Multiple Technology Appraisal

Nusinersen and risdiplam for treating spinal muscular atrophy (MA review of TA588 and TA755) [ID6195]

Committee Papers

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MULTIPLE TECHNOLOGY APPRAISAL

Nusinersen and risdiplam for treating spinal muscular atrophy (MA review of TA588 and TA755) [ID6195]

Contents:

The following documents are made available to stakeholders:

Access the **final scope** and **final stakeholder list** on the NICE website.

1. **Company submission:**
    a. Biogen
        i. Submission
        ii. Addendum
    b. Roche
        i. Submission
        ii. Addendum

2. **Company summary of information for patients (SIP):**
    a. Biogen
    b. Roche

3. **Clarification questions and company responses**
    a. Biogen
        i. Initial response
        ii. Further response
    b. Roche
        i. Initial response
        ii. Further response

4. **Patient group, professional group, and NHS organisation submissions** from:
    a. Spinal Muscular Atrophy UK-Muscular Dystrophy UK-Treat SMA (joint submission)
    b. Adult SMA Reach
    c. Association of British Neurologists
    d. SMA Reach UK
    e. NHS England

5. **External Assessment Group (EAG) report**, post consultation prepared by Newcastle NIHR TAR Team, Newcastle University - updated following consultation.
    a. EAG report post consultation
    b. Addendum of economic results

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6. **Company responses to the EAG report consultation**
    a. Biogen
    b. Roche

7. **Consultee and commentator responses to the EAG report consultation:**
    a. Spinal Muscular Atrophy UK-Muscular Dystrophy UK-Treat SMA (joint response)
    b. Adult SMA Reach
    c. Association of British Neurologists
    d. SMA Reach UK
    e. Novartis

8. **External Assessment Group critique of response to consultation** prepared by Newcastle NIHR TAR Team, Newcastle University

9. **Expert personal perspectives** from:
    a. Dr Channa Hewamadduma – clinical expert, nominated by Biogen and Roche
    b. Dr Mariacristina Scoto – clinical expert, nominated by Biogen and Roche
    c. Andrew Thornton – patient expert, nominated by Muscular Dystrophy UK and TreatSMA
    d. Lucy Frost – patient expert, nominated by Muscular Dystrophy UK and TreatSMA
    e. Portia Thorman - patient expert, nominated by Muscular Dystrophy UK

10. **Post ACM1 Company additional analyses** from
    a. Biogen
    b. Roche

11. **External Assessment Group (EAG) report addendum,** post ACM1 prepared by Newcastle NIHR TAR Team, Newcastle University.

12. **External Assessment Group (EAG) critique of DEVOTE study**

13. **SMA UK Gap filling data report,** post ACM1

Any information supplied to NICE which has been marked as confidential, has been redacted. All personal information has also been redacted.

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Multiple technology appraisal

Nusinersen for treating spinal muscular atrophy. Review of TA588

Document B

Company evidence submission

April 2024

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B.1 Decision problem, description of the technology and clinical care pathway

B.1.1 Decision problem

The technology's full marketing authorisation includes the treatment of 5q spinal muscular atrophy (SMA), which accounts for about 95% of all SMA forms [1].

The submission focuses on part of the technology's marketing authorisation, specifically people with presymptomatic, symptomatic infantile-onset (those who have type 1) and symptomatic later-onset (those who have types 2 and 3) SMA. The proposed population is narrower than the marketing authorisation (which includes all people with 5q SMA) because the evidence base on nusinersen is limited to people with presymptomatic, symptomatic infantile-onset and later-onset SMA [2]. People with SMA who do not fulfil these criteria are omitted from the submission. Clinical experts consulted by the company expressed the opinion that treatment of symptomatic infants with type 0 SMA is futile, hence this group is excluded from this submission. With regards to type 4 SMA, the available evidence is limited and insufficient for health technology assessment purposes (see Section B.2.2 for summary) and was therefore not included in cost-effectiveness modelling; however, Biogen welcomes the opportunity to discuss the available evidence, especially considering no other treatments have a marketing authorisation for use in this population.

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Table 1. The decision problem

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
Population	People with types 0, 1, 2, 3, or 4 5q SMA, or pre-symptomatic 5q SMA confirmed with genetic testing with 1 to 4 *SMN2* copies	Presymptomatic SMA and SMA types 1, 2 and 3	The evidence base on nusinersen is limited to people with presymptomatic SMA, and symptomatic infantile-onset (type 1) and later-onset SMA (types 2 and 3). Type 0 SMA was excluded from the submission due to futility of treatment for these patients. The evidence base on nusinersen in type 4 SMA is insufficient for HTA purposes, hence this population is also excluded from cost-effectiveness modelling.
Intervention	• Nusinersen • Risdiplam Interventions are monotherapies in addition to existing clinical services and established clinical management.	Nusinersen	Not applicable; Biogen are the manufacturer of nusinersen only.
Comparator(s)	• Established clinical management • Best supportive care • The interventions will be compared to each other • In addition, onasemnogene abeparvovec will be considered as a comparator for children aged ≤12 months with a biallelic mutation in the *SMN1* gene and present with a clinical diagnosis of type 1 5q SMA or pre-symptomatically with up to 3	Direct evidence is presented comparing nusinersen with established clinical management/best supportive care. Indirect evidence only is available against risdiplam and onasemnogene abeparvovec. This is subject to substantial uncertainty due to differences in trial populations and outcome assessments. See Section B.2.5 for a brief summary of the ITCs.	The sham control used in phase III ENDEAR and CHERISH trials can be considered to represent established clinical management/ best supportive care. No direct evidence is currently available against risdiplam or onasemnogene abeparvovec; consequently, ITCs were performed with the aim to inform relative efficacy. However, limitations of the ITCs render them unsuitable to inform cost-effectiveness modelling (see Section B.2.5). Therefore, this

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	copies of the *SMN2* gene		submission focuses on the comparison between nusinersen and BSC.
Outcomes	• Motor function (including, where applicable, both age-appropriate gross motor milestones and fine motor skills) • Bulbar function (including, for example, swallowing and ability to communicate) • Frequency and duration of hospitalization • Respiratory function • Complications of spinal muscular atrophy (including, for example, scoliosis and muscle contractures) • Need for non-invasive or invasive ventilation • Stamina and fatigue • Mortality • Adverse effects of treatment • Health-related quality of life (for patients and carers)	As specified in the NICE scope.	• Maintenance of respiratory function, which is most critical in type 1 SMA (see Section B.1.3.1) was included in the primary endpoint of the ENDEAR trial, i.e., time to death or permanent ventilation, with long-term assessment continued in the SHINE open-label extension. • Data on pulmonary function in later-onset SMA is limited to real-world studies and is briefly summarised in Section B.2.7. • Information on stamina and fatigue, as measured using the 6-Minute Walk Test, is limited to ambulant patients.
Economic analysis	• The reference case stipulates that the cost effectiveness of treatments should be expressed in terms of incremental cost per quality-adjusted life year. • The reference case stipulates that the time horizon for estimating clinical and cost effectiveness should be	As per the reference case	Not applicable

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	sufficiently long to reflect any differences in costs or outcomes between the technologies being compared. • Costs will be considered from an NHS and Personal Social Services perspective. • The availability of any commercial arrangements for the intervention, comparator, and subsequent treatment technologies will be taken into account. The availability of any managed access arrangement for the intervention will be taken into account.		
Subgroups to be considered	If the evidence allows the following subgroups will be considered: • Number of *SMN2* gene copies in people with presymptomatic SMA • Functional status (non-sitter, sitter, walker) • People who have had prior active treatment for SMA	• Subgroup analyses stratified by *SMN2* copy number are available for the presymptomatic population treated in NURTURE • Subgroup analyses stratified by functional status and prior therapy are available from the Managed Access Agreement established by TA588	Subgroup analyses stratified by functional status and prior therapy are at present only available from the real-world data collection as part of the Managed Access Agreement established by TA588; no data is stratified by functional status from the clinical development programme. The efficacy of nusinersen in patients who received prior therapy is currently being assessed in the ongoing studies ASCEND and RESPOND, which include patients previously treated with risdiplam and onasemnogene abeparvovec, respectively (see Section B.2.8).

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Special considerations including issues related to equity or equality	None stated	Although nusinersen will be appraised through a multiple technology appraisal, its assessment is anticipated to have several features that are commonly seen in the highly specialised technologies programme. Therefore, decision modifiers and flexibility in NICE's decision making should be taken into account.	Not applicable

Abbreviations: BSC, Best supportive care ITC, indirect treatment comparison; MTA, multiple technology appraisal; SMA, spinal muscular atrophy; *SMN*, survival of motor neuron

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B.1.2 Description of the technology being evaluated

Table 2. Technology being evaluated

UK approved name and brand name	Nusinersen (Spinraza)
Mechanism of action	Nusinersen is an antisense oligonucleotide (ASO) that increases the production of functional survival of motor neuron (SMN) protein. SMN is a ubiquitously expressed protein that provides a platform for RNA–protein interactions during the formation of ribonucleoprotein complexes, which are fundamental for cellular function.[3] Healthy individuals have two *SMN* genes, *SMN1* and *SMN2*, located on the longer (q) arm of chromosome 5. SMN1 in healthy, unaffected individuals predominantly produces the functional full-length SMN protein. *SMN2* predominantly produces a shortened, unstable, non-functioning and rapidly degraded isoform. All individuals with SMA have a loss or mutation of *SMN1*, but retain at least 1 copy of *SMN2*, which can produce a small quantity of functional SMN protein. However, the small amount of SMN protein produced does not fully compensate for the loss of *SMN1* [1,4]. Nusinersen binds to a splice silencing site in intron 7 of the SMN2 pre-messenger ribonucleic acid (mRNA), displacing factors that normally suppress splicing. Displacement of these factors leads to increased retention of exon 7 in the SMN2 mRNA transcripts and hence, increased translation to functional full-length SMN protein. [5]
Marketing authorisation/CE mark status	Nusinersen has a marketing authorisation from the MHRA for the treatment of 5q SMA.[6] It was initially approved by the EMA on 30 May 2017.[7]
Indications and any restriction(s) as described in the SmPC	The indication in the UK is for the treatment of 5q SMA.[6] Further details are available in Appendix C.
Method of administration and dosage	• Treatment with nusinersen should be started as early as possible after diagnosis with four loading doses on days 0, 14, 28, and 63. A maintenance dose should be administered once every 4 months thereafter. The recommended, licensed dose is 12 mg (5 ml) per administration for the loading dose and the maintenance dose [5]. • Nusinersen is administered as an intrathecal bolus injection over 1–3 minutes, via lumbar puncture, directly into the cerebrospinal fluid (CSF) [5].
Additional tests or investigations	• To be eligible for treatment with nusinersen on the NHS, an individual needs to have confirmed pre-symptomatic SMA, or SMA types 1, 2 or 3. No additional tests or investigations are required to initiate treatment with nusinersen, beyond those normally used to identify presymptomatic, infantile-onset, or later-onset SMA. SMA diagnosis is confirmed through genetic tests and clinical examinations, regardless of treatment choice. In the absence of a national newborn screening programme, presymptomatic SMA is identified by targeted testing of related individuals (for example, asymptomatic siblings of people diagnosed with SMA or via a pilot

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	SMA Newborn Screening Study[8]). • Lumbar puncture procedure: The use of ultrasound or other imaging techniques to assist with intrathecal administration of nusinersen can be considered at the physician's discretion, although this may only be relevant for younger patients and those with scoliosis [5]. • Thrombocytopenia and coagulation abnormalities: Thrombocytopenia and coagulation abnormalities, including acute severe thrombocytopenia, have been observed after administration of other subcutaneously or intravenously administered ASOs. If clinically indicated, platelet and coagulation laboratory testing is recommended before administration of nusinersen [5]. • Renal toxicity: Renal toxicity has been observed after administration of other subcutaneously and intravenously administered ASOs. If clinically indicated, urine protein testing (preferably using a first morning urine specimen) is recommended. For persistent elevated urinary protein, further evaluation should be considered [5].
List price and average cost of a course of treatment	The list price is £75,000 per vial (excluding VAT). At the list price, the total annual treatment cost is £450,000 for the first year and £225,000 for subsequent years.
Patient access scheme (if applicable)	A simple PAS is currently approved. The PAS price is £[redacted] per vial (excluding VAT) At the PAS price, the total annual treatment cost is [redacted] for the first year and [redacted] for subsequent years. .

Abbreviations: ASO, antisense oligonucleotide; CE, Conformité Européenne; CSF, cerebrospinal fluid; EMA, European Medicines Agency; MHRA, Medicines and Healthcare products Regulatory Agency; mRNA, messenger ribonucleic acid; RNA, ribonucleic acid; SMA, spinal muscular atrophy; SMN, survival of motor neuron; SmPC, summary of product characteristics.

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B.1.3 Health condition and position of the technology in the treatment pathway

B.1.3.1 5q SMA diagnosis

SMA is a rare, genetic, neuromuscular disease, which is debilitating and can be fatal[7]. The disease not only affects the musculoskeletal system but also the respiratory and gastrointestinal systems[9]. SMA is recognised by the European Medicines Agency (EMA) as an orphan disease and, without treatment, is the leading genetic cause of infant mortality globally[10]. Individuals with SMA have an insufficient level of functional survival of motor neuron (SMN) protein caused by loss or mutation in the *SMN1* gene. Over time, this leads to the progressive loss of motor function and respiratory failure[1,2].

In the absence of universal newborn screening, the diagnosis of SMA is prompted by family history of the condition or clinical signs. The diagnosis can be confirmed through genetic testing, with the gold standard being a quantitative analysis of both *SMN1* and *SMN2* using multiplex ligation-dependent probe amplification (MLPA), quantitative polymerase chain reaction (qPCR), or next generation sequencing (NGS)[11]. Diagnosis of SMA can be ascertained if both full *SMN1* copies are absent[11]. In patients with a single full copy of *SMN1* and clinical signs and symptoms of SMA, the remaining *SMN1* gene should be sequenced to identify any possible mutations[11]. In patients who have two full *SMN1* copies, a diagnosis of SMA is highly unlikely but the *SMN1* gene should be sequenced if there is a strong clinical indication or consanguinity[11].

B.1.3.2 Subtypes of 5q SMA

The disease presents across a spectrum of subtypes, with greater disease severity linked to younger age of onset, as shown in Table 3[12]. Type 1 and types 2 to 3 can be grouped into infantile-onset SMA and later-onset SMA, respectively, based on age of onset and motor function achieved. SMA severity is linked to *SMN2* copy number, with higher *SMN2* copy number linked to milder disease, although this is not the only phenotypic modifier[13]. All SMA patients have at least one copy of *SMN2*[11].

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Table 3. Classification and subtypes of SMA

Type	Age of onset	Maximal motor milestone	Motor ability and additional features	Prognosis[b]	Possible *SMN2* copy number (most common copy number in bold)
SMA 0	Before birth	None	Severe hypotonia; unable to sit and roll[a]	Respiratory insufficiency at birth: death within weeks	1
SMA 1	<6 months	None	Severe hypotonia; unable to sit and roll	Death/permanent ventilation by 2 years	1, **2**, 3
SMA 2	6 to <18 months	Sitting	Proximal weakness: unable to walk independently	Survival into adulthood (70% alive at age 25 years)	2, **3**, 4
SMA 3	>18 months to <18 years	Walking	May lose ability to walk	Normal life span	**3**, **4**, 5
SMA 4	>18 years	Normal	Mild motor impairment	Normal life span	>4

Table abbreviations: SMA, spinal muscular atrophy.

[a] Need for respiratory support at birth; contractures at birth, reduced foetal movements

[b] Prognosis varies with phenotype and supportive care interventions

Source: Farrar, et al. [12], Kolb and Kissel [13], Prior, et al. [14], Feldkötter, et al. [15], Calucho, et al. [16]

A presymptomatic SMA individual is defined as a patient who has genetically confirmed 5q SMA but is not exhibiting any clinical signs or symptoms of SMA. These individuals are genetically destined to develop 5q SMA. Presymptomatic SMA is identified by either newborn screening programs or targeted testing of related individuals (for example, asymptomatic siblings of individuals diagnosed with SMA). At the time of presymptomatic diagnosis, the type of SMA cannot be ascertained clinically, but it can be predicted based on *SMN2* copy number.

Type 0 SMA is often associated with reduced foetal movement *in utero*, severe weakness and respiratory distress at birth and often causes mortality due to respiratory distress within a few weeks[17-20]. Therefore, incidence data is lacking because infants do not always receive a diagnosis, which has been confirmed by clinical experts[21]. Type 0 SMA is not included in this submission, because it is unlikely that treatment would prove beneficial to affected patients. Both limited

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previous published reports on the use of nusinersen in type 0 SMA[22,23] and clinical experts consulted by Biogen during an advisory board suggest the futility of treating type 0 patients with nusinersen.

Infantile-onset SMA causes limited motor development, failure to reach motor milestones and the inability to sit without support, alongside the loss of any motor function gained before the onset of symptoms and an increased need for respiratory intervention[9,24,25]. In a US study which assessed motor milestones using the Hammersmith Infant Neurological Examination (HINE-2) in 33 untreated infants with type 1 SMA, none of the infants achieved milestones such as sitting, rolling, crawling, standing, or walking. Partial achievement, corresponding to a score of 1–4, was reported for the milestones of head control (39% of patients), kicking (46%) and hand grasp (55%)[26]. The Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders (CHOP INTEND) scale is another scale that is commonly used to assess motor function is patients with type 1 SMA. A pooled analysis of three longitudinal natural history studies of untreated patients (n=38) reported that the mean decline in CHOP INTEND score per month was 1–2 points per month in patients with two *SMN2* copies, regardless of age at symptom onset (neonatal vs post-neonatal) and baseline CHOP INTEND score (<25, 25–35, >35)[27]. People with type 1 SMA often experience pulmonary complications, which contribute to respiratory failure due to impaired secretion clearance, and insufficient ventilation and oxygenation. Other complications may include nutritional deficiencies, the need for feeding support and the risk of aspiration pneumonia as a result of gastrointestinal complications[28]. Therefore, children with infantile-onset SMA have severe physical disability and experience early morbidity due to respiratory insufficiency and aspiration pneumonia. The median age for death or permanent respiratory support (a composite endpoint used in clinical trials in this population) is approximately 9 to 13 months[29]. The differential use of life-extending symptomatic care, including permanent respiratory support, means that real-world survival may not reflect clinical trials.

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To understand real-world survival, a survey of 6 paediatric neuromuscular disease centres in England and Wales was conducted and the average age of mortality for infantile-onset was estimated to be 18.6 months (range 10 to 24 months)[30,31].

Patients with untreated later onset (type 2 and 3) SMA experience a progressive decline in motor function[32,33]. In patients with type 2 SMA, disease progression, as assessed using the Hammersmith Functional Motor Scale - Expanded (HFMSE), was non-linear with an improvement until the age of 5 years followed by a rapid deterioration until puberty and a slower decline thereafter[32,34,35]. Age and severity of functional impairment at baseline are predictive factors for overall disease progression[32,34]. Among 199 patients with type 3 SMA participating in an international study, 26 patients lost ambulation during a 12-month follow-up period, of whom 85% had SMA Type 3a[33]. Participants with type 3a SMA also lost ambulation at an earlier age than those with type 3b (11.47 vs 13.43 years). Furthermore, ambulatory participants with SMA Type 3 experience progressive loss of walking ability, with an international study of 73 patients reporting a mean annual change in the 6-minute walk test (6MWT) of -7.8m[36]. If untreated, patients with type 2 and 3 SMA also experience progressive reductions in hand function measured with the Revised Upper Limb Module (RULM), with a study of 107 patients with later-onset SMA reporting a significant decline in RULM scores over two years in type 2 but not type 3 patients[37]. Among patients with type 3 SMA, non-ambulant patients experienced a slow progressive decline in RULM over 24 months, while the scores of ambulant patients were relatively stable[37],

Later-onset SMA is associated with a gradual decline in respiratory function. In an 8-year international, retrospective, observational study including 437 patients with later-onset SMA, 39% of patients with type 2 SMA and up to 9% of non-ambulant patients with type 3 SMA required non-invasive ventilation[38]. Scoliosis was prevalent in this study, affecting 84% of type 2 patients and 80% of non-ambulant type 3 patients, and 48% and 31%, respectively, underwent surgery for scoliosis[38]. However, surgery did not slow the decline in respiratory function[38]. Although people with later-onset SMA usually survive into adulthood, the considerable morbidity of the disease is associated with lifelong impacts on health-related quality of life (HRQoL), ability to live independently, and requirements for care because of

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contractures to the lower extremities, hypermobile joints in the upper extremities and recurrent fractures[39,40]. Pain caused by severe contractures, osteoporosis, vertebral fractures, orthopaedic procedures, or muscular overuse is also a frequent occurrence and major feature of SMA[41]. Furthermore, later-onset SMA imposes a major physical and psychological burden due to the progressive decline in health, including fear of losing independence, struggle with feeding, and impaired breathing[41,42].

Patients with type 4 SMA typically present with muscle weakness in their late teens or twenties[14]. The weakness particularly affects the deltoids, triceps, and quadriceps muscles, and patients may develop hand tremor[14]. Disease progression is slower than with type 3 SMA and if patients lose ambulation, it usually occurs after the age of 50[14]. The life expectancy of affected patients is normal[14]. The evidence on the use of nusinersen in type 4 SMA is predominantly available from the SMArtCARE registry, which included 9 (4%) patients with type 4 SMA among 237 adult patients with SMA who had been treated with nusinersen for ≥14 months[43]. Although the data for the few type 4 patients were not presented separately, in the overall population of adults with SMA treatment with nusinersen resulted in increases from baseline in all outcome measures, including HFSME (primary outcome), RULM, and 6MWT scores, that were sustained through month 38[43].

Despite the widespread use of the SMA staging system, patient experts have previously commented that the SMA classification system does not always reflect the full extent of the disease. The boundaries between the different SMA types are blurred and can be subjective. It is also important to note that the classification system was not originally intended to define populations who were eligible for treatment[21].

B.1.3.3 Epidemiology of SMA

There are an estimated 1,340 patients living with SMA in the UK[44]. Infantile-onset SMA (type 1) is a severe form of the disease estimated to occur in 5.83 per 100,000 live births[45,46]. Prior to the availability of treatment, prevalence was estimated at around 0.1 per 100,000 population due to high mortality rates as patients rarely survive to their second birthday without treatment[10]. However, since the introduction of several disease modifying therapies, prevalence is likely higher at present and

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Biogen estimates that there are approximately 130–150 prevalent patients with type 1 SMA in England and Wales. Based on 2018/19 data from the National Congenital Anomaly and Rare Disease Registration Service (NCARDRS), SMA type 1 accounted for around 60% of all SMA cases[31]. In England and Wales, around 37 babies a year are born with SMA type 1. Symptoms of SMA type 1 appear before 6 months and include muscle weakness of varying severity, mainly evident as hypotonia, inability to lift head/poor head control, poor feeding, and respiratory issues[47-49]. SMA type 0 is very rare (<1% cases).

People with later-onset SMA are most likely to develop type 2 or type 3, with an estimated incidence of 1.9 and 1.7 per 100,000 live births, respectively [50]. Type 4 SMA is very rare and affects <5% of individuals with SMA[14].

Given that treatments for patients with SMA have been available for several years now, and that clinical experts consulted by Biogen stated that less than 5% of paediatric patients remain untreated (predominantly due to parental choice) and approximately 10% of adult patients known to the system are untreated. Most patients initiating treatment in England and Wales will be newly-diagnosed incident patients and/or patients identified through newborn screening if recommended by the National Screening Committee following pilot studies. To optimise clinical outcomes in these patients, it is essential to initiate treatment as early as possible following diagnosis.

B.1.3.4 Humanistic burden of SMA

The humanistic burden of SMA is substantial and small improvements in motor function, or even disease stabilisation, can have a significant impact on patients' quality of life (QoL). Average utility measured using the EQ-5D-5L across SMA patients in Canada was reported to be 0.49, with the impairment in patients with type 1 SMA (0.32), followed by patients with type 2 and 3 (0.46 and 0.65, respectively)[51]. In the UK, the averaged utility measured using the proxy version of the EQ-5D-3L was reported to be even lower (0.167 [SD: 0.277]) in a study that enrolled 34 children with SMA from the UK, of whom nearly 60% had type 2 disease[52]. Increased functional status correlates with increased QoL in patients with SMA, but nonetheless QoL in SMA remains significantly impaired and lower than in the general population[52-54].

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Mobility is important for QoL of patients with SMA at all ages. Everyday activities, such as the ability to use restrooms alone, have a wash by themselves, and perform transfers on their own have a major impact on the QoL of children with SMA[55]. Among older individuals with SMA, limited mobility and ability to participate in everyday activities are common. In a 2016 survey of 359 adults with SMA in the United States, almost all participants reported limitations with mobility, walking or ability to perform activities, resulting in a negative effect on their personal lives[56]. In a study of 62 adults with SMA in the Netherlands, the participants reported being substantially restricted and dissatisfied with their ability to participate in daily activities[57].

The impact that SMA has on patients' lives varies by disease type. Patients with type 1 SMA are typically unable to sit and have short lives with high care needs, often spending prolonged periods of time in hospital. They require respiratory support (non-invasive ventilation or cough-assist) almost daily. Some patients require permanent ventilation or tracheostomy, are unable to swallow and need tube feeding. Whilst these interventions may prolong survival, the procedures themselves are invasive. Patients with type 2 SMA and those with progressed type 3 SMA are able to sit but are not ambulatory. These patients suffer from painful musculoskeletal issues, such as scoliosis, contractures, and fractures, and often require multiple surgeries. As their disease progresses, patients with later-onset SMA can develop feeding issues and respiratory infections. Ambulatory patients with type 3 SMA achieve the ability to walk unassisted, but their mobility is still limited. Patients experience frequent falls and may require wheelchair for longer distances.

SMA poses a substantial burden on caregivers of affected patients, who report reduced working time and impaired work productivity, increased stress, limitations on social activities, concerns for their own health (including anxiety and depression), and pressures on family finances[51,58-64]. SMA affects not just the patient and their primary caregiver, but the entire family. The diagnosis of SMA, the symptoms that patients experience, and difficult treatment decisions bring stress and anxiety. Physical health of the caregivers also suffers, and they may need support services. In a Canadian survey of 962 caregivers, 45.7% reported needing respite care, 45.7% reported needing physiotherapy for an injury from a lift/transfer, and 63.3% reported

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other health impacts[51]. Furthermore, the time burden on caregivers of patients with SMA is substantial. In an Italian cohort study of 118 families affected by SMA, caregiver work productivity burden was significant with 47% of carers being unemployed, 46% employed and reporting lost work days, and only 7% employed and not reporting lost work days; the average annual number of lost work days was 38 [59]. In a cross-sectional study of 68 informal caregivers of patients with SMA in Europe, the average care time was 10 hours per day, of which the main caregiver provided an average of 6.9 hours, while the remaining care time fell on other caregivers [65]. Caregiver impairment correlates with patient age and functional status[62], as well as SMA type[64], with the highest burden reported by caregiver of patients with type 1 SMA[64,65]. Caregivers of individuals with SMA (predominantly type 1) may also experience bereavement as patients with SMA are at risk of dying, which adds further to the impact that SMA has on the patients' families. Due to the high risk of mortality, type 1 SMA qualifies for the NICE severity modifier.

B.1.3.5 Economic burden of SMA

Despite the rare nature of the disease, both infantile-onset and later-onset SMA pose a substantial economic burden to the healthcare system, families affected by SMA, and the wider society. The major cost drivers are summarised in Figure 1.

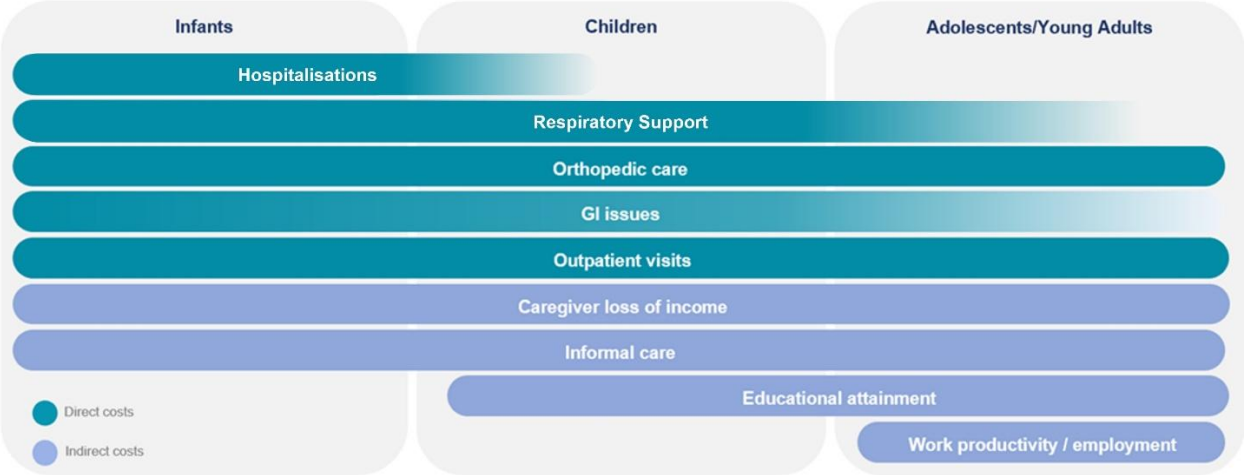
The costs of treating SMA vary by disease type and functional status. As the disease progresses, people with SMA need more intensive treatments. Total annual healthcare costs reported in the NICE approval of onasemnogene abeparvovec (HST24, also used in the economic model in this submission), ranged from £8,333 for patients able to stand and walk, through £67,567 in patients who can sit but are not ambulatory, to £112,500 in non-sitters, and £283,710 in those on permanent ventilation (Table 65). Hospitalisations were the main cost driver in all non-ambulant patients (permanent ventilation, non-sitters, and sitters), followed by social services. In ambulant patients, social services and medical visits were the two main cost drivers (Table 65).

A high proportion of parents of children with SMA have to reduce working hours or even leave their jobs, leading to financial strain and further impacting on their HRQoL [58]. A survey of families affected by SMA in Scotland found that 79% (n=15/19) of the main unpaid carers had to give up work completely or drop to part

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time [66]. This is driven by increased utilisation of healthcare resources, such as inpatient and intensive care stays, outpatient visits, non-medical costs, professional caregiving, and durable medical equipment [58,67,68]. Parents of children with SMA (types 1 to 3) in Scotland reported that they attend 2 to 6 appointments a month in connection with their child's SMA and spend up to 80 hours a month on non-caring, SMA-related tasks [66]. In a cross-sectional study, primary caregivers reported providing care to individuals with SMA for an average of 10 hours per day, with most of the time focused on assisting patients with basic activities of daily living (for example, helping with basic hygiene, dressing, and/or moving the person); caregivers of individuals with SMA type 1 were more likely to provide >10 hours of daily care than those caring for individuals with SMA type 3 [65].

Figure 1. Typical cost drivers in SMA



Abbreviations: GI, gastrointestinal

B.1.3.6 Treatment Guidelines

The International Standard of Care Committee (SCC) for SMA has issued a two-part updated consensus statement on types 1 to 4 SMA. Part 1 provides an update on diagnosis, rehabilitation, orthopaedic and spinal management in SMA, whereas part 2 discusses pulmonary management, acute care, other organ involvement, and ethical issues[11,69]. However, as the consensus process underlying this statement was completed before any of the disease-modifying therapies received regulatory approval, the Consensus Statement does not provide information relevant to disease-modifying therapy. However, the guidelines still apply for those who are not

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currently eligible for nusinersen, onasemnogene abeparvovec, or risdiplam. In addition, while therapies are available for some SMA subtypes, many of these individuals will still need multidisciplinary supportive care, including nutritional support, rehabilitation, respiratory therapy, and orthopaedic surgery.

The updated SCC for SMA consensus statement addresses 3 functional levels: non-sitter, sitter, and walker (rather than SMA subtypes)[69]. The recommendations from the SCC consensus statement are summarised in Table 4[70].

Table 4. Clinical management recommendations from the consensus statement by the SCC for SMA

<table>
<tr><th>Type of care</th><th>Non-sitters</th><th>Sitters</th><th>Walkers</th></tr>
<tr><td colspan="4">Pulmonary care</td></tr>
<tr><td>Anticipatory respiratory care</td><td colspan="3">• Understanding the patient’s baseline, deviations from his/her baseline, hypoventilation and intervention
• Acute illness management including rapid access to specialty medical care providers
• Nutrition and hydration
• A low threshold to start antibiotics
• Routine immunisations</td></tr>
<tr><td rowspan="3">Chronic respiratory management</td><td colspan="3">Airway clearance:
• Assisted cough (MI-E or manual)
• Secretion mobilisation techniques (chest physiotherapy, postural drainage)
• Oximetry to guide therapy
Respiratory support:
• NIV
CPAP (goal to transition to BiPAP)</td></tr>
<tr><td>• Option: Care without ventilation support
• Palliative care
• Tracheotomy</td><td>Airway clearance/ respiratory support, as needed</td><td rowspan="2">Airway clearance/ respiratory support not likely to be required until late into the disease course</td></tr>
<tr><td colspan="2">NIV with high span BiPAP, even for short daytime periods</td></tr>
<tr><td rowspan="2">Acute care management</td><td colspan="3">Airway clearance:
• Assisted cough (MI-E or manual), oral or airway suctioning
• Oximetry
• Chest physiotherapy
• Postural drainage
Respiratory support:
• Acute use of NIV
• Oxygen therapy</td></tr>
<tr><td colspan="2">Respiratory support:
• Daytime NIV with airway clearance
• Intubation and mechanical ventilation
• Palliative care</td><td>Respiratory support:
• NIV for home use</td></tr>
</table>

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Type of care	Non-sitters	Sitters	Walkers
Gastrointestinal and nutritional care			
Feeding and swallowing difficulties	• Changing food consistency • Positioning and seating alterations and orthotic devices • Nutritional supplementation through NG or NJ feeding • Gastrostomy tube feeding		
Gastrointestinal dysfunction	Management of gastroesophageal reflux: • Short-term use of acid neutralisers and/or inhibitors of acid secretion • Prokinetic agents • Probiotics • Laparoscopic anti-reflux Nissen fundoplication		
Growth and under or over nutrition problems	• Monitoring of growth velocity (growth charts) • Dietitian assessment of nutritional intake • Appropriate intake of calcium and vitamin D • Monitor pre-albumin levels		
Management of nutrition in acutely sick people with SMA	• Avoid prolonged fasting due to high risk of hypoglycaemia • Enteral and/or parenteral feeding to meet caloric needs within 4–6 hours of acute illness admission • Post-operative caloric supplementation		
Neuromuscular and musculoskeletal evaluation			
Managing musculoskeletal problems	• Assessments of strength and range of joint motion, relevant motor functional scales and timed tests to monitor those aspect of function that reflect ADL		
Orthopaedic care and rehabilitation			
Managing problems caused by muscle weakness	• Wheelchair mobility • Environmental controls and home modifications		
	• Posture management with supportive seating • Contracture management by splinting • Pain management • Therapy for ADL and assistive equipment • Limb orthotics	• Contracture management by stretching, bracing, serial casting, orthotics and supports/slings • Regular exercise and standing with appropriate assistive devices and orthotics • Spine orthotics and surgery	• Contracture management and education • PT and OT • Regular exercise and walking with appropriate assistive devices and orthotics • Spine/limb orthotics and surgery
Orthopaedic surgery	Non-sitters do not benefit from surgery	• Hip subluxation and contractures • Scoliosis surgery	
Other care			
Perioperative care	Due to high risk for post-anaesthesia complications, respiratory status needs to be optimised and orthotic interventions need to be adjusted before surgery. After surgery, close monitoring, aggressive respiratory management, and rapid mobilisation, may be required.		

Table abbreviations: ADL, activities of daily living; BiPAP, bi-level positive airway pressure; CPAP, continuous positive airway pressure; NIV, non-invasive ventilation; NG, nasogastric; NJ, nasojejunal; MI-E, mechanical insufflation/exsufflation; PT, physiotherapy; OT, occupational therapy; SCC, International Standard of Care Committee; SMA, spinal muscular atrophy Source: TREAT-NMD [70]; Mercuri, et al. [11]

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B.1.3.7 Clinical pathway of care for SMA

Before 2017, there were no therapies for the disease, meaning all people with SMA were managed through multi-disciplinary supportive management. In 2017, nusinersen became available in the UK through the Expanded Access Programme (EAP), where Biogen provided nusinersen free of charge, though access was limited to type 1 SMA, and only available where the clinical management team and the infant's parents agreed to the treatment. Over the period 2009–2016, infant mortality rate in patients with SMA in the UK was 4.2 per 100,000 live births[31]. This fell to 1.9 per 100,000 in 2017, which coincided with the opening of the nusinersen EAP [31]. In March 2018, NHS England issued an urgent commissioning statement to reimburse the administration costs for nusinersen provided by the EAP[71].

In 2019, NICE assessed nusinersen for people with types 1, 2, and 3 SMA and presymptomatic SMA (TA588). The main clinical effectiveness evidence for nusinersen came from two clinicals trials: ENDEAR and CHERISH, both randomised, double blind, multicentre, phase 3, sham-controlled trials [72,73]. The clinical trial evidence showed that nusinersen improved a range of outcomes that are important to people with infantile- and later-onset SMA and, at the time, that there was some evidence that nusinersen is effective for presymptomatic SMA. However, there was no long-term evidence, so the long-term benefits were highly uncertain. As such, nusinersen was made available to people with type 1, 2 and 3 SMA and presymptomatic SMA as part of a 5-year MAA, while data to address the uncertainties about the benefits of nusinersen was collected. In 2021, the MAA was updated to cover treatment for people with type 3 SMA who are unable to walk.

In 2020, the gene therapy onasemnogene abeparvovec (Zolgensma), designed to introduce a functional *SMN1* copy, was licenced by the EMA for patients with inherited mutations affecting *SMN1*, who have either been diagnosed with SMA type 1 (the most severe type) or have up to 3 copies of *SMN2*. In 2021, NICE recommended onasemnogene abeparvovec as an option for 5q SMA with a bi-allelic mutation in the *SMN1* gene for type 1 SMA in babies aged 12 months and younger[74]. NHS England expanded this eligibility criteria to include children of any age weighing up to 21 kg. However, in January 2023 there was a temporary pause when they reverted to the original NICE guidance following safety concerns, after MHRA review

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in March 2023 the expansion of eligibility criteria was resumed. In April 2023, NICE recommended onasemnogene abeparvovec for presymptomatic individuals with SMA[75].

Risdiplam (Evrysdi), an orally administered modifier of *SMN2* splicing, was licenced in 2021 for the treatment of 5q SMA in patients 2 months of age and older, with a clinical diagnosis of SMA type 1, 2 or 3, or presymptomatic with 1 to 4 *SMN2* copies; however, the 2-month age restriction was lifted in December 2023. In 2021, NICE made risdiplam available subject to terms of an MAA for SMA types 1, 2, and 3, or presymptomatic with 1 to 4 SMN2 copies [76]. This recommendation was expanded in December 2023 to remove the 2-month age restriction in line with the revisions to the marketing authorisation for risdiplam [76].

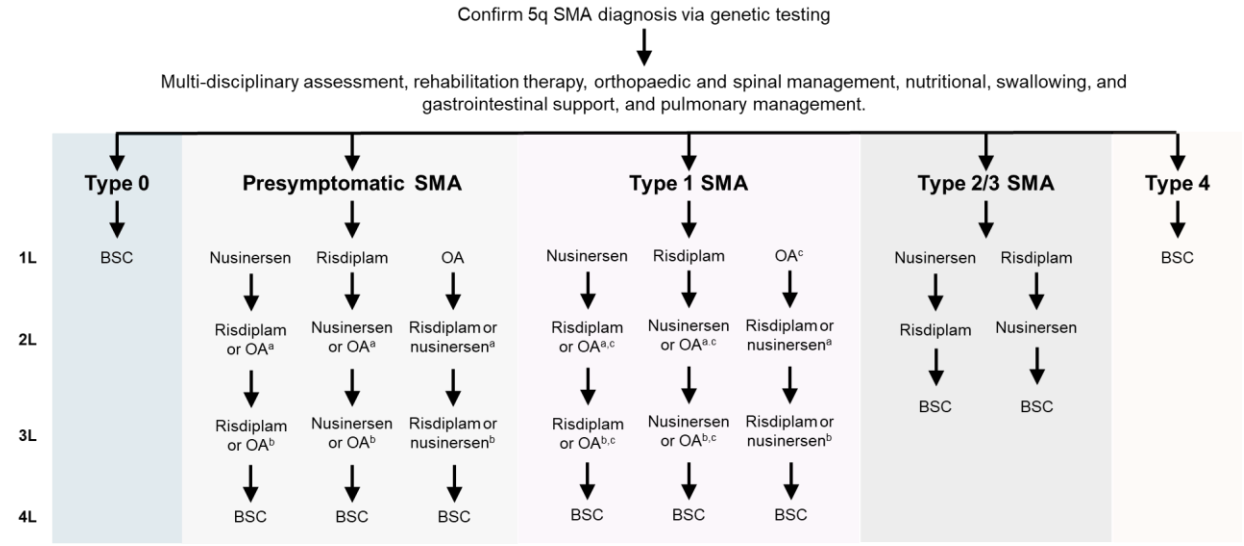
At present, there are no therapies available through routine commissioning or managed access for SMA type 0 and SMA type 4. In the previous nusinersen submission (TA588), there was no evidence for these subtypes. No new evidence is presented in this submission for patients with type 0 SMA. As described in Section B.1.3.2, both clinical expert opinion and limited published evidence suggest that treatment of these patients would be futile. For patients with type 4 SMA, clinical experts stated they would treat type 4 SMA patients should nusinersen be recommended. The limited evidence available for type 4 SMA from the SMArtCARE registry is described in Section B.2.2; however, it is not sufficient to include these patients in the cost-effectiveness modelling, although Biogen would welcome a discussion about potential routes to funding nusinersen for patients with type 4 SMA.

B.1.3.8 Proposed place of nusinersen within the clinical pathway

In line with the current use of nusinersen within NHS England, it is expected that all people with presymptomatic, type 1, type 2, and type 3 SMA can be offered nusinersen as a first-line therapy. The position of nusinersen in the overall SMA treatment pathway is shown in Figure 2. Real-world efficacy and safety outcomes of patients treated with nusinersen in England and Wales as part of the MAA are available in Section B.2.4.5, while an overview of the MAA methodology is provided in Section B.2.3.4.

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Figure 2. Clinical care pathway with nusinersen



Abbreviations: 1L, first line treatment; 2L, second line treatment; 3L, third line treatment; 4L, fourth line treatment; BSC, best supportive care (based on individual clinical need and symptom severity); OA, onasemnogene abeparvovec; SMA, spinal muscular atrophy.
a: Second-line treatment choice based on clinical decision
b: Third-line treatment choice based on clinical decision and second-line treatment
c: In line with HST15, to be eligible for treatment with onasemnogene abeparvovec, patients with type 1 SMA have to be aged ≤6 months, or ≤12 months if their treatment is approved by the national multidisciplinary team, and cannot require permanent ventilation for ≥16 hours per day or a tracheostomy[74]

B.1.4 Equality considerations

The licensed indication for nusinersen includes all people with 5q SMA, however, the economic evaluation includes presymptomatic individuals with genetically diagnosed 5q SMA and people with SMA where symptom onset begins before adulthood (Type 1 to 3). This is due to the inclusion criteria of the available clinical evidence.

Although nusinersen will be appraised through a multiple technology appraisal, its assessment is anticipated to have several features that are commonly seen in the highly specialised technologies programme. Therefore, decision modifiers and flexibility in NICE's decision making should be taken into account.

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B.2 Clinical effectiveness

Summary of key results:

- Nusinersen has been investigated in multiple controlled and uncontrolled open-label clinical studies that together cover the majority of the 5q SMA spectrum. Key results from the pivotal trials ENDEAR and CHERISH, the long-term open-label extension SHINE, the NURTURE study in presymptomatic patients, the nusinersen MAA, and the ongoing RESPOND study are summarised below.
- ENDEAR was the pivotal study demonstrating the efficacy of nusinersen vs sham control in symptomatic patients with infantile-onset SMA. The trial met both its primary endpoints, demonstrating the efficacy of nusinersen in patients with infantile-onset SMA.
  - At the interim analysis when this endpoint was formally analysed, the proportion of motor milestone responders assessed using HINE-2 was 41% in the nusinersen group vs 0% in the sham group, p<0.0001. At the final analysis, the proportions were 51% in the nusinersen group vs 0% in the sham group.
  - Patients treated with nusinersen has a 47% reduction in the risk of death or permanent ventilation compared with patients who received the sham procedure (HR: 0.530, p = 0.0046).
  - There was a 62.8% reduction in the risk of death with nusinersen vs sham control (HR : 0.372, p=0.0041).
- CHERISH was the pivotal trial demonstrating the efficacy of nusinersen in the treatment of symptomatic patients with later-onset SMA.
  - Significant and clinically meaningful differences in HFMSE scores were observed in children treated with nusinersen compared with sham control. The trial met its primary endpoint, with nusinersen-treated patients demonstrating an improvement in HFMSE scores at 15 months as compared with patients in the control group (least squares [LS] mean change, nusinersen vs sham control: 4.0 vs. -1.9; p = 0.0000002). Results from the final analysis were consistent with the interim analysis (LS mean change 3.9 with nusinersen vs -1.0 with sham control, p = 0.0000001).
  - In addition, clinically meaningful increases in RULM scores were observed in children treated with nusinersen compared with sham procedure with a LS mean difference of 3.7 between the groups (p = 0.0000001).
  - In the nusinersen group, 19.7% of patients achieved new WHO motor milestones compared with 5.9% of patients in the control group (difference of 13.8%, p = 0.0811).
- The data available from the open-label extension SHINE speak to long-term efficacy and safety of nusinersen. The data presented in this submission focus on patients transitioning from ENDEAR and CHERISH.
- SHINE results highlight the benefits of early initiation of treatment with nusinersen, [redacted] in previous nusinersen patients (i.e., patients who received nusinersen in ENDEAR/CHERISH) than previous control patients (i.e., patients who received sham treatment in ENDEAR).
  - In patients with infantile-onset SMA who transitioned from ENDEAR, [redacted] A [redacted] of previous nusinersen patients ([redacted]) died or required permanent ventilation in ENDEAR and/or SHINE compared with previous control patients ([redacted]).
  - A [redacted] of previous nusinersen patients ([redacted]) died in ENDEAR or SHINE compared with previous control patients ([redacted].

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- With regards to HINE-2, at Day 818, mean HINE-2 total motor milestone scores for previous control and previous nusinersen patients were [redacted], respectively, [redacted], respectively.
- [redacted] At Day 2790, the scores [redacted] in previous control and previous nusinersen groups, respectively.
- Mean HFMSE total scores for previous nusinersen patients [redacted] than for previous control patients. [redacted]

- NURTURE was a single-arm study that demonstrated the efficacy of nusinersen in presymptomatic individuals with SMA.
  - As of the 15 February 2021 data cut, none of the 25 infants enrolled had died or required permanent ventilation at a median age of 4.9 (range 3.8–5.5) years, which is in stark contrast with the natural history of infantile-onset SMA and also represents a substantial improvement relative to the outcomes observed in ENDEAR, where treatment with nusinersen was initiated after symptom onset.
  - Four patients met the endpoint of death or respiratory intervention (invasive or non-invasive for ≥ 6 hours/day continuously for 7 or more days OR tracheostomy), which was defined more strictly than similar endpoints in comparator trials enrolling the presymptomatic population (RAINBOWFISH and SPR1NT).
  - All 10 children with three *SMN2* copies achieved the highest WHO motor milestone of walking independently within normal developmental timeframes.
  - Among the 15 children with two *SMN2* copies, all achieved sitting without support and standing with assistance, 14 achieved hands and knees crawling and walking with assistance, and 13 achieved standing alone and walking alone, with some attaining milestones within normal developmental time frames.
- Data from the MAA support real-world efficacy of nusinersen in paediatric and adult patients with SMA in the UK.
  - Among paediatric patients treated with nusinersen and evaluable at time points up to 48 months, ≥70.8% patients attained new motor milestones or remained in the same motor milestone category relative to baseline, regardless of baseline motor function and SMA type.
  - Motor function scales generally demonstrated improvement from baseline in paediatric patients treated with nusinersen across SMA types, which is in contrast to the decline over time observed in untreated patients with SMA.
  - None of the patients included in the final analysis cohort died, and the requirement for permanent ventilation was limited to three patients with type 1 SMA who were enrolled in the nusinersen Early Access Programme (EAP) prior to enrolment in the MAA. The EAP cohort included chronic patients with type 1 SMA with a median age of 2.91 years at treatment initiation (vs 0.28 years in the SMA type 1 non-EAP cohort).
  - Contrary to the progressive nature of SMA, ≥87.5% of adult patients evaluable at time points up to 42 months attained new motor milestones or remained in the same motor milestone category relative to baseline, regardless of baseline motor function status (non-sitter, sitter, walker). It should also be noted that walking without assistance is the last WHO motor milestone, so ambulant patients could not achieve any further milestones.
  - Except for small improvements in upper limb function as measured on the RULM, there were no statistically significant changes from baseline in any of the scales, indicating that nusinersen prevented the disease-related worsening of motor function in this diverse, real-world patient cohort. In contrast, untreated adults (aged >15 years) with later-onset SMA reported a mean decline from baseline in the RULM score of 0.6 points at 12 months.

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- Three studies of nusinersen are currently ongoing: DEVOTE, ASCEND, and RESPOND.
  - DEVOTE is an ongoing phase 2/3, randomized, controlled escalating dose study using active-controlled treatment, evaluating the safety/tolerability, efficacy, and pharmacokinetics of investigational higher doses of nusinersen in patients with SMA.
  - RESPOND is a phase 4, open-label, multicentre, single-arm study of nusinersen (currently licensed dose) in children with SMA who have previously received onasemnogene abeparvovec and have suboptimal clinical status per the Investigator. In an interim analysis, most participants with suboptimal motor function at baseline improved, Mean (SD) HINE-2 scores increased across age groups, with a 5.4 (2.62) point improvement from baseline in patients with two *SMN2* copies aged ≤9 months at first dose of nusinersen and a 5.2 (2.74) point improvement in patients with two *SMN2* copies aged >9 months at first nusinersen dose.
  - ASCEND is an international, open-label, single-arm study of higher dose nusinersen in non-ambulatory patients with later-onset SMA previously treated with risdiplam.
- The safety profile of nusinersen emerging from available clinical studies is favourable, with AEs generally consistent with underlying SMA or with the lumbar puncture procedure.

B.2.1 Identification and selection of relevant studies

Published clinical studies relevant to this submission were identified through a systematic literature review that included studies of patients with 5q SMA of any age or SMA type, including pre-symptomatic patients. Eligible interventions/comparators were nusinersen, onasemnogene abeparvovec and risdiplam against any other of the three eligible interventions or sham / placebo / best supportive care. Eligible outcomes included overall survival, event-free survival, ventilation use, motor milestones, motor function scores, HRQoL, hospitalisation, bulbar function, speech and communication, respiratory function, complications of SMA, stamina and fatigue, neurological outcomes, growth measures, development of symptomatic SMA, adherence to treatment, and safety outcomes. Randomised controlled trials (RCTs), non-randomised controlled trials, single-arm trials, cohort studies (i.e. comparative observational studies) and large (≥100 participants) non-comparative observational studies were eligible for inclusion. Medline, Embase, Cochrane Database of Systematic Reviews, well-established registers of clinical trials, HTA and regulatory agency websites, and key SMA-related conference websites were searched, and no date or language restrictions were applied. A comprehensive quality assessment of included studies was undertaken as part of the systematic review process.

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A total of 52 studies described in 282 reports were included, of which five were multinational RCTs. For these RCTs, the feasibility of conducting indirect treatment comparisons between nusinersen, risdiplam, and onasemnogene abeparvovec were explored, considering separate networks for pre-symptomatic, type 1 and type 2 and 3 SMA.

There were no RCTs of pre-symptomatic SMA. Only one RCT of nusinersen was identified for type 1 SMA. In type 2 and 3 SMA, network meta-analyses were not recommended due to clinically important heterogeneity introduced by differences in patient characteristics, treatment dosage and duration, and a lack of common outcomes. Consequently, the indirect treatment comparisons between nusinersen, risdiplam, and onasemnogene abeparvovec used alternative methods (matching-adjusted indirect comparisons [MAICs] and simulated treatment comparisons [STCs]) that were subject to substantial limitations (see Section B.2.5).

The full report from the systematic literature review of clinical studies is provided in Appendix D.

B.2.2 List of relevant clinical effectiveness evidence

Nusinersen has been investigated in multiple controlled and uncontrolled open-label clinical studies that together cover the majority of the 5q SMA spectrum (see Section B.1.3.2), including presymptomatic patients (NURTURE study), infantile-onset (type 1; studies CS3A, ENDEAR) and later-onset (type 2 or type 3; studies CS2/12, CHERISH) SMA (Figure 3). In addition, patients ineligible for ENDEAR or CHERISH could have entered the phase 2 EMBRACE study (CS7). Table 5 provides an overview of the nusinersen studies described in this submission. ENDEAR and CHERISH data were presented as part of TA588; consequently, the methods and results of these studies are only briefly summarised here. A summary of the methods and results of CS3A, CS2/12, and EMBRACE is available in Appendix H.

Patients with type 4 SMA are not included in the cost-effectiveness modelling due to the limited evidence base. The evidence on the use of nusinersen in type 4 SMA is predominantly available from the SMArtCARE registry, which included 9 (4%) patients with type 4 SMA among 237 adult patients with SMA who had been treated with nusinersen for ≥14 months[43]. Although the data for the few type 4 patients were

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not presented separately, in the overall population of adults with SMA treatment with nusinersen resulted in increases from baseline in all outcome measures, including HFSME (primary outcome), RULM, and 6MWT scores, that were sustained through month 38[43].

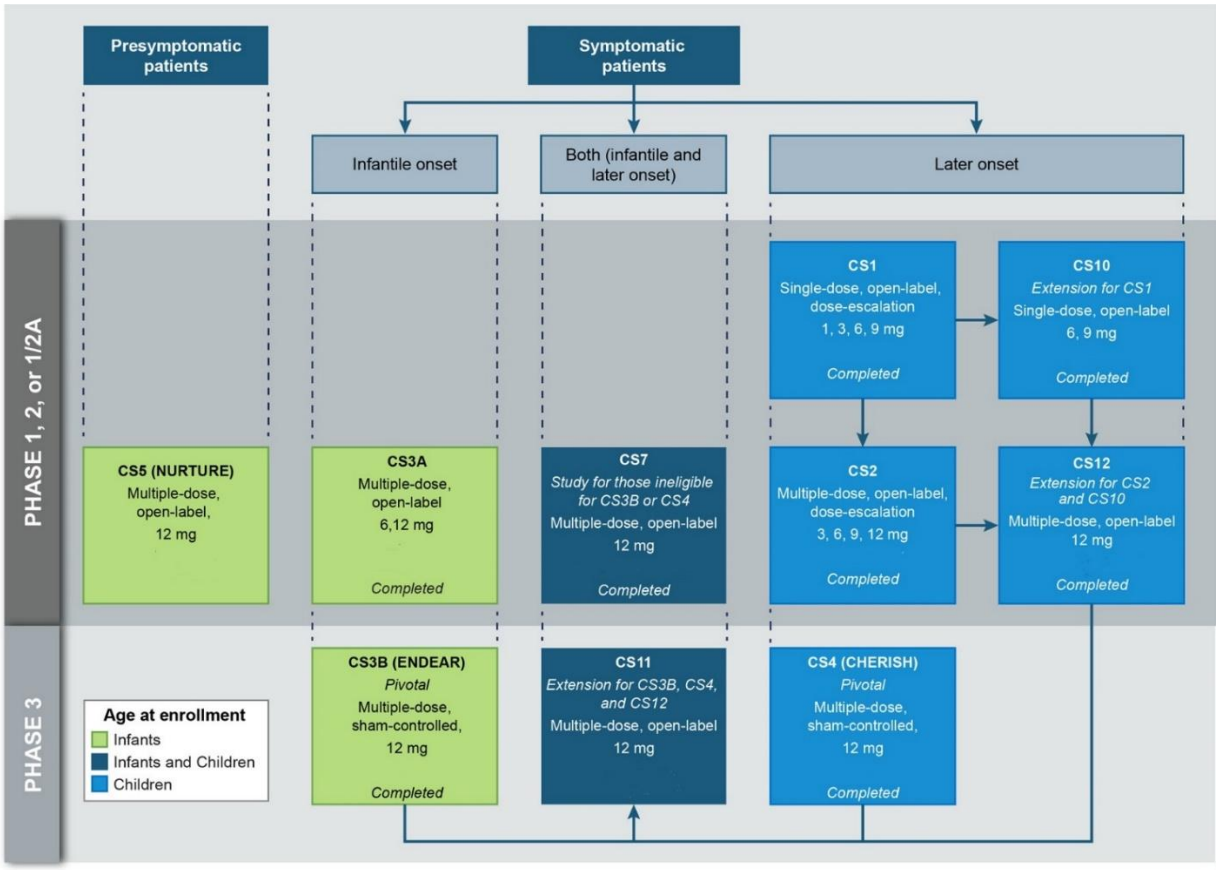
Symptomatic patients who participated in any of the nusinersen studies were eligible for the SHINE open-label extension study. Consequently, SHINE provides long-term safety, tolerability, and efficacy data on nusinersen administered to patients representing a broad range of ages and disease durations (presented in Section B.2.4.3). Long-term follow-up for presymptomatic patients treated with nusinersen was conducted as part of the NURTURE study (presented in Section B.2.4.4).

In addition, a Managed Access Agreement (MAA) was established for nusinersen as part of TA588, in which Biogen committed to collecting real-world data on the effectiveness and safety of nusinersen as used in the real-world clinical practice setting in the UK. The data collected as part of the MAA is summarised in Section B.2.4.5.

Considering that a major concern raised by the Committee as part of TA588 was uncertainty around the long-term benefits of nusinersen, the Company believes that the long-term data from SHINE and NURTURE, and the UK-specific data collected under the MAA, can largely address the concerns of the Committee expressed during the initial TA. It should also be noted that the MAA includes many prevalent patients with SMA, as no disease-modifying therapies had been available for patients with SMA in the UK prior to the nusinersen EAP/MAA. Therefore, the expectation is that outcomes in newly diagnosed incident patients treated on the NHS in the future will be better than those observed in the MAA.

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Figure 3. Overview of nusinersen clinical studies



Abbreviations: RCT, randomised controlled trial

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Table 5. Overview of clinical effectiveness evidence for nusinersen

Study	NURTURE	CS3A	ENDEAR	CS2/CS12	CHERISH	EMBRACE	SHINE
Study design	Phase II, open-label, multicentre, single-arm study	Phase II, open-label, multiple dose, single-arm, multi-centre study	Randomised, double blind, multicentre (including UK), phase III, sham-procedure controlled	CS2: Phase I/IIa, open-label, multicentre, multiple-dose, dose escalation study CS12: Phase I, multicentre, open-label, multiple-dose extension study	Randomised, double-blind, multicentre, phase III, sham-procedure controlled	Phase II, randomised, double-blind, sham-procedure controlled study	Open-label extension study
Population	Pre-symptomatic infants genetically diagnosed with SMA (likely to develop early or later onset SMA)	Symptomatic infantile-onset (type 1) SMA	Symptomatic infantile-onset (type 1) SMA	Symptomatic later-onset (type 2/3) SMA	Symptomatic later-onset (type 2/3) SMA	Patients with SMA who are not eligible to participate in ENDEAR and CHERISH	Patients who participated in the initial studies (ENDEAR, CHERISH, EMBRACE, CS3a, and CS12)
Intervention(s)	Nusinersen (N=25)	Nusinersen (N=21)	Nusinersen (N=80)	Nusinersen (N=34 in CS2 and N=47 in CS12)	Nusinersen (N=84)	Nusinersen (N=14)	Nusinersen (N=327)
Comparator(s)	None	None	Sham procedure (N=41)	None	Sham procedure control (N=42)	Sham procedure (N=7)	None
Indicate if study used in the economic model	Yes	No, phase 3 data is available from ENDEAR	Yes	No, phase 3 data is available from CHERISH	Yes	No	Yes

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B.2.3 Summary of methodology of the relevant clinical effectiveness evidence

B.2.3.1 Phase III RCTs: ENDEAR and CHERISH

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Table **6** summarises the methodology of ENDEAR and CHERISH, which were phase III, international, multicentre, double-blind, sham-controlled RCTs conducted in the infantile-onset and later-onset populations, respectively. Detailed methodology of these studies was presented as part of TA588, and a summary is presented in this section to the interpretation of data in from these trials and the long-term SHINE extension. The methods and results of the supporting uncontrolled phase II studies CS3A, CS2/12, and EMBRACE are available in Appendix H.

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Table 6. Summary of the methodology of ENDEAR and CHERISH

Study	ENDEAR	CHERISH
Location	31 centres in 13 countries: Australia, Belgium, Canada, France, Germany, Italy, Japan, Korea, Spain, Sweden, Turkey, UK, US	24 centres in 10 countries: Canada, China, France, Germany, Italy, Japan, Korea, Spain, Sweden, US
Trial design	Phase III, randomised, double blind, multicentre, sham- controlled study. Using an IXRS, eligible patients were randomised 2:1 to receive nusinersen or sham procedure control, respectively.	Phase III, randomised, double-blind, multicentre, sham-controlled study. Randomisation: 2:1 ratio using an IXRS to receive nusinersen or sham procedure control, respectively.
Patient population	Symptomatic infantile-onset SMA (type 1)	Symptomatic later onset SMA (type 2/3)
Key inclusion criteria	• Genetic documentation of 5q SMA • Two copies of the *SMN2* gene • Onset of clinical signs and symptoms consistent with SMA at less than 6 months of age (180 days) • Younger than 7 months of age (210 days) at screening • Receiving adequate nutrition and hydration (with or without gastrostomy) in the opinion of the site investigator • Measuring to at least the third percentile in body weight using country-specific guidelines • Adherence to the consensus statement for standard of care in SMA for medical care guidelines • Gestational age of 37–42 weeks	• Genetic documentation of 5q SMA • Onset of clinical signs and symptoms consistent with SMA at more than 6 months of age • Age 2 to 12 years inclusive • Able to sit independently but never had the ability to walk independently • HFMSE score of ≥10 and ≤54 or lower at screening • Estimated life expectancy more than 2 years from screening • Adequate contraception for patients of reproductive age
Key exclusion criteria	• Peripheral oxygen desaturation (oxygen saturation below 96% without ventilation support) during screening • SMA symptoms within the first week of birth • History of brain or spinal cord disease that would interfere with LP, CSF circulation, or safety assessments • Presence of an implanted shunt for the drainage of CSF or an implanted CNS catheter • History of gene therapy, prior ASO therapy, or cell transplantation	• Respiratory insufficiency at screening (defined by the medical necessity for invasive or non-invasive ventilation for >6 hours during a 24-hour period) • A gastric feeding tube, where most feeds are given by this route • Severe contractures or severe scoliosis evident on X-ray examination at screening • Hospitalisation for surgery, pulmonary event, or nutritional support within 2 months of screening or planned during the study • History of brain or spinal cord disease that would interfere with the lumbar puncture procedures or CSF circulation • Presence of an implanted shunt for the drainage of CSF or an implanted CNS catheter • History of bacterial meningitis • Dosing with nusinersen in any previous clinical study • Prior injury (e.g., upper or lower limb fracture) or surgical procedure that would impact the child's ability to perform any of the outcome measure testing required in the protocol and from which the child has not fully recovered or achieved a stable baseline

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Study	ENDEAR	CHERISH
		• History of gene therapy, ASO, or cell transplantation
Intervention	• Nusinersen (N=80): each scaled equivalent[a] 12 mg dose was administered as a single intrathecal LP injection. Four loading doses were administered on study days 1, 15, 29, and 64, followed by maintenance dosing once every 4 months (on days 183 and 302)	• Nusinersen (N=84): each 12 mg dose was administered as a single intrathecal LP injection. Three loading doses were administered on days 1, 29, 85, followed by a maintenance dose given 6 months later (day 274)[b]
Control	• Sham-control (N=41): administered as small needle prick to the skin over the lumbar spine on the same study days	• Sham-control (N=42): administered as small needle prick to the skin over the lumbar spine on the same study days
Permitted and disallowed concomitant medication	• Concomitant medications or treatments deemed necessary for AEs or to provide adequate supportive care were permitted. • Experimental agents other than nusinersen were prohibited during the study. This included marketed agents being used off-label and/or at experimental doses being tested for the treatment of SMA.	• Concomitant medications or treatments deemed necessary for AEs or to provide adequate supportive care were permitted. • Experimental agents other than nusinersen were prohibited during the study. This included marketed agents being used off-label and/or at experimental doses being tested for the treatment of SMA.
Study duration	13 months	15 months
Primary outcomes	• Proportion of motor milestone responders assessed using HINE-2 (at screening, and prior to dosing on days 64, 183, 302 and 394) • Event-free survival, i.e., time to death or permanent ventilation (tracheostomy or ≥16 hours ventilatory support per day for >21 days)	• Change from baseline in HFMSE score at 15 months. Change from baseline was assessed at screening and on days 92 (3 months), 169 (6 months), 74 (9 months), 365 (12 months) and 456 (15 months)
Secondary outcomes	• CHOP INTEND responders (≥4-point improvement from baseline) • Survival rate • Percentage of patients not requiring permanent ventilation • Proportion of CMAP responders (peroneal CMAP amplitude increasing to or maintained at ≥1 mV vs. baseline) • Time to death or permanent ventilation in the subgroups of patients above and below the median disease duration in the study	• Proportion achieving a ≥3-point increase from baseline in HFMSE score at 15 months • Proportion achieving any new WHO motor milestone at 15 months • Number of WHO motor milestones achieved per child at 15 months • Proportion achieving standing alone at 15 months • Proportion achieving walking with assistance at 15 months • Change from baseline in RULM score at 15 months
Key tertiary/exploratory outcomes:	• Change from baseline in growth parameters • Number of hours of ventilation support • Number and length of hospitalisations • Number of serious respiratory events	• Change from baseline in PedsQL score • CGI-I (investigator and caregiver assessment) • Change from baseline in ACEND score • Disease-related hospitalisations
Pre-planned subgroups	• Age at symptom onset (<=12 weeks, >12 weeks) • Disease duration at screening (<=12 weeks, >12 weeks) • Geographic region (North America, Europe, Asia-Pacific)	• Age at screening (<6 years versus ≥6 years) • Disease duration at screening by tertiles • Geographic region (North America, Europe, and Asia-Pacific)

Abbreviations: ACEND, Assessment of Caregiver Experience with Neuromuscular Disease; AE, adverse event; ASO, antisense oligonucleotide; CGI-I, Global Impression of Change – Improvement; CHOP INTEND, The Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders; CMAP, compound motor action potential; CNS, central nervous system; CSF, cerebrospinal fluid; CT, computed tomography; HFMSE, Hammersmith Functional Motor Scale – Expanded; HINE-2, Hammersmith Infant Neurological Examination Part 2; IXRS, Interactive Voice/Web Response System; LP, lumbar puncture; MRI, magnetic resonance imaging; PedsQL, Paediatric Quality of Life Inventory; RULM, Revised Upper Limb Module; SMA, spinal muscular atrophy; SMN, survival of motor neuron; WHO, World Health Organization

a: The scaling was applied to infants and based on CSF volume, so that younger patients received a lower dose of nusinersen, achieved by injecting a smaller volume that was proportional to estimated CSF volume for age, such that dose volume was equivalent to 5 mL for age 2 years to adult.

b: Note that this is less frequent than the licensed dosing regimen.

Source: TA588, ENDEAR Statistical Analysis Plan, ENDEAR Clinical Study Report, CHERISH Clinical Study Report,

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B.2.3.2 SHINE open-label extension study

SHINE was an open-label extension study in patients with SMA who previously participated in other studies of nusinersen. The purpose of the study was to provide patients with SMA who completed one of the index studies with the option to initiate or continue to receive nusinersen treatment and to evaluate the long-term safety, tolerability, and efficacy of nusinersen. The data presented in this submission focuses on SHINE patients who were previously enrolled in the pivotal ENDEAR and CHERISH phase III RCTs, in which all nusinersen-treated patients received the licensed 12 mg dose of nusinersen. SHINE completed in late 2023.

B.2.3.2.1 SHINE study design and methodology

The methodology of SHINE is summarised in Table 7.

Table 7. Summary of the methodology of SHINE

Study	SHINE
Location	46 study sites in 14 countries worldwide (Australia, Belgium, Canada, France, Germany, Hong Kong, Italy, Japan, South Korea, Spain, Sweden, Turkey, UK, and the US). These sites had participated in ≥1 index study.
Trial design	Open-label extension study
Patient population	Patients with SMA who previously participated in ENDEAR, CHERISH, EMBRACE, CS3a, or CS12
Inclusion criteria	• Signed informed consent of parent or legal guardian and signed informed assent of patient, if indicated per patient's age and institutional guidelines • Completion of the index study in accordance with the study protocol or as a result of Sponsor decision (e.g., ET of the index study) within the preceding 16 weeks. • Ability to complete all study procedures, measurements, and visits, and parent/patient had adequately supportive psychosocial circumstances, in the opinion of the Investigator. • Adequate contraception for patients of reproductive age
Exclusion criteria	• Had any new condition or worsening of existing condition, which in the opinion of the Investigator would make the patient unsuitable for enrolment or could interfere with the patient participating in or completing the study. • Clinically significant abnormalities in haematology or blood chemistry parameters or ECG, as assessed by the Site Investigator, at the Screening Visit that would render the patient unsuitable for participation in the study. • The patient's parent or legal guardian was unable to understand the nature, scope, and possible consequences of the study or did not agree to comply with the protocol's schedule of procedures.

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	• The patient's parent or legal guardian was not willing or able to meet guidelines in the consensus statement for standard of care in SMA[77] or provide nutritional and respiratory support throughout the study. Note: Routine vaccinations and RSV prophylaxis were recommended per consensus guidelines on standard of care[77] but were not required for study enrolment. Patients who were not current on vaccinations or who were not receiving RSV prophylaxis, but who otherwise met study inclusion criteria, were considered eligible for study enrolment. • Treatment with another investigational agent, biological agent, or device within 1 month of Screening or 5 half-lives of study agent, whichever was longer.
Trial drugs	Nusinersen at a dose of 12 mg administered via LP injection every four months (for patients transitioning from CHERISH, initially maintenance doses were given every 6 months, with a change to dosing every 4 months on MMDR Day 1, see Figure 5). A loading dose period was required for sham control patients rolling over from ENDEAR and CHERISH.
Permitted and disallowed concomitant medication	Throughout the study, the Site Investigators or designated licensed physicians could prescribe concomitant medications or treatments deemed necessary for AEs or to provide adequate supportive care. In addition, a mild sedative (e.g., midazolam) and a local anaesthetic (e.g., lidocaine) was permitted for the intrathecal LP procedure (per institutional guidance). Study patients were prohibited from receiving other experimental agents during the study. This included marketed agents being used off-label and/or at experimental doses that are being tested for the treatment of SMA (e.g., riluzole, creatine, sodium phenylbutyrate, valproate, or hydroxyurea).
Efficacy analyses	The study did not have pre-specified primary or secondary efficacy endpoint. The following efficacy assessments, also used in ≥1 index study, were included: • Survival rate • Time to death or permanent ventilation (tracheostomy or ≥ 16 hours ventilation/day continuously for > 21 days in the absence of an acute reversible event) • Achievement of WHO motor milestones • Change from baseline in applicable motor function assessments (CHOP INTEND, HFMSE, RULM, 6MWT, and CMAP) • Growth parameters • Number of motor milestones achieved per patient • Proportion of patients who achieved standing alone • Proportion of patients who achieved walking with assistance • Change from baseline in Cobb angle on X-ray of the thoracolumbar spine • Changes in quality of life assessment (ACEND and PedsQL) • Dysphagia assessed using the PASA survey Please see Appendix H for descriptions of the efficacy assessments used in SHINE.
Safety analyses	Clinical safety assessments included: • Monitoring of AEs and SAEs

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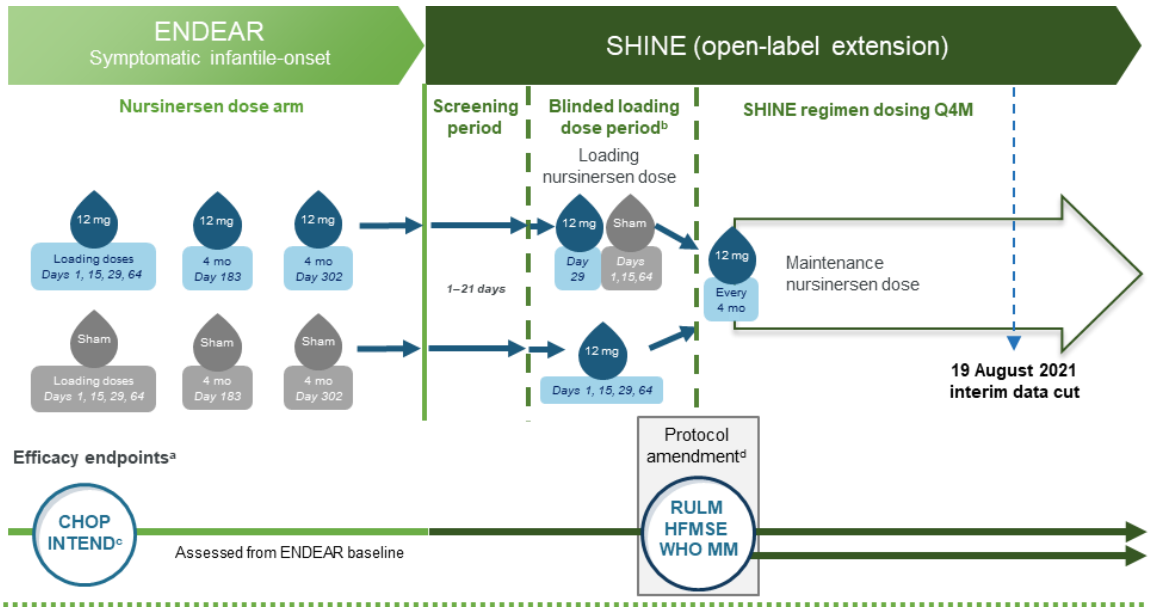
	• Physical examination • ECG, neurological examination, and vital signs (temperature, heart rate, respiratory rate, systolic and diastolic blood pressure, pulse, and pulse oximetry) • Monitoring of concomitant medications Laboratory safety assessments included haematological parameters, liver function tests, kidney function tests and electrolytes, total protein, albumin, bicarbonate, calcium, phosphorous, glucose, GGT, and coagulation parameters, as well as uranalysis.
Pre-planned subgroups	The infantile-onset and later-onset populations were analysed separately. Within each population, subgroup analyses were performed based on the following criteria: • Age at first dose of nusinersen or sham-control treatment • Disease duration at first dose

Abbreviations: 6MWT, 6-minute walk test; ACEND, Assessment of Caregiver Experience with Neuromuscular Disease; AE, adverse event; CHOP INTEND, Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders; CMAP, compound motor action potential; ECG, electrocardiogram; ET, early termination; HFMSE, Hammersmith Functional Motor Scale Expanded; LP, lumbar puncture; MMDR, modified maintenance dosing regimen; PASA, Parent Assessment of Swallowing Ability; PedsQL, Paediatric Quality of Life Inventory; RSV, respiratory syncytial virus; RULM, Revised Upper Limb Module; SAE, serious adverse event; SMA, spinal muscular atrophy; UK, United Kingdom; US, United States; WHO, World Health Organization
Source: SHINE Clinical Study Report

Patients were screened for eligibility up to 21 days prior to the administration of the first dose within this open-label extension study. Patients who entered SHINE from the double-blind RCTs ENDEAR and CHERISH required a loading dose period to ensure that patients previously receiving sham treatment receive appropriate loading doses and, at the same time, that the blinding of the original RCTs is preserved. The loading dose period was blinded until the unblinding of the original studies. After the unblinding of ENDEAR and CHERISH, the loading dose period was unblinded and sham procedures were no longer performed. The study designs of ENDEAR/SHINE and CHERISH/SHINE are presented in Figure 4 and Figure 5, respectively.

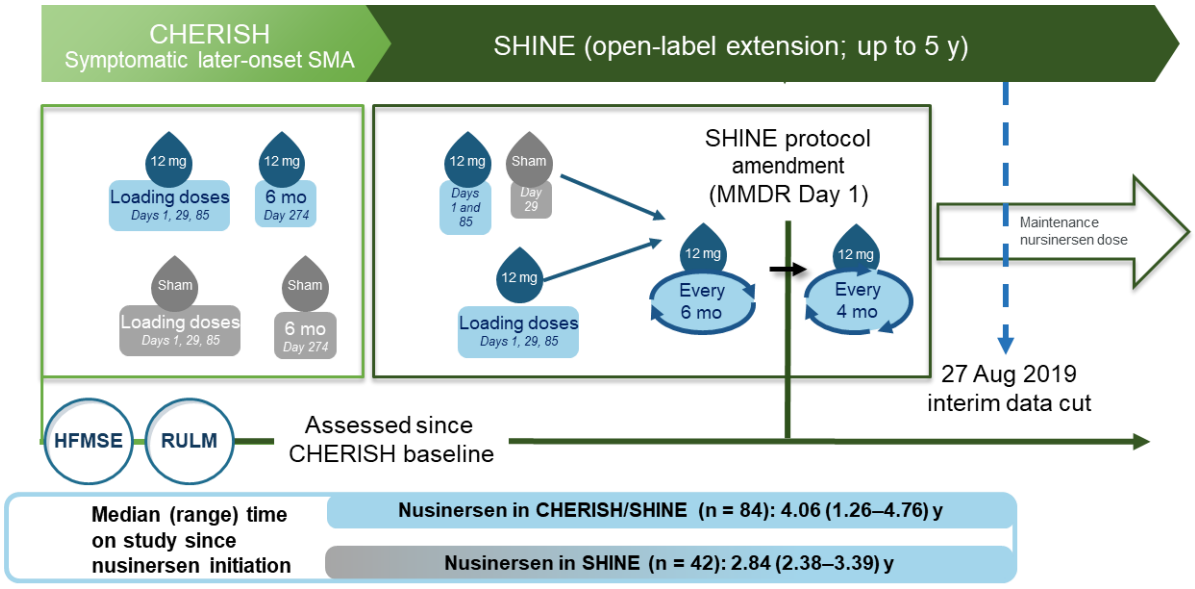
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Figure 4. Study design of SHINE for patients transitioning from ENDEAR



Abbreviations: CHOP INTEND, Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders; HFMSE, Hammersmith Functional Motor Scale – Expanded; MM, motor milestones; mo, months; Q4M, every 4 months; RULM, Revised Upper Limb Module; WHO, World Health Organization
a: Assessments were performed at Screening, and/or Day 1 and every 8 months to Day 720 of the 2017 protocol amendment, every 12 months thereafter, and at study/treatment end. The protocol amendment established a minimum of 5 years' follow-up for all patients.
b: Some patients were blinded beyond the loading dose period before the protocol amendment was in place and received maintenance doses under the original protocol.
c: CHOP INTEND was assessed until a maximum score of 64 was reached.
d: RULM was added with the protocol amendment, HFMSE and WHO MM were initiated in SHINE but revised with the protocol amendment to include all patients aged ≥ 2 years (HFMSE, previously limited to patients with CHOP INTEND total score of ≥ 50 for 2 consecutive visits) or all patients (WHO MM, previously performed only if independent sitting achieved per HINE Section 2). Source: Finkel et al. 2017[72], Tulinus et al.,[78]

Figure 5. Study design of SHINE for patients transitioning from CHERISH



Abbreviations: HFMSE, Hammersmith Functional Motor Scale – Expanded; mo, months; MMDR, modified maintenance dosing regimen; RULM, Revised Upper Limb Module; SMA, spinal muscular atrophy
Note: Prior to the implementation of Protocol Version 2.0 in SHINE, patients from CHERISH received maintenance doses every 6 months; this was later changed to every 4 months. Source: Darras B, et al. presented at Cure SMA 2020[79]

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B.2.3.2.2 Statistical analysis and definition of study groups

Statistical hypothesis testing for the primary endpoint

SHINE was an open-label extension study aiming to provide information on long-term safety, tolerability, and efficacy of nusinersen. As such, no formal statistical hypothesis was tested as part of the study and the sample size was based solely on the number of patients enrolled in index studies.

Withdrawals

With regards to withdrawals, a patient had to be withdrawn from the study if:

- the patient or the patient's parent or legal guardian withdrew consent, or
- if the patient or the patient's parent or legal guardian was unwilling or unable to comply with the protocol.

Other reasons for withdrawal of patients from the study could include the following:

- At the discretion of the Investigator for medical reasons
- At the discretion of the Investigator or Sponsor for non-compliance
- Initiation of commercial nusinersen treatment
- Significant protocol deviation
- Administrative decision by the Investigator or Sponsor

Analysis populations

The first Safety Set utilised the safety populations as defined in the index studies, which was based on patients who received ≥1 dose of nusinersen or sham-control procedure. The second Safety Set was defined as all patients who were enrolled and received ≥1 dose of nusinersen or underwent sham-control procedure during SHINE. Both Safety Sets were used for safety and efficacy analyses.

The Efficacy Set at each visit was defined as the subset of patients In the Safety Set who had the opportunity to be assessed at that visit.

B.2.3.3 NURTURE – an open-label study in presymptomatic patients

In the presymptomatic stage of SMA, the pool of motor neurons is irreversibly reduced before the onset of symptoms, with weakness only becoming apparent after

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the number of motor neurons has fallen below a critical threshold[80,81]. The presymptomatic stage of SMA is therefore the optimal time to initiate therapy; indeed immediate treatment with disease-modifying therapy is recommended by clinical experts for infants who are diagnosed with SMA through newborn screening or through siblings with an SMA diagnosis and have ≤4 *SMN2* copies[81,82]. The efficacy and safety of nusinersen for the treatment of presymptomatic patients who were most likely to develop symptomatic type 1 or 2/3 SMA was assessed in the NURTURE study described below.

B.2.3.3.1 NURTURE study design and methodology

NURTURE assessed the efficacy of nusinersen for preventing or delaying the development of SMA symptoms in infants who were genetically diagnosed with SMA but were not yet symptomatic at study entry. The methodology of the study is summarised in Table 8 and the study schematic is available in Figure 6. NURTURE is currently ongoing and will complete in 2025, providing up to 10 years of follow-up. The most recent available data is from an interim analysis with a data cut of 15 February 2021.

Table 8. Summary of the methodology of NURTURE

Study	NURTURE
Location	15 sites in 7 countries (Australia, China, Germany, Italy, Qatar, Turkey, US)
Trial design	Phase II, open-label, multicentre, single-arm study
Patient population	Pre-symptomatic infants genetically diagnosed with SMA
Key inclusion criteria	•Age ≤ 6 weeks at first dose •Genetic documentation of 5q SMA homozygous gene deletion, mutation, or compound heterozygous mutation •Genetic documentation of 2 or 3 copies of *SMN2* •CMAP ≥1 mV at baseline •Receiving adequate nutrition and hydration (without gastrostomy) in the opinion of the Investigator. •Body weight ≥3rd percentile for age using appropriate country-specific guidelines. •Gestational age of 37–42 weeks for singleton births; gestational age of 34–42 weeks for twins
Key exclusion criteria	•Hypoxaemia (oxygen saturation <96% awake or asleep without any supplemental oxygen or respiratory support) •Any clinical signs or symptoms at screening or immediately prior to the first dosing (day 1) that are, in the opinion of the Investigator, strongly suggestive of SMA •Any history of gene therapy, prior ASO treatment, or cell transplantation

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	• History of brain or spinal cord disease that would have interfered with the lumbar puncture procedures, CSF circulation or safety assessments • Presence of an implanted shunt for the drainage of CSF or an implanted central nervous system catheter • History of bacterial meningitis or viral encephalitis • Diagnosis of neonatal respiratory distress syndrome requiring surfactant replacement therapy or invasive ventilator support
Trial drugs	Nusinersen (N=25) administered at a dose of 12 mg via LP as loading doses on days 1, 15, 29, 64 and maintenance doses every 4 months thereafter (i.e., on days 183, 302, 421, 540, 659, and 778)
Permitted and disallowed concomitant medication	Patients who received prior treatment with an investigational drug given for the treatment of SMA, biological agent, or device were excluded from participation in the study. Patients with a history of gene therapy, prior ASO treatment, or cell transplantation were also excluded from the study. No disallowed concomitant medications were specified.
Primary outcomes (including scoring methods and timings of assessments)	Event-free survival defined as time to death or respiratory intervention (defined as invasive or non-invasive ventilation for ≥6 hours per day continuously for ≥7 days or tracheostomy)

Secondary outcomes:	• Overall survival i.e., proportion of patients alive
	• Attainment of motor milestones as assessed by WHO criteria
	• Percentage of patients who attained motor milestones assessed as part of HINE-2 (at 13 and 24 months of age)
	• Change from baseline in CHOP INTEND
	• Change from baseline in HFMSE
	• Change in baseline in growth parameters
	• Proportion of patients developing clinically manifested SMA as defined by:
	  ○ Age-adjusted weight <5th percentile or decrease of ≥2 major weight growth curve percentiles (3rd, 5th, 10th, 25th, or 50th) or a percutaneous gastric tube placement for nutritional support
	  ○ Failure to achieve age-appropriate attainment of the 6 WHO motor milestones

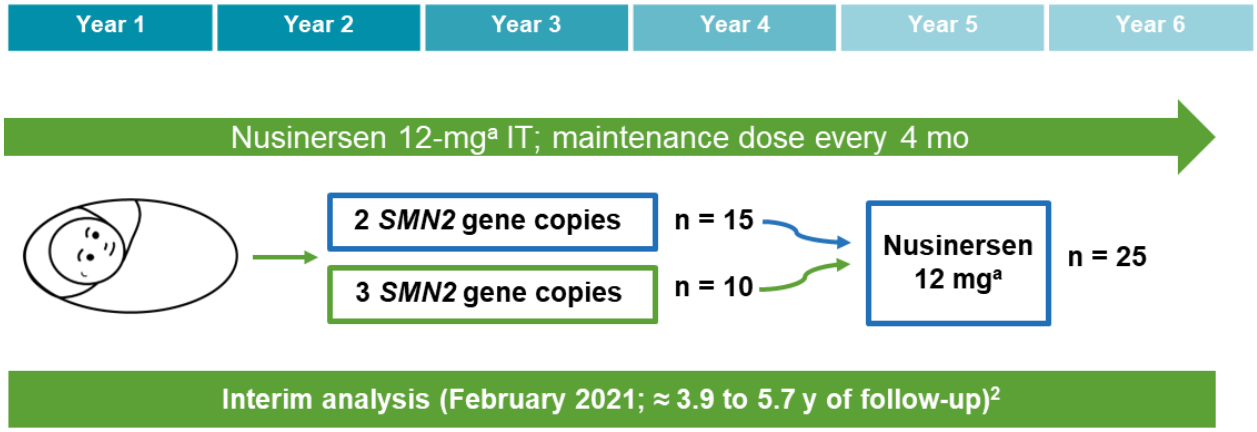
Key tertiary/exploratory outcomes:	• Change from baseline in CMAP • Measures of respiratory events: respiratory infections, hospitalizations for respiratory events, non-invasive and invasive ventilator use, and oxygen saturation • Time to death or permanent ventilation (≥16 hours ventilation/day continuously for >21 days in the absence of an acute reversible event OR tracheostomy) • Time to death or ventilation (≥6 hours ventilation/day continuously for ≥7 days OR tracheostomy) • Change from baseline in 6MWT • Change from baseline in cognitive assessments • Change from baseline in the quality of life questionnaires (PedsQL and ACEND) • Parent Assessment of Swallowing Ability

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	•Incidence of AEs and SAEs •Change from baseline in clinical laboratory parameters, ECGs, and vital signs. •Neurological examinations
Pre-planned subgroups	None

Abbreviations: 6MWT, 6-minute walk test; ACEND, Assessment of Caregiver Experience with Neuromuscular Disease; AE, adverse event; ASO, antisense oligonucleotide; CHOP INTEND, Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders; CSF, cerebrospinal fluid; CMAP, compound motor action potential; ECG, electrocardiogram; HFMSE, Hammersmith Functional Motor Scale – Expanded; HINE-2, Module 2 of the Hammersmith Infant Neurological Examination; LP, lumbar puncture; PedsQL, Pediatric Quality of Life Inventory; SAE, serious adverse event; SMA, spinal muscular atrophy; SMN, survival of motor neuron; UK, United Kingdom; US, United States; WHO, World Health Organization
Source: Biogen data on file. NURTURE Clinical Study Report and NURTURE Statistical Analysis Plan

Figure 6. Study design of NURTURE



Abbreviations: CMAP, compound muscle action potential; IT, intrathecal; SMA, spinal muscular atrophy; *SMN,* survival motor neuron
[a]Nusinersen 12 mg was administered intrathecally as 4 loading doses (Days 1, 15, 29, 64) followed by maintenance doses every 4 months; before the protocol was revised in March 2017, infants received a 12-mg scaled equivalent dose based on the patients' age on the day of the dosing.
Source: De Vivo, et al. 2019[83], Crawford et al. 2023[84].

B.2.3.3.2 Statistical analysis and definition of study groups

Statistical hypothesis testing for the primary endpoint

Given the open-label nature of the NURTURE study, no formal statistical hypothesis was tested. For the analysis of the primary endpoint, median age at respiratory intervention (≥ 6 hours/day for ≥ 7 days or tracheostomy) or death and associated 95% confidence interval (CI) were estimated using the Kaplan-Meier method. The proportion of patients who meet such an event at different ages of interest will be estimated from the Kaplan-Meier curve. Details of secondary and exploratory endpoint analyses are available in the statistical analysis plan, provided as part of the reference pack for this submission.

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Withdrawals

Patients could be withdrawn from the study if the patient's parent(s)/legal guardian(s) withdrew consent or if the patient's parent(s)/legal guardian(s) were unwilling or unable to comply with the protocol. Patients prematurely withdrawn from the study were encouraged to complete the early termination evaluation assessments at the time of withdrawal.

Analysis populations

Two analysis sets were defined. The ITT Set was defined as all patients who received at least 1 dose of nusinersen. The Efficacy Set was defined as the subset of patients in the ITT Set who had either attended the targeted visit of the analysis or who would have had the opportunity to attend the visit had they not died or discontinued.

B.2.3.4 Data collection as part of the Managed Access Agreement established by TA588

In July 2019, nusinersen was recommended within the conditions of the MAA for individuals with 5q SMA type 1, 2, and 3, and presymptomatic individuals with SMA. Three variations to the original MAA have since been implemented, modifying the treatment eligibility and/or stopping criteria, which should be taken into account when interpreting the results from the MAA. Because of these modifications, the eligibility criteria for treatment were changing during data collection, which is a potentially important confounder. The original and revised criteria for starting and stopping treatment with nusinersen are described below. Full study reports from the MAA are provided as Appendix E (paediatric report) and Appendix F (adult report) to this submission. It is important to note that the period of MAA data collection partly overlapped with the COVID-19 pandemic, during which patients may have had delayed doses or assessments.

B.2.3.4.1 Treatment eligibility and stopping criteria

In the original MAA, the following criteria applied for starting treatment with nusinersen for patients with all SMA types (excluding type 0 and 4):

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- No permanent ventilation (defined as > 16 hours/day for 21 consecutive days in the absence of acute and reversible infection/ tracheostomy requirement at baseline;
- Intrathecal injection had to be technically feasible not contraindicated in the opinion of the treating clinician;
- No previous spinal fusion surgery following a diagnosis of scoliosis which, in the opinion of the treating clinician would prohibit safe administration of nusinersen;
- No severe contractures which, in the opinion of the treating clinician, would prohibit the measurement of motor milestones;
- Patients who had gained independent ambulation (defined as ≥5 steps of independent walking in an upright position per the WHO definition) prior to treatment initiation had to remain independently ambulant, with the exception of paediatric patients who have lost independent ambulation in the previous 12 months.

For presymptomatic patients, treatment eligibility per the original MAA depended on the number of *SMN2* copies that the patient had:

- Immediate access to nusinersen was to be offered to patients with 1 *SMN2* copy where type 0 SMA was not apparent.
- Patients with 2 *SMN2* copies were eligible for treatment.
- Patients with 3 *SMN2* copies and an older sibling who was diagnosed with type 1 or 2 SMA were eligible for treatment.
- Patients with 3 copies of *SMN2* and no older sibling diagnosed with type 1 or 2 SMA, and patients with 4 copies of *SMN2* were not treated, but were instead monitored closely for the onset of symptoms.

The criteria for stopping treatment with nusinersen included:

- Total worsening in a relevant scale score, corroborated by two consecutive measurements (>2 points on the horizontal kick or 1 point on other HINE scores excluding voluntary grasp, >4 point on the CHOP INTEND, > 3 points on the Revised Hammersmith Scale [RHS]);

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- Requirement for permanent ventilation (defined as for eligibility criteria);
- For patients who were previously independently ambulant, the inability to regain ambulation within 12 months of treatment initiation;
- Inability to administer nusinersen by intrathecal administration because of spinal fusion surgery.

Since the introduction of this original MAA, three variations were implemented, introducing the following changes:

1. Variation 1 was implemented in May 2021, following a review of evidence available for non-ambulant type 3 patients. The start and stop criteria related to prior ambulation were removed and all type 3 patients were able to access nusinersen, providing they met the other eligibility criteria. In addition, stopping criteria for SMA types were updated to specify that where one or more motor function scales were measured from baseline, patients only met stopping criteria where they demonstrated total worsening in scale score(s) in the absence of any stability or improvement in other scale corroborated by two consecutive measures, subject to discussions with the NHS clinical panel; i.e., a worsening in an isolated scale no longer constituted a stopping criterion.
2. Variation 2 was implemented in January 2022 and modified both treatment starting and stopping criteria. Starting criteria were updated as follows:
    - Restrictions for presymptomatic patients with 3 and 4 copies of *SMN2* were lifted so that presymptomatic patients with one to four *SMN2* copies became eligible for treatment;
    - Nusinersen had to be used as a monotherapy;
    - Patients were not permitted to have had successful treatment with onasemnogene abeparvovec. Unsuccessful treatment was permitted and was defined as total worsening in motor scale score corroborated by two consecutive measurements from any two of the following three scales: HINE, CHOP INTEND and RHS; and/or a deterioration in respiratory function defined as an increasing requirement for respiratory support overnight and/or, an uncharacteristic for the patient increase in

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respiratory infections requiring hospital treatment that cannot be accounted for by aspiration or intrinsic lung disease;

- Patients who were receiving permanent ventilation but would otherwise meet the eligibility criteria were to be discussed with the NHS England clinical panel.

Stopping rules were updated to include the requirement to discuss the case with the NHS England clinical panel if a patient required permanent ventilation whilst receiving treatment.

3. The third and final variation came into effect in November 2022 and updated the data collection agreement to include patient-reported outcome measures (PROMs). In addition, considering the difficulties associated with data collection during the COVID-19 pandemic, the MAA was extended for 12 months to cover a maximum of 6 years of data collection (up to July 2025).

B.2.3.4.2 Data sources

The data was collected through two registries, SMA Research and Clinical Hub (REACH) UK and Adult SMA REACH. SMA REACH UK is an established registry of paediatric SMA patients in the UK, while Adult SMA REACH is a new registry that focuses on the adult SMA population in the UK. These registries are networks with transparent governance and independent from Biogen. Neither registry is specific to patients receiving nusinersen; however, analysis of only those patients were accessible to Biogen. Results are presented separately for paediatric and adult patients with SMA treated with nusinersen as data could not be consolidated into a single dataset at the time of the analysis. Patients are transitioned from the paediatric to the adult registry from the age of 16 years, so that the latter registry includes patients aged ≥16 years. In addition, linked PRO data (using parents as proxies for paediatric patients) from the established UK SMA Patient Registry was used.

Data collection as part of the nusinersen MAA started on 24 July 2019, although patients with type 1 SMA who started treatment before that date as part of the EAP were also included and their baseline was re-defined as the visit closest to the MAA start date. The data collection is ongoing; this submission uses the data cut of 9 October 2023 for paediatric patients and 3 August 2023 for adult patients.

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B.2.3.4.3 Outcome measures

The primary outcome measures for paediatric patients were motor function scales and milestones as assessed in physiotherapy clinics using scales that were clinically appropriate for patient's age and motor function. These included CHOP-INTEND, HINE-2, Revised Hammersmith Scale (RHS), and RULM, as well as the achievement of WHO motor milestones. Other outcomes included time to permanent ventilation (defined as any ventilation type for ≥ 16 hours/day continuously for > 21 days or tracheostomy), tracheostomy procedure, overall survival, and PROMs.

The primary outcomes collected in adult patients were motor function scales such as the RHS and RULM. Exploratory outcomes, not mandated as part of the MAA, included the 6MWT, Adapted Test of Neuromuscular Disorders (ATEND, a functional motor outcome assessment used among SMA patients who are not able to sit or transfer out of the wheelchair developed for the testing of non-infants with severe contractures for whom motor assessments are a challenge), WHO motor milestones, and PROMs.

Mixed-effects repeated measures (MMRM) models were fitted to provide a summary statistical measure of longitudinal changes for motor function scales. The models for both registries were adjusted for baseline score, SMA type (2 vs 3, where appropriate), baseline function (non-sitters, sitters, walkers), weight at baseline visit, age at symptom onset, age at treatment initiation, duration of disease at baseline visit (age of diagnosis to age at treatment initiation), and time between treatment initiation and baseline visit. Sensitivity analyses without weight as a covariate due to the extent of missing data. Please see Appendix E and F for full details of the models fitted in paediatric and adult patients, respectively.

The following PROMs were collected for both paediatric and adult patients:

1. Patient Global Impression of severity score (PGI-S): a single item 7-point ordinal scale (higher value is worse)
2. Patient Global Impression of improvement score (PGI-I: a single item 7-point ordinal scale (higher value is worse)

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3. SMA independence scale (SMAIS): a 22 item scale, range 0–44 (higher values indicate greater independence)
4. EQ-5D 5L in adults and EQ-5D-Y in paediatric patients

Despite the use of various established scales, it was difficult to capture the all the benefits of treatment with nusinersen due to the heterogeneity of the patient population of this real-world cohort and confounding factors, such as patients growing. In addition, the floor and ceiling effect of the different scales may contribute to underestimating the treatment benefit.

B.2.4 Clinical effectiveness results of the relevant studies

B.2.4.1 Summary of efficacy results from ENDEAR

Efficacy data from ENDEAR and CHERISH RCTs were presented as part of TA588, as the trials were completed at the time. Nonetheless, the key results are briefly summarised here for completeness. Baseline characteristics of patients included in ENDEAR are presented in Table 9 and a brief summary of key efficacy data is presented in Table 10. In addition, the two co-primary endpoints are presented graphically in Figure 7 (HINE-2) and Figure 8 (event-free survival). Additional efficacy data from ENDEAR is presented in combination with the long-term SHINE extension data in Section B.2.4.3.1.

The intent-to-treat population of ENDEAR included 121 patients, of whom 80 were randomised to nusinersen and 41 to sham injection (Table 9).

Table 9. Baseline characteristics of patients enrolled in ENDEAR

Characteristic	Nusinersen (N=80)	Sham Control (N=41)
Female, n (%)	43 (54)	24 (59)
Mean age at first dose, days (range)	163 (52–242)	181 (30–262)
Mean age at symptom onset, weeks (range)	7.9 (2–18)	9.6 (1–20)
Mean age at SMA diagnosis, weeks (range)	12.6 (0–29)	17.5 (2–30)
Mean disease duration, weeks (range)	13.2 (0–25.9)	13.9 (0–23.1)
SMA symptoms, n (%)		
Hypotonia	80 (100)	41 (100)
Developmental motor delay	71 (89)	39 (95)
Paradoxical breathing	71 (89)	27 (66)
Pneumonia or respiratory symptoms	28 (35)	9 (22)
Limb weakness	79 (99)	41 (100)

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Swallowing or feeding difficulties	41 (51)	12 (29)
Other	20 (25)	14 (34)
Use of ventilation support, n (%)	21 (26)	6 (15)
Use of a gastrointestinal tube, n (%)	7 (9)	5 (12)
Total HINE-2 score, mean (SD)	1.29 (1.07)	1.54 (1.29)
CHOP INTEND score, mean (SD)	26.63 (8.13)	28.43 (7.56)
Peroneal CMAP amplitude, mean (SD)	0.371 (0.31)	0.317 (0.29)
Ulnar CMAP amplitude, mean (SD)	0.226 (0.19)	0.225 (0.12)

Abbreviations: CMAP, compound muscle action potential, CHOP INTEND, Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders, HINE–2, Hammersmith Infant Neurological Exam, Part 2; SD, standard deviation, SMA, spinal muscular atrophy.
Source: Finkel et al. 2017[72]

Table 10. Summary of key efficacy data in ENDEAR

	Key efficacy data in ENDEAR (ITT population: N=121, including N=80 in the nusinersen group and N=41 in the sham control group)
Primary endpoints:	•Proportion of motor milestone responders assessed using HINE-2: o At interim analysis when this endpoint was formally analysed: 41% in the nusinersen group vs 0% in the sham group, p<0.0001. o At final analysis: 51% in the nusinersen group vs 0% in the sham group •Event-free survival, i.e., time to death or permanent ventilation (tracheostomy or ≥16 hours ventilatory support per day for >21 days): o Formally tested at final analysis: 47% reduction in the risk of death or permanent ventilation compared with patients who received the sham procedure (HR: 0.530, p = 0.0046)
Secondary endpoints:	•CHOP INTEND responders (≥4-point improvement from baseline): o 71% in the nusinersen group vs 3% in the sham control group, a difference of 68.53%, (p<0.0001) •Survival rate o 62.8% reduction in the risk of death with nusinersen vs sham control (HR : 0.372, p=0.0041) •Percentage of patients not requiring permanent ventilation o 34% reduction in the risk of permanent ventilation vs sham control; however, this endpoint did not reach statistical significance (HR: 0.66, p=0.1329) •Proportion of CMAP responders (peroneal amplitude increased to, or maintained at, 1 mV or more compared to baseline): o 36% in the nusinersen arm vs 5% in the sham control arm

Abbreviations: CHOP INTEND, Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders; CMAP, compound muscle action potential; HINE, Hammersmith Infant Neurological Exam; ITT, intent-to-treat;
Source: ENDEAR Clinical Study Report, Finkel et al. 2017[72]

ENDEAR was a pivotal clinical study that demonstrated the efficacy and safety of nusinersen in symptomatic patients with infantile-onset SMA, providing evidence of

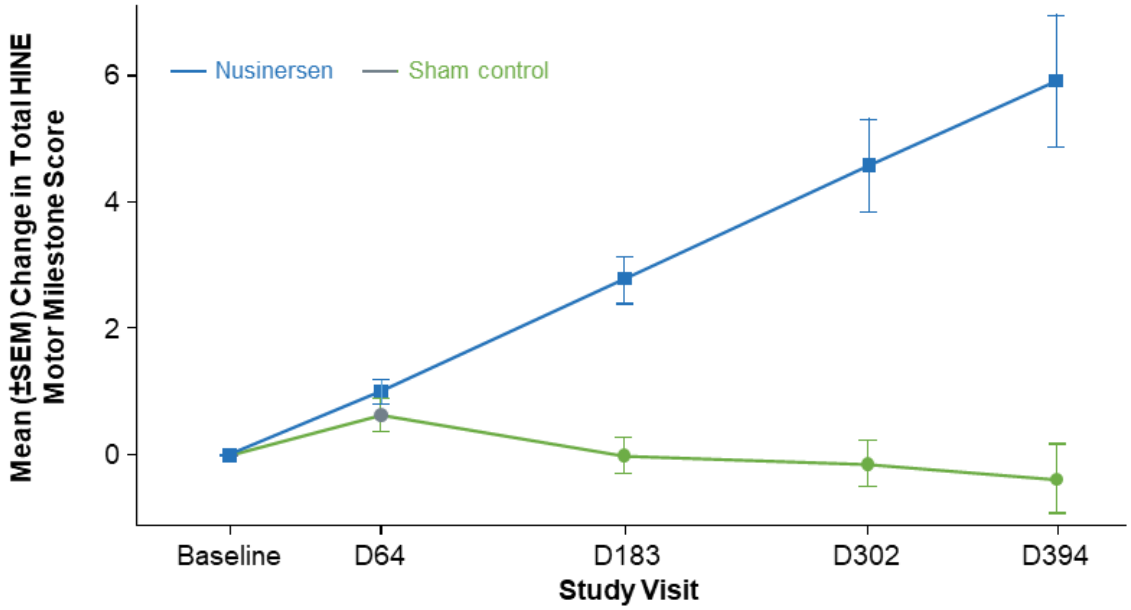
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clinically meaningful improvement in motor function and survival, alongside a favourable safety profile. Median event-free survival (time to death or permanent ventilation) was 22.6 weeks in the sham control group and was not reached in the nusinersen group (Figure 8). There was also a 63% reduction in the risk of death with nusinersen. Furthermore, infants treated with nusinersen showed progressive mean increases in HINE-2 motor milestone score (Figure 7) and achieved HINE-2 milestones unexpected for individuals with type 1 SMA without disease-modifying treatment, such as full head control (22%), supine to prone rolling (10%), independent sitting (8%), and standing (1%); all versus 0% for infants treated with sham control.

In a subgroup analysis assessing the primary endpoint of event-free survival in patients with a disease duration above the median duration of 13.1 weeks, the risk of death or permanent ventilation was 76% lower in patients treated with nusinersen, and the median time to death or permanent ventilation was 25.4 weeks in patients treated with sham control and was not reached in nusinersen-treated patients. Among patients with a disease duration above the study median, there was no significant difference in the proportion of patients who died or required permanent ventilation between treatment arms. These results highlight the importance of early treatment with nusinersen.

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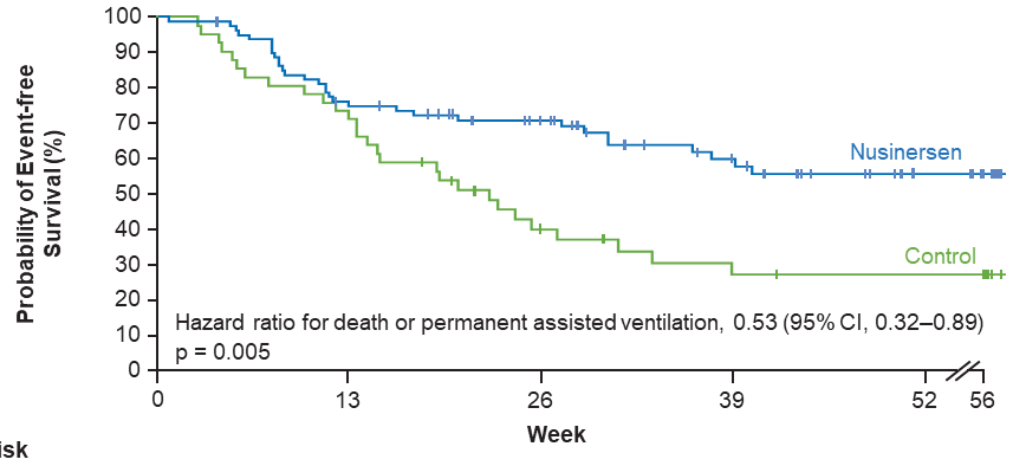
Figure 7. Change in HINE-2 motor milestone score over time in ENDEAR



Sham control	37	30	23	16	11
Nusinersen	73	66	59	36	26

Abbreviations: D, day; HINE-2, Hammersmith Infant Neurological Exam – Part 2; SEM, standard error of the mean.
Source: Finkel et al. 2017 [85]

Figure 8. Event-free survival in ENDEAR



No. at Risk						
Nusinersen	80	59	46	29	16	13
Control	41	30	14	9	7	7

Abbreviations: CI, confidence interval.
Source: Finkel et al. 2017[72]

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B.2.4.2 Summary of efficacy results from CHERISH

As noted above, efficacy data from ENDEAR and CHERISH were presented in full within TA588, as both trials were completed at the time. Therefore, only the key results from CHERISH are briefly summarised in this section. Baseline characteristics of patients included in CHERISH are presented in Table 11 and a brief summary of key efficacy data is presented in Table 12. In addition, the primary endpoint of change from baseline in HFMSE (Figure 9), the RULM (Figure 10), and WHO motor milestone achievement (

Table 13) are presented below. Additional efficacy data from CHERISH is presented in combination with the long-term SHINE extension data in Section B.2.4.3.2. The intent-to-treat population of CHERISH included 126 patients, of whom 84 were randomised to nusinersen and 42 to sham injection (Table 11).

Table 11. Baseline characteristics of patients enrolled in CHERISH

Characteristic	Nusinersen (N=84)	Sham control (N=42)
Female, n (%)	46 (55)	21 (50)
Median (range) age at screening, years	4.0 (2–9)	3.0 (2–7)
Median (range) age at symptom onset, months	10.0 (6–20)	11.0 (6–20)
Median (range) age at diagnosis, months	18.0 (0–48)	18.0 (0–46)
Median (range) disease duration, months[a]	39.3 (8–94)	30.2 (10–80)
SMN2 copy number, n (%)		
2	6 (7)	4 (10)
3	74 (88)	37 (88)
4	2 (2)	1 (2)
Unknown	2 (2)	0
Ever sat without support, n (%)[b]	84 (100)	42 (100)
Ever walked with support, n (%)[b]	20 (24)	14 (33)
Ever walked ≥15 feet independently, n (%)[b]	0	0
Mean (SD) HFMSE score	22.4 (8.3)	19.9 (7.2)
Mean (SD) WHO motor milestone achieved	1.4 (1.0)	1.5 (1.0)
Mean (SD) RULM score	19.4 (6.2)	18.4 (5.7)

Abbreviations: HFMSE, Hammersmith Functional Motor Scale – Expanded; SD, standard deviation; SMN, survival of motor neuron; RULM, Revised Upper Limb Module; WHO, World Health Organization.
[a] Disease duration is the child's age at screening minus age at symptom onset.
[b] Children who had ever achieved the milestone; does not reflect the maximal milestone achieved.
Source: Mercuri et al. 2018[73]

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Table 12. Summary of key efficacy data in CHERISH

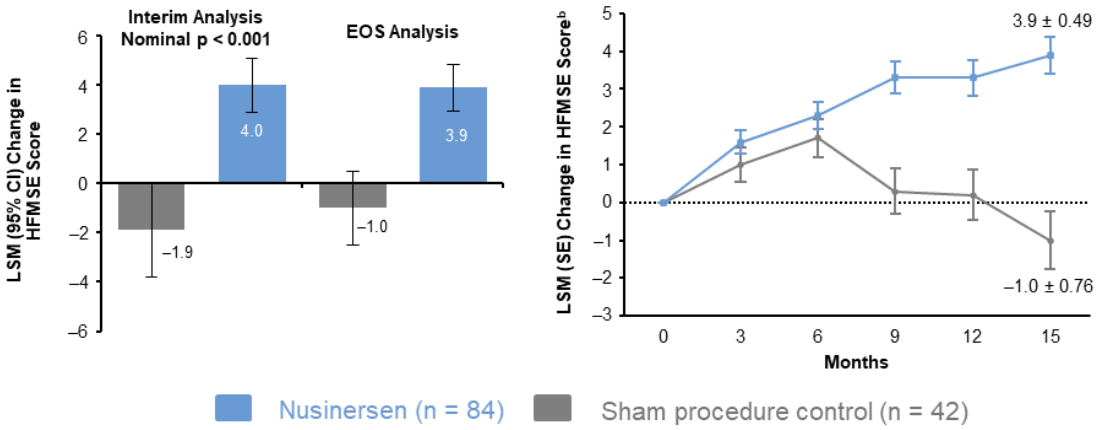
Key efficacy data in CHERISH (ITT population: N=126, including N=84 in the nusinersen group and N=42 in the sham group)	
Primary endpoint:	•Change from baseline in HFMSE score at 15 months: o The primary endpoint was formally tested for the interim analysis: patients treated with nusinersen showed an improvement in HFMSE scores at 15 months as compared with patients in the control group (LS mean change, nusinersen vs sham control: 4.0 vs. -1.9; p = 0.0000002). o Results from the final analysis were consistent with the interim analysis with patients receiving nusinersen demonstrating improvement in HFMSE scores as compared with those in the control group at 15 months (LS mean change 3.9 with nusinersen vs -1.0 with sham control, p = 0.0000001)
Secondary endpoints:	•Proportion of children achieving a response (≥3-point increase from baseline) in HFMSE score at 15 months o The nusinersen group had a significantly higher proportion of responders achieving an increase of ≥3 points in HFMSE score at 15 months than the control group did: 56.8% versus 26.3%, respectively (p = 0.0006). •Proportion of children achieving any new WHO motor milestone at 15 months: o In the nusinersen group, 19.7% of patients achieved new motor milestones compared with 5.9% of patients in the control group (difference of 13.8% (p = 0.0811). • Number of WHO motor milestones achieved per child at 15 months o There was a slight increase in the number of motor milestones gained in the nusinersen group (0.2), as well as a slight decrease in the control group (-0.2) with a LS mean difference of 0.4 between the groups (p = 0.0001) • Proportion of children achieving standing alone at 15 months o One patient in the nusinersen group (1.5%) and one patient in the control group (2.9%) achieved the milestone of standing alone • Proportion of children achieving walking with assistance at 15 months o One patient in the nusinersen group (1.5%) and no patients in the control group achieved the milestone of walking with assistance •Change from baseline in RULM score at 15 months o The nusinersen group (LS mean change of 4.2) had a greater improvement in RULM score from baseline to 15 months than the control group (LS mean change of 0.5) with a LS mean difference of 3.7 between the groups (p = 0.0000001).

Abbreviations: HFMSE, Hammersmith Functional Motor Scale Expanded; ITT, intent-to-treat; LS, least squares; RULM, Revised Upper Limb Module; WHO, World Health Organization
Sources: Biogen Data on File. CHERISH Clinical Study Report; Mercuri et al. 2018[73].

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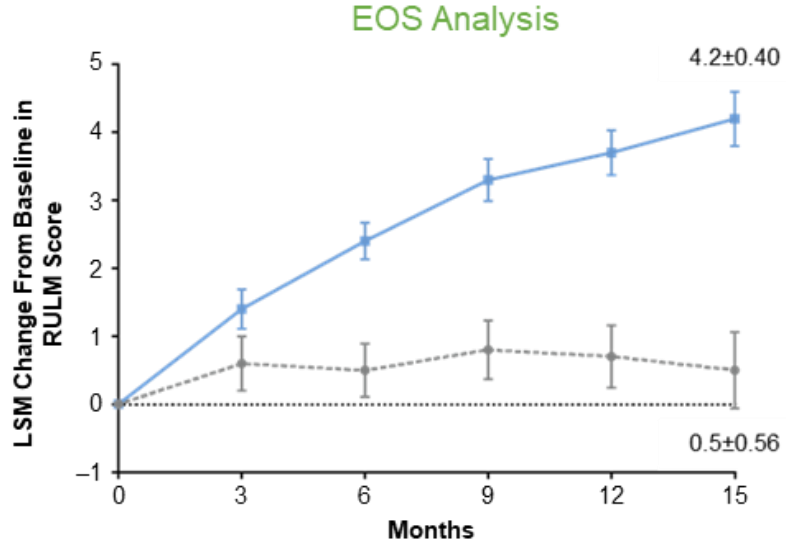
CHERISH was the pivotal trial demonstrating the efficacy of nusinersen in the treatment of later-onset SMA, providing evidence of substantial efficacy accompanied by a favourable safety profile. Significant and clinically meaningful differences in HFMSE scores were observed in children treated with nusinersen compared with sham control (Figure 9). In addition, clinically meaningful increases in RULM scores were observed in children treated with nusinersen compared with sham procedure (Figure 10).

Figure 9. HFMSE scores in CHERISH, including LS mean differences between arms (left) and LS mean change in scores from baseline over time for both arms (right)



Abbreviations: CI, confidence interval; EOS, end-of-study; HFMSE, Hammersmith Functional Motor Scale Expanded; LSM, least-squares mean; SE, standard error
Sources: Mercuri et al. 2018[73]

Figure 10. RULM scores in CHERISH



Abbreviations: CI, confidence interval; EOS, end-of-study; LSM, least-squares mean
Sources: Mercuri et al. 2018[73]

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The percentages of children with later-onset SMA who attained WHO motor milestones increased from baseline to Month 15 with nusinersen but not sham treatment (

Table 13). This difference was consistent across the six WHO milestones except for standing alone, as two (6%) sham-treated patients achieved this ability, compared with three patients treated with nusinersen (5%). There were no significant between-group differences in the proportions of children who achieved standing alone or walking with assistance at Month 15.

Table 13. Attainment of WHO motor milestones in CHERISH

WHO Motor Milestone	Nusinersen n = 66			Sham Procedure Control n = 34			Difference in % Change at Month 15 (nusinersen minus sham procedure control)
	Baseline, n (%)	Month 15, n (%)	Change at Month 15, %	Baseline, n (%)	Month 15, n (%)	Change at Month 15, %	
Sitting without support	65 (98)	66 (100)	+2	34 (100)	34 (100)	0	+2
Hands and knees crawling	13 (20)	20 (30)	+10	7 (21)	1 (3)	–18	+28
Standing with assistance	5 (8)	9 (14)	+6	6 (18)	4 (12)	–6	+12
Walking with assistance	4 (6)	5 (8)	+2	2 (6)	2 (6)	0	+2
Standing alone	2 (3)	3 (5)	+2	1 (3)	2 (6)	+3	–1
Walking alone	0	1 (2)	+2	0	0	0	+2

Source: Mercuri et al. Presented at Cure SMA - 2017 Annual Conference. 2017

B.2.4.3 Long-term nusinersen efficacy in SHINE

SHINE has recently been completed and the following sections present data based on the final data cut of 21 August 2023. The efficacy results from SHINE are presented separately for the infantile-onset and later-onset populations, due to the largely different endpoints used in both populations.

The data available from SHINE speak to long-term efficacy and safety of nusinersen. Median total follow-up (including the parent study and SHINE) for the [redacted] infantile-onset patients in the safety set (enrolled and received ≥1 dose of nusinersen in the

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parent study or SHINE) was [redacted] (range [redacted] to [redacted]) and the median number of nusinersen doses administered was [redacted] (range [redacted]). Among the [redacted] later-onset SMA patients included in the SHINE safety set, median total follow-up was [redacted] (range [redacted] to [redacted]) and the median number of nusinersen doses per patient was [redacted] (range[redacted]).

Although patients participating in any nusinersen study for symptomatic SMA populations could enrol in SHINE, the following sections focus on patients entering SHINE from the pivotal ENDEAR and CHERISH trials, where all nusinersen-treated patients received the approved 12 mg dose.

B.2.4.3.1 Infantile-onset SMA

B.2.4.3.1.1 Patient disposition

Of the 121 patients with infantile-onset SMA in ENDEAR, 80 received nusinersen and 41 received sham treatment. Baseline characteristics of this population are presented in Table 9. Sixteen patients in the sham control arm and 15 patients in the nusinersen arm discontinued treatment during ENDEAR, mostly due to adverse events which were largely consistent with type 1 SMA. All the adverse events that led to discontinuation had fatal outcomes. Twenty-four patients from the sham control arm of ENDEAR and 65 patients from the nusinersen arm of ENDEAR enrolled in SHINE (Figure 11). Since their enrolment in SHINE, [redacted] patients from the control arm of ENDEAR and [redacted] patients from the nusinersen arm of ENDEAR discontinued treatment with nusinersen and withdrew from SHINE (Figure 11). Therefore, [redacted] patients from the sham arm of ENDEAR and [redacted] patients from the nusinersen arm of ENDEAR completed treatment in ENDEAR and SHINE.

In subsequent sections, patients from the sham arm of ENDEAR are referred to as “previous control” patients, while patients from the nusinersen arm of ENDEAR are referred to as “previous nusinersen” patients.

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Figure 11. Disposition of patients in ENDEAR/SHINE



Source: Biogen Data on File. SHINE CSR

B.2.4.3.1.2 Time to death or permanent ventilation

[redacted] A [redacted] of previous nusinersen patients ([redacted]) died or required permanent ventilation in ENDEAR and/or SHINE compared with previous control patients ([redacted]). During ENDEAR, 28 patients (68%) in the sham arm died or required permanent ventilation [redacted].

The median estimated time to death or permanent ventilation was [redacted] and [redacted], respectively for previous control and previous nusinersen patients (Figure 12).

Figure 12. Event-free survival in ENDEAR/SHINE



Source: Biogen Data on File. SHINE CSR

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B.2.4.3.1.3 Survival

[redacted] A [redacted] of previous nusinersen patients ([redacted]) died in ENDEAR or SHINE compared with previous control patients ([redacted]. During ENDEAR, 16 patients (39%) in the sham control arm died[redacted] The median estimated time to death for previous control patients was [redacted] and [redacted] (Figure 13). [redacted]

Figure 13. Survival in ENDEAR/SHINE



Source: Biogen Data on File. SHINE CSR

B.2.4.3.1.4 Motor milestones

As detailed in Appendix H, motor milestones were assessed using WHO motor milestones. Patients <2 years of age who did not achieve sitting without support were also assessed using HINE-2. [redacted] (Table 14). Please note that this table presents data from the first dose of nusinersen, i.e., starting from the ENDEAR baseline for previous nusinersen and from the SHINE baseline from previous control patients who enrolled in SHINE.

With regards to HINE-2, at Day 818, mean HINE-2 total motor milestone scores for previous control and previous nusinersen patients were [redacted], respectively, [redacted], respectively. At the last visit for HINE-2 assessment (after which patients were assessed using the WHO motor milestones), [redacted]previous control patients [redacted] previous nusinersen patients had full head control. The corresponding figures for being able to sit or pivot were [redacted]for the previous control group and [redacted] for the previous nusinersen group.

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Table 14. WHO motor milestones in ENDEAR/SHINE

Milestone	Previous control (n=24)	Previous nusinersen (n=81)	
	Patients achieving the milestone, n (%)	Patients achieving the milestone, n (%)	Median (range) time to achieve the milestone, months
Sitting without support	[redacted]	[redacted]	[redacted]
Standing with assistance	[redacted]	[redacted]	[redacted]
Standing alone	[redacted]	[redacted]	[redacted]
Walking with assistance	[redacted]	[redacted]	[redacted]

Source: Biogen Data on File. SHINE CSR

B.2.4.3.1.5 CHOP INTEND

[redacted] (Figure 14). [redacted] (Figure 14).

Figure 14. CHOP INTEND scores over time in ENDEAR/SHINE

[redacted]

Abbreviations: Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders; SEM, standard error of the mean.
Source: Biogen Data on File. SHINE CSR

The mean CHOP INTEND total score at [redacted] for was [redacted] for previous control patients and [redacted] for previous nusinersen patients. Relative to ENDEAR baseline, this corresponded to [redacted] and [redacted], respectively. As shown in Figure 14, patients in the sham arm experienced a [redacted] in CHOP INTEND from baseline during the sham treatment in ENDEAR (from ENDEAR baseline [redacted], red line in Figure 14), followed by a mean [redacted] after initiating treatment with nusinersen in SHINE (green line in Figure 14). Patients who had ≥ 4 points improvement in CHOP INTEND total score from ENDEAR baseline were considered responders. At [redacted], [redacted] and [redacted] were responders on the CHOP INTEND scale, i.e., experienced ≥4-point improvement from ENDEAR baseline.

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B.2.4.3.1.6 Growth parameters

[redacted]. At Day 2102, mean weight for age percentile (per WHO criteria) for previous control patients was [redacted] which [redacted]. For previous nusinersen patients, mean weight for age percentile at Day 2102 was [redacted], which corresponded to [redacted].

B.2.4.3.1.7 Dysphagia

Dysphagia was assessed using the Parent Assessment of Swallowing Ability (PASA) questionnaire developed by Biogen; this assessment was introduced in SHINE following a protocol amendment in January 2017. Therefore, the data is presented from modified maintenance dosing regimen (MMDR) Day 1, i.e., the point from which all patients in SHINE (including later-onset patients transitioning from CHERISH who initially had less frequent dosing, see Figure 5) received nusinersen per the licensed dosing regimen. [redacted]

B.2.4.3.1.8 Scoliosis and contractures

Patients ≥2 years of age (except for patients treated at German sites) had approximately annual X-rays of the thoracolumbar region to determine the severity of scoliosis by measuring the Cobb angle. Assessments of scoliosis were not performed in ENDEAR and were introduced for previous ENDEAR patients in SHINE following a protocol amendment in January 2017. Therefore, the data is presented from MMDR Day 1.

[redacted]. At MMDR Day 1800, median Cobb angles of previous control and previous nusinersen patients were [redacted] and [redacted] respectively, which corresponded to median [redacted]from first assessment of [redacted] and [redacted], respectively. [redacted]. [redacted] previous control patients and [redacted] previous nusinersen patients had surgery to correct scoliosis [redacted].

Contractures which limited the ability of the patient to perform motor outcome scales were assessed in SHINE following a protocol amendment in January 2017; consequently, the data is presented from MMDR Day 1. [redacted]. At MMDR Day 1800, [redacted] and [redacted] had at least one contracture at any location. Severe contractures (assessed at five locations: hip flexors, knee flexors, ankle plant flexors, elbow flexors, and forearm pronators) were observed in [redacted]) previous control patients and [redacted] previous nusinersen patients.

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[redacted]. This data from is presented in Figure 15 [redacted]. In general, [redacted] from ENDEAR baseline ([redacted]), [redacted] patients in the previous control group [redacted]. The proportion of previous nusinersen patients experiencing contractures was [redacted] compared with previous control patients. [redacted]. Note, that the data in Figure 15 is presented using [redacted] as the denominator, [redacted]. This is because, at most time points, a [redacted] (see tabulation at the bottom of Figure 15).

Figure 15. Percentage of patients with contractures over time in ENDEAR/SHINE[a]



B.2.4.3.1.9 Quality of life

Quality of life was assessed for previous ENDEAR patients in SHINE following a protocol amendment implemented in January 2017 and the data presented in this section refer to the MMDR Day 1800 assessment, with baseline being defined as MMDR Day 1. Mean PedsQL scores of patients with infantile-onset SMA previously enrolled in ENDEAR were [redacted]and were [redacted] for previous nusinersen than previous control patients (Table 15).

Table 15. Summary of PedsQL scores in SHINE (previous ENDEAR patients)

Measure	Previous control	Previous nusinersen
Mean patient-rated inventory total score, points	[redacted]	[redacted]
Mean patient-rated neuromuscular score, points	[redacted]	[redacted]
Mean parent-rated inventory total score (mean change from baseline), points	[redacted]	[redacted]
Mean parent-rated neuromuscular score (mean change from baseline), points	[redacted]	[redacted]

Note that baseline was the first PedsQL measurement in SHINE. No change from baseline data are available for patient-rated scores due to the young age of the patients.
Source: Biogen Data on File. SHINE CSR

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[redacted] (Figure 16). [redacted](Figure 16). [redacted]Figure 16).

Mean feeding/grooming/dressing total scores for previous control and previous nusinersen groups were [redacted], respectively, which corresponded to mean [redacted] from baseline (first ACEND measurement in SHINE) of [redacted], respectively.

Mean sitting/play total scores were [redacted] for previous control and [redacted] for previous nusinersen groups, respectively, which corresponded to a mean [redacted]from baseline of [redacted] a mean [redacted] from baseline [redacted], respectively.

Mean mobility total scores for previous control and previous nusinersen groups were [redacted], respectively, which corresponded to mean [redacted], respectively.

[redacted]Figure 16. ACEND scores over time in SHINE (previous ENDEAR patients)



Abbreviations: ACEND, Assessment of Caregiver Experience with Neuromuscular Disease; SEM, standard error of the mean
Source: Biogen Data on File. SHINE CSR

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B.2.4.3.1.10 SMA-related hospitalisations

The annualised rate of hospitalisation for serious respiratory events [redacted] in ENDEAR/SHINE. The annualised rates of hospitalisation for serious respiratory events during the first year (Days 1–360) in ENDEAR/SHINE were [redacted] hospitalisations per patient-year in the previous control group and [redacted] hospitalisations per patient-year in the previous nusinersen group. The corresponding rates during the eighth year (Days 2521–2880) [redacted].

B.2.4.3.2 Later-onset SMA

B.2.4.3.2.1 Patient disposition

Of the 126 patients with later-onset SMA in CHERISH, 84 received nusinersen and 42 received sham treatment. Baseline characteristics of this population are presented in Table 11. No patients discontinued treatment during CHERISH. All 42 patients from the sham control arm of CHERISH and 83 of 84 patients from the nusinersen arm enrolled in SHINE (Figure 17). Since their enrolment in SHINE, [redacted] patients from the control arm of CHERISH and [redacted] patients from the nusinersen arm of CHERISH discontinued treatment with nusinersen and withdrew from SHINE (Figure 17). Therefore, [redacted] patients from the sham arm of CHERISH and [redacted] patients from the nusinersen arm of CHERISH completed treatment in CHERISH and SHINE.

In subsequent sections, patients from the sham arm of CHERISH are referred to as “previous control” patients, while patients from the nusinersen arm of CHERISH are referred to as “previous nusinersen” patients.

Figure 17. Disposition of patients in CHERISH/SHINE

[redacted]

Source: Biogen Data on File. SHINE CSR

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B.2.4.3.2.2 Survival

[redacted] with later-onset SMA who initially participated in CHERISH [redacted]in the previous control group and [redacted] in the previous nusinersen group. [redacted]

B.2.4.3.2.3 WHO motor milestones

[redacted]Table 16[redacted]

Table 16. WHO motor milestones in CHERISH/SHINE

Milestone	Patients able to perform the milestone at last assessment, n (%)	
	Previous control (n=42)	Previous nusinersen (n=84)
Sitting without support	[redacted]	[redacted]
Standing with assistance	[redacted]	[redacted]
Standing alone	[redacted]	[redacted]
Walking with assistance	[redacted]	[redacted]

Source: Biogen Data on File. SHINE CSR

B.2.4.3.2.4 HFMSE

Mean HFMSE total scores for previous nusinersen patients [redacted] than for previous control patients (

Figure 18). [redacted] (

Figure 18). Mean HFSME total scores at CHERISH baseline for previous control and previous nusinersen patients were [redacted], respectively. At Day 2790, the scores in the two groups were [redacted], respectively, which corresponded to [redacted], respectively. At Day 2790, [redacted] previous control patients ([redacted]) and [redacted] previous nusinersen patients ([redacted]) had ≥3-point improvement from CHERISH baseline in HFMSE total score.

[redacted]

Figure 18. HFMSE scores over time in CHERISH/SHINE

[redacted]

spinal muscular atrophy

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Abbreviations: HFMSE, Hammersmith Functional Motor Scale Expanded; SEM, standard error of the mean
Source: Biogen Data on File. SHINE CSR.

B.2.4.3.2.5 RULM

[redacted] (Figure 19). Mean RULM total scores at CHERISH baseline were [redacted] points in previous control and previous nusinersen groups, respectively. At Day 2790, the scores [redacted] in the two groups, respectively, for a mean total RULM score of [redacted] in previous control patients and [redacted] in previous nusinersen patients. At Day 2790, [redacted] previous control patients [redacted] and [redacted] previous nusinersen patients [redacted] were responders on the RULM scale, i.e., had ≥ 2-points improvement from CHERISH baseline in RULM total score.

Figure 19. RULM scores over time in CHERISH/SHINE

[redacted]

Abbreviations: RULM, Revised Upper Limb Module; SEM, standard error of the mean
Source: Biogen Data on File. SHINE CSR.

B.2.4.3.2.6 Scoliosis and contractures

[redacted]Median Cobb angle at CHERISH baseline was [redacted] for patients in the previous control group and [redacted] for patients in the previous nusinersen group. At Day 2790, median Cobb angles were [redacted] and [redacted] in the previous control and previous nusinersen groups, respectively. This corresponded to median [redacted]in the previous control group and [redacted] in the previous nusinersen group from baseline over the duration of follow-up in CHERISH/SHINE. [redacted] had growing rod or spinal fixation surgery to correct scoliosis during the follow-up in CHERISH/SHINE.

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[redacted] At MMDR Day 1800, [redacted] previous control patients and [redacted] previous nusinersen patients had at least one contracture at any location. Severe contractures (assessed at five locations: hip flexors, knee flexors, ankle plant flexors, elbow flexors, and forearm pronators) affected [redacted] and [redacted] patients in the two groups, respectively.

A post-hoc analysis was performed to assess contractures across CHERISH and SHINE from CHERISH baseline. [redacted] (Figure 20).

Figure 20. Contractures over time in CHERISH/SHINE[a,b]



[redacted]

As noted in Section B.2.4.3.2.4, [redacted]

B.2.4.3.2.7 Dysphagia

Symptoms related to dysphagia, measured using the PASA questionnaire, were [redacted].

B.2.4.3.2.8 Quality of life

Quality of life of patients with later-onset SMA was assessed throughout CHERISH/SHINE. [redacted] (Table 17).

Table 17. Summary of PedsQL scores in CHERISH/SHINE

Score at last visit	Previous control	Previous nusinersen
Mean patient-rated inventory total score (mean change from baseline), points	[redacted]	[redacted]
Mean patient-rated neuromuscular score (mean change from baseline), points	[redacted]	[redacted]
Mean parent-rated inventory total score (mean change from baseline), points	[redacted]	[redacted]
Mean parent-rated neuromuscular score (mean change from baseline), points	[redacted]	[redacted]

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Note that baseline was the CHERISH baseline.
Source: Biogen Data on File. SHINE CSR

[redacted] (Figure 21). [redacted] (Figure 21).

Mean feeding/grooming/dressing total scores at Day 2070 (approximately 5.7 years from first dose of nusinersen) were [redacted] points for previous control and previous nusinersen patients respectively, corresponding to [redacted] (first dose of nusinersen) of [redacted] points, respectively.

Mean transfers total scores at Day 2070 were [redacted] in previous control patients (mean increase from baseline of [redacted] points) and [redacted] points in previous nusinersen patients ([redacted] of [redacted] points).

Mean mobility total scores at Day 2070 were [redacted]and [redacted] points, respectively, for previous control and previous nusinersen patients, which corresponded to mean [redacted] of [redacted], respectively.

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Figure 21. ACEND scores over time in CHRISH/SHINE



Abbreviations: ACEND, Assessment of Caregiver Experience with Neuromuscular Disease; SEM, standard error of the mean
Source: Biogen Data on File. SHINE CSR

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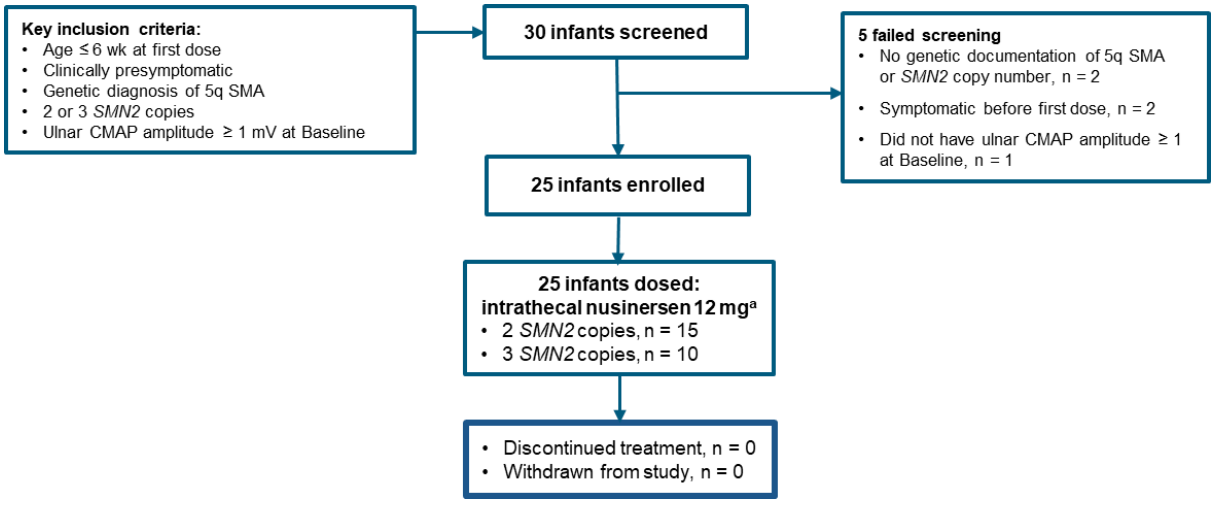
B.2.4.3.2.9 SMA-related hospitalisations

[redacted]. The annualized rate of hospitalisation for serious respiratory events in the first year of CHERISH/SHINE (Days 1–360) were [redacted] and [redacted]hospitalisations per patient year in previous control and nusinersen patients, respectively. [redacted] and was [redacted] [redacted] in the eighth year of follow-up in CHERISH/SHINE (Days 2521–2880).

B.2.4.4 Long-term efficacy of nusinersen in presymptomatic patients (NURTURE)

A total of 30 infants were screened and 25 infants were enrolled in NURTURE (Figure 22). As of the clinical data cut of 15 February 2021, all enrolled patients remained on study with a median time on study of 4.9 (3.9–5.7) years[84]. Among the 25 participating infants, 15 had two *SMN2* copies and 10 had three *SMN2* copies.[84] Baseline patient characteristics are listed in Table 18. Median age at first nusinersen dose was 19.0 days in patients with two copies of *SMN2* and 23.0 days in patients with three copies (Table 18). Total HINE-2 scores were similar between patients with two and three *SMN2* copies (median scores of 3.0 in both groups), while the median CHOP-INTEND score was higher in infants with three *SMN2* copies (median of 53.5) than in those with two *SMN2* copies (median of 45.0) (Table 18).[84]

Figure 22. Patient flow diagram for the NURTURE study



[a] Nusinersen 12 mg administered intrathecally as 4 loading doses (Days 1, 15, 29, and 64) followed by maintenance doses every 4 months; some infants received a 12-mg scaled equivalent dose before the protocol was revised in March 2017.
Source: De Vivo et al. 2019[83], Crawford et al. 2023[84]

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Table 18. Baseline characteristics of patients enrolled in NURTURE

Characteristic	2 *SMN2* copies $n = 15$[a]	3 *SMN2* copies $n = 10$	Total $N = 25$
Age at first dose, days, n (%)			
≤14	6 (40)	3 (30)	9 (36)
>14 and ≤28	7 (47)	5 (50)	12 (48)
>28	2 (13)	2 (20)	4 (16)
Median (range)	19.0 (8–41)	23.0 (3–42)	22.0 (3–42)
Mean (SD)	19.5 (9.29)	22.3 (12.45)	20.6 (10.51)
Male, n (%)	8 (53)	4 (40)	12 (48)
CHOP INTEND total score	n = 15	n = 10	n = 25
Median (range)	45.0 (25.0–60.0)	53.5 (40.0–60.0)	50.0 (25.0–60.0)
Mean (SD)	47.0 (10.04)	51.9 (6.10)	49.0 (8.87)
HINE total motor milestones	n = 15	n = 10	n = 25
Median (range)	3.0 (0–5)	3.0 (0–7)	3.0 (0–7)
Mean (SD)	2.7 (1.59)	3.2 (1.87)	2.9 (1.69)
Ulnar CMAP amplitude, mV	n = 14	n = 10	n = 24
Median (range)	2.30 (1.0–6.7)	2.90 (1.8–4.9)	2.65 (1.0–6.7)
Mean (SD)	2.69 (1.516)	3.11 (1.119)	2.87 (1.354)
Peroneal CMAP amplitude, mV	n = 12	n = 10	n = 22
Median (range)	3.20 (1.1–9.7)	4.00 (0.2–7.0)	3.30 (0.2–9.7)
Mean (SD)	3.52 (2.159)	3.75 (2.188)	3.62 (2.123)
Plasma pNF-H, pg/mL[b]	n = 13	n = 9	n = 22
Geometric mean (95% CI)	20880.9 (9639.4–45231.9)	1870.7 (1152.9–3035.5)	7782.7 (3828.6–15820.3)
Range	845–52,900	959–7950	845–52,900
CSF pNF-H, pg/mL[b]	n = 14	n = 9	n = 23
Geometric mean (95% CI)	20139.2 (10075.0–40256.7)	951.5 (366.5–2470.2)	6099.8 (2646.0–14062.0)
Range	342–37,200	261–9140	261–37,200

Abbreviations: CHOP INTEND, Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders; CI, confidence interval; CMAP, compound muscle action potential; CSF, cerebrospinal fluid; HINE, Hammersmith Infant Neurological Examination; pNF-H, phosphorylated neurofilament heavy chain; *SMN2*, survival motor neuron 2.
a: Included one set of twins; each child had two *SMN2* copies;
b: The number of decimal places reported in summary statistics is not indicative of biomarker assay precision or sensitivity.
Source: De Vivo et al. 2019[83]

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B.2.4.4.1 Primary endpoint (time to death or respiratory intervention)

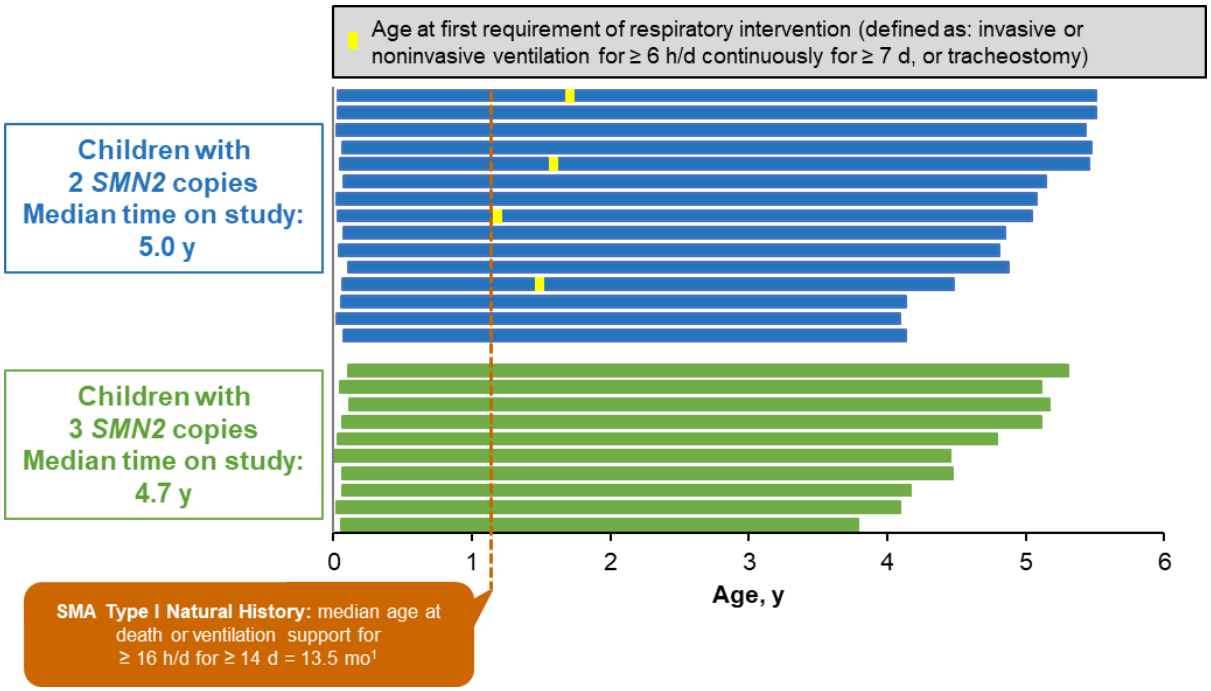
As of the 15 February 2021 data cut, none of the 25 infants enrolled had died or required permanent ventilation at a median age of 4.9 (range 3.8–5.5) years[84]. This is in stark contrast with the natural history of infantile-onset SMA both in the US, where median age at death or requiring at least 16 hours/day of ventilation support was reported at 13.5 months (IQR 8.1–22.0 months)[86], and in the UK, where average age of mortality for SMA was estimated to be approximately 1.5 years (18.6 months; range 10–24 months)[30].

Four patients met the primary NURTURE endpoint of time to death or respiratory intervention (invasive or non-invasive for ≥ 6 hours/day continuously for 7 or more days OR tracheostomy) at an age of 14.9, 18.1, 19.1, and 20.7 months (Figure 23) [84]. All of these patients had two copies of *SMN2*[84]. One of these infants first met the definition for respiratory intervention at age 1.5 years but as of the last assessment has not required respiratory intervention since age 3.3 years[84]. However, the patient used twice daily cough assist for prophylactic respiratory support. The remaining three patients received non-invasive ventilation for 9–10 h/day for prophylactic support (n = 2) or microaspiration treatment (n = 1)[84]. At baseline, all four patients who met the primary endpoint had either complete areflexia (n = 3), ulnar CMAP amplitude <2 mV (n = 3), or peroneal CMAP <2 mV (n = 1)[84].

It is worth noting that the definition of respiratory intervention used in the primary endpoint of NURTURE was stricter than in comparator trials enrolling presymptomatic patients. RAINBOWFISH assessing risdiplam used a cut-off of ≥16 hours for >21 days to define permanent ventilation[87], while the SPR1NT study of used a cut-off of ≥16 hours for ≥14 days[88]; similar to NURTURE, the definitions in both comparator trials also included tracheostomy[87,88].

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Figure 23. NURTURE primary endpoint: time to death or respiratory intervention



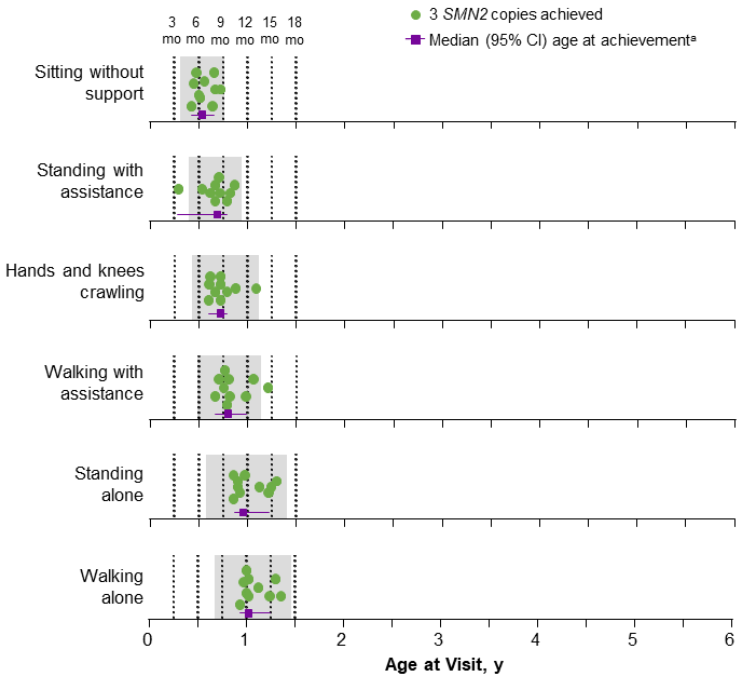
Abbreviations: SMA, spinal muscular atrophy; *SMN2*, survival motor neuron 2.
The horizontal bars show the age of each child at the last visit the child attended.
References: 1. Finkel et al. 2014[86]
Source: Crawford et al. 2023[84]

B.2.4.4.2 WHO motor milestones

The 10 children with three *SMN2* copies achieved the highest WHO motor milestone of walking independently within normal developmental timeframes [84] (Figure 24). Among the 15 children with two *SMN2* copies, all achieved sitting without support and standing with assistance, 14 achieved hands and knees crawling and walking with assistance, and 13 achieved standing alone and walking alone, with some attaining milestones within normal developmental time frames[84] (Figure 25). All children who achieved a WHO motor milestone retained this achievement at the last study visit[84].

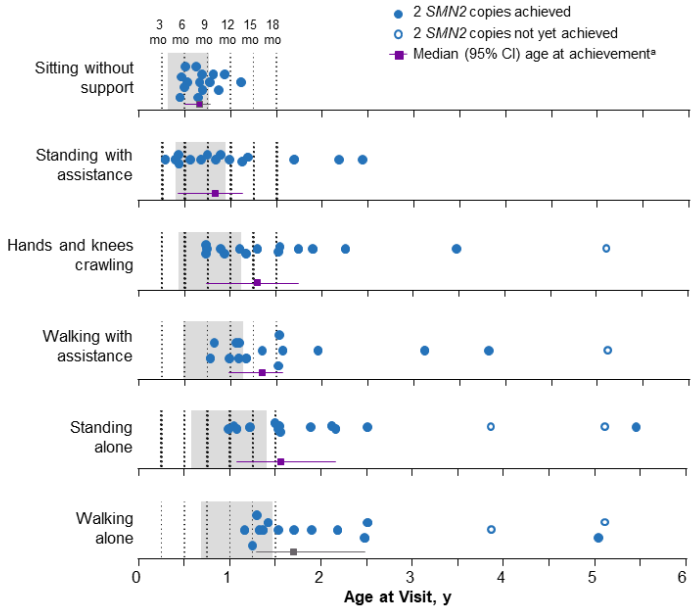
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Figure 24. Achievement of WHO motor milestones by patients with three *SMN2* copies enrolled in NURTURE



Abbreviations: *SMN2*, survival motor neuron 2; WHO, World Health Organization; y, years.
Note: Gray shading indicates the WHO motor milestone first and 99th percentiles of age at achievement for healthy, typically developing children based on the WHO Multicenter Growth Reference Study[89].
[a] Median age at achievement of milestone and 95% CI estimated from Kaplan-Meier curve.
Source: Crawford et al. 2023[84]

Figure 25. Achievement of WHO motor milestones by patients with two *SMN2* copies enrolled in NURTURE



Abbreviations: *SMN2*, survival motor neuron 2; WHO, World Health Organization; y, years.
Note: Gray shading indicates the WHO motor milestone first and 99th percentiles of age at achievement for healthy, typically developing children based on the WHO Multicenter Growth Reference Study[89].
[a] Median age at achievement of milestone and 95% CI estimated from Kaplan-Meier curve.
Source: Crawford et al. 2023[84]

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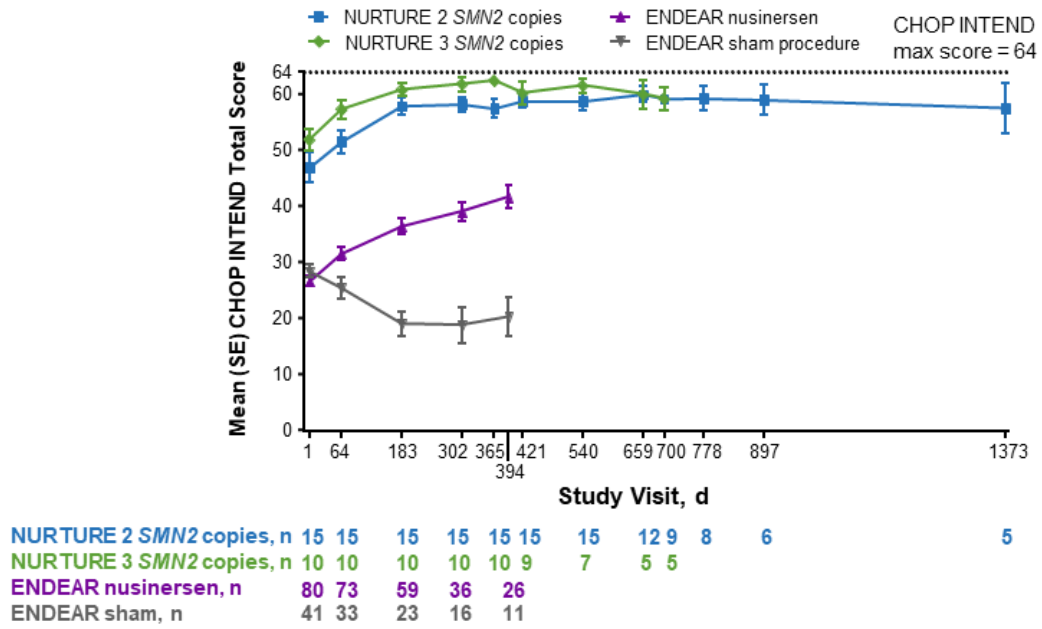
B.2.4.4.3 CHOP INTEND

A total of 22 children achieved the maximal CHOP INTEND score of 64, including all 10 (100%) patients with three *SMN2* copies and 12 (80%) patients with two *SMN2* copies[84]. Mean CHOP INTEND scores increased steadily from baseline before stabilizing around the maximum score [84] (Figure 26). CHOP INTEND scores in NURTURE patients were higher than the scores of children with symptomatic infantile-onset SMA who participated in ENDEAR (Figure 26). It is worth noting that all patients enrolled in ENDEAR had two *SMN2* copies as per the trial's inclusion criteria (see

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Table 6).

Figure 26. Mean total CHOP INTEND score over time in NURTURE (timepoints with ≥ 5 children) compared with symptomatic infantile-onset patients from ENDEAR



Abbreviations: CHOP INTEND, Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders; d, days; *SMN2*, survival motor neuron 2.
Note: Only study visits with n ≥ 5 are included. Per Version 6 of the study protocol, CHOP INTEND is assessed in children until they have a maximum score of 64. Once a score of 64 is achieved, CHOP INTEND will no longer be assessed.
Source: Crawford et al. 2023[84] and Finkel et al. 2017[72]

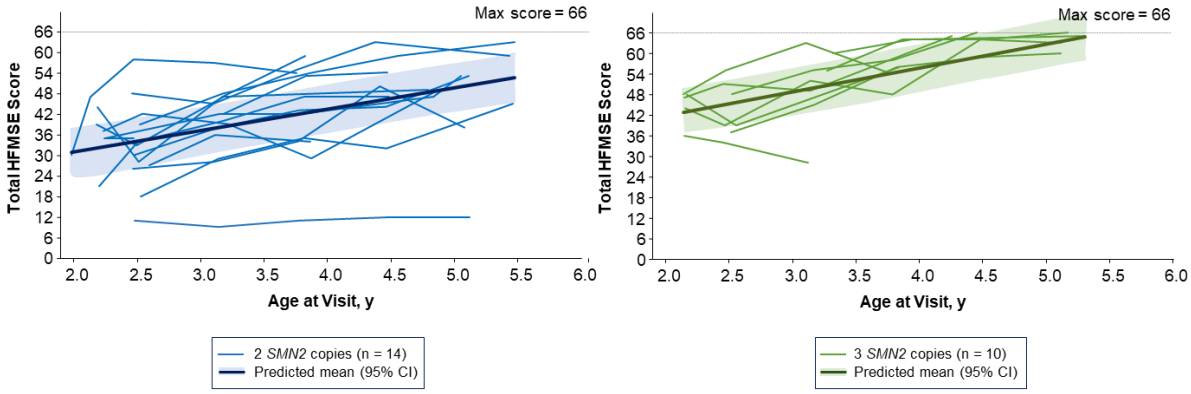
B.2.4.4.4 HFMSE

Beginning at an age of 2 years, initial HFSME assessments were obtained in 14 out of 15 children with two *SMN2* copies (assessed at age: 2.1–3.2 years) and all 10 children with three *SMN2* copies (assessed at age: 2.1–3.8 years), with mean (SD; range) total scores of 33.1 (11.31; 11–48) and 46.4 (7.44; 36–60), respectively[84].

Overall, HFMSE mean and individual total scores showed continued improvement both in patients with two and three *SMN2* copies[84] (Figure 27). However, one child with two copies had stable, low scores with baseline characteristics suggestive of neurodegeneration at baseline, including low weight-for-age (6.7th percentile), areflexia, and low ulnar CMAP amplitude (1.5 mV)[84]. In addition, one child with three copies had scores of 36 and 34 at Days 778 and 897, but a score of 28 was noted at Day 1135 at age 3.1 years[84]. However, the physical therapist noted that this score was not reflective of the child's abilities and resulted from poor patient cooperation[84].

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Figure 27. Mean HFMSE total scores over time among patients in NURTURE with two (left) or three (right) *SMN2* copies



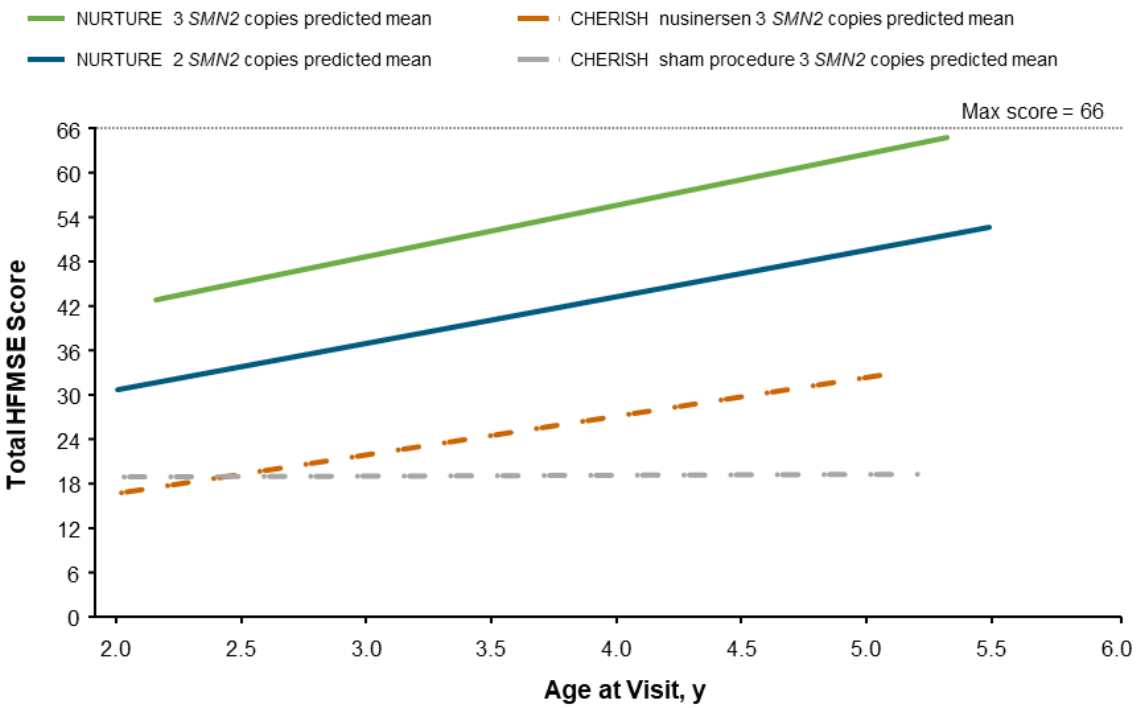
Abbreviations: HFMSE, Hammersmith Functional Motor Scale Expanded; *SMN2*, survival motor neuron 2; WHO, World Health Organization; y, years.
Note: HFMSE was assessed in children aged ≥ 2 years. The first evaluable HFMSE score was identified, excluding Day 700 records. A mixed-effects model with random intercept was used to determine predicted mean and 95% CI.
Source: Crawford et al. 2023[84]

Predicted mean total scores and improvements over time were higher in NURTURE patients with two or three *SMN2* copies than in CHERISH patients with symptomatic later-onset SMA who were treated with nusinersen or sham control[84] (Figure 28).

A total of 11 children had at least one valid 6-Minute Walk Test (6MWT) assessment[84]. Total distances were 150–325 m among the five patients with two *SMN2* copies and 238–444 m among the six patients with three *SMN2* copies, indicating that patients treated at the presymptomatic stage could achieve and sustain independent walking[84].

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Figure 28. Predicted means slopes of HFMSE total scores in NURTURE compared with symptomatic later-onset SMA patients from CHERISH



Group	n	Slope (95% CI)
NURTURE 3 *SMN2* copies	10	6.99 (4.98–9.00)
NURTURE 2 *SMN2* copies	14[a]	6.30 (4.70–7.90)
CHERISH 3 *SMN2* copies nusinersen[b]	34	5.22 (4.51–5.94)
CHERISH 3 *SMN2* copies sham[b]	24	0.14 (−0.79 to 1.06)

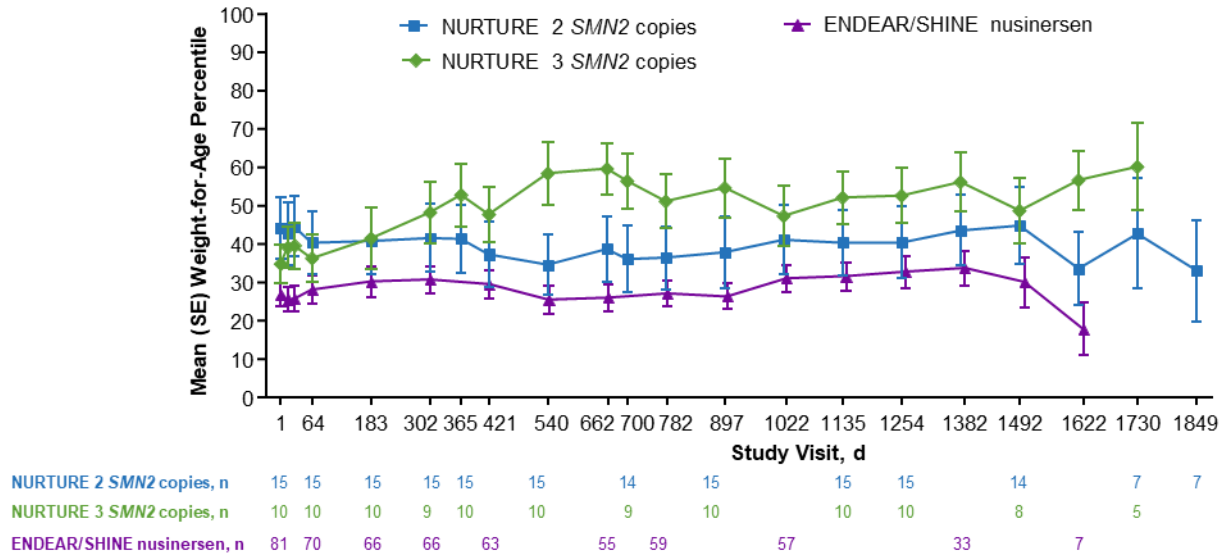
Abbreviations: HFMSE, Hammersmith Functional Motor Scale – Expanded; max, maximum; SMN, survival motor neuron.
HFMSE was assessed in children age ≥ 2 years. The first evaluable HFMSE score was identified, excluding Day 700 records. A mixed-effects model with random intercept was used to determine predicted mean and 95% CI.
Notes: [a] One child was not included because of inability to perform an evaluable HFMSE. [b] CHERISH children who were age 2–4 years at baseline were included for this comparison. All CHERISH children were non-ambulatory at Baseline per enrolment criteria.
Source: Crawford et al. 2023[84]

B.2.4.4.5 Growth parameters

All children continued to grow and gain weight. Mean weight-for-age stabilized over time (Figure 29), and half of the patients (n=12 [48%]) were between the 25th and 75th percentiles of weight-for-age at last visit while 7 (28%) were in the <25th percentile and 6 (24%) were in the >75th percentile[84]. Mean weight for age was higher in NURTURE patients than in ENDEAR-SHINE patients treated with nusinersen after symptom onset[84] (Figure 29).

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Figure 29. Mean weight for age in NURTURE patients compared with ENDEAR-SHINE



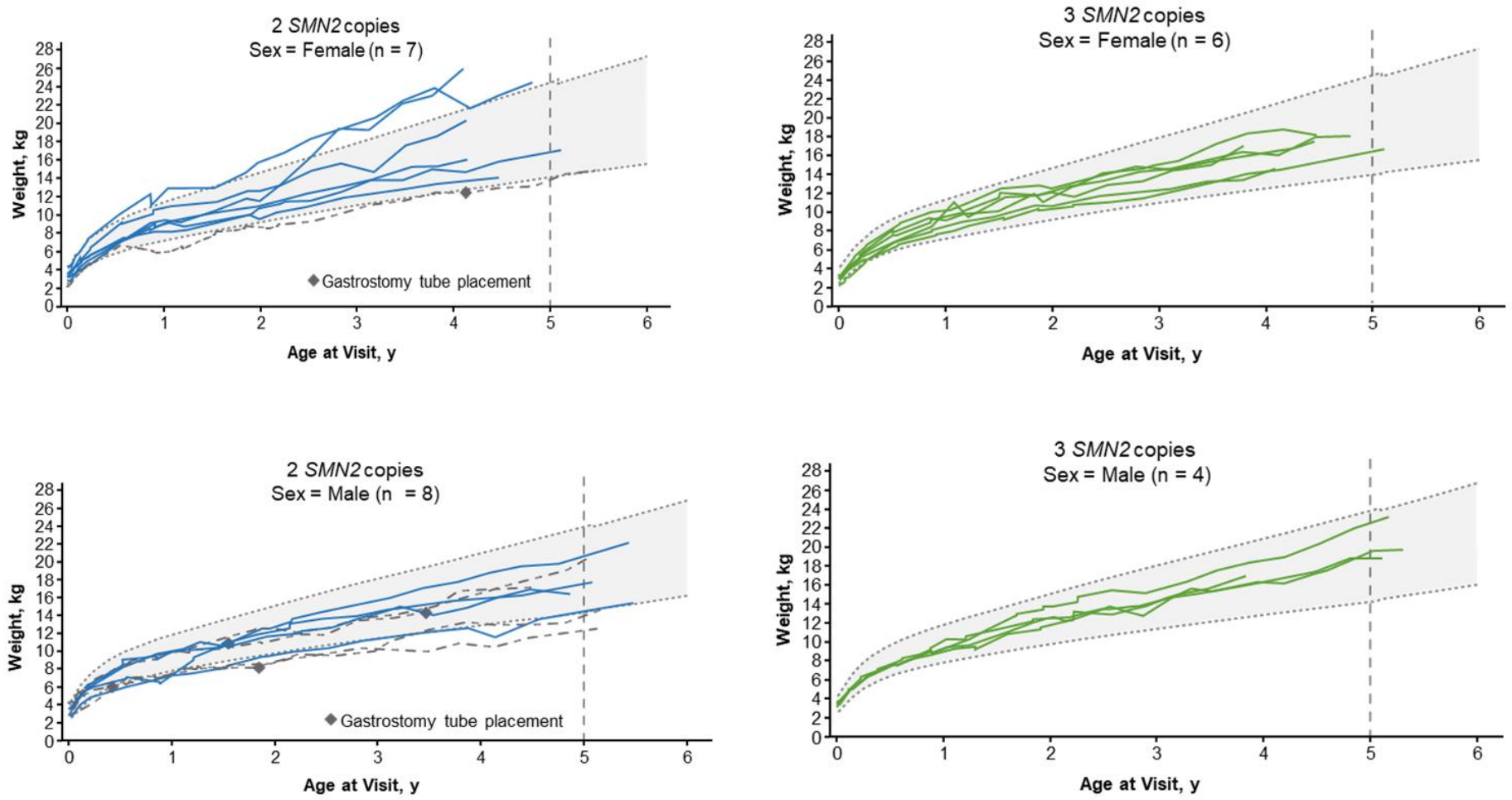
Abbreviations: *SMN2*, survival motor neuron 2; d, day
Source: Crawford et al. 2023[84]

At the last visit when length was measured (age: 3.2–5.1 years), 10 patients (40%) were between the 25th and 75th percentiles for length-for-age, 11 (44%) were in were in the <25th percentile, and 4 (16%) were in the >75th percentile[84].

A total of five patients, all with two *SMN2* copies has a gastrostomy tube placed. Gastrostomy tube placement occurred at ages 5.9, 19.4, 22.5, 41.9, and 50.1 months[84] (Figure 30). The reason for tube placement was dysphagia (n = 3; 1 used as needed), and low weight (n = 2) [84]. At baseline, one of these patients had low peroneal CMAP amplitude (1.1 mV), three had low ulnar CMAP amplitude (1–1.5 mV); three were areflexic, and four were in the <50th percentile for weight-for-age[84]. Four of these five patients also required respiratory intervention during the study. Nonetheless, all five patients with gastrostomy tubes continued to achieve motor milestones after tube placement, three attained independent walking, and two reached the CHOP INTEND maximum score[84].

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Figure 30. Body weight of NURTURE patients in relation to WHO weight-for-age percentiles



Abbreviations: *SMN2,* survival motor neuron 2; WHO, World Health Organization
WHO third and 97th growth percentiles for healthy children are shown in grey. The grey dotted lines denote children who received gastrostomy tube and diamonds denote age of child at insertion of gastrostomy tube.
Source: Crawford et al. 2023[84]

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B.2.4.4.6 Dysphagia

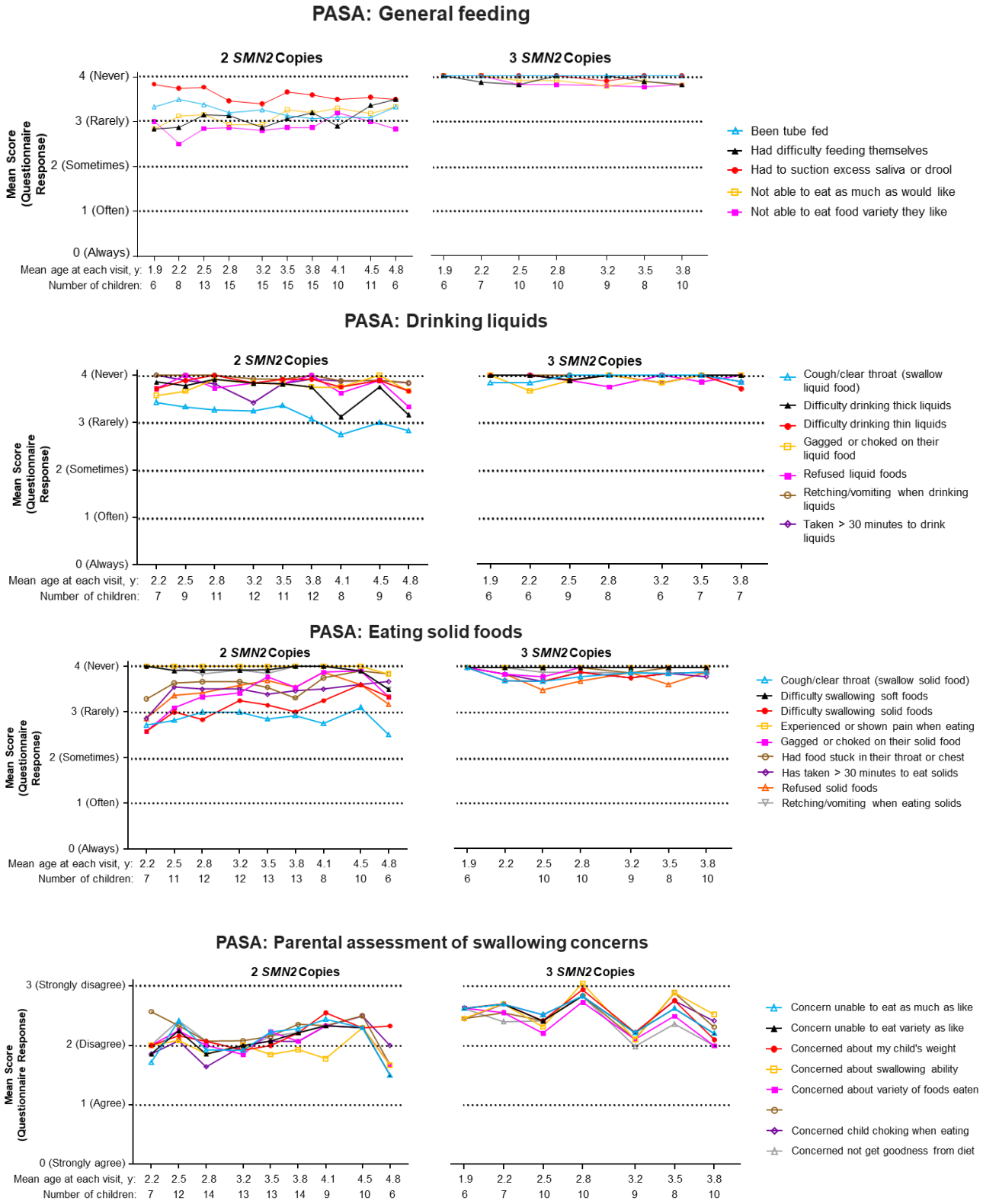
Dysphagia was assessed using the PASA questionnaire developed by Biogen. This questionnaire consists of 33 items across four domains: general feeding, drinking liquids, eating solid foods and assessment of swallowing concerns. The first three of these domains are generally assessed with five levels of response: Never, Rarely, Sometimes, Often and Always, although two items are assessed with a simple 'Yes'/'No' answer. The assessment of swallowing concerns has four levels of response: Strongly agree, Agree, Disagree and Strongly disagree. In answering each item, the parent is directed to consider the previous 7 days. The questionnaire domains were completed as applicable, e.g. the eating solid foods domain was completed only by parents/caregivers of children who attempted to eat solid foods in the last 7 days.

For most PASA items, NURTURE patients were consistently rated, on average, as never to rarely experiencing difficulty swallowing over a mean of 2.6 years (assessments began >1 y after treatment initiation)[84] (Figure 31). As of their last assessment, 23 patients (92%) maintained the ability to swallow, and parents/caregivers did not have concerns about swallowing independent of the patient's *SMN2* copy number[84]. At the patient's last PASA assessment, 19 of 25 (76%) parents/caregivers disagreed or strongly disagreed with being concerned about their child choking, and 20 (80%) (20/25) disagreed or strongly disagreed with being concerned about their child aspirating on food while eating[84].

Of the five children with two *SMN2* copies ever identified by PASA as being tube-fed, two were "always" tube-fed, and three were "often" tube-fed in the 7 days preceding the last assessment[84].

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Figure 31. Parent Assessment of Swallowing Ability responses over time in NURTURE



Abbreviations: PASA, Parent Assessment of Swallowing Ability; *SMN2*, survival motor neuron 2
Mean scores are reported for every visit with >5 children with PASA data in both *SMN2* copy number groups.
Data for two items in the eating solid foods domain (had difficulty swallowing pills, required food to be cut up into smaller pieces) are not shown, because they were not developmentally relevant.
Source: Crawford et al. 2023[84]

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B.2.4.5 Real-world efficacy of nusinersen in the UK

Consistent with the separate data collection efforts for paediatric and adult patients with SMA treated with nusinersen in the UK, the results are presented separately for the two age-based populations. See Section B.2.3.4 for an overview of MAA methodology and Appendices E and F for full study reports. Because nusinersen was the first therapy to become available for patients with SMA in the UK, both the paediatric and adult MAA cohorts included prevalent patients, some of whom had a long disease duration. Real-world outcomes can be expected to be substantially better among patients treated nowadays and in the future, who are expected to be almost exclusively newly-diagnosed, incident patients and therefore are likely to have a lower symptom burden at baseline compared with the MAA cohorts.

B.2.4.5.1 Nusinersen in paediatric patients in the UK

B.2.4.5.1.1 Patient and treatment characteristics

Among 287 patients identified initially as receiving nusinersen in England and Wales through the MAA, a total of 220 patients were included in the analyses. All of these patients were diagnosed at the symptomatic stage; 5 patients diagnosed presymptomatically were identified but not included in the analyses. Patients were classified into five cohorts based on SMA type and motor function at baseline: type 1 patients enrolled in the EAP (n=46), type 1 patients who were not enrolled in the EAP (n=35), type 2/3 non-sitters (n=21), type 2/3 sitters (n=88), and type 2/3 walkers (n=30). The distinction between type 1 patients enrolled and not enrolled in the EAP was introduced in because when the EAP was opened in UK for SMA type 1, many older and chronic patients were offered the possibility to access nusinersen. These patients were often already receiving feeding and/or respiratory support and had contractures. Baseline characteristics and duration of treatment with nusinersen for patients in the total paediatric MAA population as well as in the individual cohorts are available in Table 19. In total, 78 patients had stopped nusinersen before the final data cut of 9 October 2023; of these, 75 (96.2%) switched to another treatment, including risdiplam in 43 (55.1%) patients and onasemnogene abeparvovec in 32 patients (41.0%). Reasons for switching treatment included increased difficulty with performing lumbar puncture (most switchers to risdiplam), spinal fusion surgery, and patients'/caregiver's preference after clinical consideration.

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Table 19. Baseline characteristics of paediatric patients treated with nusinersen in the UK and included in the MAA data collection.

	Type 1- EAP	Type 1- Non-EAP	Type 2/3- Non-Sitters	Type 2/3- Sitters	Type 2/3- Walkers	All SMA types
Number of Patients	46	35	21	88	30	220
SMA Type						
Type 1, n (%)	46 (100.00)	35 (100.00)	0 (0.00)	0 (0.00)	0 (0.00)	81 (36.82)
Type 2, n (%)	0 (0.00)	0 (0.00)	20 (95.24)	62 (70.45)	0 (0.00)	82 (37.27)
Type 3, n (%)	0 (0.00)	0 (0.00)	1 (4.76)	26 (29.55)	30 (100.00)	57 (25.91)
Age at symptom onset (months), mean (SD), median (range)	3.57 (2), 3.24 (0.00–8.52)	2.22 (2), 1.56 (0.00–8.04)	8.96 (3.2), 8.04 (5.28–7.16)	16.05 (25), 12.00 (0.00–189.72)	24.97 (12), 23.52 (6.00–48.96)	11.71 (18), 8.04 (0.00– 189.72)
Age at first treatment with nusinersen (years), mean (SD), median (range)	3.75 (2.6), 2.91 (0.52–13.29)	0.54 (0.67),0.28 (0.03–2.91)	7.32 (5.3) 6.73 (1.15–16.79)	6.84 (4.3), 6.66 (0.03–17.67)	9.22 (4.1), 9.44 (2.58– 17.26)	5.56 (4.6), 4.22 (0.03– 17.67)
Female gender, n (%)	25 (54.35)	13 (37.14)	7 (33.33)	37 (42.05)	19 (63.33)	101 (45.91)
Number of *SMN2* copies, n (%)						
1	0 (0.00)	1 (2.86)	0 (0.00)	1[a] (1.14)	0 (0.00)	2 (0.91)
2	30 (65.22)	31(88.57)	2 (9.52)	7 (7.95)	0 (0.00)	70 (31.82)
3	12 (26.09)	2 (5.71)	6 (28.57)	46 (52.27)	12 (40.00)	78 (35.45)
4	0 (0.00)	0 (0.00)	0 (0.00)	8 (9.09)	10 (33.33)	18 (8.18)
Unknown	4 (8.70)	1 (2.86)	13 (61.90)	26 (29.55)	8 (26.67)	52 (23.64)
Scoliosis, n (%)						
No	23 (50.00)	31 (88.57)	8 (38.10)	48 (54.55)	25 (83.33)	135 (61.36)
Yes	20 (43.48)	4 (11.43)	13 (61.90)	36 (40.91)	5 (16.67)	78 (35.45)
Unknown	3 (6.52)	0 (0.00)	0 (0.00)	4 (4.55)	0 (0.00)	7 (3.18)
CHOP INTEND						
N	43	33	9	10	0	95
Mean (SD), median (range)	36.86 (12), 39.00 (2.00–55.00)	22.79 (10), 22.00 (3.00–45.00)	34.44 (6.9), 33.00 (26.00–45.00)	44.60 (12), 44.00 (29.00–64.00)	-	32.56 (13), 34.00 (2.00–64.00)
HINE-2						
N	32	31	13	52	7	135

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Mean (SD), median (range)	5.59 (4.4), 4.00 (0.00– 16.00)	2.03 (1.8), 2.00 (0.00– 7.00)	6.23 (2.9), 6.00 (1.0– 12.00)	14.08 (5.2), 13.00 (6.00–24.00)	24.57 (1.8), 25.00 (22.00–26.00)	9.09 (7.3), 8.00 (0.00–26.00)
RHS						
N	17	2	16	79	28	142
Mean (SD), median (range)	6.12 (3.6), 6.00 (1.00–17.00)	4.00 (2.8), 4.00 (2.00–6.00)	4.12 (2.7), 3.50 (0.00–11.00	15.27 (8.8), 14.00 (2.00–48.00)	49.79 (13), 48.50 (27.00–67.00)	19.56 (18), 13.00 (0.00–67.00)
RULM						
N	5	0	8	50	15	78
Mean (SD), median (range)	12.80 (2.8), 14.00 (8.00–15.00)	-	8.50 (5.1), 8.50 (2.00–18.00)	19.44 (7.7), 20.00 (0.00–37.00)	33.67 (5.7), 37.00 (16.00–37.00)	20.63 (10), 20.00 (0.00–37.00)
WHO Motor Milestone Achievement, n (%)						
Non-sitters	22 (47.83)	32 (91.43)	21 (100.00)	0 (0.00)	0 (0.00)	75 (34.09)
Sitting without support	10 (21.74)	0 (0.00)	0 (0.00)	54 (61.36)	0 (0.00)	64 (29.09)
Crawling	0 (0.00)	0 (0.00)	0 (0.00)	11 (12.50)	0 (0.00)	11 (5.00)
Standing with assistance	0 (0.00)	0 (0.00)	0 (0.00)	3 (3.41)	0 (0.00)	3 (1.36)
Walking with assistance	0 (0.00)	0 (0.00)	0 (0.00)	11 (12.50)	0 (0.00)	11 (5.00)
Standing alone	0 (0.00)	0 (0.00)	0 (0.00)	6 (6.82)	0 (0.00)	6 (2.73)
Walking alone	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	30 (100.00)	30 (13.64)
Unknown	14 (30.43)	3 (8.57)	0 (0.00)	3 (3.41)	0 (0.00)	20 (9.09)
Feeding problems, n (%)						
No	13 (28.26)	14 (40.00)	15 (71.43)	75 (85.23)	27 (90.00)	144 (65.45)
Yes	25 (54.35)	16 (45.71)	3 (14.29)	6 (6.82)	0 (0.00)	50 (22.73)
Unknown	8 (17.39)	5 (14.29)	3 (14.29)	7 (7.95)	3 (10.00)	26 (11.82)
TLSO Brace use, n (%)						
No	15 (32.61)	23 (65.71)	7 (33.33)	48 (54.55)	18 (60.00)	111 (50.45)
Yes	13 (28.26)	3 (8.57)	8 (38.10)	18 (20.45)	1 (3.33)	43 (19.55)
Unknown	18 (39.13)	9 (25.71)	6 (28.57)	22 (25.00)	11 (36.67)	66 (30.00)
At least one fracture, n (%)						
No	37 (80.43)	28 (80.00)	18 (85.71)	76 (86.36)	24 (80.00)	183 (83.18)
Yes	0 (0.00)	1 (2.86)	0 (0.00)	2 (2.27)	2 (6.67)	5 (2.27)
Unknown	9 (19.57)	6 (17.14)	3 (14.29)	10 (11.36)	4 (13.33)	32 (14.55)

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Upper limb contractures, n (%)						
No	12 (26.09)	24 (68.57)	9 (42.86)	53 (60.23)	21 (70.00)	119 (54.09)
Yes	10 (21.74)	7 (20.00)	7 (33.33)	16 (18.18)	0 (0.00)	40 (18.18)
Unknown	24 (52.17)	4 (11.43)	5 (23.81)	19 (21.59)	9 (30.00)	61 (27.73)
Lower limb contractures, n (%)						
No	3 (6.52)	18 (51.43)	2 (9.52)	16 (18.18)	8 (26.67)	47 (21.36)
Yes	21 (45.65)	14 (40.00)	14 (66.67)	54 (61.36)	13(43.33)	116 (52.73)
Unknown	22 (47.83)	3 (8.57)	5 (23.81)	18 (20.45)	9(30.00)	57 (25.91)
Spinal surgery, n (%)						
No	21 (45.65)	25 (71.43)	11 (52.38)	61(69.32)	20 (66.67)	138 (62.73)
Yes	3 (6.52)	0 (0.00)	2 (9.52)	5 (5.68)	0 (0.00)	10 (4.55)
Unknown	22 (47.83)	10 (28.57)	8 (38.10)	22 (25.00)	10 (33.33)	72 (32.73)
Salbutamol use, n (%)						
No	28 (60.87)	27 (77.14)	12 (57.14)	46 (52.27)	16 (53.33)	129 (58.64)
Yes	7 (15.22)	0 (0.00)	5(23.81)	32 (36.36)	10 (33.33)	54 (24.55)
Unknown	11 (23.91)	8 (22.86)	4 (19.05)	10 (11.36)	4 (13.33)	37 (16.82)
Other treatments, n (%)						
No	11 (23.91)	20 (57.14)	3 (14.29)	38 (43.18)	14 (46.67)	86 (39.09)
Yes	12 (26.09)	5 (14.29)	8 (38.10)	22 (25.00)	3 (10.00)	50 (22.73)
Unknown	23 (50.00)	10 (28.57)	10 (47.62)	28 (31.82)	13 (43.33)	84 (38.18)
Duration of treatment with at last follow-up (months), mean (SD), median (range)	36.91 (12), 39.23 (3.62–50.82)	15.76 (12), 10.62 (3.09–47.50)	29.30 (11), 29.64 (5.59–47.40)	30.91 (12), 30.35 (4.01–49.51)	33.16 (11), 35.97 (7.83–47.14)	Not available
Ongoing treatment with nusinersen at last follow-up, n (%)	25 (54.35)	12 (34.29)	15 (71.43)	63 (71.59)	27 (90.00)	142 (64.55)

Abbreviations: CHOP INTEND, Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders; EAP, Early Access Programme; HINE-2, Hammersmith Infant Neurological Examination — Part 2; RHS, Revised Hammersmith Scale; RULM, Revised Upper Limb Module; SD, standard deviation; SMA, spinal muscular atrophy; SMN, survival of motor neuron; TLSO, thoracic-lumbar-sacral orthosis; WHO, World Health Organization

a: The number of *SMN2* copies for this patient is being queried

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B.2.4.5.1.2 Motor function

Among paediatric patients treated with nusinersen and evaluable at time points up to 48 months, ≥70.8% patients attained new motor milestones or remained in the same motor milestone category relative to baseline, regardless of baseline motor function and SMA type (Table 20). Substantial proportions of patients gained new motor milestones. At timepoints with >1 patient assessed, up to 80.0% of type 1 non-EAP patients, up to 72.7% of non-sitters with type 2/3 SMA, and up to 30% of sitters with type 2/3 SMA achieved new milestones. WHO motor milestones are clearly defined and walking alone is the last milestone, so that achievement of new milestones did not apply to patients able to walk at baseline. Almost all ambulant type 2/3 patients maintained the ability to walk independently for up to 4 years; however, one patient lost ambulation at 1 year and remained non-ambulant up to and including their most recent visit at 3.5 years. At baseline, 22% of type 1 EAP patients had achieved the ability to sit without support (although it should be noted ~30% had an unknown baseline WHO milestone), during the MAA the proportion of patients gaining new milestones from baseline was lower among type 1 EAP patients (up to 33.3%), with most of this cohort demonstrating stabilisation. This is expected, considering that the EAP included many chronic patients with a long duration of SMA.

SMA is a progressive disease associated with an inevitable decline in motor function in the absence of treatment. In type 1 patients, death before two years of age preceded by loss of previously achieved motor milestones would be expected without treatment. Therefore, improvements and maintenance of motor function in patients with SMA in this real-world cohort is noteworthy. It should also be noted that the maintenance and achievement of motor milestones, particularly in non-ambulant patients with type 2/3 SMA, could be affected by SMA-related comorbidities such as scoliosis, contractures, and surgery for scoliosis.

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Table 20. Attainment or maintenance of motor milestones in paediatric patients treated with nusinersen in the UK real-world setting

Parameter	Type 1- EAP	Type 1- Non-EAP	Type 2/3- Non-Sitters	Type 2/3- Sitters	Type 2/3- Walkers
6 months (± 3 months) following baseline: n	24	29	15	73	27
Net attainment of a motor milestone: n (%), 95% CI	3 (12.50), 0.03, 0.32	1 (3.45), 0.00, 0.18	7 (46.67), 0.21, 0.73	13 (17.81), 0.10, 0.29	N/A[a]
Either Net attainment of a motor milestone or remained in the same motor milestone category: n (%), 95% CI	24 (100.00), 0.86, 1.00	29 (100.00), 0.88, 1.00	15 (100.00), 0.78, 1.00	66 (90.41), 0.81, 0.96	27 (100.00), 0.87, 1.00
12 months (± 3 months) following baseline: n	22	18	18	69	25
Net attainment of a motor milestone: n (%), 95% CI	3 (13.64), 0.03, 0.35	3 (16.67), 0.04, 0.41	10 (55.56), 0.31, 0.78	14 (20.29), 0.12, 0.32	N/A[a]
Either Net attainment of a motor milestone or remained in the same motor milestone category: n (%), 95% CI	22 (100.00), 0.85, 1.00	18 (100.00), 0.81, 1.00	18 (100.00), 0.81, 1.00	59 (85.51), 0.75, 0.93	24 (96.00), 0.80, 1.00
18 months (± 3 months) following baseline: n	25	11	10	62	21
Net attainment of a motor milestone: n (%), 95% CI	3 (12.00), 0.03, 0.31	4 (36.36), 0.11, 0.69	7 (70.00), 0.35, 0.93	15 (24.19), 0.14, 0.37	N/A[a]
Either Net attainment of a motor milestone or remained in the same motor milestone category: n (%), 95% CI	24 (96.00), 0.80, 1.00	11 (100.00), 0.72, 1.00	10 (100.00), 0.69, 1.00	50 (80.65), 0.69, 0.90	20 (95.24), 0.76, 1.00
24 months (± 3 months) following baseline: n	23	6	11	60	20
Net attainment of a motor milestone: n (%), 95% CI	6 (26.09), 0.10, 0.48	4 (66.67), 0.22, 0.96	8 (72.73), 0.39, 0.94	14 (23.33), 0.13, 0.36	N/A[a]
Either Net attainment of a motor milestone or remained in the same motor milestone category: n (%), 95% CI	22 (95.65), 0.78, 1.00	6 (100.00), 0.54, 1.00	11 (100.00), 0.72, 1.00	48 (80.00), 0.68, 0.89	19 (95.00), 0.75, 1.00

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30 months (± 3 months) following baseline: n	22	5	14	40	13
Net attainment of a motor milestone: n (%), 95% CI	5 (22.73), 0.08, 0.45	4 (80.00), 0.28, 0.99	7 (50.00), 0.23, 0.77	8 (20.00), 0.09, 0.36	N/A[a]
Either Net attainment of a motor milestone or remained in the same motor milestone category: n (%), 95% CI	22 (100.00), 0.85, 1.00	5 (100.00), 0.48, 1.00	14 (100.00), 0.77, 1.00	32 (80.00), 0.64, 0.91	12 (92.31), 0.64, 1.00
36 months (± 3 months) following baseline: n	15	3	6	37	18
Net attainment of a motor milestone: n (%), 95% CI	4 (26.67), 0.08, 0.55	2 (66.67), 0.09, 0.99	4 (66.67), 0.22, 0.96	7 (18.92), 0.08, 0.35	N/A[a]
Either Net attainment of a motor milestone or remained in the same motor milestone category: n (%), 95% CI	15 (100.00), 0.78, 1.00	3 (100.00), 0.29, 1.00	6 (100.00), 0.54, 1.00	30 (81.08), 0.65, 0.92	17 (94.44), 0.73, 1.00
42 months (± 3 months) following baseline: n	9	0	5	24	10
Net attainment of a motor milestone: n (%), 95% CI	3 (33.33), 0.07, 0.70	-	2 (40.00), 0.05, 0.85	5 (20.83), 0.07, 0.42	N/A[a]
Either Net attainment of a motor milestone or remained in the same motor milestone category: n (%), 95% CI	8 (88.89), 0.52, 1.00	-	5 (100.00), 0.48, 1.00	17 (70.83), 0.49, 0.87	9 (90.00), 0.44, 0.97
48 months (± 3 months) following baseline: n	7	2	1	10	3
Net attainment of a motor milestone: n (%), 95% CI	2 (28.57), 0.04, 0.71	0 (0.00), 0.00, 0.84	1 (100.00), 0.03, 1.00	3 (30.00), 0.07, 0.65	N/A[a]
Either Net attainment of a motor milestone or remained in the same motor milestone category: n (%), 95% CI	7 (100.00), 0.59, 1.00	2 (100.00), 0.16, 1.00	1 (100.00), 0.03, 1.00	8 (80.00), 0.44, 0.97	3 (100.00), 0.29, 1.00

Abbreviations: CI, confidence interval; EAP, Early Access Programme; N/A, not applicable to the cohort able to walk independently

Note: a: The data in Appendix E include 95% CIs with a non-zero upper bound; however, these are not presented since independent walking is the last WHO motor milestone

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Motor function scales generally demonstrated improvement from baseline in patients treated with nusinersen across SMA types, which is in contrast to the decline over time observed in untreated patients with SMA. Table 21 presents data for 48 months, i.e., the latest available time point and for 24 months, since the number of patients with available data at 48 months is relatively low. For patients with type 1 SMA who were initially assessed using the CHOP INTEND scale, data for RHS and RULM is presented at 12 months and at 30 months, with the latter being the latest data point available. The RHS and RULM enable measurement of treatment effect in patients who had achieved a ceiling effect on the CHOP INTEND, or achieved skills not tested on that scale, such as sitting and rolling.

Table 21. Change from baseline in motor function scales in paediatric patients treated with nusinersen in the UK real-world setting

Motor function scale, SMA type	Visit	Number of patients	Estimated score	SE	Predicted change from baseline	95% CI	P value
CHOP INTEND, type 1	Baseline	54	30.5	0.92	-	-	-
	24 months	15	39.6	1.60	9.13	5.60, 12.65	< 0.001
	48 months	3	49.2	3.77	18.67	11.06, 26.28	< 0.001
RHS, type 1[a]	Baseline	30	6.8	0.34	-	-	-
	12 months	19	8.3	0.43	1.49	0.42, 2.57	< 0.01
	30 months	3	9.0	1.65	2.22	-1.10, 5.53	0.19
RULM, type 1[a]	Baseline[b]	20	9.0	0.38	-	-	-
	12 months	13	11.4	0.46	2.49	1.33, 3.64	< 0.001
	30 months	3	14.5	0.99	5.58	3.48, 7.69	< 0.001
RHS, type 2/3	Baseline[b]	96	22.8	0.46	-	-	-
	24 months	59	25.5	0.53	2.75	1.53, 3.97	< 0.001
	48 months	11	25.1	1.12	2.36	0.008, 4.71	0.05
RULM, type 2/3	Baseline	58	20.9	0.34	-	-	-
	24 months	36	22.5	0.40	1.54	0.58, 2.51	< 0.01
	48 months	6	23.6	1.00	2.69	0.62, 4.75	0.01

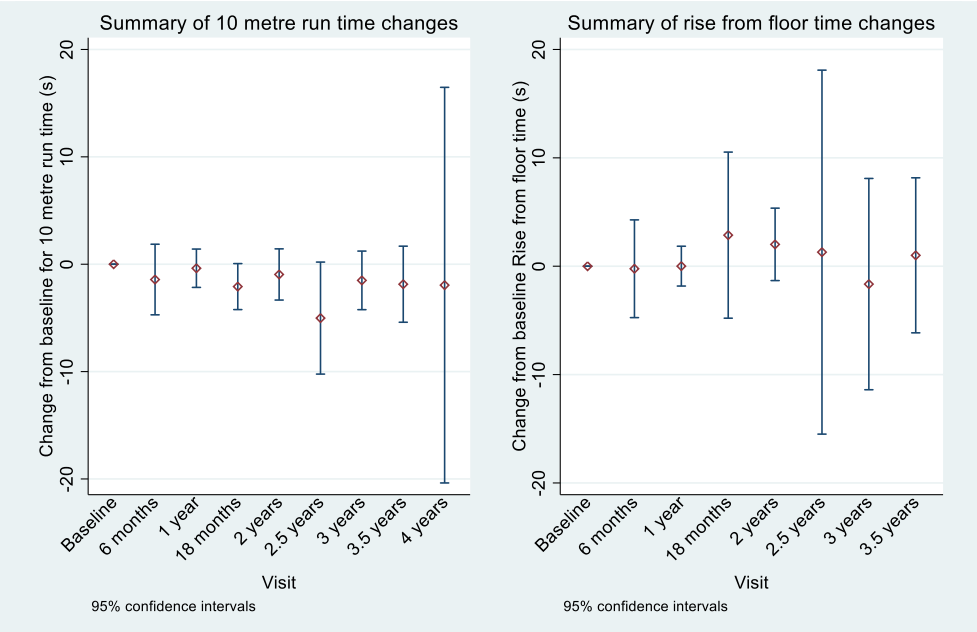
Abbreviations: CHOP INTEND, Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders; CI, confidence interval; RHS, Revised Hammersmith Scale; RULM, Revised Upper Limb Module; SE, standard error
a: Type 1 patients were initially evaluated with the CHOP INTEND scale.
b: This is the "new" baseline, i.e., baseline at the start of RHS/RULM administration.

In addition to the motor function scales presented in Table 21, two timed motor function tests were evaluated in ambulant patients. Fourteen ambulant patients had

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data available for the 10-metre run test (RHS item 19) and 17 patients for the rise from floor test (RHS item 25). These data were insufficient to run statistical models and should therefore be interpreted with caution, however the observed data are available in Figure 32. Both the 10-metre run test and the rise from floor test demonstrated long-term stability from baseline.

Figure 32. Summary of changes and 95% confidence interval for timed tests for ambulant paediatric type patients with type 2/3 SMA



A responder analysis, identifying patients who achieved a clinically meaningful benefit, was performed for two motor function scales, CHOP INTEND and HINE-2. Responders were defined as patients whose score improved from baseline by ≥1 point for HINE-2 and ≥9 points for CHOP INTEND.

The proportion of responders at selected time points of 6, 12, 24, and 48 months from baseline is listed in Table 22. Please see Appendix E for full results. Among patients with type 1 SMA, the proportion of responders on both CHOP INTEND and HINE-2 was consistently lower in the EAP cohort (which included prevalent patients with a long disease duration at treatment initiation) than the non-EAP cohort, highlighting the benefits of early treatment with nusinersen. The data for type 2/3 patients were scarce, especially for the CHOP INTEND scale, and are presented for completeness only. At time points at which data for more than 10 patients were available per cohort, the proportion of responders was ≥60%.

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Table 22. Proportion of CHOP INTEND and HINE-2 responders among paediatric patients treated with nusinersen in the UK real-world setting

	Type 1- EAP	Type 1- Non-EAP	Type 2/3- Non-Sitters	Type 2/3- Sitters	Type 2/3- Walkers
Time point: 6 months from baseline					
Number of Patients with Evaluable CHOP-INTEND Data	27	31	5	7	0
Patients who achieved important improvement, N (%), 95% CI	4 (14.81), 0.04, 0.34	22 (70.97), 0.52, 0.86	0 (0.00), 0.00, 0.52	3 (42.86), 0.10, 0.82	0, NA
Number of Patients with Evaluable HINE-2 Data	22	29	9	30	2
Patients who achieved important improvement, N (%), 95% CI	13 (59.09), 0.36, 0.79	24 (82.76), 0.64, 0.94	6 (66.67), 0.30, 0.93	18 (60.00), 0.41,0.77	2 (100.00), 0.16, 1.00
Time point: 1 year from baseline					
Number of Patients with Evaluable CHOP-INTEND Data	24	19	5	6	0
Patients who achieved important improvement, N (%), 95% CI	3 (12.50), 0.03, 0.32	14 (73.68), 0.49, 0.91	3 (60.00), 0.15, 0.95	3 (50.00), 0.12, 0.88	0, NA
Number of Patients with Evaluable HINE-2 Data	19	18	11	29	2
Patients who achieved important improvement, N (%), 95% CI	12 (63.16), 0.38, 0.84	17 (94.44), 0.73, 1.00	7 (63.64), 0.31, 0.89	18 (62.07), 0.42, 0.79	2 (100.00), 0.16, 1.00
Time point: 2 years from baseline					
Number of Patients with Evaluable CHOP-INTEND Data	16	5	0	1	0
Patients who achieved important improvement, N (%), 95% CI	4 (25.00), 0.07, 0.52	3 (60.00), 0.15, 0.95	0, NA	0 (0.00), 0.00, 0.97	0, NA
Number of Patients with Evaluable HINE-2 Data	19	4	5	13	1
Patients who achieved important improvement, N (%), 95% CI	14 (73.68), 0.49, 0.91	4 (100.00), 0.40, 1.00	5 (100.00), 0.48, 1.00	11 (84.62), 0.55, 0.98	1 (100.00), 0.03, 1.00
Time point: 4 years from baseline					
Number of Patients with Evaluable CHOP-INTEND Data	3	2	0	0	0
Patients who achieved important improvement, N (%), 95% CI	1 (33.33), 0.01, 0.91	1 (50.00), 0.01, 0.99	0, NA	0, NA	0, NA
Number of Patients with Evaluable HINE-2 Data	3	2	0	0	0
Patients who achieved important improvement, N (%), 95% CI	2 (66.67), 0.09, 0.99	2 (100.00), 0.16, 1.00	0, NA	0, NA	0, NA

Abbreviations: CHOP INTEND, Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders; CI, confidence interval; Hammersmith Infant Neurological Examination — Part 2; NA, not applicable

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B.2.4.5.1.3 Mortality

None of the patients included in the final analysis cohort died. Since nusinersen has been made available to SMA patients, >90% of patients with SMA type 1 treated within routine UK clinical practice have survived beyond 2 years of age. Age at most recent visit is summarised in Table 23.

Table 23. Age at most recent visit in paediatric patients treated with nusinersen in the UK real-world setting

Cohort	Age at last visit (years), median (range)
Type 1- EAP (N=46)	6.6 (2.9–14.5)
Type 1- Non-EAP (N=35)	1.3 (0.4–6.8)
Type 2/3- Non-Sitters (N=21)	8.5 (2.3–17.4)
Type 2/3- Sitters (N=88)	9.1 (2.1–18.7)
Type 2/3- Walkers (N=30)	12.5 (3.5–18.9)
All SMA types (N=220)	**7.3 (0.4–18.9)**

Abbreviations: EAP, Early Access Programme, SMA, spinal muscular atrophy

It should be noted that although none of the patients included in the analysis died, some deaths occurred in patients not eligible for the analysis. Five type 1 SMA non-EAP patients died at <1 month, 3.3 months, 3.5 months, 4.8 months, and 6.4 months after their first nusinersen injection. The cause of death was respiratory disease in 3 patients, disease of the circulatory system in 1 patient, and not reported in one patient. In addition, one patient with type 1 SMA who previously participated in the EAP patient died from respiratory disease 14 months after their first MAA dose.

B.2.4.5.1.4 Permanent ventilation

Permanent ventilation was defined as any ventilation type for ≥16 hours/day continuously for >21 days or tracheostomy. No patients in the non-EAP cohort required permanent ventilation by the time of the data-cut. Three patients with SMA type 1 enrolled in the EAP required ventilation for > 16 hours per day as assessed at ≥1 visit. One patient progressed to receive permanent ventilation after 3.5 years of treatment with nusinersen at an age of 5.5 years. The date of starting permanent ventilation is not available for the remaining two patients; however, for one of these patients, daily time of ventilation later reduced to <16 hours. Two patients with type 1 SMA enrolled in the EAP had a tracheostomy at baseline, and no additional patients had the procedure during the study.

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Importantly, permanent ventilation was only required for patients in the EAP, which included more chronic patients with type 1 SMA with a median age of 2.91 years at treatment initiation (vs 0.28 years in the SMA type 1 non-EAP cohort). Despite a total of four nusinersen-treated patients progressing to permanent ventilation (including one type 1 EAP patient not eligible for this analysis), these results represent substantial improvement from the natural history of SMA, where most patients are expected to die or require permanent ventilation by 2 years of age.

Due to a high percentage of missing data (approximately 30%), no time-to-event analysis could be performed, so time to permanent ventilation is not available.

B.2.4.5.1.5 Patient-reported outcomes

Limited PRO data were available, and the cohorts defined based on SMA type and motor function a baseline were not analysed separately. The analyses were descriptive. EQ-5D-5L data is not presented, as this version of the questionnaire was completed by only two patients. Nonetheless, available PRO data clearly demonstrated stability or improvement at last available follow-up relative to baseline. No patients at baseline or last follow-up reported severe of extreme problems in any of the EQ-5D Y domains (Table 24). EQ-5D VAS scores were stable, while SMAIS scores showed some improvement (Table 25). PGI-S scores are available in Table 26. At last follow-up 6 had no change in severity from baseline and 4 had a reduction of 1 unit. PGI-I data are presented in Table 27. At last follow-up, 7 patients had reported no change from baseline, 2 patients reported a reduction (of 1 and 3 units), and 3 patients reported an improvement (of 1 and 2 units). Please consult Appendix E for full PRO results in this cohort.

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Table 24. Patients reporting problems on each EQ-5D Y dimension at baseline and last available follow-up

	Mobility n (%)	Self-care n (%)	Usual activity n (%)	Pain/ Discomfort n (%)	Anxiety/ Depression n (%)
Baseline					
Level 1 (No problem)	0 (0.0)	3 (9.7)	3 (9.7)	11 (36.7)	15 (50.0)
Level 2 (Slight problems)	3 (10.7)	6 (19.3)	17 (54.8)	19 (63.3)	15 (50.0)
Level 3 (Moderate problems)	25 (89.3)	22 (71.0)	11 (35.5)	0 (0.0)	0 (0.0)
Level 4 (Severe problems)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Level 5 (Extreme problems/ unable to do)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Last follow-up					
Level 1 (No problem)	0 (0.0)	0 (0.0)	1 (11.1)	5 (50.0)	4 (40.0)
Level 2 (Slight problems)	0 (0.0)	5 (55.6)	5 (55.6)	4 (40.0)	6 (60.0)
Level 3 (Moderate problems)	9 (100)	4 (44.4)	3 (33.3)	1 (10.0)	0 (0.0)
Level 4 (Severe problems)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Level 5 (Extreme problems/ unable to do)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

Table 25. Summary of EQ-5D VAS and SMAIS scores at baseline and the last follow-up time in paediatric patients treated with nusinersen in the UK real-world setting

PRO	Timepoint	n	Mean (SD)	Median	Min	Max
EQ-5D VAS	Baseline	33	78.8 (17.9)	80	20	100
	Last follow-up	12	79.6 (15.5)	82.5	50	100
SMAIS	Baseline	31	21.4 (11.2)	21	4	44
	Last follow-up	11	25.6 (8.9)	25	9	44

Abbreviations: SMAIS, SMA independence scale, VAS, visual analogue scale.

Table 26. Summary of PGI-S scores at baseline and the last follow-up time in paediatric patients treated with nusinersen in the UK real-world setting

	Number of patients	Score 1 (not at all)	Score 2 (mildly)	Score 3 (moderately)	Score 4 (severely)
Baseline	32	0 (0.0)	5 (15.6)	15 (46.9)	12 (37.5)
Last follow-up	10	0 (0.00)	2 (20.0)	6 (60.0)	2 (20.0)

Abbreviations: PGI-S, Patient Global Impression of severity score

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Table 27. Summary of PGI-I scores at baseline and the last follow-up time in paediatric patients treated with nusinersen in the UK real-world setting

	Number of patients	Score 1 (very much improved)	Score 2 (Much improved)	Score 3 (Minimally improved)	Score 4 (No change)
Baseline	35	3 (8.6)	6 (17.1)	17 (48.6)	4 (11.4)
Last follow-up	13	0 (0.00)	5 (38.4)	3 (23.1)	4 (30.8)

Abbreviations: PGI-I, Patient Global Impression of improvement score

B.2.4.5.2 Nusinersen in adult patients in the UK

B.2.4.5.2.1 Patient and treatment characteristics

Among all 333 patients in the Adult SMA Reach Registry, a total of 94 adult type 2/3 SMA patients treated with nusinersen were included in the study and classified into three cohorts based on motor function status at baseline (non-sitters: n=16; sitters: n=40; walkers n=38). Baseline demographics and duration of treatment with nusinersen for patients in the three cohorts are presented in Table 28.

By the 3 August 2023 data cut, 4 patients (4.3%) discontinued treatment with nusinersen. Reasons for discontinuation included adverse effects of the procedure and of nusinersen, and elective choice of other treatment, and was not known in the final patient.

Table 28. Baseline characteristics of adult patients treated with nusinersen in the UK and included in the MAA data collection.

Parameter	Type 2/3 non-sitters (N = 16)	Type 2/3 sitters (N=40)	Type 2/3 walkers (N=38)
Age (years) at symptom onset, mean (SD), median (range)	1.63 (1.81), 1 (0.75–8)	3.21 (3.93), 2 (0.33–18)	9.22 (6.28), 7.25 (1–30)
Age (years) at first receipt of nusinersen, mean (SD), median (range)	37.87 (12.29), 41.08 (17.8–58.55)	32.6 (13.93), 28.97 (17.42–65.27)	34.34 (14.30), 31.01 (16.48–76.13)
Female gender, n (%)	8 (50)	13 (32.5%)	15 (39.47%)
SMA Type, n (%)			
2	9 (56.25)	3 (7.5%)	0 (0%)
3	7 (43.75)	37 (92.5%)	38 (100%)
Number of *SMN2* copies, n (%)			
1	0 (0)	0 (0%)	0 (0%)
2	1 (6.25)	2 (5%)	2 (5.26%)
3	3 (18.75)	4 (10%)	5 (13.16%)
4 and over	2 (12.5)	6 (15%)	10 (26.32%)

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Unknown	10 (62.5)	28 (70%)	21 (55.26%)
Total number of comorbid medical conditions	2 (1.86), 1.5 (0-6)	1.08 (1.29), 1 (0–4)	2 (2.32), 1.5 (0–9)
Scoliosis, n (%)			
Yes	14 (87.5)	19 (47.5%)	9 (23.68%)
No	1 (6.25)	18 (45%)	27 (71.05%)
Unknown	1 (6.25)	3 (7.5%)	2 (5.26%)
Total number of non–disease-modifying medications, mean (SD), median (range)	3.75 (3.36), 4 (0–12)	1.62 (1.75), 1.5 (0–7)	1.73 (2.56), 1 (0–12)
RHS total baseline score, mean (SD), median (range)	Not relevant to this cohort	18.38 (7.09), 18 (15–30)	42.06 (11.62), 42 (17–67)
RULM total baseline score, mean (SD), median (range)	8.31 (5.92), 7 (2–19)	24.09 (7.75), 24 (2–36)	31 (6.77), 34 (13–37)
6MWT total baseline distance, mean (SD), median (range)	Not relevant to this cohort	Not relevant to this cohort	273.63 (168.94), 285 (25–700)
ATEND total right baseline score, mean (SD), median (range)	24.17 (6.85), 23.5 (15–34)	35.17 (5.64), 36 (21-42)	Not relevant to this cohort
ATEND total left baseline score, mean (SD), median (range)	20 (8.46), 17 (11–31)	34.08 (5.43), 34.5 (19–39)	Not relevant to this cohort
Number of nusinersen doses at last follow-up, mean (SD), median (range)	7.63 (2.7), 8 (1–11)	7.88 (2.02), 8 (2-11)	10.66 (2.57), 11 (1–15)
Duration of treatment with nusinersen at last follow-up (months), mean (SD), median (range)	16.48 (7.09), 16.82 (5.1–30.87)	16.43 (8.12), 17.72 (0	26.91 (6.84), 29.38 (10.59–42.61)
Ongoing treatment with nusinersen at last follow-up, n (%)	12 (75)	27 (68)	26 (68)

Abbreviations: 6MWT, 6-minute walk test; ATEND, Adapted Test of Neuromuscular Disorders; RHS, Revised Hammersmith Scale; RULM, Revised Upper Limb Module; SD, standard deviation SMA, spinal muscular atrophy; SMN, survival of motor neuron.

B.2.4.5.2.2 Motor function

Contrary to the progressive nature of SMA, ≥87.5% patients evaluable at time points up to 42 months attained new motor milestones or remained in the same motor milestone category relative to baseline, regardless of baseline motor function status (non-sitter, sitter, walker) (Table 29). The vast majority of these patients achieved stabilisation rather than gained new motor milestones (Table 29). It should also be noted that walking without assistance is the last WHO motor milestone, so ambulant patients could not achieve any further milestones.

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Table 29. Attainment or maintenance of motor milestones in adult patients treated with nusinersen in the UK real-world setting

Parameter: n (%), 95% CI	**Type 2/3 non-sitters (N = 16)**	**Type 2/3 sitters (N=40)**	**Type 2/3 walkers (N=38)**
6 months (± 3 months) following baseline: n	10	30	29
Net attainment of a motor milestone: n (%), 95% CI	1 (10%), 0.25%-45.5%	1 (3.33%), 0.08%-17.22%	N/A
Either Net attainment of a motor milestone or remained in the same motor milestone category	10 (100%), 69.15%-100%	27 (90%), 73.47%-97.89%	29 (100%), 88.06%-100%
12 months (± 3 months) following baseline: n	12	32	33
Net attainment of a motor milestone:	1 (8.33%), 0.21%-38.48%	0 (0%), 0%-10.89%	N/A
Either Net attainment of a motor milestone or remained in the same motor milestone category	12 (100%), 73.54%-100%	31 (96.88%), 83.78%-99.92%	33 (100%), 89.42%-100%
18 months (± 3 months) following baseline: n	8	23	32
Net attainment of a motor milestone: n (%), 95% CI	1 (12.5%), 0.32%-52.65%	2 (8.7%), 1.07%-28.03%	N/A
Either Net attainment of a motor milestone or remained in the same motor milestone category	8 (100%), 63.6%-100%	22 (95.65%), 78.05%-99.89%	31 (96.88%), 83.78%-99.92%
24 months (± 3 months) following baseline: n	6	8	26
Net attainment of a motor milestone: n (%), 95% CI	1 (16.67%), 0.42%-64.12%	1 (12.5%), 0.32%-52.65%	N/A
Either Net attainment of a motor milestone or remained in the same motor milestone category	6 (100%), 54.07%-100%	7 (87.5%), 47.35%-99.68%	25 (96.15%), 80.36%-99.9%
30 months (± 3 months) following baseline: n	2	4	20
Net attainment of a motor milestone: n (%), 95% CI	1 (50%), 1.26%-98.74%	0 (0%), 0%-60.24%	N/A
Either Net attainment of a motor milestone or remained in the same motor milestone category	2 (100%), 15.81%-100%	4 (100%), 39.76%-100%	19 (95%), 75.13%-99.87%
36 months (± 3 months) following baseline: n	0	0	5
Net attainment of a motor milestone: n (%), 95% CI	-	-	N/A
Either Net attainment of a motor milestone or remained in the same motor milestone category	-	-	5 (100%), 47.82%-100%
42 months (± 3 months) following baseline: n	0	1	2
Net attainment of a motor milestone: n (%), 95% CI	-	1 (100%), 2.5%-100%	N/A
Either Net attainment of a motor milestone or remained in the same motor milestone category	-	1 (100%), 2.5%-100%	2 (100%), 15.81%-100%

Abbreviations: CI, confidence interval ; N/A, not applicable to the cohort able to walk independently

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Changes from baseline at months 12 and 24 (the latest common available time point for all scales) in the RULM, 6MWT, ATEND and RHS scales are presented in Table 30. Except for small improvements in upper limb function as measured on the RULM, there were no statistically significant changes from baseline in any of the scales, indicating that nusinersen prevented the disease-related worsening of motor function in this diverse, real-world patient cohort. In contrast, untreated adults (aged >15 years) with later-onset SMA reported a mean decline from baseline in the RULM score of 0.6 points at 12 months

Table 30. Change from baseline in motor function scales in adult patients treated with nusinersen in the UK real-world setting

Motor function scale	Visit	Number of patients	LS Mean	SE	Predicted change from baseline	95% CI	P value
RULM	Baseline	53	22.74	0.41	-	-	-
	12 months	49	24.16	0.44	1.42	0.48, 2.36	0.003
	24 months	25	24.53	0.64	1.79	0.37, 3.22	0.0136
6MWT	Baseline	19	268.77	14.4	-	-	-
	12 months	18	289.97	15.8	21.2	-10.31, 52.70	0.1873
	24 months	15	295.8	16.2	27.02	-11.02, 65.07	0.1639
ATEND Right	Baseline	15	31.87	0.7	-	-	-
	12 months	22	31.5	0.8	-0.37	-1.87, 1.13	0.6307
	24 months	7	31.58	1.8	-0.29	-3.87, 3.29	0.8744
ATEND Left	Baseline	15	30.28	0.6	-	-	-
	12 months	22	30.36	0.7	0.08	-1.58, 1.74	0.9253
	24 months	7	30.75	2.4	0.47	-4.28, 5.21	0.8467
RHS	Baseline	47	36.6	0.8	-	-	-
	12 months	40	38.07	0.85	1.47	-0.27, 3.21	0.0973
	24 months	26	38.23	1.01	1.63	-0.67, 3.92	0.1653

Abbreviations: 6MWT, 6-minute walk test; ATEND, Adapted Test of Neuromuscular Disorders; CI, confidence interval; RHS, Revised Hammersmith Scale; RULM, Revised Upper Limb Module; SE, standard error;

B.2.4.5.2.3 Patient-reported outcomes

Limited PRO data were available, and the cohorts defined based on motor function at baseline were not analysed separately. The analyses were descriptive. Nonetheless, available PRO data clearly demonstrated stability or improvement at

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last available follow-up relative to baseline (Table 31 and Table 32). Substantial proportions of patients reported extreme problems with mobility and self-care at baseline (56.9% and 35.3%, respectively, Table 31). At last follow-up, the proportion of patients reporting extreme problems with self-care declined to 29.0% (Table 31). The proportion of patients reporting no problems increased at last follow-up relative to baseline for mobility, usual activity, and anxiety/depression domains (Table 31). Mean EQ-5D VAS, SMAIS, PGI-S, and PGI-I scores remained stable at last follow-up, while median EQ-5D VAS and SMAIS scores increased, indicating improvement in general health and greater independence/less assistance needed, respectively (Table 32). Median PGI-I and PGI-S scores remained stable (Table 32). Please consult Appendix F for full PRO results in this cohort.

Table 31. Patients reporting problems on each EQ-5D 5L domain at baseline and last available follow-up

	Mobility n (%)	Self-care n (%)	Usual activity n (%)	Pain/ Discomfort n (%)	Anxiety/ Depression n (%)
Baseline					
Level 1 (No problem)	2 (3.92)	17 (33.33)	13 (25.49)	17 (33.33)	26 (50.98)
Level 2 (Slight problems)	5 (9.80)	6 (11.76)	10 (19.61)	11 (21.57)	13 (25.49)
Level 3 (Moderate problems)	8 (15.69)	5 (9.80)	14 (27.45)	20 (39.22)	10 (19.61)
Level 4 (Severe problems)	7 (13.73)	5 (9.80)	9 (17.65)	2 (3.92)	2 (3.92)
Level 5 (Extreme problems/ unable to do)	29 (56.86)	18 (35.29)	5 (9.80)	1 (1.96)	0 (0.00)
Total	51 (100)	51 (100)	51 (100)	51 (100)	51 (100)
Last follow-up					
Level 1 (No problem)	3 (7.89)	12 (31.58)	15 (39.47)	10 (26.32)	20 (52.63)
Level 2 (Slight problems)	4 (10.53)	6 (15.79)	10 (26.32)	16 (42.11)	11 (28.95)
Level 3 (Moderate problems)	2 (5.26)	5 (13.16)	4 (10.53)	10 (26.32)	6 (15.79)
Level 4 (Severe problems)	8 (21.05)	4 (10.53)	6 (15.79)	2 (5.26)	1 (2.63)
Level 5 (Extreme problems/ unable to do)	21 (55.26)	11 (28.95)	3 (7.89)	0 (0.00)	0 (0.00)
Total	38 (100)	38 (100)	38 (100)	38 (100)	38 100)

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Table 32. Summary of PRO scores at baseline and the last follow-up time in adult patients treated with nusinersen in the UK real-world setting

PRO	Timepoint	n	Mean (SD)	Median	Min	Max
EQ-5D VAS	Baseline	51	69.57 (19.39)	70	20	100
	Last follow-up	39	72.05 (14.99)	74	39	97
SMAIS	Baseline	51	32.35 (12.62)	35	1	44
	Last follow-up	37	33.70 (11.87)	39	1	44
PGI-S	Baseline	33	3.18 (0.73)	3	2	4
	Last follow-up	15	3.27 (0.70)	3	2	4
PGI-I	Baseline	49	3.63 (1.35)	3	1	7
	Last follow-up	38	3.50 (1.13)	3	1	6

Abbreviations: PGI-I, Patient Global Impression of improvement score; PGI-S, Patient Global Impression of severity score; SMAIS, SMA independence scale, VAS, visual analogue scale.

B.2.5 Indirect and mixed treatment comparisons

As noted in Section B.2.1 standard network meta-analyses were not recommended due to lack of data from RCTs and/or clinically important heterogeneity between studies of nusinersen, risdiplam, and onasemnogene abeparvovec. Consequently, ITCs were performed using alternative methods, that is MAICs or STCs, which use reweighting and regression, respectively, to compare individual patient data from the intervention trial (nusinersen) to aggregate data from published comparator trials.

A total of 14 comparisons were conducted, including 12 MAICs and two STCs (for changes in HFMSE and RULM scores from baseline to 12 months vs risdiplam). The results of all comparisons are summarised in Figure 33. Further details are provided in Appendix D.

The ITCs were undertaken in attempt to provide relative effectiveness estimates for nusinersen versus risdiplam and onasemnogene. However, following the completion of all analyses, it was clear that were major limitations associated with the ITCs. In particular, all MAICs were unanchored and this means that the benefits of within-study randomisation and comparison to a placebo arm do not apply to these comparisons. In this case, NICE TSD 18 recommends that '…those presenting such estimates should give evidence that the degree of bias due to imbalance in unaccounted for covariates is acceptable, bearing in mind the size of the observed treatment effect.' In the context of substantial heterogeneity in patient characteristics,

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treatment dosage, and treatment duration between the studies of nusinersen, risdiplam, and onasemnogene included in the comparisons presented in Figure 33, the amount of bias in the estimates from the ITCs is likely to be substantial and could even exceed the magnitude of treatment effects that were estimated.

Other major limitations were also present that are expected to have introduced bias into the analyses. Firstly, for all ITCs related to the achievement of motor milestones, covering the comparisons versus both risdiplam and onasemnogene, the outcome timepoints did not align between the studies. For example, for the type 1 population, motor milestone attainment was measured at 18 months for onasemnogene in the STR1VE-EU and STR1VE-US trials, whereas these outcomes were not measured at 18 months in the ENDEAR trial for nusinersen. Therefore, for the inclusion of nusinersen data in the motor milestone ITCs, the nearest timepoint prior to 18 months was used. Given the outcomes were measured at a later timepoint for onasemnogene this gave these patients longer to achieve each motor milestone, which biases the analysis in favour of onasemnogene. The available timepoints for the measurement of motor milestone attainment were also biased in favour of risdiplam for the nusinersen versus risdiplam ITCs.

All ITCs were based on small patient numbers, as shown by the effective sample size (ESS) of the nusinersen populations that were included in each analysis. The highest ESS was 34.13 for the comparison of overall survival for nusinersen versus onasemnogene in the type 1 population. This number reduced to 8.78 for the analyses of achieving standing with support and walking independently in the presymptomatic population for nusinersen versus onasemnogene. Experts at the advisory board noted that it is difficult to draw meaningful conclusions for analyses that are based on small sample sizes, such as was the current ITCs.

For all ITCs related to motor milestone attainment in the type 1 population, different outcomes were used within the available clinical studies. In terms of nusinersen versus onasemnogene, the effectiveness of the interventions was based on BSID-III and HINE-2 for onasemnogene and nusinersen, respectively. Therefore, the completion of these ITCs required the assumption that BSID-III and HINE-2 are equivalent in terms of how they measure milestone attainment. However, the clinical experts at the advisory board noted that like-for-like comparisons cannot be made

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using these two instruments as they are not equivalent. For example, the measurement of ‘sitting without support’ using BSID-III incorporates an element of upper limb function (unlike HINE-2) and, therefore, it can be easier for people to achieve that particular motor milestone when this is measured using BSID-III.

For the comparison of nusinersen versus risdiplam in the type 1 population, within the ENDEAR trial, nusinersen patients were initially assessed based on HINE-2 and if patients were able to sit at 2 years the WHO motor milestone system was used instead. Consequently, for the purpose of completing the ITC, these records were combined with a HINE-2 score ≥ 3 in the sitting category being considered equivalent to the achievement of the WHO motor milestone ‘sitting without support’. Alternatively, the mobility of patients in the risdiplam trial were assessed using HINE-2 only. This indicates that there was also inconsistency in the outcome measures that were used for the nusinersen versus risdiplam comparison of motor milestone attainment.

For the comparison of nusinersen versus risdiplam in the type 2/3 population, a simulated treatment comparison (STC) was completed to compare and RULM HFMSE scores. An STC was necessary because the attempt to complete a MAIC failed, likely due to a poor overlap for the age at screening and age at symptom onset for the nusinersen and risdiplam trials, which were judged to be key covariates. However, the differences in age between the study population still had a major impact on the STC outputs. In particular, the median age at screening was 108 months and 49.2 months within the risdiplam and nusinersen studies, respectively. Additionally, the maximum age of screening for nusinersen patients was 101.8 months. Therefore, to enable a comparison, the STC was estimating nusinersen patient outcomes that were beyond the observed data for this covariate (i.e. it was estimating the efficacy of nusinersen for patients with a median age of 108 months but the oldest patient in the nusinersen study had an age of 101.8 months at screening).

Overall, the limitations described above introduced levels very high levels of bias in the estimates produced by the ITCs. Therefore, it was concluded that the ITC should not be used to inform the cost-effectiveness models. Nonetheless, the full ITC report is provided as Appendix D for transparency and completeness.

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Figure 33. Summary results from ITCs



Abbreviations: BSID, Bayley Scales of Infant Development; HFMSE, Hammersmith Functional Motor Scale – Expanded; HINE-2, Hammersmith Infant Neurological Examination – Part 2; MM, motor milestone; OA, onasemnogene abeparvovec; RULM, Revised Upper Limb Module; WHO, World Health Organization.

B.2.6 Adverse reactions

Nusinersen has been available on the market since 2017 and can therefore be considered an established treatment. Headache, vomiting, and back pain are the most common adverse events associated with the administration of nusinersen. These adverse events are considered related to lumbar puncture and mostly occur within 72 hours after the procedure. For a more detailed overview of safety data, please see the summary of product characteristics for nusinersen provided as Appendix C to this submission.

Among the presymptomatic SMA population, no adverse events (AEs) were considered to be related to nusinersen over a median follow-up of 4.9 (range: 3.9–5.7) years[84]. In symptomatic patients with infantile-onset and later-onset SMA who entered the long-term SHINE extension study, [redacted]. AEs were generally consistent with underlying SMA or with the lumbar puncture procedure. Please see the SHINE clinical study report for detailed safety data.

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B.2.7 Interpretation of clinical effectiveness and safety evidence

As of last year (2023), more than 14,000 patients received nusinersen across clinical studies, EAPs, and post-marketing real-world settings, demonstrating a favourable benefit to risk profile. Prior to the availability of nusinersen, SMA was associated with progressive loss of motor function and, especially in patients with type 1 disease, early mortality. As the first disease-modifying therapy to receive approval for patients with SMA, nusinersen has changed the natural history of this condition, establishing a new standard of care. The advances in treatment available to NHS patients mean that, in 2023, 73% of children with type 1 SMA were older than 2 years, an age few patients survived to before the availability of disease-modifying therapy[90].

Addressing the concerns raised during TA588, this submission presents long-term evidence on the efficacy and safety of nusinersen in presymptomatic patients with SMA based on the NURTURE study (B.2.4.4) as well as in symptomatic patients with SMA types 1, 2, and 3 based on the SHINE study (B.2.4.3). Despite the challenges of fully capturing the benefits of nusinersen due to the floor and ceiling effect of the scales, efficacy outcomes showed long-term benefits of treatment with nusinersen that are inconsistent with the progressive declines seen in the natural history of infantile-onset and later-onset SMA. In terms of safety, nusinersen was well tolerated and the reported AEs were generally consistent with SMA symptoms or with events observed in the context of intrathecal lumbar puncture procedures. [redacted]

SHINE results presented in this submission demonstrate long-term efficacy and safety of nusinersen across a range of participants treated in the symptomatic stages of infantile-onset and later-onset SMA over a median of 6 years. [redacted] that are in stark contrast with the early mortality of untreated patients with type 1 SMA who have a median age at death or permanent ventilation of approximately 9–13 months[29]. [redacted].

[redacted]

The NURTURE study further demonstrated sustained benefits of early intervention with nusinersen. In this study, patients initiated treatment before the onset of SMA symptoms. NURTURE patients showed features of normal development and improvement in motor skills, which is in stark contrast with the progressive decline observed in untreated patients with SMA types 1 and 2[86,91]. Furthermore, compared

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with patients who initiated treatment with nusinersen after the onset of symptoms in ENDEAR or CHERISH, motor outcomes (CHOP INTEND, HMFSE) were improved in NURTURE patients. Infants treated at the presymptomatic stage also showed improved growth over time, with higher mean weight-for-age than observed in infants treated after symptom onset in ENDEAR/SHINE. With a median follow-up of approximately 5 years, the results of NURTURE show sustained, long-term benefits of treatment with nusinersen, combined with a favourable safety and tolerability profile.

Data from SHINE are further supported by the results from the nusinersen MAA, which involved collection of real-world data from patients who received nusinersen on the NHS in several centres in England and Wales. Although any naïve comparisons between this real-world dataset and the clinical studies of nusinersen should be made with extreme caution, if at all (especially given the impact that COVID likely had on MAA data collection and treatment schedule), it is clear from the data collected that treatment with nusinersen resulted in clinically meaningful improvement or disease stabilisation for many patients with SMA in the UK; a remarkable improvement on the natural history of the disease in the absence of disease-modifying therapy.

Overall, the entirety of the evidence presented in this submission points to the benefits of initiating nusinersen treatment for patients with SMA as early as possible, and ideally before the symptoms of the disease occur, to optimise long-term clinical outcomes. Universal newborn screening for SMA could increase the number of patients diagnosed at the presymptomatic stage, offering more individuals with SMA the chance of achieving optimal benefits from disease-modifying therapy.

While comprehensive, the evidence presented in this submission is subject to some limitations and data gaps. One major data gap is the paucity of clinical trial data in adult patients with SMA, [redacted]. Real-world evidence further supports the use of nusinersen in teens and adults with SMA. The MAA included 94 adults with SMA treated with nusinersen and their motor function was generally maintained over time (see Section B.2.4.5.2). Furthermore, several large published real-world studies demonstrated benefits of treatment with nusinersen in adults with SMA[43,92,93].

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Another data gap relates to pulmonary function in patients with later-onset SMA. While the ventilation requirements of patients with infantile-onset SMA are described in this submission based on ENDEAR, SHINE, and the MAA, data for later-onset patients is very limited. [redacted], which is consistent with published real-world evidence suggesting that treatment with nusinersen improves respiratory outcomes in patients with type 2/3 SMA[94-97].

[redacted] These considerations highlight the importance of using the most clinically appropriate scale for a given patient with SMA, incorporating the patient's baseline functional status when evaluating treatment effect. In this submission, clinical data are stratified by functional status based on gross motor milestones where possible (particularly for the MAA) and the economic models are driven by motor milestone achievement.

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B.2.8 Ongoing studies

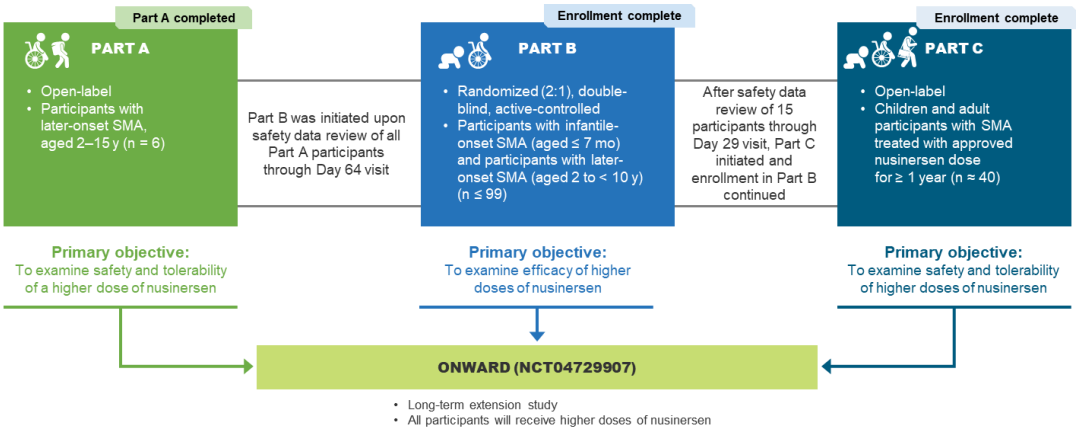
Three studies of nusinersen are currently ongoing: DEVOTE, ASCEND, and RESPOND.

DEVOTE is an ongoing phase 2/3, randomised, controlled escalating dose study using active-controlled treatment, evaluating the safety/tolerability, efficacy, and pharmacokinetics of investigational higher doses of nusinersen in patients with SMA. The long-term efficacy and safety profile of nusinersen studied in a broad range of patients as well as pharmacokinetic /pharmacodynamic modelling and preclinical safety studies provide the basis to explore whether higher doses of nusinersen can offer improved clinical outcomes while maintaining a favourable safety profile. DEVOTE has 3 distinct parts (A, B, and C) where the next part starts after a confirmatory safety evaluation of the preceding part (Figure 34):

- Part A is an open-label study in later-onset SMA evaluating the safety and tolerability of a higher loading and maintenance dosing regimen of nusinersen before exposing patients to the proposed high dosing regimen in Part B, the pivotal portion of the study. Patients in Part A received 3 loading doses of intrathecal 28 mg nusinersen at 14-day intervals followed by 28 mg maintenance doses every 4 months. The safety data profile suggests adequate safety and tolerability of the higher dose of nusinersen. Furthermore, although DEVOTE Part A was not designed to assess the efficacy of the higher dose, most patients showed improvement or stabilization in motor function after treatment with 28 mg nusinersen. Safety and limited efficacy results from Part A were reported in 2023[98].
- Part B is a pivotal, randomized, double-blind, active-controlled study. Enrolment is complete and a total of 126 patients with early- or later-onset SMA were randomized (1:2) to receive the approved 12mg dose of nusinersen or high dose nusinersen, i.e., two loading doses (50 mg) 14 days apart followed by maintenance doses (28 mg) every 4 months.
- Part C has been initiated based on the initial favourable safety findings in Part B. This part evaluates the safety of transitioning from the approved maintenance dose of nusinersen (12 mg) to the investigational higher loading dose (50 mg) and maintenance dose (28 mg).

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Figure 34. Overview of the DEVOTE study design



Final results from DEVOTE are expected [redacted] and Biogen is planning [redacted] for high-dose nusinersen [redacted].

RESPOND is a phase 4, open-label, multicentre, single-arm study of nusinersen in children with SMA who have previously received onasemnogene abeparvovec and have suboptimal clinical status per the Investigator. Enrolment in RESPOND began in 2021 in 30 sites globally. The target enrolment is 60 patients. Data from an interim analysis of RESPOND support the potential benefit and safety profile of nusinersen treatment in infants and children with suboptimal clinical response to onasemnogene abeparvovec[99]. At Day 183, most participants with suboptimal motor function at baseline improved[99]. Mean (SD) HINE-2 scores increased across age groups, with a 5.4 (2.62) point improvement from baseline in patients with two *SMN2* copies aged ≤9 months at first dose of nusinersen and a 5.2 (2.74) point improvement in patients with two *SMN2* copies aged >9 months at first nusinersen dose[99]. Mean (SD) CHOP INTEND scores improved from baseline by 6.7 (6.76) points in the younger group and remained stable in the older group with a change of 0.6 (5.50) points[99]. No emerging safety concerns were identified[99].

ASCEND is an international, open-label, single-arm study of higher dose nusinersen (two loading doses of 50 mg 2 weeks apart followed by 28 mg maintenance doses every 4 months) in non-ambulatory patients with later-onset SMA previously treated with risdiplam. Both nusinersen-naïve patients and patients previously treated with nusinersen are eligible. Target recruitment is approximately 135 patients and enrolment is currently ongoing.

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B.3 Cost effectiveness

B.3.1 Published cost-effectiveness studies

All the previous health technology appraisals that have been completed for interventions for SMA, as identified from the economic SLR, are summarised in Table 33. Full results of the economic SLR are provided in Appendix G.

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Table 33. Previous health technology appraisals of interventions for SMA

Study ID	Year	Summary of model	Patient population (average age)	QALYs (intervention, comparator)	Costs (currency) (intervention, comparator)	ICER (per QALY gained)
Nusinersen						
CADTH SR0525 - nusinersen (plus resubmission) 2017/2019 [100]	2017 (published)	Multi-state Markov models based upon milestone achievement. Separate models for Type 1 SMA, Type 2 SMA and Type 3 SMA. Effectiveness of treatments taken from published trials. Utilities and costs largely taken from confidential information submitted by the company.	Type 1 to 3 SMA. (Average age not reported)	**Company** Type 1 SMA RWC: -0.881 Nusinersen: 3.919 Type 2 SMA RWC: 19.602 Nusinersen: 23.278 Type 3 SMA RWC: 10.490 Nusinersen: 12.053 **Committee** Type 1 SMA RWC: 0.65 Nusinersen: 0.90 Type 2 SMA RWC: 4.64 Nusinersen: 4.93 Type 3 SMA RWC: 10.82 Nusinersen: 11.38	**Company** Type 1 SMA RWC: $339,683 Nusinersen: $3,534,854 Type 2 SMA RWC: $708,620 Nusinersen: $8,336,271 Type 3 SMA RWC: $1,091,307 Nusinersen: $5,554,707 **Committee** Type 1 SMA RWC: $341,060 Nusinersen: $2,410,906 Type 2 SMA RWC: $704,769 Nusinersen: $7,653,525 Type 3 SMA RWC: $1,096,196 Nusinersen: $5,271,475	ICER per QALY gained nusinersen vs RWC **Company** Type 1 SMA: $665,570 Type 2 SMA: $2,075,435 Type 3 SMA: $2,855,818 **Committee** Type 1 SMA: $9,161,397 Type 2 SMA: $24,387,422 Type 3 SMA: $7,429,834
CADTH SR0713 - nusinersen (reassessment) 2022 [101]	2022	Seven-state Markov models based upon milestone achievement. Effectiveness of treatments taken from published trials. Utilities and costs taken from published studies, prior submissions or company research.	Type 2 to 3 SMA. (Model mean age: 33 to 36)	**Company** RWC: 5.43 Nusinersen: 7.09 **Committee** CADTH did not generate results as the model was too flawed. The model generated different QALYs for nusinersen and RWC even when all parameters for both arms were equalised	**Company** RWC: $337,386 Nusinersen: $6,253,061 Risdiplam is cheaper than nusinersen at list price **Committee** CADTH did not generate any results.	**Company** ICER per QALY gained nusinersen vs RWC: $3,568,727 **Committee** No ICERs were produced by CADTH.

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Study ID	Year	Summary of model	Patient population (average age)	QALYs (intervention, comparator)	Costs (currency) (intervention, comparator)	ICER (per QALY gained)
				meaning the company results had no face validity.		
Garau 2018 [102]	2018	An eight-state Markov model for Type 1 SMA with health states defined by HINE-2 and CHOP-INTEND scores and a seven state Markov model for Type 2 to 3 SMA with health states determined of HFMSE scores or WHO criteria. Patients could maintain, improve or lose function each cycle. Parameter values taken from clinical trials, expert opinion and published sources.	Type 1 SMA and Type 2 to 3 SMA. (Model start age Type 1 SMA: 4.4 months SMA 2: 2.1 years)	QALYS Type 1 SMA Nusinersen: 8.49 RWC: 2.56 Type 2 to 3 SMA Nusinersen: 22.99 RWC: 19.46	Type 1 SMA Nusinersen: €3,376,122 RWC: €399,757 Type 2 to 3 SMA Nusinersen: €6,016,370 RWC: €2,277,175	ICER Nusinersen versus RWC (societal perspective) **Company** Type 1 SMA: €502,289 Type 2 SMA: €1,059,269 **Committee** The Zorginstituut considered the ICERs would be approximately €600,000 for Type 1 SMA and €1,700,000 for Type 2 to 3 SMA. How this was determined is not clear.
National centre for Pharmacoeconomics 2017 [103]	2017	Two Markov models (early and later onset SMA) populated using nusinersen trial data.	Type 1 to 3 SMA (although not explicitly stated). (Average age not reported)	NR	NR	Nusinersen vs RWC **Company** ICER per QALY gained Early onset: €501,069 Later-onset: €2,107,108 ICER per life year gained Early onset: €453,079 Later-onset: €3,906,818 **Committee** The HTA agency did not generate their own results.
NICE TA588 - nusinersen 2019 [104]	2019	An eight-state Markov model (infantile-onset) and seven state Markov model (later onset) with health states defined by	Type 1 to 3 SMA. (The infantile-infantile model start age is 5.58 months. The later-onset	**Company - original submission** Infantile-onset model Excluding carers utilities Nusinersen: 7.86	**Company - original submission** Infantile-onset model Nusinersen: £2,258,852 Usual care: £71,540	**Company - original submission** Infantile-onset model Excluding carers utilities: £407,605

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Study ID	Year	Summary of model	Patient population (average age)	QALYs (intervention, comparator)	Costs (currency) (intervention, comparator)	ICER (per QALY gained)
		HINE-2 (infantile-onset) and HFMSE (later onset). Depending on cycle number and treatment, patients can maintain, improve or lose function each cycle. Parameter values taken from clinical trials, published sources and clinical advice/opinion.	model start age is 43.71 months.)	Usual care: 2.49 Including carers utilities Nusinersen: 7.61 Usual care: 2.17 Later onset model Excluding carers utilities Nusinersen: 16.88 Usual care: 14.52 Including carers utilities Nusinersen: 15.66 Usual care: 12.36 **Company - revised submission** Infantile-onset onset model Excluding carers utilities Nusinersen: 0.57 Usual care: -0.48 Including carers utilities Nusinersen: -0.96 Usual care: -2.34 Later onset model Excluding carers utilities Nusinersen: 5.83 Usual care: 1.09 Including carers utilities Nusinersen: -3.56 Usual care: -14.30	Later onset model Nusinersen: £3,148,754 Usual care: £184,312 **Company - revised submission** with EAG suggested amendments and additional scoliosis surgery health states and with plateauing of treatment effect (early onset) and 1% worsening each cycle with nusinersen (later onset) Infantile-onset onset model Nusinersen: £1,116,254 Usual care: £176,108 Later onset model Nusinersen: £2,943,909 Usual care: £1,074,004	Including carers utilities: £402,361 Later onset model Excluding carers utilities: £1,252,991 Including carers utilities: £898,164 **Company - revised submission** Infantile-onset onset model Excluding carers utilities: £895,865 Including carers utilities: £684,389 Later onset model Excluding carers utilities: £394,343 Including carers utilities: £174,106

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Study ID	Year	Summary of model	Patient population (average age)	QALYs (intervention, comparator)	Costs (currency) (intervention, comparator)	ICER (per QALY gained)
SMC 2018 [105]	2018	Two ten-state Markov models using trial and published data.	Type 1 SMA and Type 2 to 3 SMA (Type 1 SMA model start age of 5.6 months. Type 2 to 3 SMA model start age 43.7 months.)	Incremental QALYs with nusinersen vs RWC **Company** Infantile-onset onset: 5.02 Later onset: 2.29 **Committee** SMC did not generate any results.	Incremental costs with nusinersen (list price) vs RWC **Company** Infantile-onset onset: £2,151,509 Later onset: £3,728,246 **Committee** SMC did not generate any results.	**Company** Infantile-onset onset: £428,964 Later onset: £1,624,951 **Committee** SMC did not generate any results.
Onasemnogene abeparvovec						
CADTH SR0649 - onasemnogene abeparvovec 2021 [106]	2021	Markov model using data from trials and previously published.	Type 1 SMA (Average age not reported although patients had to enter the model before 6 months of age)	**Company** BSC: 0.21 OA: 10.89 Nusinersen: 4.54 **Committee** BSC: 0.567 OA: 9.883 Nusinersen: 6.295	**Company** BSC: $132,600 OA: £3,266,544 Nusinersen: £3,938,147 **Committee** BSC: $137,171 OA: £3,249,578 Nusinersen: £4,881,630	**Company** OA vs BSC: $293,521 OA dominated nusinersen **Committee** OA vs BSC: $334,090 OA dominated nusinersen
NICE HST15 2021 [107]	2021	Six-state Markov model based upon milestone achievement with transitions that can occur for the first three years. Each cycle for three years patients can maintain or gain function or, if in the sitting state, lose function and require PAV. After three years milestones achieved are maintained for life.	Symptomatic Type 1 SMA with 2 copies of SMN2 gene (base case) – a presymptomatic population was explored in a scenario analysis (Model start age was birth)	**Company – 2019 submission** OA: 11.42 Nusinersen: 1.81 BSC: 0.65 **Company – 2020 resubmission** OA: 10.007 BSC: 0.210 **Evidence Assessment Group** OA + BSC: 13.74 BSC: 0.21	**Company – 2019 submission** OA: £2,614,400 Nusinersen: £2,270,315 BSC: £707,836 **Company – 2020 resubmission** OA: £2,640,022 BSC: £381,131 **Evidence Assessment Group** Onasemnogene + BSC: redacted BSC: £381,131	**Company – 2019 submission** OA vs BSC: £177,061 Nusinersen vs BSC: £1,354,762 **Company – 2020 resubmission** OA vs BSC: £230,568 **Evidence Assessment Group** Onasemnogene + BSC vs BSC: redacted

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Study ID	Year	Summary of model	Patient population (average age)	QALYs (intervention, comparator)	Costs (currency) (intervention, comparator)	ICER (per QALY gained)
NICE HST24 2023 [108]	2023	For OA, a short term (2 year) six state Markov model followed by a long term (2 years to lifetime) seven state Markov model. The short term model established the maximum function gained by each child. The long term model allowed patients to lose but not gain function. Only one milestone could be lost. In both models milestone achievement was used as a proxy for SMA type. For BSC, just the long term model was used with patients with milestone achievement (SMA type) based upon natural history data. Only one milestone could be lost.	Presymptomatic SMA with up to three copies of the SMN2 gene. (Model start age was birth)	**Company** QALYs were redacted **Committee** QALYs were redacted	**Company** OA: £2,096,927 BSC: £882,564 **Committee** Redacted	**Company** OA (list price) vs BSC: £70,610 per QALY gained **Committee** All redacted but with the PAS applied for OA the ICER was reported as being under £100,000 per QALY gained for the whole population and for patients with two copies or three copies of the SMN2 gene analysed separately, if there was a loss of milestones with OA and if social care costs were removed.
SMC - onasemnogene abeparvovec 2021 [109]	2021	A six-state Markov model using published trial evidence on OA and nusinersen with an ITC to produce comparative efficacy. Other parameter values were generated through clinical advice, other published sources or company gathered evidence.	Type 1 SMA. (Model starts at birth)	**Company** OA: 7.50 Nusinersen: 3.77 **Committee** SMC did not generate any results.	**Company** OA: £2,704,737 Nusinersen: £2,800,590 **Committee** SMC did not generate any results.	**Company** OA dominated nusinersen **Committee** SMC did not generate any results.
Onasemnogene abeparvovec or nusinersen						
ICER – onasemnogene abeparvovec	2019	Five-state Markov models (infantile onset: Type 1 SMA and	Type 1 to 3 SMA	Presymptomatic model OA: 21.94 Nusinersen: 21.94	Presymptomatic model OA: $3,264,000 Nusinersen: $11,929,000	Presymptomatic model OA vs BSC: $157,000 (assumed OA same

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Study ID	Year	Summary of model	Patient population (average age)	QALYs (intervention, comparator)	Costs (currency) (intervention, comparator)	ICER (per QALY gained)
and nusinersen 2019 [110]		presymptomatic) and three state Markov model later onset (Type 2 to 3 SMA). The models had two parts – a short-term model based upon trial data and long term extrapolation. Parameter values were taken from published sources.	(Presymptomatic model start age: 21 days Infantile onset model start age: 4.4 months Later onset model start age: 2 years)	BSC: 6.25 Infantile onset model OA: 21.94 Nusinersen: 21.94 BSC: 6.25 Later onset model Nusinersen: 12.28 BSC: 11.34	BSC: $801,000 Infantile onset model OA: $3,657,000 Nusinersen: $3,884,000 BSC: $789,000 Later onset model Nusinersen: $9,148,000 BSC: $1,442,000	efficacy as nusinersen) Nusinersen vs BSC: $709,000 Infantile onset model OA vs BSC: $243,000 Nusinersen vs BSC: $1,112,000 Later onset model Nusinersen vs BSC: $8,156,000
Risdiplam						
CADTH SR0661 – risdiplam 2021 [111]	2021	Six-state Markov model based upon milestone achievement. Separate models for Type 1 SMA and Types 2 to 3 SMA. Effectiveness of treatments taken from published trials with assumed equal effectiveness of OA and risdiplam. Utilities and costs largely taken from confidential information submitted by the company.	Type 1 SMA and Type 2 to 3 SMA (Average age not reported)	**Company** Type 1 SMA BSC: 3.53 Nusinersen: 10.17 Risdiplam: 10.19 Type 2 to 3 SMA BSC: 70.11 Nusinersen: 70.91 Risdiplam: 71.04 **Committee** Type 1 SMA BSC: 0.34 Nusinersen: 1.06 Risdiplam: 1.08 Type 2 to 3 SMA BSC: 15.05 Nusinersen: 15.20 Risdiplam: 15.34	**Company** Type 1 SMA BSC: $68,293 Nusinersen: $1,865,665 Risdiplam: $961,580 Type 2 to 3 SMA BSC: $825,656 Nusinersen: $11,892,866 Risdiplam: $11,454,583 **Committee** Type 1 SMA BSC: $69,311 Nusinersen: $1,869,652 Risdiplam: $965,780 Type 2 to 3 SMA BSC: $823,674 Nusinersen: $11,890,396 Risdiplam: $11,452,152	ICER per QALY gained **Company** Type 1 SMA Risdiplam vs BSC: $134,229 Risdiplam vs nusinersen: risdiplam dominated nusinersen Type 2 to 3 SMA Risdiplam vs BSC: $11,343,198 Risdiplam vs nusinersen: risdiplam dominated nusinersen **Committee** Type 1 SMA Risdiplam vs BSC: $1,203,108 Risdiplam vs nusinersen: risdiplam dominated nusinersen

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Study ID	Year	Summary of model	Patient population (average age)	QALYs (intervention, comparator)	Costs (currency) (intervention, comparator)	ICER (per QALY gained)
						Type 2 to 3 SMA Risdiplam vs BSC: $33,378,163 Risdiplam vs nusinersen: risdiplam dominated nusinersen
NICE TA755 – risdiplam 2021 [112]	2021	Two six-state Markov models (Type 1 SMA and Type 2 to 3 SMA) with health states defined by HINE-2 scores (Type 1 SMA) and MFM-32 scores (Type 2 to 3 SMA). Patients can maintain, improve or lose function each cycle. Parameter values were taken from clinical trials, a MAIC, previous NICE technology appraisals, published sources and clinical advice/opinion.	Type 1 to 3 SMA. (The Type 1 model start age is 5.8 months. The Type 2/3 model start age is redacted.)	QALYs **Company** Type 1 SMA BSC: 8.59 Risdiplam: 31.33 Type 2 to 3 SMA BSC: 23.04 Risdiplam: 45.19 **Committee** Type 1 SMA BSC: -1.91 Risdiplam: -3.12 Type 2 to 3 SMA BSC: -4.08 Risdiplam: 7.82	Redacted	ICER per QALY gained risdiplam vs BSC For list price; PAS price ICERs all redacted **Company** Type 1 SMA: £97,729 Type 2 SMA: £185,197 **Committee** Redacted but above £50,000 (Type 1 SMA) and £30,000 (Type 2 to 3 SMA)

Abbreviations: BSC, Best supportive care; CADTH, Canadian Agency for Drugs and Technologies in Health; EAG, Evidence Assessment Group; ICER, Incremental cost-effectiveness ratios; NR- Not reported; OA, Onasemnogene abeparvovec; PAS, Patient access scheme; QALY, Quality adjusted life-year; RWC- Real world care; SMA, Spinal muscular atrophy; UK, United Kingdom.

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B.3.2 Economic analysis

B.3.2.1 Patient population

Nusinersen has a marketing authorisation for 5q SMA, which encompasses presymptomatic SMA and symptomatic SMA types 0 to 4. However, there is currently insufficient evidence to inform the efficacy and survival benefits of nusinersen for people with type 4 SMA, while treatment of patients with type 0 SMA is considered futile, as described in Section B.1.3.2. Therefore, to avoid introducing uncertainty into the models, the economic analysis assessed the cost-effectiveness of nusinersen in three populations, namely, presymptomatic, infantile onset (type 1), and later-onset (types 2 and 3) SMA. This means that the model cohort is narrower than both the current marketing authorisation for nusinersen and the population listed in the final NICE scope.

Three separate de-novo economic models were developed to assess the cost-effectiveness of nusinersen in the three SMA populations described above. This approach was primarily taken because each population has a different natural disease history (see Section B.1.3.3) and because the current evidence from the completed, pivotal clinical trials for nusinersen, NURTURE (presymptomatic, described in see Section B.2.3.3; ENDEAR (infantile-onset, type 1, described in Section B.2.3.1); CHERISH (later-onset, type 2/3, described in SectionB.2.3.1), and SHINE (long-term follow-up study for symptomatic patients with type 1, 2, and 3 SMA, described in Section B.2.3.2), considers these three populations separately.

For each population, the model cohort were designed to match the baseline characteristics of the ITT population in the appropriate pivotal trials for nusinersen. The detailed eligibility criteria for the NURTURE; ENDEAR; CHERISH, and SHINE clinical trials are presented in Section B.2.3.

The population assessed in the cost-effectiveness analysis for the presymptomatic model were infants with genetically confirmed, presymptomatic SMA, aligning with the population in the NURTURE clinical trial. The model also considered two sub-populations, namely, people with two or three copies of the *SMN2* gene. The inclusion of these subgroups was completed because the number of *SMN2* copies

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has been shown to be a key factor (although not the only one) when predicting an individual's prognosis [15,16,113,114].

Typically, people with a more severe disease phenotype will have fewer copies of *SMN2*. Furthermore, this sub-population was listed in the NICE scope [115] and, in the 2023 NICE appraisal of onasemnogene abeparvovec for people with presymptomatic SMA [116], the EAG noted that this stratification of the presymptomatic population was important to model. For decision making purposes, the presymptomatic population should be treated as a single population as it is not possible to reliably predict the prognosis of SMA in individual people diagnosed pre-symptomatically.

The population assessed in the cost-effectiveness analysis for the later-onset economic model also stratified the population into two sub-populations, namely, a sub-population of people with type 2 SMA, and a sub-population of people with type 3 SMA. While these sub-populations were not listed explicitly in the NICE scope, this scope did state that subgroups based on functional status would be considered. Given that people with type 2 SMA are generally defined as "sitters" and people with type 3 SMA are generally defined as "walkers" [117], the inclusion of sub-population was judged important to capture long-term outcomes more accurately. Key clinical experts highlighted the heterogeneity of the two types of SMA in terms of survival and ambulatory status [117]. This separation was also considered in the CADTH pharmacoeconomic review report for nusinersen [118]. Further details of the impact of this separation are provided in Section B.3.3.

B.3.2.2 Model structure

The structure for the three economic models was informed by several sources including systematic reviews; clinical guidelines and prior health technology assessment (HTA) reports. At the date of submission, four cost-effectiveness models (CEM) have been submitted as part of the following NICE appraisals:

- Nusinersen for treatment spinal muscular atrophy (TA588) [119].
- Risdiplam for treating spinal muscular atrophy (TA755) [120].
- Onasemnogene abeparvovec for treating spinal muscular atrophy (HST15) [107].

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- Onasemnogene abeparvovec for treating presymptomatic spinal muscular atrophy (HST24) [116].

Additionally, the Institute for Clinical and Economic Review (ICER) in the US has previously undertaken an assessment of both nusinersen and onasemnogene for the treatment of SMA [110]. The model developed for this assessment was taken into consideration. A UK advisory board with five clinical experts and three health economics experts was also conducted to further validate the model structures.

A key finding from these sources was that SMA is highly driven by the development of gross motor milestones. Indeed, type 1, type 2 and type 3 SMA are classified by the maximal motor milestone achieved by the person with SMA, namely, 'non-sitters', 'sitters' and 'walkers' respectively [117]. Therefore, the achievement of gross motor milestones is associated with healthcare resource use, treatment costs and health related quality of life (HRQoL) for both the person with SMA and their caregiver, as well as overall survival outcomes for the person with SMA. Three proportion in state cohort models, with a partitioned survival element, were therefore developed to capture the impact of nusinersen on the achievement of gross motor milestones in a cohort with either presymptomatic, type 1 or type 2/3 SMA. The following health states were included in all three models: 'non-sitting', 'sitting without support', 'standing with support' and 'walking independently'. In both the pre-symptomatic and type 1 models, permanent ventilation was also captured via a specific health state and this is discussed in further detail below. Finally, the absorbing health state in all three models was 'death'.

For the type 1 model, the definitions of each gross motor milestone-based health state (excluding death) relied on two separate outcome measures: HINE-2 and WHO motor development milestones (referred to as WHO henceforth). The use of two separate outcome measures was necessary because one consistent measure was not used across the ENDEAR and SHINE clinical trials. HINE-2 is a measurement that is only used in children aged two years or less [121]. Therefore, within the nusinersen clinical trial programme, the HINE-2 score was used to measure the motor milestone development in children younger than two. When these children exceeded the age of two and were able to sit without support, the WHO instrument was used. The definitions for milestone attainment do differ across the two

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measures, as outlined in Table 34. However, for the purpose of populating the economic models it was necessary to assume equivalence between the HINE-2 and WHO measures. The pre-symptomatic and type 2/3 models were based only on the measurement of gross motor milestones using the WHO instrument given NURTURE and CHERISH/ SHINE did not use the HINE-2 for these populations.

When selecting the appropriate motor milestone-based health states, consideration was given to whether a person required support. The lowest motor milestone a person can achieve is 'sitting without support', however, both HINE-2 and WHO measures have distinct definitions for 'standing with support'; 'standing without support'; 'walking with support', and 'walking independently'. Based on the advice of clinical experts, it was determined that 'sitting without support', 'standing with support' and 'walking independently' would be the most appropriate definitions to use for the model states. Indeed, the achievement of 'standing with support' was deemed by clinical experts to have a greater impact on the outcomes of people with SMA than the achievement of 'standing without assistance'. This is because 'standing with support' facilitates a greater increase in the number of daily activities that can be completed. Similarly, clinical experts advised that the achievement of 'walking independently' had a greater impact on the outcomes of people with SMA than the achievement of 'walking with support.

Table 34. Definitions of health states for HINE-2 section 2 and WHO measures of motor skills

	HINE-2 section 2 definition [26]	WHO motor milestone definition [122]
Sitting without support	Score 3-4 in sitting ability (stable sitting or pivot achievement) and a score of less than 2 in standing ability.	Sits up straight with head erect for 10 seconds without support from hands.
Standing with support	Score of 2 in standing ability. Any score in other items except walking ability.	Stands in an upright position on both feet holding onto a stable object with support from hands only for 10 seconds. The body does not touch the stable object.
Walking independently	Score of 3 in walking ability. Any score in other items.	5 steps independently. One leg moves while the other supports weight.

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The inclusion of the health states described above were deemed appropriate as they capture clinically meaningful changes in the health of people with SMA. Therefore, the attainment or loss of each gross motor milestone is associated with substantial changes in healthcare costs and outcomes for both people with SMA and their caregivers. However, interim milestones are often also measured for people with SMA including head control, rolling, and hands and knees crawling. The inclusion of these interim milestones as additional health states was considered and would have provided a more granular model structure. However, this would have required the development of a more complex model structure and, importantly, a higher data burden to fully populate the models. Given that SMA is a rare disease, such that the majority of clinical studies associated with the disease have small sample sizes, there would have been a substantially higher number of data gaps for a model structure that included these interim milestones as explicit health states. Therefore, to reduce the number of assumptions in the model it was judged appropriate to exclude these interim milestones. However, clinical experts advised that an 'on-treatment' utility increment should be included to capture additional benefits of treatment on the achievement of interim milestones. This is discussed further in Section B.3.4.

The final model structures are presented in Figure 35 for the presymptomatic and type 1 populations, and Figure 36 for the type 2/3 sub-population. Figure 35 incorporates a fifth health state that captured people within the presymptomatic and type 1 populations who required permanent ventilation because of a deterioration in health meaning unassisted breathing was no longer possible. It was assumed that only the cohort in the 'not sitting' health state could deteriorate to the point to which they require a tracheostomy or greater than or equal to 16 hours of ventilatory support per day for more than 21 days. Once the cohort entered the 'permanent ventilation' heath state, it was assumed that they could not improve and, therefore, they discontinued any active treatment regimen (only applicable to nusinersen arms) and remained in 'permanent ventilation' until death. The methods adopted to include permanent ventilation in the model, in particular the assumption that patients could only transition to this state from 'not sitting' was validated by clinical experts at the advisory board.

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As presented in Figure 36, ‘permanent ventilation’ was not included as a health state for the type 2/3 model. This decision aligns with the available data, which indicates that permanent ventilation is very rarely required for people with type 2 and type 3 SMA. Indeed, Trucco et al. reported that, within a natural history study incorporating 306 people with type 2 and 3 SMA, only 1% required a tracheostomy, which is indicative of permanent ventilation. Additionally, only 3% of the cohort required non-invasive ventilation, which typically precedes permanent ventilation. It should also be noted that this study was undertaken in the US and Italy, and the interventional approach taken may not fully reflect UK practice. As such, the rate of invasive ventilation may be even lower in the UK. The exclusion of permanent ventilation from the type 2/3 model was also validated by clinical experts at the advisory board.

In both the presymptomatic and type 1 models, at baseline the starting age of the cohort was less than 6 months and all patients started the model in the ‘not sitting’ health state. In the type 2/3 model, the starting age of the cohort was older and patients were separated between the ‘sitting without support’, ‘standing with support’ and ‘walking independently’ (if type 3) health states. See Section B.3.3 for more information on the baseline characteristics that were applied in all models.

In terms of transitioning between each gross motor milestone health state (either improve or deteriorate), patients could only transition by a maximum of one motor milestone each cycle. For example, those in the “not sitting” health state could only transition to “sitting without support” and not jump directly to “standing with support”. However, patients were able to move by more than one motor milestone over multiple cycles (i.e. it was possible for a patient to decline from ‘walking independently’ to ‘not sitting’ over three or more cycles). As described previously, those in the “not sitting” state could also transition to the “permanent ventilation” state and patients in all health states were at risk of mortality, as described further in Section B.3.3.

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Figure 35. Model structure for presymptomatic and type 1 SMA populations

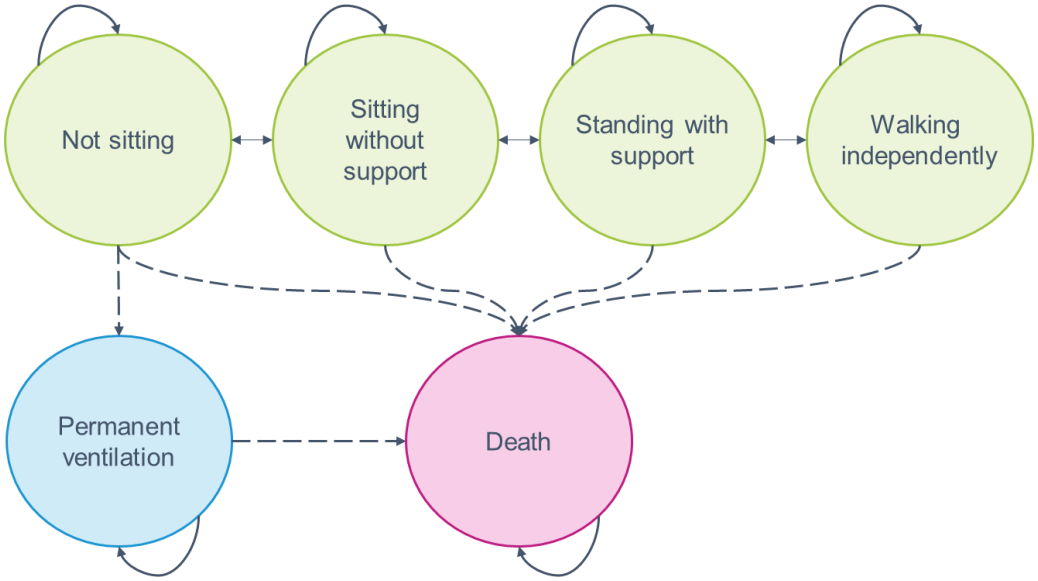
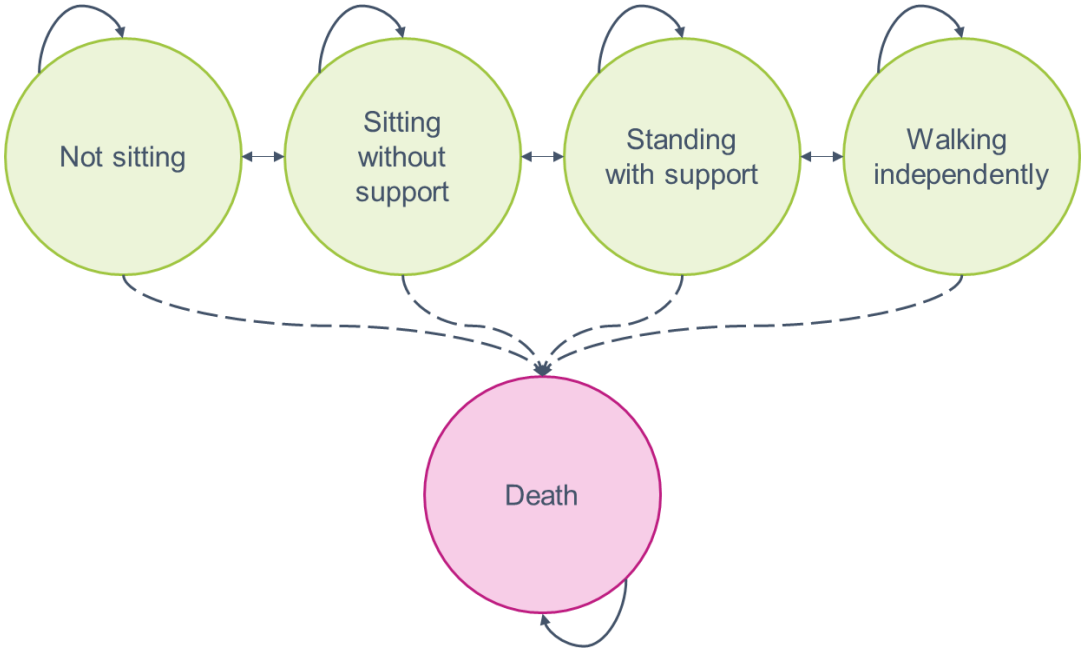


Figure 36. Model structure for the later-onset SMA population



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Table 35. Features of the economic analysis

	Previous evaluations		Current evaluation	
Factor	**TA755**	**HST24**	**Chosen values**	**Justification**
Time horizon	Lifetime (90 years)	Lifetime (100 years)	Lifetime	Nusinersen will have effects on costs and outcomes over the lifetime of a person with SMA, therefore, a lifetime horizon is appropriate [123]. This is in line with NICE guidance section 4.2.22 to 4.2.25.
Treatment waning effect	Type 1 SMA Treatment effects on transition probabilities were assumed constant up to 50 years then a constant waning effect to reach BSC values after 5 years was applied. No survival impact was assumed. Type 2/3 SMA Treatment effects on transition probabilities were assumed constant up to 30 years then a constant waning effect was applied to reach BSC values after 10 years. No survival impact was assumed.	It is stated in HST24 that a one-time administration of onasemnogene abeparvovec at the therapeutic dose provides prolonged efficacy, with no evidence to indicate that SMN protein expression would stop or wane over time.	The models include the option to allow long term, cyclic decline of motor milestones to capture treatment waning. It is assumed people can decline by several motor milestones (but only one milestone per cycle). The cyclic rate of decline for BSC is informed using a natural history study conducted by Wadman et al [35]. The rate of decline is assumed to be slower for the treatment arms, proportional to the difference motor milestone response, for nusinersen compared to the sham/ BSC, that was observed in the nusinersen ENDEAR [85] (to inform the presymptomatic and type 1 models) and CHERISH [124] (to inform the presymptomatic and later-onset model).	There is a lack of data to inform the long-term efficacy and waning of treatment for SMA. Therefore, this was not included in the base case to avoid introducing uncertainty into the model. However, this was explored further in the scenario analysis
Source of utilities	Patient utilities For the type 1 model, health state utility values provided by the ERG clinical advisors in TA588 were selected for the base case due to their greater face validity and clinical plausibility. For the type 2 model, utility values from the Lloyd et al. 2019 EQ-5D vignette study were selected to inform the base case in accordance with the ERG and Committee's	Followed the approach taken by US ICER and adapted to the UK general population. They were derived using the calculation from Ara and Brazier (2010)[126] for health state 3a (delayed walker), health state 3b (experiences later onset SMA), and HS-BRND (within a broad range of normal development). The 'Loses walking' sub-health states was taken from Thompson et al. 2017 [127].	Health state utilities In the base case, the three models utilise the utilities from the company submission for NICE HST24 [130] Carer utilities In the base case, the three models utilise the utilities elicited by clinical experts and preferred by the EAG for TA588 [131]	A SR was undertaken to search for sources for health state utility. However, there was a lack of consistency across studies. Furthermore, whilst EQ-5D data were collected in the MAA the data were limited (in particular, small sample size and limited follow-up visits) and insufficient for the purpose of populating the models. Therefore, the values utilised in the company submission for NICE HST24 [130] were used. The EAG had

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	preference for final decision making in TA588 [125]. The utility values provided by the ERG's clinical advisors were explored in a scenario analyses. <u>Carer utilities</u> In line with the approach taken in TA588, carer health state utility values in the model were informed by Bastida et al. 2017 and general population utility [53,126]. EQ-5D-5L utility values were additionally collected from care givers of SMA patients in a Roche UK burden of illness study, and cross-walked to the EQ-5D-3L and valued using UK tariffs. These health state utility values were applied in a scenario analysis.	Health state 2 (sitter) was taken from Tappenden et al. 2018 [128]. Health state 1 (non-sitter, no PAV) and 'lose sitting' sub-health state were taken from Thompson et al. 2017 [127]. Health state 1 (non-sitter, PAV) was also informed by HST15, Edwards et al. 2020 [129].		no concerns with the utilities that were applied in that appraisal.
Source of costs	Cost and resource use in the base case analysis was informed by the UK-based real-world study and estimates that informed the final NICE decision-making in TA588.	Cost were sourced from a UK HCRU study [116], the NHS Schedule of Reference Costs 2019–2020 [132], Prescription Cost Analysis 2021/22 [133] and from literature searches (inflated to 2021/22 values where necessary).	Health state costs were sourced from the company submission NICE HST24 [130] and inflated to 2021/22 using NHS cost inflation index (NHSCII) pay and prices from PSSRU [134]. Drug acquisition costs were sourced from British National Formulary, [135-138] administration costs were from NHS 2021/22 National Cost Collection data [139].	A SR identified a reasonably large number of studies. However, there was a serious paucity of data based on the motor milestones that are achieved by people with SMA. NICE HST24 [130] is the most recent source for health state costs and has the benefit of incorporating costs for social services. Also, the EAG had no concerns with the health state costs applied in that appraisal.

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B.3.2.3 Intervention technology and comparators

B.3.2.3.1 Intervention

Nusinersen was modelled as a first-line therapy, with best supportive care (BSC) applied according to health state, as is described in the NURTURE, ENDEAR, CHERISH and SHINE trials and according to the marketing authorisation for nusinersen.

The modelled treatment regimen for nusinersen adhered to the regimen described by the SmPC [140]. Therefore, the cohort on active treatment with nusinersen received four loading doses of 12 mg nusinersen on days 0, 14, 28 and 63. For modelling purposes, the four loading doses were applied in the first four-month cycle. In each subsequent 4-monthly cycles, the cohort received one 12 mg administration per cycle. Given that nusinersen is packaged in a 5ml vial, containing 2.4 mg/ml of nusinersen, only one vial was required per administration. The same dose is administered intrathecally for all ages.

Best supportive care (BSC) was a comparator in all populations and was implemented in the models based on a mix of gastrointestinal, respiratory, nutritional and orthopaedic interventions delivered by a multidisciplinary team. More details on the resources incurred for BSC are provided in Section B.3.5. The efficacy of BSC was determined by a combination of data from the pivotal nusinersen trials, external natural history data and assumptions. More details are provided in Section B.3.3.

As described in Section B.2.5, whilst an ITC was undertaken in an attempt to compare nusinersen with risdiplam and onasemnogene it was judged that the outputs from the analyses could not be used due to major limitations. Additionally, a naïve comparison was judged to be inappropriate as major differences in the study populations precluded the possibility of generating robust comparative effectiveness estimates using this method. Therefore, risdiplam and onasemnogene were excluded as comparators from the models.

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B.3.3 Clinical parameters and variables

B.3.3.1 Presymptomatic Model

B.3.3.1.1 Baseline Characteristics

Baseline characteristics utilised in the model, from the NURTURE trial, are presented in Table 36 for the total population and each sub population.

Table 36. Model baseline characteristics (informed by NURTURE [141,142])

Time point	Total population	Two copies of *SMN2*	Three copies of *SMN2*
Baseline population			
Total population of trial (N)	[redacted]	[redacted]	[redacted]
Baseline age (years, mean [SE])	[redacted]	[redacted]	[redacted]
Sex (female, %)	[redacted]	[redacted]	[redacted]
Baseline weight (kg, mean [SE])	[redacted]	[redacted]	[redacted]
Health state at baseline			
Not sitting (%)	100.0%	100.0%	100.0%
Sitting without support (%)	0.0%	0.0%	0.0%
Standing with support (%)	0.0%	0.0%	0.0%
Walking independently (%)	0.0%	0.0%	0.0%

B.3.3.1.2 Nusinersen Effectiveness

The ongoing NURTURE (NCT02386553) clinical trial is currently investigating the safety, efficacy and tolerability of nusinersen in 25 people with genetically diagnosed and pre-symptomatic SMA [141,142].

Over the first 72 months, WHO motor milestone achievement from the most recent data cut from the NURTURE clinical trial (dated 15 November 2021 at the time of the submission) were used directly in the model to capture the proportion of the cohort in each health state. The data, presented in Table 39 for the total population, and the sub-populations with two and three copies of SMN2, reflects the highest WHO motor milestones achieved in NURTURE. It should be noted that no nusinersen patients required permanent ventilation or died during NUTURE.

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As shown in Table 39, and reported by Crawford et al, 87% and 100% of the presymptomatic population receiving nusinersen with 2 and 3 copies of SMN2 respectively, 92% of the total pre-symptomatic population, were able to walk independently at 72 months [84]. Therefore, long-term effectiveness related to the ability of nusinersen to allow people with SMA to maintain the ability to walk. No data were available to quantify these long-term outcomes. Therefore, a rate of decline was incorporated into the model base case to capture people moving back by a maximum of one health state. This rate of decline for the nusinersen cohort was estimated relative to the BSC. Further details about the rate of decline for BSC are provided below.

As described in Section B.3.3.2, the long-term effectiveness of nusinersen versus BSC was based on the relative efficacy measured during the follow-up periods of the ENDEAR and CHERISH studies, for type 1 and type 2/3 SMA, respectively. However, the NUTURE trial was single-arm and, therefore, relative estimates of efficacy for nusinersen versus BSC were not available from this trial, nor any other clinical study related to the pre-symptomatic population. Therefore, in the absence of alternative data, the relative efficacy estimates from the ENDEAR and CHERISH studies were applied to the pre-symptomatic population. It was judged that the data from ENDEAR would be most applicable to the pre-symptomatic sub-population with two copies of SMN2, whilst CHERISH would be most applicable to the sub-population with three copies of SMN2. Details of these relative efficacy estimates are provided in Section B.3.3.2 and Section B.3.3.3.

In order to estimate the probability of a nusinersen patient declining, the relative efficacy estimates described above were applied to probabilities for BSC, which are described in more detail below. The probability of decline utilised for the cohort on nusinersen is presented in Table 38 and this was applied to all cycles in the model from 6 years onwards (i.e. the end of the follow-up period for the NUTURE study for the pre-symptomatic population). This is a conservative assumption as clinical experts stated that if a patient treated pre-symptomatically achieved milestones within a normal timeframe it was unlikely they would be lost, but there is an absence of long-term data to support this.

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Table 37. Relative risk of decline for nusinersen

Population	Relative risk of decline	Reference
Total presymptomatic population	[redacted]	Weighted average over the total presymptomatic population.
Presymptomatic population with 2 SMN2 copies	[redacted]	In the final analysis in ENDEAR, [redacted] people on nusinersen experienced a motor milestone response. Therefore, [redacted] did not have a motor milestone response. The probability of no response with nusinersen is, therefore, [redacted]. In the control arm, [redacted] people had a motor milestone response so the probability of no response with BSC is, therefore, [redacted] The relative risk is 49.3%/100% = 49.3%
Presymptomatic population with 3 SMN2 copies	[redacted]	Mercuri et al (2018) reporting on the CHERISH study. Informed by the proportion of people who gained 1≥ WHO motor milestone for sham control and nusinersen. This was [redacted] people on treatment [redacted] people on sham control. The difference (95% CI): [redacted] Assumed to be equivalent for all populations within the model. • Odds ratio: OR = P1/P2 = [redacted] • Relative risk for motor milestone improvement: RRI = OR/(1-P1+(P1*OR) • Relative risk for motor milestone maintenance or decline: RRD = 1/RRI = [redacted]

Table 38. Per cycle probability of decline for nusinersen

Health state	Year after which people decline	Per cycle probability of decline (%) (total presymptomatic)	Per cycle probability of decline (%) (2-copies)	Per cycle probability of decline (%) (3-copies)
Sitting without support to not sitting	6.25	[redacted]	[redacted]	[redacted]
Standing with support to sitting without support	6.25	[redacted]	[redacted]	[redacted]
Walking independently to standing with support	6.25	[redacted]	[redacted]	[redacted]

There is uncertainty around the age at which the cohort would start to decline and the rate of the decline. Indeed, nusinersen has shown durability in efficacy in infants with pre-symptomatic SMA over 6 years in NURTURE and therefore the base case

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could be potentially a pessimistic analysis. Therefore, to alleviate this uncertainty, a scenario adhering to the precents set in other models, namely HST24, was explored. In this scenario, the cohort on nusinersen maintained the maximum motor milestone achieved at the end of the clinical trial period until death.

Table 39. Achievement of WHO motor milestones for all nusinersen patients in NURTURE [141,142]

Time point	Not Sitting	Sitting without support	Standing with support	Walking independently
Total population				
Baseline				
Month 6				
Month 9				
Month 12				
Month 15				
Month 18				
Month 24				
Month 36				
Month 48				
Month 60				
Month 72				
Two copies of SMN2				
Baseline				
Month 6				
Month 9				
Month 12				
Month 15				
Month 18				
Month 24				
Month 36				
Month 48				
Month 60				
Month 72				
Three copies of SMN2				
Baseline				
Month 6				
Month 9				
Month 12				
Month 15				
Month 18				
Month 24				
Month 36				
Month 48				
Month 60				
Month 72				

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B.3.3.1.3 Best supportive Care Effectiveness

The NURTURE clinical trial did not include a control arm. Therefore, the distribution of the BSC arm across each of the motor milestone-based health states was based on a weighted average of the BSC data that were applied for the type 1 population (see Section B.3.3.2) and both the type 2 and type 3 population (see Section B.3.3.3). This is possible because all pre-symptomatic patients will utility develop SMA type 1 to 3. The distribution of the total population and sub-populations (by copy number) across each SMA type was based on a worldwide epidemiology study conducted by Calucho et al[16]. Within this study, the authors analysed the phenotype–genotype correlations using data from 625 Spanish patients and 2,834 patients worldwide, based on data extracted from SMA studies published after 1999. This distribution is presented in Table 40.

A summary of the motor milestone data by SMA type is presented in Table 41. More details of these datapoints are provided in Section B.3.3.2 and Section B.3.3.3. The data in Table 41 shows that if these data were applied directly in the pre-symptomatic model then implausible levels of motor milestone attainment would have been achieved. For example, [redacted] of type 3 patients were walking by month 6. However, this data was based on patients with a mean age of [redacted] during the CHERISH trial. The pre-symptomatic population in the model had a mean age of [redacted] at baseline. Therefore, it was not feasible for these patients to be walking by 6 months. To ensure that implausible estimates were not included in the model the data in Table 41 were adjusted by up to two health states. Details for this adjustment are presented as footnotes to that table.

Table 40. Distribution of SMA population by SMA type and copy number

	Type 1	Type 2	Type 3	Total
2 SMN2 copies	919	192	54	1165
3 SMN2 copies	245	902	515	1662
Total	1164	1094	569	2827

The values that were applied in the pre-symptomatic model, following the adjustments described above, are presented in Table 42.

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Table 41. Summary of BSC motor milestone attainment, by SMA type

	Pre-adjustment			Post-adjustment		
	Type 1	Type 2	Type 3	Type 1	Type 2	Type 3
Not sitting						
Baseline	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Month 6	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Month 9	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Month 12	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Month 15	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Sitting without support						
Baseline	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Month 6	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Month 9	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Month 12	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Month 15	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Standing with support						
Baseline	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Month 6	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Month 9	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Month 12	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Month 15	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Walking independently						
Baseline	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Month 6	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Month 9	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Month 12	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Month 15	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

*Assumed to be 'not sitting' for inclusion in the model (see 'post-adjustment').
¥Assumed to be 'sitting without support' for inclusion in the model (see 'post-adjustment')
†Assumed to be 'standing with support' for inclusion in the model (see 'post-adjustment')

Table 42. Summary of motor milestone attainment values applied for the BSC population in the pre-symptomatic model

Time point	Not Sitting	Sitting without support	Standing with support	Walking independently
Total population				
Baseline	[redacted]	[redacted]	[redacted]	[redacted]
Month 6	[redacted]	[redacted]	[redacted]	[redacted]
Month 9	[redacted]	[redacted]	[redacted]	[redacted]
Month 12	[redacted]	[redacted]	[redacted]	[redacted]
Month 15	[redacted]	[redacted]	[redacted]	[redacted]
Two copies of SMN2				
Baseline	[redacted]	[redacted]	[redacted]	[redacted]
Month 6	[redacted]	[redacted]	[redacted]	[redacted]
Month 9	[redacted]	[redacted]	[redacted]	[redacted]
Month 12	[redacted]	[redacted]	[redacted]	[redacted]
Month 15	[redacted]	[redacted]	[redacted]	[redacted]

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Time point	Not Sitting	Sitting without support	Standing with support	Walking independently
Three copies of SMN2				
Baseline	[redacted]	[redacted]	[redacted]	[redacted]
Month 6	[redacted]	[redacted]	[redacted]	[redacted]
Month 9	[redacted]	[redacted]	[redacted]	[redacted]
Month 12	[redacted]	[redacted]	[redacted]	[redacted]
Month 15	[redacted]	[redacted]	[redacted]	[redacted]

Once the motor milestone was achieved, it was assumed that the cohort on BSC was able to decline by a maximum of one WHO motor milestone per cycle. It was necessary to assume decline initiated at the same timepoint for each motor milestone. Therefore, decline was applied in all cycles of the model from 1.25 years (15 months) and onwards (i.e. the maximum follow-up period observed in the BSC arms of the ENDEAR and CHERISH clinical trials).

The per-cycle probability of decline for each health state, presented in Table 43, was derived from Wadman et al [35], assuming a uniform distribution from the average age the motor milestone was attained to the average age the motor milestone was lost. Copy number was not included as a subgroup and, therefore, it was necessary to assume equivalent per-cycle probabilities of decline for the total population and the sub-populations. In the absence of a control arm in the NUTURE trial, it was assumed that decline was possible after 15 months, which is the longest follow-up point that was available for the sham control arm in the nusinersen clinical trail programme (which informed the effectiveness of BSC, as described previously). These probabilities were applied to all subsequent cycles after these timepoints.

Table 43. Per cycle probability of decline for BSC in the total presymptomatic population [35]

Health state	Year after which people decline	Per cycle probability of decline (%)
Sitting without support to not sitting	1.5	0.8%
Standing with support to sitting without support	1.5	7.2%
Walking independently to standing with support	1.5	13.9%

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Table 44. Per cycle probability of decline for BSC in the presymptomatic population with 2 SMN2 copies [35]

Health state	Year after which people decline	Per cycle probability of decline (%)
Sitting without support to not sitting	1.5	1.2%
Standing with support to sitting without support	1.5	13.2%
Walking independently to standing with support	1.5	25.5%

Table 45. Per cycle probability of decline for BSC in the presymptomatic population with 3 SMN2 copies [35]

Health state	Year after which people decline	Per cycle probability of decline (%)
Sitting without support to not sitting	1.5	0.3%
Standing with support to sitting without support	1.5	1.2%
Walking independently to standing with support	1.5	2.3%

B.3.3.1.4 Permanent ventilation

Permanent ventilation was defined in line with the NURTURE clinical trial, namely, either tracheostomy or at least 16 hours ventilation per day continuously for more than 21 days in the absence of an acute reversible event.

No patients in the individual patient-level time-to-event data from the NURTURE clinical trial required permanent ventilation. Therefore, it was assumed that anyone receiving nusinersen would not progress to permanent ventilation. However, it was assumed that a proportion of people in the BSC arm progressed to permanent ventilation from the 'non-sitting' health state in each cycle for a fixed number of cycles. The proportion of BSC patients progressing to permanent ventilation was informed by Wijngaarde et al [143], in line with the approach taken in HST24. Wijngaarde et al found that, at 4.8 years, 21.9% of people with SMA receiving no active treatment required permanent ventilation. In the presymptomatic model, the proportion of patients progressing to permanent ventilation was assumed to follow a uniform distribution over the model cycles for the first 4.8 years of the model. Therefore, the percentage from Wijngaarde et al was converted to a per-cycle

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probability of decline from ‘sitting without support’ to ‘permanent ventilation’ of 1.7% and this value was applied to BSC patients in the ‘not sitting’ health state for all cycles in the model.

B.3.3.1.5 Survival

The cohort with presymptomatic SMA could transition to ‘death’ from any health state. Individual patient-level time to death data from NURTURE could not be utilised to inform the proportion of the cohort in the nusinersen arm moving to the ‘death’ health state at any point in time because at the time of the latest available data cut all patients were alive and free of permanent ventilation. Instead, the model aligned with the approach in HST24. Therefore, parametric curves derived in HST24 for the permanent ventilation (figure 14 in HST24), not sitting (figure 16 in HST24) and sitting (figure 17 in HST24) cohorts were used. The curves themselves, rather than the Kaplan Meier plots, were digitised to allow for consistency of curves between the models. The curves had the EAG’s preferred extrapolations of exponential for ‘permanent ventilation’ and gamma for ‘not sitting’ and ‘sitting without support’.

The digitised curves were bound by the survival of the next-highest health state to ensure the cohort in more severe health states did not live for longer than those in less severe health states.

The proportion of the cohort moving to the ‘death’ health state from the ‘standing’ and ‘walking’ health states was informed by general population mortality data [144]. As of the date of the submission, the most recent publications of national life tables were from 2020-2022. However, NICE TSD23 states that: “The impact of COVID-19 on long term mortality rates will remain unknown for some years. For current NICE assessments, it would be prudent to use figures from the three-year band 2017 - 2019 and for the Institute to commit to regular reviews of recommended data sources” [145]. Therefore, national life tables from 2017-2019 were utilised.

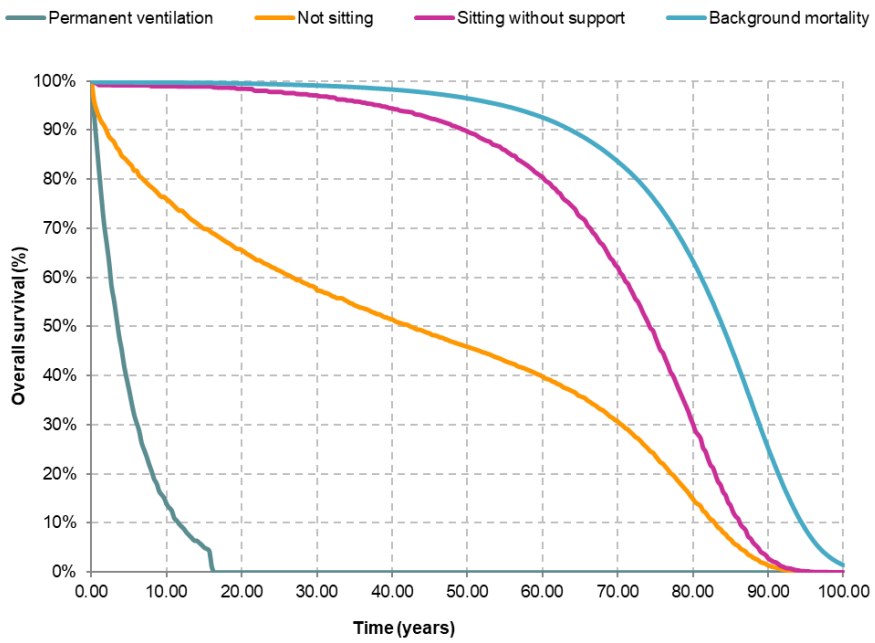
There is a paucity of long-term survival data for people who have received a disease modifying treatment for SMA. Furthermore, there is no comparative data to suggest that survival differs by treatment. Therefore, the same survival curves were used for nusinersen and BSC. Given that more severe health states progress to death faster than the less severe health state, extended life years, as a result of treatment,

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accumulated based on extended time in the less severe health states (e.g. standing and walking).

It was assumed that people with 2 copies of SMN2 will have the same overall survival as people with 3 copies. This was because the survival estimates for the 2-copy cohort presented in figure 15 of HST24 dipped below the overall survival of the permanent ventilation cohort. This did not seem clinically valid. Survival curves are presented in Figure 37.

Figure 37. Overall survival curves [35] for the presymptomatic model



B.3.3.1.6 Discontinuation

The MAA for nusinersen outlines criteria to determine whether people on active treatment with nusinersen would discontinue. These criteria were as follows:

"Where 1 scale has been measured: from baseline: total worsening in scale score corroborated by two consecutive measurements. A scaled equivalent of these losses would apply if a domain was unmeasurable / not suitable. For example, >2 points on horizontal kick or 1 point on other HINE scores excluding voluntary grasp; >4 points on the CHOP INTEND scale; >3 points on the RHS scale. These scores are derived from the minimal clinical indicators of difference. Where 2 (or more) scales have been measured from baseline: total worsening in scale score(s) in the absence of any stability or improvement in other scales corroborated by two consecutive

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measurements. A scaled equivalent of these losses would apply if a domain was unmeasurable / not suitable. For example, if a patient deteriorates on one scale (e.g. loses >3 points on the RHS scale) but maintains stability or demonstrates improvement on another scale that has been measured since baseline (e.g. RULM), AND in the opinion of the treating clinician the patient continues to receive clinical benefit from treatment then continuation of treatment may be considered. These cases should be discussed with the NHS England Clinical Panel: In order to allow for confirmation of worsening and not an 'off' assessment day if contractures develop or fracture occurs, then the unmeasurable domain of the scale is removed, and the delta change of remaining domains are scaled up to ensure the total achievable score of the scale remains. Permanent ventilation (≥16 hours/day for 21 consecutive days in the absence of acute reversible infection) or requirement of insertion of permanent tracheostomy. Inability to administer nusinersen by intrathecal administration because of spinal fusion surgery. All patients stop due to mortality. Therefore, it was assumed the proportion of the cohort that deteriorate from not sitting to permanent ventilation will automatically discontinue treatment.

The MAA was utilised to inform the discontinuation, for reasons other than permanent ventilation, for nusinersen. Therefore, this was utilised, as described below. It should be noted that only 5 pre-symptomatic patients were included in the MAA and, as such, there were insufficient data to estimate discontinuation rates for this population. This also means that separate discontinuation rate by SMN2 copy number were not available. As noted in Section B.3.9, the outputs from all three models indicate that the prognosis of the pre-symptomatic population is more similar to the type 2/3 population. This is because type 1 patients have much lower life years and QALYs then the other populations. Therefore, the discontinuation data for the type 2/3 population were applied in the pre-symptomatic model as it was judged this data would be most applicable to the pre-symptomatic population. More details on the discontinuation data for the type 2/3 population are provided in Section B.3.3.3. These probabilities were applied consistently to all cycles across the full model time horizon. Data on 'standing with support' were not available from the MAA and, therefore, the discontinuation data from the 'walking independently' health state were applied to patients in this health state.

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Table 46. Per-cycle probability discontinuation with nusinersen

Treatment discontinuation / loss of response	Total population
Per-cycle discontinuation in not sitting (%)	3.2%
Per-cycle discontinuation in sitting without support (%)	3.1%
Per-cycle discontinuation in standing with support (%)	1.0%
Per-cycle discontinuation in walking independently (%)	1.0%

After discontinuing treatment, it was assumed that the cohort was redistributed as per the BSC efficacy at the time point they discontinued and then incurred outcomes and costs specific to BSC.

B.3.3.2 Infantile-onset (type 1) Model

B.3.3.2.1 Baseline Characteristics

Baseline characteristics are presented in Table 47.

Table 47. Model baseline characteristics (informed by ENDEAR) [146]

Time point	Total population
Baseline population	
Total population of trial (N)	[redacted]
Baseline age (years, mean [SE])	[redacted]
Sex (female, %)	[redacted]
Baseline weight (kg, mean [SE])	[redacted]
Health state at baseline	
Not sitting (%)	100%
Sitting without support (%)	0%
Standing with support (%)	0%
Walking independently (%)	0%

*In the ENDEAR trial one patient (0.8%) was able to sit without support at baseline. This is a discrepancy in the data as, by definition, no type 1 patients should be able to sit without support if they are not receiving active treatment. Therefore, this patient was excluded from consideration and it was assumed 100% of patients were not sitting at baseline.

B.3.3.2.2 Nusinersen Effectiveness

The ENDEAR (NCT02193074) and SHINE (NCT02594124) clinical trials investigated the safety, efficacy and tolerability of nusinersen in 121 people with diagnosed type 1 SMA. Over the first 60 months, a combination of HINE-2 and WHO motor milestone achievement data was informed by patient-level data from ENDEAR and SHINE. This data was used directly in the model to capture the proportion of the

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cohort in each health state. The data reflects the highest motor milestones achieved in SHINE. A summary of the population from SHINE achieving each motor milestone is presented in Table 48 for the total type 1 population.

There was no long-term data available to inform the efficacy outcomes for nusinersen, after the SHINE follow-up. Therefore, the type 1 SMA model uses the same approach as the presymptomatic SMA model (Section B.3.3.1) to extrapolate the data over a lifetime horizon. A proportion of the type 1 population could have the ongoing capacity to achieve additional motor milestones. However, in the absence of data to prove additional gains in motor milestone following the trial follow-up, it was assumed that from 60 months in the model patients could only maintain their current milestone or decline. It was assumed that the cohort could decline by a maximum of one motor milestone per cycle. Over the course of a lifetime, a proportion of the cohort could lose several motor milestones, for example, declining from walking independently to standing with support, to sitting without support to not sitting.

Table 48. Achievement of WHO motor milestones for all nusinersen patients in ENDEAR and SHINE

Time point	Not Sitting	Sitting without support	Standing with support	Walking independently
Baseline				
Month 3				
Month 6				
Month 9				
Month 12				
Month 15				
Month 18				
Month 24				
Month 36				
Month 48				
Month 60				

The final analysis in ENDEAR (at 13 months) indicated that [redacted] out of [redacted] people receiving nusinersen ([redacted]) did not experience a motor milestone response. Alternatively, in the control arm [redacted] of the cohort did not experience a response, as defined by improvement in at least one category of HINE-2 (i.e., an increase in the score for head control, rolling, sitting, crawling, standing, or walking of ≥1 point, an increase in the score for kicking of ≥2 points, or achievement of the maximal score

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for kicking) and more categories with improvement than categories with worsening (i.e., a decrease in the score for head control, rolling, sitting, crawling, standing, or walking of ≥1 point or a decrease in the score for kicking of ≥2 points).

Patients were evaluated in seven of the eight categories of the HINE-2 (excluding voluntary grasp): i.e. kicking, head control, rolling, sitting, crawling, standing, and walking. These estimates were used to estimate the relative efficacy of nusinersen versus BSC, as measured by a relative risk of [redacted]. It was assumed that this difference in efficacy would remain constant for the remainder of the model time horizon. Therefore, this relative risk was applied to the probability of decline values that were estimated for BSC (more details below), to estimate probabilities for the nusinersen cohort, and these probabilities were then applied to all cycles in the model from month 60 onwards (i.e. the first cycle after the follow-up period for SHINE ended). Given that this relative risk was calculated using data for improvement of motor milestones, it is more reflective of the decline and maintenance of motor milestones, rather than only decline. Therefore, this is potentially a conservative estimate. The values for nusinersen are presented in Table 49.

Table 49. Per cycle probability of decline for nusinersen

Health state	Year after which people decline	Per cycle probability of decline (%)
Sitting without support to not sitting	5.00	0.3%
Standing with support to sitting without support	5.00	0.6%
Walking independently to standing with support	5.00	0.7%

B.3.3.2.3 Best Supportive Care Effectiveness

In total, 41 of the 121 patients in the ENDEAR clinical trial received a sham procedure. This control arm was chosen because, at the time of the design of the clinical trial, no disease-modifying therapies were approved or routinely used in SMA. Outcomes from the control arm were considered to be equivalent to best-supportive care and this was validated by clinical experts at the advisory board. Therefore, patient-level data from ENDEAR from the sham arm were used to capture the proportion of the BSC cohort in each health state over the first 12 months of the

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model time horizon (reflects the maximum follow-up period for sham arm patients within ENDEAR). It should be noted that data were available up to 13 months in ENDEAR for sham control and the data for the 13-month follow-up were applied at month 12 in the model. As per the definition of type 1 SMA, BSC patients never achieved the ability to sit without support.

Table 50. Achievement of WHO motor milestones for BSC patients in ENDEAR

Time point	Not Sitting	Sitting without support	Standing with support	Walking independently
Baseline	[redacted]	[redacted]	[redacted]	[redacted]
Month 6	[redacted]	[redacted]	[redacted]	[redacted]
Month 9	[redacted]	[redacted]	[redacted]	[redacted]
Month 12	[redacted]	[redacted]	[redacted]	[redacted]

The probability of decline per cycle was derived for BSC based on data reported by Wadman et al,. This study reported the following information:

- The proportion of the natural history cohort that achieved a specific motor milestone and the mean age that this milestone was achieved.
- For those that achieved this milestone, the proportion that subsequently declined to the previous milestone and the mean age of this loss.

Therefore, the proportion of the overall cohort that experienced a decline and the number of cycles (i.e. 4-months) between the two mean ages was used to estimate the probability of declining one milestone per cycle. It was assumed that the decrease started as soon the milestone was achieved and that it occurred at a linear rate in each 4 monthly cycle. Separate probabilities were calculated for each health state in the model and these are summarised in Table 51.

It should be noted that [redacted] of patients in the control arm of ENDEAR remained in the 'not sitting' health state as [redacted] achieved any motor milestones during the 13-month follow-up. Therefore, the data from the Wadman study did not actually affect the outcomes of BSC patients in the model, as they could not decline to a worse health state (except for permanent ventilation but transitions to this health state were informed separately – more details below). However, the data reported in Table 51 did impact the probability of decline values for nusinersen, as described above.

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Table 51. Per-cycle probability of decline for BSC [35]

Health state	Year after which people decline	Per cycle probability of decline (%)
Sitting without support to not sitting	1.00	0.7%
Standing with support to sitting without support	1.00	1.3%
Walking independently to standing with support	1.00	1.5%

B.3.3.2.4 Survival

The cohort with type 1 SMA could transition to 'death' from any health state. For people in either the 'permanent ventilation', 'no sitting' and 'sitting without support' health states, patient-level data from ENDEAR and SHINE was utilised to inform the time to all-cause mortality. This was defined as time from the date of randomisation to the date of death due to any cause, censored at the last date known alive reported in ENDEAR and SHINE.

As described previously, patients in the sham arm of the ENDEAR study were switched to nusinersen at the start of the SHINE study. Therefore, to inform the ITT dataset used to model the survival for the nusinersen arm in ENDEAR and SHINE, rank preserving structural failure time models (RPSFTM) were required to adjust for this treatment switching in the SHINE clinical trials [147]. This method was chosen in line with NICE recommendations (TSD16).

RPSFTM works by estimating a causal effect of the treatment in order to derive counterfactual survival times that are independent of treatment. The method does not depend on the assumption that adjustments have been made for all possible confounders and that there are no unmeasured confounds which could influence the outcome. Instead, the RPSFTM method assumes a common treatment effect, that is, the treatment effect is the same for all patients independent of when treatment was received. Due to the limited amount of data available at baseline for all patients (i.e. unlikely to capture all observable confounders) and because patient crossover was independent of disease progression (i.e. a common treatment effect can be assumed as patients did not switch treatments due to disease state), the RPSFTM was chosen as the most appropriate method of adjusting survival outcomes due to treatment switching.

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The RPSFTM method is designed to estimate what would have happened to participants in the trial if they had not switched treatments. It attempts to preserve the rank order of event times for participants who switched treatments and allows the estimation of counterfactual outcomes, which can be combined with the observed data. RPSFTM was conducted to generate time-to-event estimates using covariables age, sex and treatment arm. The new survival times for the control arm (which switched treatments) were then combined with the observed treatment arm (who remained on the same treatment throughout the study) as part of the parametric time-to-event analysis to allow extrapolation beyond the end of the trial.

No imputation was conducted for missing observations other than the censoring of incomplete observations. The resulting Kaplan Meier curve is presented in Figure 38.

Figure 38. Kaplan-Meier curve for overall survival



In line with guidelines outlined NICE TSD 14[148] a parametric survival analysis of IPD OS data was used to extrapolate data over the model time horizon. A range of six conventional parametric functions were utilised for the analysis, and models controlling for age, sex and treatment arm. The proportional hazards assumptions were met for all covariables and therefore a single parametric survival model was used (i.e. treatment arms were not modelled independently).

The resulting survival curves are presented in Figure 39. Goodness-of-fit statistics, namely the Akaike information criterion (AIC) and the Bayes information criterion (BIC), were calculated to understand which parametric curve best fits the observed data. Parametric curves were also assessed visually to determine their fit to the Kaplan-Meier curve and the clinical plausibility of the long-term extrapolations. The AIC and BIC, presented in Table 52, determined that the Gompertz curve is the best

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fitting to the available data. However, when looking at the long-term extrapolation, the Gompertz curve lacks plausibility due to the very long tail that can be observed in Figure 40 for nusinersen and Figure 41 for BSC. When not bound by overall survival, 50% of the BSC population survive to age 80. When bound by overall survival 19% of the BSC population survive to age 80. Given that the prognosis for type 1 SMA is 2-years to death or permanent ventilation (outlined in Table 3), this is not clinically plausible.

To further validate the choice of survival curve, clinical experts were consulted. They concluded that, out of the exponential, Weibull, Gompertz, log-logistic or log-normal (note that the generalised gamma failed to converge), the Weibull parametric curve was the best approximation of long-term clinical practice. Therefore, the Weibull distribution was selected for the base case analysis in the economic model.

When implemented in the model, the Weibull parametric curve was bounded by general population mortality [144], to ensure that the life expectancy did not exceed that of the general population. This was done by selecting the highest instantaneous hazard between the two curves. When compared with the general population, it was assumed that there is no increased risk of mortality for people who achieve the ‘standing with support' and ‘walking independently’ motor milestones. Therefore, the proportion of the cohort moving to the death health state at any point in time from these health states was informed by general population mortality data.

There is a paucity of long-term survival data for people who have received a disease modifying treatment for SMA. Furthermore, there is no available comparative data to suggest that survival differs by treatment. Therefore, the same survival curves were used for nusinersen and all model comparators. Given that it is expected that the more severe health states progress to death faster than the less severe health state, extended live years, as a result of treatment, accumulated based on extended time in the less severe health states (e.g. standing and walking). The survival curves utilised in the model are presented in Figure 42.

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Figure 39. Parametric survival curves for the type 1 SMA model



Table 52. Goodness of fit statistics for survival

	AIC	BIC
Exponential	[redacted]	[redacted]
Weibull	[redacted]	[redacted]
Gompertz	[redacted]	[redacted]
Log-normal	[redacted]	[redacted]
Log-logistic	[redacted]	[redacted]
Generalised gamma	N/A	N/A

Figure 40. Long-term extrapolation of parametric survival curves for the type 1 SMA model (nusinersen arm)



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Figure 41. Long-term extrapolation of parametric survival curves for the type 1 SMA model (BSC arm)



Figure 42. Overall survival curves (using the Weibull distribution) for the type 1 SMA model



B.3.3.2.5 Permanent ventilation

It was assumed that the cohort with type 1 SMA could transition to 'permanent ventilation' from the 'not sitting' health state only. The proportion of the cohort moving to the permanent ventilation from the nusinersen and the BSC cohort were informed by independent parametric survival analysis, with no covariables controlled for, on the ITT dataset over the follow-up period in ENDEAR and SHINE. A joint model was not possible because the treatment effect violated the proportional

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hazards assumption. In line with NICE guidelines, curves were modelled independently. Time-to-permanent ventilation data was calculated from either:

- Study enrolment date to the date of permanent ventilation.
- Study enrolment date to the date the person was last alive.

Therefore, the time-to-permanent ventilation curve considered death as a censoring event, so the data represents only time-to-permanent ventilation rather than time-to-permanent ventilation or death. As per the overall survival curves, no imputation was conducted for missing observations other than the censoring of incomplete observations. The resulting Kaplan Meier curve is presented in Figure 43 and the survival curves are presented in Figure 46.

The AIC and BIC, presented in Table 53, determined that the generalised gamma and Gompertz curves were the best fitting for nusinersen, and the log-normal or exponential curves were the best fitting for BSC. Conversely, clinical experts agreed that log-normal curve for nusinersen and the log-logistic distribution for BSC were the most plausible. These distributions were utilised in the base case analysis.

The methods used in the analysis adhered to guidance outlined in NICE TSD 14 and the methods outlined for OS.

Figure 43. Kaplan-Meier curve for permanent ventilation



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Figure 44. Time-to-permanent ventilation survival curves for nusinersen



Figure 45. Time-to-permanent ventilation survival curves for BSC



Table 53. Goodness of fit statistics for permanent ventilation

	Nusinersen		BSC	
	AIC	BIC	AIC	BIC
Exponential	[redacted]	[redacted]	[redacted]	[redacted]
Weibull	[redacted]	[redacted]	[redacted]	[redacted]
Gompertz	[redacted]	[redacted]	[redacted]	[redacted]
Log-normal	[redacted]	[redacted]	[redacted]	[redacted]
Log-logistic	[redacted]	[redacted]	[redacted]	[redacted]
Generalised gamma	[redacted]	[redacted]	[redacted]	[redacted]

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Figure 46. Permanent ventilation curves for the type 1 SMA model



B.3.3.2.6 Discontinuation

The per-cycle probability of discontinuation for nusinersen for the type 1 model, as determined by data from the MAA, are presented in Table 54. During the MAA, 44 people out of a total cohort of 81 discontinuing from nusinersen over a 3.5-year period. However, of those that discontinued, 32 patients switched to onasemnogene, which only became available to the UK SMA population during the period of the MAA analysis. In the future, it is expected that patients who are eligible for onasemnogene and would have the option to receive this treatment prior to initiating nusinersen. Therefore, a high rate of switching from nusinersen to onasemnogene is not expected, which indicates the MAA data is not reflective of the true nusinersen discontinuation rates experienced in clinical practice. For this reason, it has been assumed that all patients who switched to onasemnogene during the MAA would have remained on nusinersen if the gene therapy had not become available during the course of the MAA study. The discontinuation data in the model are based on those patients that stopped treatment as they were unable to receive nusinersen safely and due to scoliosis issues.

Based on this assumption, 14.81% (12/81) of nusinersen patients discontinued over the 3.5-year period of the MAA and this was converted to a 4-month probability of 1.5% to align with the model cycle length. This probability was assumed to remain constant and, thus, was applied to all cycles in the model.

For the Type 1 population, discontinuation data were not presented by motor milestone attainment. Therefore, it was assumed that the data from the MAA were applicable to the ‘not sitting’ and ‘sitting without support’ health states. This is

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because no type 1 patients achieved the ability to stand or walk during the MAA, which is a reflection of the short follow-up period of the study. If the type 1 population are able to stand or walk due to nusinersen then the treatment will have been highly effective, given the natural history of the disease. Therefore, it is expected that the rate of discontinuation will be low for these two health states in the model. To reflect this expected low rate of discontinuation, an assumed probability of discontinuation of 1% per cycle was applied to these two health states.

Table 54. Per-cycle probability of discontinuation

Treatment discontinuation / loss of response	Total population
Per-cycle discontinuation in not sitting (%)	1.5%
Per-cycle discontinuation in sitting without support (%)	1.5%
Per-cycle discontinuation in standing with support (%)	1.0%
Per-cycle discontinuation in walking independently (%)	1.0%

B.3.3.3 Later-onset (type 2 and 3) Model

B.3.3.3.1 Baseline Characteristics

CHERISH and SHINE were predominantly comprised of a type 2 population. While there were some type 3 patients included (as evident by those who achieved walking independently), clinical experts advised that the data included in CHERISH and SHINE did not adequately reflect a type 3 population. Therefore, the model utilised CHERISH and SHINE data to accurately model a sub-population of people with type 2 SMA. Robust, real-world evidence and informed assumptions were used to inform a sub-population of people with type 3 SMA. An overall population was also incorporated into the model, that combined these two sub-populations.

Baseline characteristics utilised in the model are presented in Table 55 for the population with later-onset (types 2 and 3) SMA and two sub-populations. The baseline characteristics for the sub-population with type 2 SMA was informed by the CHERISH clinical trial[124]. The baseline population characteristics sub-population with type 3 SMA was informed by baseline data from a natural history study conducted by Wadman et al[35]. Given that the clinical definition of type 3 SMA is “acquire autonomous ambulation" or “walkers”, it was assumed that 100% of the cohort with

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type 3 SMA were walking at baseline. The total population of later-onset SMA was informed by a mean over the two sub-populations.

Table 55. Model baseline characteristics for the later-onset model

Time point	Total later-onset SMA	Type 2 SMA*	Type 3 SMA**
Baseline population			
Total population of trial (N)	[redacted]	[redacted]	[redacted]
Baseline age (years, mean [SE])	[redacted]	[redacted]	[redacted]
Sex (female, %)	[redacted]	[redacted]	[redacted]
Baseline weight (kg, mean [SE])	[redacted]	[redacted]	[redacted]
Health state at baseline			
Not sitting (%)	[redacted]	[redacted]	[redacted]
Sitting without support (%)	[redacted]	[redacted]	[redacted]
Standing with support (%)	[redacted]	[redacted]	[redacted]
Walking independently (%)	[redacted]	[redacted]	[redacted]

*Based on the baseline characteristics of all nusinersen and control patients in the CHERISH study

**Informed by baseline data from the natural history study reported by Wadman et al.

B.3.3.3.2 Nusinersen Effectiveness

As mentioned above, the effectiveness data for CHERISH and SHINE was used to inform the sub-population with type 2 SMA. Over the first 96 months, WHO motor milestone achievement data was informed by patient-level data from CHERISH and SHINE. This data was used directly in the model to capture the proportion of the cohort in each health state (see Table 56). The data reflects the highest WHO motor milestones achieved in SHINE.

Clinical experts advised that the patients enrolled in the CHERISH trial were indicative of a type 2 population. Therefore, as described in the previous section, the nusinersen data from CHERISH and SHINE were applied to the type 2 sub-population only. However, as presented in Section B.3.3.3.3, a small number of sham control patients (which represents BSC) were able to walk by the end of the trial follow-up. Based on the standard definition for SMA, type 2 patients following natural history (i.e. no active treatment) should not be able to walk. Therefore, to incorporate the data from CHERISH and SHINE into the model for the type 2 sub-population, it was assumed that all BSC patients in the 'walking independently' health state should be defined as 'standing with support' and were allocated accordingly. To avoid biasing the model in favour of nusinersen, the same

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assumption was also applied to the nusinersen data. However, this is a conservative assumption as it is feasible for type 2 patients to achieve the ability to walk if they are administered an active treatment early enough.

For the sub-population with type 3 SMA, it was assumed that the motor milestone achieved at baseline (everyone walking) was maintained throughout the horizon of the SHINE clinical trial. While it is expected that, without treatment, a person with type 3 SMA will lose the ability to walk, Wadman et al found people with type 3 SMA lost the ability to walk at a mean age of 11 years and 34 years for type 3A and 3B respectively[35]. Therefore, it was judged reasonable that all type 3 people would maintain the ability to walk over the first 96 months of the model time horizon. The total population was calculated using the mean of the two sub-populations.

Table 56. Achievement of WHO motor milestones for all nusinersen patients in CHERISH and SHINE

Time point	Not Sitting	Sitting without support	Standing with support	Walking independently
Baseline	[redacted]	[redacted]	[redacted]	[redacted]
Month 6	[redacted]	[redacted]	[redacted]	[redacted]
Month 9	[redacted]	[redacted]	[redacted]	[redacted]
Month 12	[redacted]	[redacted]	[redacted]	[redacted]
Month 15	[redacted]	[redacted]	[redacted]	[redacted]
Month 18	[redacted]	[redacted]	[redacted]	[redacted]
Month 24	[redacted]	[redacted]	[redacted]	[redacted]
Month 36	[redacted]	[redacted]	[redacted]	[redacted]
Month 48	[redacted]	[redacted]	[redacted]	[redacted]
Month 60	[redacted]	[redacted]	[redacted]	[redacted]
Month 72	[redacted]	[redacted]	[redacted]	[redacted]
Month 84	[redacted]	[redacted]	[redacted]	[redacted]
Month 96	[redacted]	[redacted]	[redacted]	[redacted]

*Includes patients who were reported as walking independently but were reallocated to meet the definition for type 2 SMA.

There was no long-term data available to inform the efficacy outcomes of the cohort on nusinersen beyond the follow-up period of SHINE (month 96). Therefore, the later-onset SMA model uses the same approach as the presymptomatic and type 1 SMA models (Section B.3.3.1 and Section B.3.3.2 respectively) to extrapolate the data over a lifetime horizon. Therefore, the model cohort was able to decline by a maximum of one milestone per cycle or by multiple milestones over their lifetime.

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This adheres to what clinical experts observe in clinical practice, whereby it is possible for a person to decline from ‘walking independently’ to ‘standing with support’ and, in a later cycle, the same person could decline from ‘standing with support’ to ‘sitting without support’ and beyond.

For the total population and each sub-population, the probability of decline per cycle was derived for BSC by Wadman et al [35] using the same methods as outlined for the presymptomatic and type 1 SMA models (Section B.3.3.1 and Section B.3.3.2 respectively).

The probability of decline with nusinersen was estimated by applying a relative risk of [redacted] to the probabilities for BSC, which are described below. The values for nusinersen are presented in Table 57. These were based on the final analysis in CHERISH (at month 15) and the outcome of the proportion of people who gained at least one WHO motor milestone. In total [redacted] and [redacted] of people on nusinersen and BSC, respectively, achieved this outcome. Therefore, an odds ratio of [redacted] was estimated ([redacted]). A relative risk of improvement ([redacted]) was derived and converted into a relative risk of maintenance or decline. This was assumed to be equivalent across all populations.

It was assumed that the rate of decline would start at the point in which the available clinical trial data for nusinersen ended. Therefore, the probability of decline was applied for all cycles in the model from 8 years onwards.

Table 57. Per-cycle probability of decline for nusinersen

Health state	Per cycle probability of decline (%)		
	Total later-onset SMA	Type 2 SMA	Type 3 SMA
Sitting without support to not sitting	[redacted]	[redacted]	[redacted]
Standing with support to sitting without support	[redacted]	[redacted]	[redacted]
Walking independently to standing with support	[redacted]	[redacted]	[redacted]

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B.3.3.3.3 Best supportive Care Effectiveness

In total, 42 of the 126 patients in the CHERISH clinical trial received a sham procedure. This control arm was chosen because, at the time of the design of the clinical trial, no disease-modifying therapies were approved or routinely used in SMA. Outcomes from the control arm were considered to be equivalent to best-supportive care.

Therefore, patient-level data from CHERISH for the sham arm were used to capture the proportion of the BSC cohort in each health state over the first 15 months of the model time horizon. A summary of the population from CHERISH achieving each WHO milestone included in the model is presented in Table 58 for the total population.

Table 58. Achievement of WHO motor milestones for BSC patients in CHERISH

Time point	Not Sitting	Sitting without support	Standing with support	Walking independently
Baseline	[redacted]	[redacted]	[redacted]	[redacted]
Month 6	[redacted]	[redacted]	[redacted]	[redacted]
Month 9	[redacted]	[redacted]	[redacted]	[redacted]
Month 12	[redacted]	[redacted]	[redacted]	[redacted]
Month 15	[redacted]	[redacted]	[redacted]	[redacted]

*Includes patients who were reported as walking independently but were reallocated to meet the definition for type 2 SMA.

There was no long-term data available to inform the efficacy outcomes of the BSC cohort from CHERISH and SHINE. Therefore, as described above for the nusinersen cohort, a rate of decline was included for all subsequent cycles in the model to reflect a potential loss of motor milestone as the cohort ages. Additionally, the cohort was able to decline multiple milestones over their lifetime, instead of just one as was included in the presymptomatic and type 1 models.

The probability of decline per cycle is presented in Table 59 for the total population (average over type 2 and 3) and each sub-population, with the values derived for BSC by Wadman et al, as outlined in Section B.3.3.1. It was assumed that the rate of decline would start at the point in which the available clinical trial data for BSC

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ended. Therefore, the probability of decline was applied for all cycles in the model from 15 months onwards.

Table 59. Per-cycle probability of decline for BSC [35]

Health state	Per cycle probability of decline (%)		
	Total later-onset SMA	Type 2 SMA	Type 3 SMA
Sitting without support to not sitting	0.7%	1.2%	0.2%
Standing with support to sitting without support	1.3%	2.2%	0.9%
Walking independently to standing with support	1.5%	1.5%	1.5%

B.3.3.3.4 Overall Survival

The cohort with later-onset SMA can transition to the 'death' state from any health state. Therefore, health state-dependent mortality data was incorporated into the model.

During the nusinersen clinical trials for later-onset SMA, [redacted], which means mortality data from the trials were too immature for use in the models. Instead, health state specific survival was modelled using survival curves equivalent to those utilised in the presymptomatic model. Using this data was considered to be appropriate for the 'not sitting' and 'sitting without support' health states as, the original source was a large, Dutch, natural history study conducted by Wijngaarde et al, 2020 [143]. A gamma distribution was fitted to data on 32 people with type 1c SMA in HST24 to inform the OS for the 'not sitting' health state. This corresponds with the clinical definition of type 1 SMA.

For the 'sitting without support' health state, HST24 fit an exponential distribution to data from patients in the Wijngaarde et al study with type 2a and type 2b, pooled with Dutch lifetables [143]. A hazard ratio was applied to ensure the data reflected England and Wales setting. This corresponds with the clinical definition of type 2 SMA being 'sitters'.

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As per the presymptomatic and type 1 model, people achieving 'standing with support' or 'walking independently' were assumed to have overall survival equivalent to the general population. While people with type 2 or 3 SMA may incur different survival outcomes for different health states, clinical experts found the survival curves and their estimates long-term estimates to be appropriate for both populations. Please see Section B.3.3 for the survival curves used in the model.

B.3.3.3.5 Discontinuation

The per-cycle probability of discontinuation for nusinersen for the type 2/3 model, as determined by data from the MAA, are presented in Table 60. These were based on the following numbers of patients discontinuing from each health state during the MAA over a 3.5 year period:

- 6 out of 21 patients who could not sit discontinued (28.6%).
- 22 out of 88 patients who could sit without support discontinued (28.41%).
- 3 out of 30 patients who walk independently discontinued (10%).
- No data were available for patients who could stand and, therefore, the discontinuation rate for walkers was applied to this health state (10%).

These rates over the 3.5 year period of the MAA were converted to a 4-month probability to align with the model cycle length. These probabilities were assumed to remain constant and, thus, were applied to all cycles in the model. For this model, equivalent values were applied to the Type 2 and Type 3 sub-populations.

Table 60. Per-cycle probability of discontinuation

Treatment discontinuation / loss of response	Total population
Per-cycle discontinuation in not sitting (%)	3.2%
Per-cycle discontinuation in sitting without support (%)	3.1%
Per-cycle discontinuation in standing with support (%)	1.0%
Per-cycle discontinuation in walking independently (%)	1.0%

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B.3.4 Measurement and valuation of health effects

B.3.4.1 Health-related quality-of-life data from clinical trials

PedsQL health-related quality-of-life (HRQoL) data, collected in the CHERISH trial, was mapped to EQ-5D utility values. These were utilised in the previous NICE appraisal for nusinersen (TA588). However, this approach was strongly criticised by the EAG who concluded that the mapped utility values had poor face validity, a conclusion that was shared by clinical advisors to the EAG. Due to the issues with the mapped data from CHERISH, the EAG adopted alternative utility data taken from a vignette study [125] in their preferred analysis. This study was also the preference of the EAG for the NICE appraisal for risdiplam (TA755). Given the reservations of the EAG during the previous nusinersen appraisal, the PedsQL HRQoL data, collected in the nusinersen clinical trials, was not utilised in the current appraisal.

B.3.4.2 Mapping

No mapping was completed for the current appraisal.

B.3.4.3 Health-related quality-of-life studies

The primary studies identified following the systematic searches for relevant health-related quality-of-life data, and the utility values reported for each study, are summarized in Table 61. In total, 17 primary studies were identified from the systematic search. Of these studies, only 3 reported utility values for the health states that were included in the economic models. These studies have been briefly summarized below. The full report from the utility SLR is provided in Appendix G.

Hu 2022 [149]: reported utilities for Type 1 SMA based on vignettes developed for 10 paediatric neurologists and Type 2/3 SMA based on a mixed cohort of 112 patients and 301 caregivers. Within the Type 2/3 population, data were collected using the EQ-5D-Y-3L, EQ-5D-3L and CHU9D. The results of the study indicated that the achievement of motor milestones was associated with an increase in utility. For example, based on the EQ-5D-3L data, utility increased from 0.30 for those “not sitting” to 0.83 for those “walking unsupported”. All data were collected based on a Chinese cohort, and using Chinese values sets. Therefore, the data were not incorporated into the current economic models due to generalizability issues.

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Sutherland 2022 [150]: presented a conference abstract that reported data from a prospective natural history study of 81 people with untreated SMA (perspective unknown). Data were reported based on the Health Utility Index Mark 2 (HUI-2). The study identified a positive association between the achievement of motor milestones and utility with values increasing from 0.49 for “non-sitters” to 0.84 for “walkers”. As the utility data were not reported based on the EQ-5D, which is a requirement of the NICE reference case, the data were not incorporated into the current economic models.

Lloyd 2019 [125]: developed a series of case studies that described the impact of Type 1 and Type 2 SMA and these case studies were then used by 5 clinical experts (with knowledge of SMA) to estimate utilities using the EQ-5D-Y and PedsQL-NMM. The outputs from this analysis were utilized in both of the previous NICE appraisals for nusinersen [TA588] and risdiplam [TA755]. However, in both appraisals, the EAGs noted that there were major limitations associated with the data reported by Lloyd et al. In particular, it was noted that the values lacked face validity, such as negative utilities being presented. Due to the plausibility issues associated with the data from Lloyd et al, the EAG in both previous appraisals adopted utilities that were obtained from the EAG’s clinical advisors during TA588, using non-preference-based methods. As the utilities from Lloyd et al have been judged to be not plausible by two previous EAGs they were also excluded from consideration for the current economic models.

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Table 61. Utility values for patients with SMA identified in the literature

Study ID	Perspective	Population	Tool / tariff	Health state	Mean Utility	Measure of uncertainty
Australia						
Chambers 2020 [63]	Patient (if over 8) carers as proxy if under 8	Type 1 SMA (n=4)	EQ-5D-3L-Y using EQ-5D-3L Australian valuation weights	NR	0.104	SD: 0.278
		Type 2 SMA (n=26)			0.067	SD: 0.158
		Type 3 SMA (n=10)			0.252	SD: 0.332
		Type 1 to 3 SMA (n=40)			0.115	SD: 0.227
Belgium						
Dangouloff 2023 [151]	Patients and carers	Patients with SMA (n=149)	EQ-5D-5L using Belgium value set and EQ-5D-Y using the same set after conversion to 5L data	Not identified by symptoms & 2 copies	1	NA
				Treated 2 copies of SMN2	0.34	NA
				Treated and 3 copies of SMN2	0.45	NA
				Treated and 4 copies of SMN2	0.7	NA
				Treated symptomatic patients	0.52	NA
				Untreated and 3 copies of SMN2	0.43	NA
				Untreated and 4 copies of SMN2	0.34	NA
				Untreated	0.4	NA
			HUI2 (no other detail provided)	Not identified by symptoms & 2 copies	1	NA
				Not identified by symptoms & 3 copies	0.97	NA
				Treated and 2 copies of SMN2	0.47	NA
				Treated and 3 copies of SMN2	0.51	NA
				Treated and 4 copies of SMN2	0.79	NA
				Treated symptomatic patients	0.52	NA
				Untreated and 2 copies of SMN2	0.42	NA
				Untreated and 3 copies of SMN2	0.52	NA
				Untreated and 4 copies of SMN2	0.69	NA
				Untreated symptomatic patients	0.54	NA
			HUI3 (no other detail provided)	Not identified by symptoms & 2 copies	1	NA
				Not identified by symptoms & 3 copies	0.96	NA
				Patients not identified by symptoms	1	NA
				Treated and 2 copies of SMN2	0.19	NA
				Treated and 3 copies of SMN2	0.19	NA
				Treated and 4 copies of SMN2	0.74	NA
				Treated symptomatic patients	0.26	NA
				Untreated and 2 copies of SMN2	0.12	NA
				Untreated and 3 copies of SMN2	0.22	NA

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Study ID	Perspective	Population	Tool / tariff	Health state	Mean Utility	Measure of uncertainty
				Untreated and 4 copies of SMN2	0.42	NA
				Untreated symptomatic patients	0.28	NA
Canada						
McMillan 2021 [51]	Patient	SMA (n=965)	EQ-5D-5L using a Canadian value set	SMA	0.49	SD: 0.26
		Type 1 SMA (n=241)			0.32	SD: 0.25
		Type 2 SMA (n=399)			0.46	SD: 0.23
		Type 3 SMA (n=283)			0.65	SD: 0.21
China						
Hu 2022 [149]	Clinician based on vignettes	Type 1 SMA (n=10)	EQ-5D-Y-3L Chinese version using EQ-5D-3L Chinese value set	PAV	0.19	0.06
				Non-sitters	0.29	0.08
				Sitting	0.39	0.19
				Standing	0.6	0.21
				Walking	0.72	0.21
	Patients and carers	Type 2 to 3 SMA under 16 (n=88)		Not sitting	Mean: 0.33 Median: 0.32	SD: 0.07 IQR: 0.04
				Sitting supported	Mean: 0.37 Median: 0.36	SD: 0.09 IQR: 0.06
				Sitting unsupported	Mean: 0.39 Median: 0.36	SD: 0.10 IQR: 0.06
				Standing supported	Mean: 0.47 Median: 0.39	SD: 0.18 IQR: 0.25
				Standing unsupported	Mean: 0.50 Median: 0.40	SD: 0.17 IQR: 0.26
				Walking supported	Mean: 0.53 Median: 0.46	SD: 0.18 IQR: 0.26
				Walking unsupported	Mean: 0.82 Median: 0.85	SD: 0.16 IQR: 0.14
				Overall	Mean: 0.49 Median: 0.39	SD: 0.21 IQR: 0.30
		Type 2 to 3 SMA over 16 (n=125)	EQ-5D-3L using Chinese value set	Not sitting	Mean: 0.30 Median: 0.32	SD: 0.71 IQR: 0.06
				Sitting supported	Mean: 0.42 Median: 0.35	SD: 0.17 IQR: 0.26
				Sitting unsupported	Mean: 0.46 Median: 0.38	SD: 0.16 IQR: 0.28
				Standing supported	Mean: 0.46 Median: 0.39	SD: 0.13 IQR: 0.24

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Study ID	Perspective	Population	Tool / tariff	Health state	Mean Utility	Measure of uncertainty
				Standing unsupported	Mean: 0.52 Median: 0.57	SD: 0.11 IQR: 0.21
				Walking supported	Mean: 0.70 Median: 0.70	SD: 0.11 IQR: 0.24
				Walking unsupported	Mean: 0.83 Median: 0.85	SD: 0.14 IQR: 0.14
				Overall	Mean: 0.56 Median: 0.57	SD: 0.24 IQR: 0.46
		Type 2 to 3 SMA under 16 (n=288)	CHU9D China value set	Not sitting	Mean: 0.46 Median: 0.45	SD: 0.22 IQR: 0.36
				Sitting supported	Mean: 0.55 Median: 0.55	SD: 0.21 IQR: 0.33
				Sitting unsupported	Mean: 0.61 Median: 0.62	SD: 0.20 IQR: 0.31
				Standing supported	Mean: 0.65 Median: 0.71	SD: 0.20 IQR: 0.32
				Standing unsupported	Mean: 0.65 Median: 0.70	SD: 0.22 IQR: 0.28
				Walking supported	Mean: 0.70 Median: 0.60	SD: 0.21 IQR: 0.22
				Walking unsupported	Mean: 0.75 Median: 0.82	SD: 0.18 IQR: 0.23
				Overall	Mean: 0.62 Median: 0.66	SD: 0.21 IQR: 0.33
Xu 2023 [152]	Carers	Patients with Type 2 to 4 SMA (n=228)	EQ-5D-5L using Chinese weighting	SMA	0.18 Median: 0.45	SD: 0.31 Range: -0.39 to 1
				Swallowing problems	0.02	SD: 0.17
				No swallowing problems	0.15	SD: 0.27
				Breathing difficulties	-0.02	SD: -0.24
				No breathing difficulties	0.16	SD: 0.33
				Sleep disorder	0.02	SD: 0.23
				No sleep disorder	0.15	SD: 0.31
				Floppy or weak arms and legs	0.02	SD: 0.31
				No floppy or weak arms and legs	0.42	SD: 0.29
				Twitching or shaking muscles	0.08	SD: 0.33
				No twitching or shaking muscles	0.25	SD: 0.27
				Difficulty walking	0.09	SD: 0.31
				No difficulty walking	0.31	SD: 0.29
				Bone and joint problems	0.04	SD: 0.18
				No bone and joint problems	0.39	SD: 0.33

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Study ID	Perspective	Population	Tool / tariff	Health state	Mean Utility	Measure of uncertainty
				Difficulty sitting up	0.03	SD: 0.15
				No difficulty sitting up	0.27	SD: 0.34
				Difficulty crawling	0.05	SD: 0.16
				No difficulty crawling	0.35	SD: 0.35
				Depression/anxiety	0.02	SD: 0.23
				No depression/anxiety	0.15	SD : 0.32
				Family registry - urban	0.47	SD: 0.37
				Family registry - rural	0.43	SD: 0.35
France						
Pena Longobardo 2020 [52]	Patient (unclear who completed)	SMA (n=27)	EQ-5D-3L using TTO social tariff	SMA	0.116	0.285
Germany						
Heinrich 2023 [153]	Patient	SMA (n=37)	EQ-5D-3L using German value set	Adults with SMA ("mostly later onset")	0.39	NR
Pena Longobardo 2020 [52]	Patient (unclear who completed)	SMA (n=25)	EQ-5D-3L using TTO social tariff	SMA	0.532	0.335
Wohnrade [154]	Patient (patient only group)	Type 2 to 4 SMA (n=22)	EQ-5D-5L	Type 2 to 4 SMA	Median: 0.469	Range: 0.031 to 0.918
		Type 2 to 4 SMA (n=11)	EQ-5D-5L	Type 2 to 4 SMA - EQ-5D-5L Index Value >0.679	Median: 0.806	Range: 0.679 to 0.918
		Type 2 to 4 SMA (n=11)	EQ-5D-5L	Type 2 to 4 SMA - EQ-5D-5L Index Value <0.259	Median: 0.175	Range: 0.031 to 0.259
	Patient (patient/ caregiver matched group)	Type 2 to 4 SMA (n=28)	EQ-5D-5L	Type 2 to 4 SMA	Median: 0.208	Range: -0.018 to 1
		Type 2 to 4 SMA (n=NR)	EQ-5D-5L	Type 2 to 4 SMA - low caregiver burden (ZBI<24)	Median: 0.175	Range: -0.018 to 1
		Type 2 to 4 SMA (n=NR)	EQ-5D-5L	Type 2 to 4 SMA - high caregiver burden (ZBI >=24)	Median: 0.241	Range: 0.063 to 0.755
Spain						
Hernandez Rojo 2020 [155]	Patient	Patients with SMA (n=9)	EQ-5D	Type 3 to 4 SMA (Before starting nusinersen)	0.67	NR
Lopez Bastida 2017 [53]	Carers	Patients with SMA (n=81)	EQ-5D-3L using TTO social tariff	SMA	0.158	0.44
UK						
Bromilow [156]	General population	Type 1 to 3 SMA (n=321)	TTO	PAV	-0.0243	95% CI: -0.0914 to 0.0428
				Non-sitters	-0.0264	95% CI: -0.0966 to 0.0438

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Study ID	Perspective	Population	Tool / tariff	Health state	Mean Utility	Measure of uncertainty
				Sitting	0.0977	95% CI: 0.0291 to 0.1664
				Walking	0.3844	95% CI: 0.3225 to 0.4463
			SG	PAV	0.0028	95% CI: -0.0611 to 0.0677
				Non-sitters	0.0139	95% CI: -0.0505 to 0.0783
				Sitting	0.0946	95% CI: -0.0302 to 0.1591
				Walking	0.3782	95% CI: 0.3176 to 0.4388
Lloyd 2019 [125]	Clinician	Type 1 SMA (n=5)	EQ-5D-Y using UK weights	Baseline	-0.12	0.19
				Worsened	-0.24	0.14
				Improvement	-0.17	0.17
				Sits without support	-0.04	0.12
				Stands with assistance	0.04	0.09
				Walks with assistance	0.52	0.22
				Stands/walks unaided	0.71	0.14
				SMA after scoliosis surgery	-0.22	0.22
				Gastric/NG tube	-0.17	0.17
				Requires ventilation	-0.33	0.27
		Type 2 SMA (n=5)		Baseline	0.04	0.1
				Worsened	-0.13	0.06
				Mild improvement	0.04	0.11
				Moderate improvement	0.1	0.09
				Stands/walks with assistance	0.39	0.29
				Stands/walks unaided	0.72	0.12
				Loss of ambulation with/without assistance	-0.12	0.16
Lo 2022 [157]	General population	Type 2 SMA and Non-ambulatory Type 3 SMA (n=84)	TTO (no other detail provided)	Can sit, stand and walk with assistance	-0.068	95% CI: -0.083 to -0.053
				Can sit but cannot stand	-0.222	95%CI: -0.242 to -0.201
				Cannot sit	-0.408	95%CI: -0.440 to -0.377
				Mechanical support for some of the day (<16 h)	-0.159	95%CI: -0.174 to -0.143
				Mechanical support for >16 h of the day	-0.304	95%CI: -0.328 to -0.281
				Injection into spine in hospital every 4 months	-0.071	95%CI: -0.085 to -0.057
				Treatment reaction for 12 h every 4 months	-0.057	95%CI: -0.071 to -0.042
				Reaction for 1–2 days every 4 months	-0.06	95%CI: -0.078 to -0.042
				Reaction for 3–4 days every 4 months	-0.087	95%CI: -0.103 to -0.071
				Monitoring if symptoms present	-0.024	95%CI: -0.036 to -0.012
				Monitoring twice a year for the first 2 years	-0.023	95%CI: -0.037 to -0.009
				Must agree to use effective contraception	-0.012	95%CI: -0.021 to -0.002
Pena-Longobardo 2020 [52]	Patient (unclear who completed)	SMA (n=34)	EQ-5D-3L using TTO social tariff	SMA	0.167	0.277
US						
Belter				PAV	-0.05	SD: 0.10

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Study ID	Perspective	Population	Tool / tariff	Health state	Mean Utility	Measure of uncertainty
2020 [158]	Patient (completed by carer for under 18s)	Type 1 SMA (n=121)	HUI3 (no other detail provided)	Non-sitters	0.06	SD: 0.10
				Sitters	0.11	SD: 0.21
				PAV	0.1	SD: 0.11
		Type 2 SMA (n=225)		Non-sitters	0.12	SD: 0.12
				Sitters	0.26	SD: 0.16
				Walk with support	0.44	SD: 0.12
				Walk independently	0.58	SD: 0.15
		Type 3 SMA (n=132)		Non-sitters	0.14	SD: 0.13
				Sitters	0.23	SD: 0.11
				Walk with support	0.35	SD: 0.21
				Walk independently	0.64	SD: 0.24
Multi-country						
Toro 2023a [159]	Patient (Carer completed)	SMA OA treated: 16 SMN2 gene)	HUI2, tariff NR	OA treated ≥2 copies of SMN2 gene	0.5	SD: 0.1
				non-OA treated ≥2 copies of SMN2 gene	0.5	SD: 0.2
				OA treated 2 copies of SMN2 gene	0.5	SD: 0.1
				non-OA treated 2 copies of SMN2 gene	0.4	SD: 0.1
				OA treated ≥3 copies of SMN2 gene	0.5	SD: 0.1
				non-OA treated ≥3 copies of SMN2 gene	0.7	SD: 0.2
Country not reported						
Sutherland 2022* [150]	NR	Type 2 to 3 SMA (n=81)	HUI2 (no other detail provided)	Non-invasive ventilation (baseline)	0.46	NR
				Feeding support (baseline)	0.38	NR
				Scoliosis (baseline)	0.54	NR
				Respiratory tract infection (baseline)	0.58	NR
				Sleep apnea (baseline)	0.5	NR
			HUI2 estimated by mixed model for repeated measures	Non-sitters	0.49	NR
				Sitters	0.54	NR
				Standers	0.56	NR
				Walkers	0.84	NR
				Non-invasive ventilation	Decrement:-0.04	NR

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B.3.4.4 Adverse reactions

There is a precedent in previous NICE appraisals for SMA to not incorporate separate utility decrements for treatment-related adverse events (TRAEs). For example, within TA588, TA755 and HST15 TRAEs were not explicitly incorporated into the economic models. Indeed, the company submission for HST15 noted that, given the nature of SMA, it was difficult to separate utility decrements caused by TRAEs from the complications associated with SMA. It follows that the impact of any adverse events on HRQoL would be accounted for in health state utility values. Therefore, utility decrements as a result of TRAEs were not explicitly modelled.

B.3.4.5 Health-related quality-of-life data

EQ-5D-5L data were collected as part of the MAA. However, there was a limited number of patients and only a short follow-up period. Therefore, it was not possible to utilise the utility data from the MAA in the models.

The most recent appraisal related to SMA is HST24. The utilities that were used in the company submission for this appraisal are presented in Table 62. The EAG did not challenge the use of these values within the company submission. Therefore, these utilities were adopted for the base case analysis of the current models.

Equivalent health state utilities have been applied to all three models, based on the assumption that it is the health state itself, and not the type of SMA, that determines the impact of the disease on patient health-related quality of life.

SMA utilities were also available from TA588 and TA755. The model structure in this appraisal is more similar to TA755 with the key difference being the use of compounded health states for standing with and without support and walking with and without support. As part of TA755, the company considered the feedback from both the EAG and NICE committee in TA588 when selecting utilities for their economic model. The EAG for TA755 judged that the health state utilities that were derived by clinical advisors to Biogen during TA588 were the most clinically plausible values to utilised in an economic model, despite the limitations associated with these utilities (namely these utilities were based on the opinion of experts rather than a formal elicitation of preferences for competing health states). These utilities are presented in Table 63 and were included in a scenario analysis.

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Table 62. Summary of health state utilities used in the current models, as derived from the onasemnogene appraisal [HST24]

Health state	Utility	Notes
Permanent ventilation	0.00	Based on HS1 (non-sitter, PAV) health state
Not sitting	0.19	Based on HS1 (non-sitter, no PAV) health state
Sitting	0.60	Based on HS2 (sitter) health state
Standing	0.77	Assumed to be equivalent to HS3a (delayed walker, loses walking) and HS3b (experiences later onset SMA, loses walking)
Walking	Equivalent to general population utility	Assumed to be equivalent to HS-BRND health state

Table 63. Summary of EAG exploratory analysis from TA755

TA755 health state	EAG exploratory analysis (Type 1)	EAG exploratory analysis (Type 2/3)
Permanent ventilation	-0.02	N/A
Not sitting	0.10	0.10
Sitting	0.20	0.20
Standing	0.70	0.70
Walking	0.85	0.85

Age and sex-adjusted population norm have been applied to the utilities, using a multiplicative approach as per NICE guidelines, to derive total QALYs for each treatment arm. Population norms were obtained from a NICE Decision Support Unit (DSU) report, authored by Hernández et al [160]. At the date of the submission, there is no available data reporting population norms for children or adolescents under the age of 16 years. In line with guidance from NICE technical support document (TSD) 23, it was assumed that population norm estimates for children or adolescents are equivalent to the population norm estimate for a person aged 16 years [145].

Clinical experts noted at the advisory board that patients receiving active treatment are likely to obtain additional gains in health-related quality of life that are not captured in the health state utilities associated with gross motor milestones. For example, those in the “sitting without support” health state are likely to gain

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additional upper limb function when on active treatment, which can help them complete a larger number of typical daily activities thus improving quality of life. These “on-treatment” utilities were captured as part of the cost-utility analysis undertaken by ICER for nusinersen and onasemnogene. Within this analysis, an on-treatment utility of 0.10 and 0.05 was applied to patients in the “not sitting” and “sitting” health states, respectively, if the patients in these health states were receiving nusinersen or onasemnogene.

To capture these potential gains in health-related quality of life, an on-treatment utility of 0.10 was applied to all nusinersen patients whilst they continued to receive treatment (i.e. the utility was no longer applied once patients discontinued).

B.3.4.6 Caregiver health-related quality-of-life data

In an exploratory scenario analysis, HST15 (onasemnogene) initially used caregiver disutilities derived from spina bifida research and applied to SMA health states using calculations from Wittenberg et al (2013) [107,161,162]. The EAG critiqued the values for being too high and recommended using values from Lopez-Bastida et al (2017), a cross-sectional Spanish study assessing utilities of people with types 1-3 SMA and their carers (n=81) [74].

Therefore, Lopez-Bastida et al (2017) was used in the risdiplam submission (TA755) for people in the most severe health state, and population norm utilities from Ara et al (2010) were applied in the least severe health state [53,115,126]. Intermediate health states were estimated assuming a linearly proportional relationship between utilities and health states. The EAG commented that the fact the paper focuses on a Spanish cohort is not ideal but approved of the approach overall. The EAG acknowledged that neither the company’s additive approach nor the EAG’s preferred caregiver disutility approach is ideal. The impact of bereavement on HRQoL was not acknowledged in TA755. This, and the approach that the model assumes caregivers die or survive with a utility of 0 after the person they were caring for dies, was critiqued by the EAG [115].

Following feedback from the advisory board, a novel approach to calculating the utility impact of carers was taken in the model. Instead of applying a utility decrement to the population norm of the caregiver, which causes the QALYs in the model to

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decrease regardless of whether the person with SMA is in a better or worse health state, the model applies a caregiver utility increment. Using the EAG's preferred caregiver utility value of the person with SMA being in the lowest health state as a baseline, namely 'permanent ventilation' for the presymptomatic and type 1 models, and 'not sitting' for the later-onset model, a utility increment for each health state is calculated. These are presented in Table 64.

When the person with SMA moves into the death state, utility increments are no longer captured for the caregiver. This is a conservative approach taken to show the maximal impact of bereavement of the caregiver following the death of their loved one. Therefore, this avoids the risk of assuming the caregiver dies or lives with a utility of 0 or that the caregiver utility immediately reverts to the population norm. The latter could cause a scenario where the most cost-effective intervention is the one that has the highest mortality rate.

Similar to the utility values for the people with SMA, equivalent health state caregiver utility increments have been applied to all three models, based on the assumption that it is the health state itself, and not the type of SMA, that determines the impact of the disease on patient health-related quality of life.

It was assumed that people with SMA who are sitting without support, unable to sit or require permanent ventilatory support will require 2 caregivers. Alternatively, people with SMA in the less severe health states ('standing with support' and 'walking independently' required fewer caregivers.

In accordance with findings from a SR of 24 articles conducted by Brandt et al. [163], caregivers are assumed to have an average age of 40 years old at baseline. The utility value of caregivers of people with SMA who are able to walk independently was consistent with the population norm of a 40-year-old, as defined by Hernández et al [160]. As per the utilities of people with SMA, age and sex-adjusted population norms from Hernández et al [160] have been applied to caregiver utilities using a multiplicative approach as per NICE guidelines.

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Table 64. Summary of caregiver utility values for cost-effectiveness analysis

State	Number of caregivers	Mean utility	95% CI	Reference	Justification
Permanent ventilation	2	0.484	N/A	[164]. Table 3 (number of caregivers) and Table 58 (caregiver utility).	Based on the preferred base case for the EAG in TA755 [164].
Not sitting	2	0.484	N/A		
Sitting without support	2	0.628	N/A		
Standing with assistance	1	0.771	N/A		
Walking independently	1	Population norm	N/A		

N/A: not available

* Because of a lack of data to inform uncertainty estimates, the standard error is assumed to be 10% of the mean.

B.3.5 Cost and healthcare resource use identification, measurement and valuation

B.3.5.1 Intervention and comparators' costs and resource use

Costs for nusinersen, consist of drug acquisition costs, administration costs and concomitant medication costs.

A 12mg/ 5ml vial of nusinersen (one dose) is priced at £75,000 (list price) [135,136]. Nusinersen is administered intrathecally by lumbar puncture [140]. The cost of intrathecal administration was £836, based on a weighted average of outpatient and day case procedures listed under HRG code HC72 (Diagnostic Spinal Puncture) listed in the 2020/21 NHS reference costs (version 3). The procedure codes used do not correspond exactly to lumbar puncture for the administration of nusinersen but were the closest available proxies. This approach was utilised during the company submission for TA588 and was not criticised by the EAG during that appraisal. The total costs and activity from the total HRG were utilised for the CEM.

The cost of nusinersen in the first cycle of treatment (4 loading doses doses) [140] was £300,000 with an additional intrathecal administration cost of £3,899. Costs thereafter for maintenance doses are £75,000 with an intrathecal administration cost of £836 per cycle. There are no concomitant medication costs applied in the model specifically for nusinersen.

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A simple PAS of [redacted] is available and was applied in the model, which reduced the per cycle nusinersen maintenance costs to [redacted]

There were no additional costs for drug acquisition, administration or concomitant medication associated with BSC.

B.3.5.2 Health-state unit costs and resource use

Relevant health states costs were reported in the company submission for the most recent NICE appraisal of onasemnogene [HST24]. These costs are presented in Table 65. During this appraisal, the EAG reported that they were satisfied with the company approach to estimating health state costs. Therefore, these costs have been incorporated into the current models. It should be noted that no health-state costs were produced for the "standing" health state. Therefore, in the base case analysis it was assumed that the costs in this state are equivalent to the "walking" health state. This matches the approach adopted in TA755.

Table 65. Total annual health state costs applied in the base case analysis (taken from HST24)

Resource category	Permanent ventilation	Non-sitter	Sitting	Standing and Walking
Drugs	£619	£810	£781	£1,012
Medical tests	£880	£1,152	£917	£ 675
Medical visits	£3,669	£4,801	£2,805	£2,461
Hospitalisations	£218,987	£70,829	£40,577	£276
Accident and Emergency	£375	£490	£201	£80
Health material	£3,590	£4,400	£2,274	£652
Social services	£55,590	£30,019	£20,013	£3,177
Total	**£283,710**	**£112,500**	**£67,567**	**£8,333**

In the original nusinersen NICE appraisal (TA588) health state costs were informed by a study from Lopez-Bastida et al [165], but this approach was criticised by both the EAG and NICE committee who noted that the data from this study likely underestimated the true costs associated with SMA disease management. Instead, the EAG preferred the use of costs derived from a real-world study that was completed by Biogen in which paediatric neurological consultants from nine UK centres were surveyed to derive healthcare resource use for SMA Type 1, Type 2

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and Type 3. The costs from this real-world study were subsequently used in the base case analysis for the risdiplam NICE appraisal (TA755). These costs are presented in Table 66 and were utilised in a scenario analysis.

Additionally, as part of TA755, the company also presented data from a UK burden of illness study, based on a survey of 122 patients and 80 carers with Types 1 to 3 SMA. The data from this study were used in a scenario analysis within the company submission. However, the data were redacted and, therefore, cannot be utilized for the current submission.

Table 66. Alternative health state costs applied in a scenario analysis

Health state	Annual cost reported in TA588	Inflated annual cost (applied in CEM) ¥	Inflated cost per 4-month cycle	Source
Permanent ventilation*	£136,444	£150,989	£50,330	Burden of illness and resource utilisation in SMA survey, 2017 [166].
Not sitting	£77,968	£86,280	£28,760	
Sitting	£55,185	£61,068	£20,356	
Standing	£20,229	£22,385	£7,462	
Walking	£20,229	£22,385	£7,462	

* The annual cost for 'permanent ventilation' is assumed to be equivalent to the cost of 'not sitting' as per TA588 with a 175% increase in costs as applied in TA577

¥ Costs are inflated from cost year 2016/17 to 2021/22 using an inflation index of 1.11 using indices derived from PSSRU 2022, NHSCII pay and prices [134].

B.3.5.3 Adverse reaction unit costs and resource use

As described in Section B.3.4, adverse events have not been incorporated into the model.

B.3.5.4 Miscellaneous unit costs and resource use

There are no additional costs or items of health care resource use which have not been covered elsewhere.

B.3.6 Severity

In order to investigate whether presymptomatic, type 1 and later-onset SMA meets the criteria to be classified as a severe disease under the severity modifier framework, the lifetime QALY gain of people receiving BSC is expressed as a proportional (i.e., proportional QALY shortfall) and an absolute decrement (i.e.,

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absolute QALY shortfall) of the estimated lifetime QALY gain of healthy patients of the same age and sex distribution.

Table 67. Alternative health state costs applied in a scenario analysis.

QALY weight	Proportional QALY shortfall	Absolute QALY shortfall
1	Less than 0.85	Less than 12
x1.2	0.85 to 0.95	12 to 18
x1.7	At least 0.95	At least 18

The economic base case includes caregiver utility increments, however, NICE TSD23 states that proportional severity estimates cannot be included when caregiver increments are applied. Therefore, two sets of results have been provided in the presented in Table 68, Table 69, and Table 70. One of these explores the base case with caregiver utility increments applied, and one explores a scenario whereby caregiver utility increments are removed to adhere to TSD23.

For all the QALY deterministic, discounted outcomes, nusinersen is ineligible for an additional weight. The QALY results from the economic model base case and the subsequent calculation are presented in Table 68, Table 69, and Table 70 and for presymptomatic, type 1 and later-onset SMA models respectively. The highest QALY shortfall (1.7) could be applied to the type 1 model and the mid QALY shortfall (1.2) could be applied to the presymptomatic model. However, given that caregiver utility increments are included, this will not be done in the reference case. For the later-onset model, no QALY shortfall is applicable.

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Table 68. Summary of QALY shortfall analysis for presymptomatic SMA

Factor	Value		Reference
Sex distribution (female, %)	50%		NURTURE (NCT02386553) [167]
Starting age	20.6 days		NURTURE (NCT02386553) [167]
QALYs of population without the disease	70.27 (undiscounted) 24.30 (discounted)		Calculated by summing the probability of being alive by age in the general population at each cycle of the model using the UK life tables[144] with the half-cycle corrected population norms[160] over the model time horizon, adjusted for the model's four-monthly cycle length
	With caregiver utility increments	Without caregiver utility increments	
QALYs	8.67	7.99	Estimated from reference case model (Section B.3.9.1)
Absolute QALY shortfall	15.63	[redacted]	Calculated
Proportional QALY shortfall	0.64	[redacted]	Calculated
QALY weight based on proportional QALY shortfall	1.2	1.2	NICE health technology evaluations: the manual (PMG36)
QALY weight based on absolute QALY shortfall	1.0	1.0	NICE health technology evaluations: the manual (PMG36)

Table 69. Summary of QALY shortfall analysis for type 1 SMA

Factor	Value		Reference
Sex distribution (female, %)	0.46		ENDEAR
Starting age	55.4%		ENDEAR
QALYs of population without the disease	70.07 (undiscounted) 24.2 (discounted)		Calculated by summing the product of the probability of being alive by age in the general population at each cycle of the model using the UK life tables [144] with the half-cycle corrected population norms [160] over the model time horizon, adjusted for the model's four-monthly cycle length
	With caregiver utility increments	Without caregiver utility increments	
QALYs with BSC	0.25	0.20	Estimated from reference case model (Section B.3.9.2)
Absolute QALY shortfall	24.03	[redacted]	Calculated
Proportional QALY shortfall	0.99	[redacted]	Calculated
QALY weight based on proportional QALY shortfall	1.7	1.7	NICE health technology evaluations: the manual (PMG36)
QALY weight based on absolute QALY shortfall	1.7	1.7	NICE health technology evaluations: the manual (PMG36)

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Table 70. Summary of QALY shortfall analysis for later-onset SMA

Factor	Value		Reference
Sex distribution (female, %)	51.72		Average of CHERISH and Wadman et al, 2022
Starting age	4.54		Average of CHERISH and Wadman et al, 2022
QALYs of population without the disease	66.42 (undiscounted) 23.97 (discounted)		Calculated by summing the product of the probability of being alive by age in the general population at each cycle of the model using the UK life tables [144] with the half-cycle corrected population norms [160] over the model time horizon, adjusted for the model's four-monthly cycle length
	With caregiver utility increments	Without caregiver utility increments	
QALYs with BSC	13.72	12.60	Estimated from reference case model (Section B.3.9.3)
Absolute QALY shortfall	10.26	[redacted]	Calculated
Proportional QALY shortfall	0.43	[redacted]	Calculated
QALY weight based on proportional QALY shortfall	1.0	1.0	NICE health technology evaluations: the manual (PMG36)
QALY weight based on absolute QALY shortfall	1.0	1.0	NICE health technology evaluations: the manual (PMG36)

B.3.7 Uncertainty

Given the very rare nature of SMA, the population enrolled in the NURTURE clinical trial (for presymptomatic SMA) was relatively small. Indeed, within the trial, only 15 people had two SMN2 copies and 10 people had three copies. In an advisory board, clinical experts observed that many of the people assumed to be presymptomatic were already exhibiting symptoms of SMA. This trial was also single-arm with no sham control arm. Therefore, it was necessary to use natural history data to compare active treatments with BSC, potentially resulting in uncertainty in the clinical outcomes included in the model.

Another potential source of uncertainty in the model is the limited follow-up data available to inform the treatment effect over patients' lifetime, resulting in a need for extrapolation of clinical data. This is shown by the maximum follow-up periods for the available nusinersen clinical trials, which are as follows…

- Pre-symptomatic: 72 months for nusinersen (NUTURE).

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- Type 1: 60 months for nusinersen and 13 months for sham control (ENDEAR and SHINE).
- Type 2/3: 96 months for nusinersen and 15 months for sham control (CHERISH and SHINE).

Due to these limitations, it was decided to make conservative assumptions in regard to the long-term outcomes of SMA patients. In particular, that patients receiving nusinersen could only maintain or decline in terms of their gross motor milestones and this may underestimate the potential benefits of active SMA treatment.

Noting that there is uncertainty in the model outputs, the base case results have been reported using those derived from a probabilistic sensitivity analysis (PSA).

This, and other well-characterised and researched methods, including a deterministic sensitivity analysis (DSA), and scenario analyses were utilized to explore the impact of uncertainty on economic outcomes (Section B.3.10.1.3). These include a testing key model assumptions and inputs (discounting rates, utility values, and costs of SMA-related care).

B.3.8 Summary of base-case analysis inputs and assumptions

B.3.8.1 Summary of base-case analysis inputs

These base case parameters are summarised in Appendix I.

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B.3.8.2 Assumptions

Table 71. Summary of the Key Modelling Assumptions

Report section	Model(s)	Assumption	Justification
Section B.3.3 (Clinical parameters and variables)	▪ Presymptomatic ▪ Type 1 SMA ▪ Later-onset SMA	Interim motor milestones, including standing and crawling, are assumed to be captured in the health state specific cost and utility values.	This approach allows for the costs and effects of interim milestones to be captured, without explicitly modelling them with complex transitions and tunnel states. This approach is consistent with the precedent set in previous NICE HTAs.
Section B.3.3 (Clinical parameters and variables)	▪ Presymptomatic ▪ Type 1 SMA ▪ Later-onset SMA	Improvement in motor milestones because of disease modifying treatment could only occur during the follow-up period of the available clinical studies (up to 72 months). Data from the Wadman et al study was used to estimate the long-term probability that BSC patients lose a motor milestone each cycle. These probabilities when then applied consistently for all model cycles, starting from timepoint whereby control arm data were no longer collected in the nusinersen clinical trial programme.	Natural history studies showed that people with SMA achieving less severe motor milestones would be expected to lose motor milestones over time. This was supported by clinical experts. However, this is a conservative assumption for the potential long-term effectiveness of nusinersen.
Section B.3.3.1.2; B.3.3.2.2 and B.3.3.3.2 (nusinersen effectiveness)	▪ Presymptomatic ▪ Type 1 SMA ▪ Later-onset SMA	The relative risk of a motor milestone decline was estimated based on the available trial data for each population and this was applied to the long-term probability of decline for BSC, to estimate the relative long-term decline with nusinersen.	No data is currently available to estimate the long-term relative effectiveness of nusinersen. However, it is expected that a treatment effect will remain, and this should be captured in the models.
Section B.3.3.1.2 and B.3.3.2.2 (nusinersen effectiveness)	▪ Type 1 SMA	The models assumed equivalence between different measures of motor milestones (i.e. HINE-2 and WHO motor milestones).	Infants aged 2 years and under were assessed using HINE-2. When their age exceeded 2 years, they were assessed using WHO. This assumption is therefore necessary to inform the analysis for people of all ages in the model.
Section B.3.3.3.3 (nusinersen effectiveness)	▪ Later-onset SMA	Data from the CHERISH and SHINE clinical trial are assumed to apply only the sub-population of people with type 2 SMA, not type 3 SMA.	CHERISH and SHINE was predominantly comprised of a type 2 population. While there were a few type 3 patients included (as evident by those who achieved walking independently), KOLs advised that the patients included in CHERISH and SHINE did not adequately reflect a type 3 population.
Section B.3.3.3.3 (nusinersen effectiveness)	▪ Later-onset SMA	The type 3 sub-population are assumed to walk independently for the duration of the initial follow-up period of the CHERISH and SHINE studies.	By definition, a person with type 3 SMA can walk independently, and, over time, will lose this ability. Natural history data (Wadman et al) found people with type 3 SMA lost the ability to walk at a mean age of 11 years and 34 years (type 3A and 3B respectively).

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Report section	Model(s)	Assumption	Justification
Section B.3.3.3.3 (nusinersen effectiveness)	▪ Presymptomatic ▪ Type 1 SMA ▪ Later-onset SMA	It was possible for the model cohort to lose more than one motor milestone. For example, from walking to standing with support to sitting independently to not sitting.	Clinical expert advised that they observed people with SMA achieving higher motor milestone to decline, for example, from walking to not sitting within their lifetime. This is also supported by data from the Wadman et al study.
Section B.3.3.1.2; B.3.3.2.2 and B.3.3.3.2 (nusinersen effectiveness)	▪ Presymptomatic ▪ Type 1 SMA ▪ Later-onset SMA	The discontinuation rate for the 'standing with support' health state were equivalent to the costs for the 'walking independently' health state.	In the absence of data for the 'standing with support' health state (which was not reported in the MAA), this assumption was required and was consistent with the assumptions utilised in the health state costs and overall survival.
Section B.3.3.1.5; B.3.3.2.5 and B.3.3.3.5 (Survival)	▪ Presymptomatic ▪ Type 1 SMA ▪ Later-onset SMA	Overall survival in a particular health state is bound by the overall survival of the next highest health state.	It is clinically implausible for the estimated life years of a person with a more severe disease to exceed the life years of either someone with a less severe disease or the general population.
Section B.3.3.1.5; B.3.3.2.5 and B.3.3.3.5 (Survival)	▪ Presymptomatic ▪ Type 1 SMA ▪ Later-onset SMA	The overall survival attributed to those in the less severe health states ('standing without support' and 'walking independently') are assumed to be consistent with the general population survival.	This is a precedent observed in previous NICE HTAs. The assumption is required because of a paucity of long-term survival data.
Section B.3.3.1.5	▪ Presymptomatic	People with 2 copies of SMN2 will have the same overall survival as people with 3 copies	The survival estimates for the 2-copy cohort presented in figure 15 of HST24 lacked visual validity because the survival curve presented estimated worse survival outcomes for the 2-copy cohort unable to sit compared to those on permanent ventilation.
Section 3.3 (discontinuation)	▪ Presymptomatic ▪ Type 1 SMA ▪ Later-onset SMA	If a proportion of the cohort declines by one or several WHO motor milestones, they remain on active treatment. Long term decline does not impact discontinuation.	The MAA outlines multiple stopping rules, including a total worsening in scale score (e.g. HFMSE or RULM) corroborated by two consecutive measurements. In the advisory board, clinicians stated that it would be unethical to deprive a sick person of treatment because of loss of one score. A worsening in one score did not correlate with worsening across all scores. A drop in HMFSE and an increase in RULM was frequently observed by the clinical experts.
Section 3.3.1 and Section 3.3.2 (discontinuation)	▪ Presymptomatic ▪ Type 1 SMA	The proportion of the cohort in the 'permanent ventilation' health state automatically discontinue treatment.	Clinical experts agreed that it was unlikely people would continue treatment with permanent ventilation and this aligned with the stopping rules that were used for nusinersen in the MAA.

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Report section	Model(s)	Assumption	Justification
Section 3.3.1.5 (discontinuation)	▪ Type 1 SMA	People who switched to onasemnogene during the MAA would have remained on nusinersen if the gene therapy had not become available during the MAA study.	Onasemnogene became available to the UK SMA population during the period of the MAA analysis. In the future, it is expected that people who are eligible for onasemnogene and would prefer this treatment option would receive the treatment prior to initiating nusinersen. Therefore, a high rate of switching from nusinersen to onasemnogene is not expected.
Section 3.3.1.5 (discontinuation)	▪ Type 1 SMA	The probability of discontinuing nusinersen per cycle in the "standing with support" and "walking independently" health states was 1.0%.	No data were available for the rates of discontinuation for patients residing in those two health states. However, it was hypothesized that the rate would be lower for these two health states, versus "not-sitting" and "sitting without support" as the treatment would have been highly effective, given the natural history of type 1, if it enabled patients to enter these states. A probability of 1.5% was applied for the "not-sitting" and "sitting without support" health states. Therefore, this value was reduced to 1.0%, which was seen as a reasonable proxy.
Section 3.3 (discontinuation)	▪ Presymptomatic ▪ Type 1 SMA ▪ Later-onset SMA	The probability of discontinuation was assumed to remain constant across the model time horizon and, thus, were applied to all cycles in the model	There is a paucity of long-term data for people who discontinued nusinersen.
B.3.4 (Measurement and valuation of health effects)	▪ Presymptomatic ▪ Type 1 SMA ▪ Later-onset SMA	The costs and utilities were consistent across all populations and sub-populations	This approach was taken to minimise the data requirements in the models, which is relevant given the general paucity of robust resource use and utility data for SMA.
B.3.4 (Measurement and valuation of health effects)	▪ Presymptomatic ▪ Type 1 SMA ▪ Later-onset SMA	The health state specific utilities (for the population with SMA and the caregivers) are bound by the population norm for the appropriate age range, e.g. if the health state utility is larger than the population norm, the population norm is used in the model.	It is clinically implausible for the utility of an SMA population to exceed the utility of the general population.
B.3.4 (Measurement and valuation of health effects)	▪ Presymptomatic ▪ Type 1 SMA ▪ Later-onset SMA	Adverse event utilities were captured in the health state utility values. Therefore, adverse event utility decrements were not explicitly modelled.	This assumption is based on precedent set-in former models. TA588 (nusinersen), HST15 (onasemnogene) and the ICER assessment of onasemnogene and nusinersen highlighted the difficulty in separating utilities due to treatment from the complications associated with SMA. Including adverse event utility

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Report section	Model(s)	Assumption	Justification
			decrements could lead to increased uncertainty caused by double counting.
B.3.4 (Measurement and valuation of health effects)	▪ Presymptomatic ▪ Type 1 SMA ▪ Later-onset SMA	Nusinersen patients received an “on-treatment” utility of 0.1	To quantify the potential benefits of treatment that are not captured based on the gross motor milestone health states that are included in the model. For example, whilst in the “sitting without support” health state patients receiving nusinersen are expected to have improved upper limb function that will enable them to undertake additional activities of daily living that are not captured in the health state utility that has been applied in the model. On-treatment utilities were previously included in the cost-utility analysis undertaken by ICER to assess nusinersen and onasemnogene.
B.3.4 (Measurement and valuation of health effects)	▪ Presymptomatic ▪ Type 1 SMA ▪ Later-onset SMA	That people with SMA who are either unable to sit or require permanent ventilatory support required 2 caregivers	As a result of lack of data on the number of caregivers. These are the most severe health states and therefore it is plausible that they would require more than one caregiver.
B.3.5.2 (Health-state unit costs and resource use)	▪ Presymptomatic ▪ Type 1 SMA ▪ Later-onset SMA	The costs for the ‘standing with support’ health state were equivalent to the costs for the ‘walking independently’ health state.	In the absence of cost and resource use data for the ‘standing with support’ health state, this assumption was required and was consistent with the assumptions in TA755.

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B.3.9 Base-case results

In accordance with new NICE methods guidance, the base case cost-effectiveness results were derived from a probabilistic sensitivity analysis (PSA) to account for second order uncertainty around parameter values. Please see Section B.3.10.1 for more detail about the methods used in the PSA. The deterministic results are presented along side the probabilistic results.

B.3.9.1 Base-case results for the presymptomatic model

Table 72 and Table 73 report the deterministic and probabilistic lifetime costs, life years and QALYs gained for a presymptomatic SMA population (with either 2 or 3 copies of the SMN2 gene), and the associated ICER for nusinersen versus BSC. Both analyses found that treatment with nusinersen accrued greater QALYs than BSC. Indeed, for every QALY gained, treatment with nusinersen cost [redacted] and [redacted] in the deterministic and probabilistic analyses respectively. Therefore, it was concluded that treatment with nusinersen [redacted] compared with BSC at a cost-effectiveness threshold of £30,000. This conclusion was attained in [redacted] PSA iterations.

BSC patients spent most of the model time horizon in the 'not sitting' ([redacted]) and 'sitting without support' ([redacted]) health states, suggesting that they developed either type 1 or type 2 SMA. Conversely, the cohort on nusinersen spent more time in the less severe health states, [redacted] in 'standing with support' and 'walking independently' respectively. Therefore, nusinersen patients, and their caregivers, experienced better HRQoL from achieving more advanced motor milestones.

A breakdown of deterministic costs is provided in Table 78 by health state. Health state and treatment costs for nusinersen are offset by the extremely high cost accrued in the 'permanent ventilation', 'sitting without support' and 'sitting' health states for people receiving BSC.

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Table 72. Deterministic base-case results for the pre-symptomatic population

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER versus baseline (£/QALY)	NHB at £30,000 / QALY
Nusinersen	[redacted]	20.84	14.59					
BSC	[redacted]	19.91	8.67	[redacted]	0.92	5.92	[redacted]	[redacted]

Abbreviations: BSC, best supportive care; ICER, incremental cost-effectiveness ratio; LYG, life years gained; NHB, net health benefit; QALYs, quality-adjusted life years

Table 73. Probabilistic base-case results for the pre-symptomatic population

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£/QALY)	Likelihood of cost-effectiveness	NHB at £30,000 / QALY
Nusinersen	[redacted]	20.88 (20.54 to 21.19)	14.58 (13.23 to 15.84)						
BSC	[redacted]	19.92 (19.57 to 20.22)	8.67 (7.65 to 9.68)	[redacted]	0.97 (0.70 to 1.24)	5.91 (4.81 to 7.03)	[redacted]	[redacted]	[redacted]

Abbreviations: BSC, best supportive care; ICER, incremental cost-effectiveness ratio; LYG, life years gained; NHB, net health benefit; QALYs, quality-adjusted life years

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Table 74. Deterministic life years (discounted) per person disaggregated by health state, pre-symptomatic population

Health state	Nusinersen	BSC	Incremental
Permanent ventilation	[redacted]	[redacted]	[redacted]
Not sitting	[redacted]	[redacted]	[redacted]
Sitting without support	[redacted]	[redacted]	[redacted]
Standing with support	[redacted]	[redacted]	[redacted]
Walking independently	[redacted]	[redacted]	[redacted]

Table 75. Deterministic life years (discounted) per person disaggregated by treatment, pre-symptomatic population

Treatment	Nusinersen	BSC	Incremental
Life years on nusinersen	[redacted]	[redacted]	[redacted]
Life years on BSC (following discontinuation)	[redacted]	[redacted]	[redacted]

Table 76. Deterministic QALYs (discounted) per person disaggregated by health state, pre-symptomatic population

Health state	Nusinersen	BSC	Incremental
Permanent ventilation	[redacted]	[redacted]	[redacted]
Not sitting	[redacted]	[redacted]	[redacted]
Sitting without support	[redacted]	[redacted]	[redacted]
Standing with support	[redacted]	[redacted]	[redacted]
Walking independently	[redacted]	[redacted]	[redacted]

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Table 77. Impact of deterministic QALY increments (discounted) per person pre-symptomatic population

Treatment	Nusinersen	BSC	Incremental
Active treatment utility increment	[redacted]	[redacted]	[redacted]
Caregiver utility increments	[redacted]	[redacted]	[redacted]

Table 78. Deterministic health state costs per person disaggregated by health state

Health state	Nusinersen	BSC	Incremental
Permanent ventilation	[redacted]	[redacted]	[redacted]
Not sitting	[redacted]	[redacted]	[redacted]
Sitting without support	[redacted]	[redacted]	[redacted]
Standing with support	[redacted]	[redacted]	[redacted]
Walking independently	[redacted]	[redacted]	[redacted]

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B.3.9.2 Base-case results for the type 1 model

Table 79 and Table 80 reports the deterministic and probabilistic results for the type 1 population. The deterministic ICER is reported at [redacted] per QALY gained and the average probabilistic ICER is reported at £[redacted], which is in excess of the threshold of cost-effectiveness referenced in the NICE manual (£20,000 to £30,000 per QALY gained). See Section 3.10.1.2 for further details about the methods used in the probabilistic analysis and the cost-effectiveness plane.

As per the definition of type 1 SMA, the cohort on BSC never gain the ability to sit independently. Conversely, the cohort receiving nusinersen achieved more advanced motor milestones. Indeed, they were, on average, able to spend [redacted] deterministic life years in 'sitting independently'; 'standing with support', and 'walking independently' respectively. Therefore, the nusinersen cohort, and their caregivers, experienced better HRQoL from achieving more advanced motor milestones than the BSC cohort.

The breakdown of deterministic costs are shown in Table 81 by health state. Costs across the health states were higher for the cohort receiving nusinersen as a result of the greater survival when compared with BSC. Health state costs for nusinersen were partially offset by the cost of permanent ventilation, however, these had a minor impact when compared with the cost of treatment.

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Table 79. Deterministic base-case results for the type 1 population

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER versus baseline (£/QALY)	NHB at £30,000 / QALY
Nusinersen	[redacted]	8.38	5.03					
BSC	[redacted]	2.91	0.25	[redacted]	5.47	4.78	[redacted]	[redacted]

Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years

Table 80. Probabilistic base-case results for the type 1 population

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER versus baseline (£/QALY)	Likelihood of cost-effectiveness £30,000/QALY	NHB at £30,000 / QALY
Nusinersen	[redacted]	8.37 (6.95 to 9.84)	4.95 (3.98 to 5.92)						
BSC	[redacted]	3.05 (1.54 to 5.19)	0.25 (0.16 to 0.38)	£[redacted]	5.32 (3.85 to 6.65)	4.70 (3.73 to 5.66)	[redacted]	[redacted]	[redacted]

Abbreviations: CI, confidence interval; ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years

Table 81. Deterministic life years (discounted) per person disaggregated by health state, type 1 population

Health state	Nusinersen	BSC	Incremental
Permanent ventilation	[redacted]	[redacted]	[redacted]
Not sitting	[redacted]	[redacted]	[redacted]
Sitting without support	[redacted]	[redacted]	[redacted]
Standing with support	[redacted]	[redacted]	[redacted]
Walking independently	[redacted]	[redacted]	[redacted]

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Table 82. Deterministic life years (discounted) per person disaggregated by treatment, type 1 population

Treatment	Nusinersen	BSC	Incremental
Life years on nusinersen	[redacted]	[redacted]	[redacted]
Life years on BSC (following discontinuation)	[redacted]	[redacted]	[redacted]

Table 83. Deterministic QALYs (discounted) per person disaggregated by health state, type 1 population

Health state	Nusinersen	BSC	Incremental
Permanent ventilation	[redacted]	[redacted]	[redacted]
Not sitting	[redacted]	[redacted]	[redacted]
Sitting without support	[redacted]	[redacted]	[redacted]
Standing with support	[redacted]	[redacted]	[redacted]
Walking independently	[redacted]	[redacted]	[redacted]

Table 84. Impact of deterministic QALY increments (discounted) per person, type 1 population

Treatment	Nusinersen	BSC	Incremental
Active treatment utility increment	[redacted]	[redacted]	[redacted]
Caregiver utility increments	[redacted]	[redacted]	[redacted]

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Table 85. Deterministic health state costs per person, disaggregated by health state, type 1 population

Health state	Nusinersen	BSC	Incremental
Permanent ventilation	[redacted]	[redacted]	[redacted]
Not sitting	[redacted]	[redacted]	[redacted]
Sitting without support	[redacted]	[redacted]	[redacted]
Standing with support	[redacted]	[redacted]	[redacted]
Walking independently	[redacted]	[redacted]	[redacted]

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B.3.9.3 Base-case results for the later-onset (type 2 and 3) model

For the base case analysis, results for the total later-onset population, those with a combined type 2 SMA and type 3 SMA are presented in the current section. The results of these two sub-populations are presented in Section B.3.11.1.

Table 86 and Table 87 report the deterministic and probabilistic results for a person with later-onset SMA. The deterministic ICER is reported at £[redacted] per QALY gained and the average probabilistic ICER is reported at £[redacted]. [redacted]of the threshold of cost-effectiveness referenced in the NICE manual (£20,000 to £30,000 per QALY gained). See Section B.3.10.1.3 for further details about the methods used in the probabilistic analysis.

Table 88 presents the life years for the two cohorts with the greatest percentage of life years spent in the 'not sitting' and 'sitting without support' health states. These outcomes contradict the definition of later-onset SMA, namely, sitters for type 2 and walkers for type 3. However, those treated with nusinersen spent less time in the more severe health states and more time in the less severe health states than BSC.

The cohort treated with nusinersen accrued more life years in the less severe health states compared to BSC ([redacted] in 'standing with support' and [redacted] in 'walking independently'). However, the overall costs were greater for patients receiving nusinersen.

The breakdown of deterministic costs are shown in Table 92 by health state. Costs across the health states were higher for the cohort receiving nusinersen because of the longer longevity and fewer life years spent in permanent ventilation compared to BSC. Health state costs for nusinersen were partially offset by the cost of permanent ventilation, however, these had a minor impact when compared with the cost of treatment.

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Table 86. Deterministic (discounted) base-case results for the later onset population

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER versus baseline (£/QALY)	NHB at £30,000 / QALY
Nusinersen	[redacted]	23.14	16.56					
BSC	[redacted]	22.86	13.72	[redacted]	0.29	2.85	[redacted]	[redacted]

Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years

Table 87. Probabilistic (discounted) base-case results the later onset population

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER versus baseline (£/QALY)	Likelihood of cost-effectiveness at £30,000 / QALY	NHB at £30,000 / QALY
Nusinersen	[redacted]	23.16 (23.06 to 23.27)	16.45 (14.90 to 17.93)						
BSC	[redacted]	22.86 (22.81 to 22.91)	13.67 (12.11 to 15.20)	[redacted]	0.30 (0.21 to 0.41)	2.78 (2.04 to 3.54)	[redacted]	[redacted]	[redacted]

Abbreviations: CI, confidence interval; ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years

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Table 88. Deterministic life years (discounted) per person disaggregated by health state, later onset population

Health state	Nusinersen	BSC	Incremental
Not sitting	[redacted]	[redacted]	[redacted]
Sitting without support	[redacted]	[redacted]	[redacted]
Standing with support	[redacted]	[redacted]	[redacted]
Walking independently	[redacted]	[redacted]	[redacted]

Table 89. Deterministic life years (discounted) per person disaggregated by treatment, later onset population

Treatment	Nusinersen	BSC	Incremental
Life years on nusinersen	[redacted]	[redacted]	[redacted]
Life years on BSC (following discontinuation)	[redacted]	[redacted]	[redacted]

Table 90. Deterministic QALYs (discounted) per person disaggregated by health state, later onset population

Health state	Nusinersen	BSC	Incremental
Not sitting	[redacted]	[redacted]	[redacted]
Sitting without support	[redacted]	[redacted]	[redacted]
Standing with support	[redacted]	[redacted]	[redacted]
Walking independently	[redacted]	[redacted]	[redacted]

Table 91. Impact of deterministic QALY increments (discounted) per person

Treatment	Nusinersen	BSC	Incremental
Active treatment utility increment	[redacted]	[redacted]	[redacted]
Caregiver utility increments	[redacted]	[redacted]	[redacted]

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Table 92. Deterministic health state costs per person disaggregated by health state, later onset population

Health state	Nusinersen	BSC	Incremental
Not sitting	[redacted]	[redacted]	[redacted]
Sitting without support	[redacted]	[redacted]	[redacted]
Standing with support	[redacted]	[redacted]	[redacted]
Walking independently	[redacted]	[redacted]	[redacted]

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B.3.10 Exploring uncertainty

B.3.10.1 Probabilistic sensitivity analysis

In the PSA, uncertain parameters in the model were each sampled from an appropriate distribution, fitted using the mean and SE associated with the uncertain parameter. In cases where the SE was unknown, it was assumed to be 10% of the mean value. Efficacy data from clinical trials reporting motor milestone achievement summed to 100% for each health state, therefore, a Dirichlet distribution was used. For other probabilities and utilities, beta distributions were used, while cost parameters were fitted with gamma distributions and relative risks were fitted with log normal distributions, as per recommendations from Briggs et al. Uncertainty around estimates provided by the regression equations were incorporated into the model by utilising the Cholesky matrix derived from the regression variance-covariance matrix. The final models used 2,000 iterations for each PSA run to allow for convergence.

B.3.10.1.1 Presymptomatic SMA model

In the model base case, convergence of the NMB was achieved after approximately 500 iterations. The convergence plot is presented in Figure 47.

Results from the PSA are presented in Table 73. The cost-effectiveness plane (Figure 48) presents the distribution of the incremental costs and QALYs generated for 2,000 iterations. The deterministic outcomes sit centrally within the PSA iterations, thereby increasing the certainty associated with the conclusions drawn in the deterministic model results. The points on the cost-effectiveness plane are distributed vertically, thereby showing more variation within the costs instead of the QALYs. Indeed, Table 73 shows a much wider 95% confidence interval for the incremental costs than the incremental QALYs. Therefore, given that, nusinersen accrued more QALYs than BSC in every PSA iteration, this adds certainty to the conclusion that nusinersen is an effective treatment. The wide range of costs supports the hypothesis that health state costs are key drivers of the cost-effectiveness. Nusinersen was found to be cost-effective, compared with BSC, in [redacted] of iterations at a cost-effectiveness threshold of £30,000. Please see Section B.3.11.1.1 and B.3.11.1.2 for the PSA results for the sub-populations with either 2 or 3 copies.

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Figure 47. Convergence plot for the presymptomatic SMA model



Figure 48. Cost-effectiveness plot for the presymptomatic SMA model



Figure 49. CEAC for the presymptomatic SMA model



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B.3.10.1.2 Type 1 SMA model

In the model base case, convergence of the NMB was achieved after approximately 500 iterations. The convergence plot is presented in Figure 50.

Results from the PSA are presented in Table 80. The deterministic incremental cost and QALY outcome sits centrally within the thickest cluster of the PSA iterations, thereby reducing the uncertainty associated with the conclusions drawn in the deterministic model results. The scatterplot shows long tails in both directions, suggesting greater uncertainty in the costs than the QALYs, and supporting the conclusion that health state costs are key drivers of the cost-effectiveness. Figure 51 shows nusinersen was cost-effective compared with BSC in [redacted] of cases in the probabilistic base case analysis. In these scenarios, cost-effectiveness was likely driven by a combination of sampling of the following parameters:

- Higher costs for permanent ventilation and lower costs for the remaining health states
- Lower utility estimates for permanent ventilation and higher utility estimates for the remaining health states
- A smaller proportion of the nusinersen cohort discontinuing treatment and initiating BSC.
- A higher proportion of the BSC, and a lower proportion of the nusinersen cohort, moving to permanent ventilation.

Figure 50. Convergence plot for the type 1 SMA model



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Figure 51. Cost-effectiveness plot for the type 1 SMA model



Figure 52. CEAC for the type 1 SMA model



B.3.10.1.3 Later-onset (type 2 and 3) SMA model

In the model base case, convergence of the NMB was achieved after approximately 500 iterations. The convergence plot is presented in Figure 53.

Results from the PSA are presented in Table 87. The deterministic incremental cost and QALY outcome sits centrally within the thickest cluster of points of the PSA iterations, indicating certainty around the base case deterministic outcomes. The spread of the incremental costs and QALYs [redacted] shows that treatment with nusinersen will increase overall quality of life for people with later-onset SMA. In contrast to Sections B.3.10.1.1 and B.3.10.1.2, there is a narrower distribution of incremental costs for the later-onset model and a slightly wider distribution of incremental QALYs than the presymptomatic and type 1 SMA models. This suggests that the incremental QALYs are key parameters in determining cost effectiveness. Furthermore, there is more certainty in the deterministic cost estimate.

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For all iterations of the PSA, nusinersen was cost-incurring in the later-onset population. Please see Section B.3.11.2.1 and B.3.11.2.2 for the PSA results for the type 2 and 3 sub-populations.

Figure 53. Convergence plot for the later-onset SMA model



Figure 54. Cost-effectiveness plot for the later-onset SMA model



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Figure 55. CEAC for the later-onset SMA model



B.3.10.2 Deterministic sensitivity analysis

Where possible, DSA was conducted by varying key input parameters within their 95% confidence interval. If the uncertainty estimates were not available in literature, an arbitrary range of ±20% around the mean was used.

B.3.10.2.1 DSA results - presymptomatic SMA model

The results of the top nine parameters identified using the DSA as the parameters that had the greatest impact on the ICER are shown in a tornado diagram (Figure 56) and summarised in Table 93. All parameters allowed for nusinersen to be within NICE's preferred cost-effectiveness thresholds of £20,000 and £30,000 per QALY gained. The top parameters within the DSA show that the time spent in the most severe, and therefore most costly, health states were key in determining cost-effectiveness. Parameters that had this effect included the per cycle discontinuation, and the relative risk of motor milestone decline. when the model allowed a smaller proportion of the cohort to either decline (move to a more severe motor milestone) or discontinue to BSC (moving to less efficacious treatment), compared to the base case. the cost of these severe health states caused nusinersen

None of the parameters caused the conclusion from the deterministic results to change. Therefore, for all parameters varied in the DSA, nusinersen was compared to BSC at a cost-effectiveness threshold of £30,000 per QALY.

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Table 93. DSA outcomes for the pre-symptomatic SMA model

Parameter	Base case parameter	Lower scenario		Higher scenario	
		Lower parameter	ICER	Higher parameter	ICER
Per-cycle health state costs: Not sitting (£30,000 to £45,000)	£37,500	£30,000	[redacted]	£45,000	[redacted]
Per-cycle health state costs: Sitting without support (£18,018 to £27,027)	£22,522	£18,018	[redacted]	£27,027	[redacted]
Per-cycle health state costs: Permanent ventilation (£75,656 to £113,484)	£94,570	£75,656	[redacted]	£113,484	[redacted]
Relative risk of decline (Nusinersen vs BSC) (0.35 to 0.52)	0.43	0.35	[redacted]	0.52	[redacted]
Per-cycle discontinuation in sitting without support (%) (2.5% to 3.8%)	3.1%	2.5%	[redacted]	3.8%	[redacted]
Per-cycle health state costs: Walking independently (£2,222 to £3,333)	£2,778	£2,222	[redacted]	£3,333	[redacted]
Per-cycle progression to permanent ventilation (%): BSC (1.4% to 2.0%)	1.7%	1.4%	[redacted]	2.0%	[redacted]
Per-cycle health state costs: Standing with support (£2,222 to £3,333)	£2,778	£2,222	[redacted]	£3,333	[redacted]
Per-cycle discontinuation in standing with support (%) (0.8% to 1.2%)	1.0%	0.8%	[redacted]	1.2%	[redacted]

Figure 56. Tornado diagram for the pre-symptomatic SMA model



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B.3.10.2.2 DSA results - Type 1 SMA model

The results of the top nine parameters identified using the DSA as the parameters that had the greatest impact on the ICER are shown in a tornado diagram (Figure 57) and summarised in Table 94.

The parameter that had the biggest impact on the ICER were the annual health state utilities. Given that the health state utility for 'permanent ventilation' is 0, the percentage change in the DSA does not allow it to increase or decrease with the other health states. Therefore, increasing or decreasing health state utilities will primarily impact the nusinersen QALYs, while the BSC QALYs will stay very similar.

Table 81 in the Section B.3.9.2 presents the deterministic disaggregated life years. They show that the cohort receiving BSC accrued most LYs in 'permanent ventilation', compared to those on nusinersen who accrued most live years in 'sitting without support'. It follows that lowering the costs for 'not sitting' and 'sitting without support' and increasing the cost for 'permanent ventilation' will cause the ICER to decrease, causing nusinersen to [redacted]. As per the DSA outcomes for the pre-symptomatic model, varying parameters that caused the cohort to spend less time in the more costly, severe health states, in particular, allowing higher percentage to remain on nusinersen by lowering the discontinuation rate and decreasing the percentage of the cohort declining, resulted in a lower ICER than the base case.

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Table 94. DSA outcomes for the type 1 SMA model

Parameter	Base case parameter	Lower scenario		Higher scenario	
		Lower parameter	ICER	Higher parameter	ICER
Health state utilities (Percentage change (-20%) to Percentage change (+20%))	Baseline	Percentage change (-20%)	[redacted]	Percentage change (+20%)	[redacted]
Per-cycle health state costs: Permanent ventilation (£76,034 to £113,106)	£94,570	£76,034	[redacted]	£113,106	[redacted]
Per-cycle health state costs: Not sitting (£30,150 to £44,850)	£37,500	£30,150	[redacted]	£44,850	[redacted]
Per-cycle health state costs: Sitting without support (£18,108 to £26,937)	£22,522	£18,108	[redacted]	£26,937	[redacted]
Per-cycle discontinuation for not sitting (%) (1.2% to 1.8%)	1.5%	1.2%	[redacted]	1.8%	[redacted]
Annual utility increments for the cohort on active treatment (0.08 to 0.12)	0.10	0.08	[redacted]	0.12	[redacted]
Annual caregiver utility (Percentage change (-20%) to Percentage change (+20%))	Baseline	Percentage change (-20%)	[redacted]	Percentage change (+20%)	[redacted]
Relative risk of decline (Nusinersen vs BSC) (0.39 to 0.59)	0.49	0.39	[redacted]	0.59	[redacted]
Per-cycle discontinuation for sitting without support (%) (1.2% to 1.8%)	1.5%	1.2%	[redacted]	1.8%	[redacted]

Figure 57. Tornado diagram for the type 1 SMA model



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B.3.10.2.3 DSA results - Later-onset (type 2 and 3) model

The results of the top nine parameters identified using the DSA as the parameters that had the greatest impact on the ICER are shown in a tornado diagram (Figure 58) and summarised in Table 95.

The results observed in the DSA support the PSA conclusions, adding greater certainty to the model structure and outcomes. Indeed, the top parameters found to be key in determining the cost-effectiveness were the annual health state utilities. Furthermore, annual utility increments caregiver utilities were also one of the nine key parameters.

Given that nusinersen helps the population to remain in the less severe health states for longer, it follows that reducing all utilities will decrease the QALYs, therefore [redacted] from cost-effectiveness. This is observed in Section B.10.3.2.2 for the type 1 SMA DSA. However, unlike the type 1 model, increasing utilities [redacted] from cost-effectiveness. This phenomenon occurred because the higher utilities were bound by the population norms. Given that the health state utility for 'walking independently' was assumed to be equivalent to the population norm in the base case, increasing this did not increase the QALY gain for time spent in this health state. This was the health state where the greatest incremental difference in life years were incurred. The increase in utility for the more severe health states offsets results in the overall QALYs for BSC increasing and offsetting the QALYs gained by the nusinersen cohort for the life years spent in the 'walking independently' health state.

Per cycle health state costs and probability of discontinuation were also important in determining cost-effectiveness, especially those influencing the 'sitting without support' health state. Indeed, for both treatment arms, most life years were within sitting without support. See Table 88 for the full breakdown in life years. Decreasing the discontinuation rate for the more severe health states results in [redacted] in the ICER, suggesting that nusinersen is [redacted] if utilised in the most severe people with later-onset SMA.

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Table 95. DSA outcomes for the later onset (type 2 and 3) SMA model

Parameter	Base case parameter	Lower scenario		Higher scenario	
		Lower parameter	ICER	Higher parameter	ICER
Annual health state utilities (Percentage change (-20%) to Percentage change (+20%))	Baseline	Percentage change (-20%)	[redacted]	Percentage change (+20%)	[redacted]
Per-cycle health state costs: Sitting without support (£18,018 to £27,027)	£22,522	£18,018	[redacted]	£27,027	[redacted]
Annual utility increments for the cohort on active treatment (0.08 to 0.12)	0.10	0.08	[redacted]	0.12	[redacted]
Per-cycle health state costs: Not sitting (£30,000 to £45,000)	£37,500	£30,000	[redacted]	£45,000	[redacted]
Per-cycle discontinuation in sitting without support (%) (2.5% to 3.8%)	3.1%	2.5%	[redacted]	3.8%	[redacted]
Per-cycle discontinuation in standing with support (%) (0.8% to 1.2%)	1.0%	0.8%	[redacted]	1.2%	[redacted]
Per-cycle discontinuation in walking independently (%) (0.8% to 1.2%)	1.0%	0.8%	[redacted]	1.2%	[redacted]
Per-cycle discontinuation in not sitting (%) (2.5% to 3.8%)	3.2%	2.5%	[redacted]	3.8%	[redacted]

Figure 58. Tornado diagram for the later-onset SMA model

[redacted]

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B.3.10.3 Scenario analysis

B.3.10.3.1 Presymptomatic SMA

For presymptomatic SMA, six probabilistic scenario analyses were conducted. These scenario analyses are summarised in Table 96 and their results presented in Table 97.

The cost-effectiveness outcome changed in [redacted]. When the health state costs were sourced from TA588 this caused the values to decrease for the 'permanent ventilation', 'not sitting', 'sitting without support' health states but increase for the 'standing with support' and 'walking independently' health states. As nusinersen patients spend more time in standing and walking health states, relative to BSC, this caused a [redacted] for that particular scenario. For all other scenarios, the ICER remained[redacted].

B.3.10.3.2 Type 1 SMA

Six probabilistic scenario analyses were conducted. These scenario analyses are summarised in Table 96 and their results presented in Table 98.

The cost-effectiveness outcome changed in [redacted] This scenario was included to explore the impact of health state costs on the overall results. As described in Section B.3.9, in the type 1 population, nusinersen causes gains in both life years and QALYs but the majority of this time is spent in the 'not sitting' and 'sitting without support' health states. However, these health states are associated with very large background costs of £112,500 and £67,567. [redacted]. This also means that nusinersen [redacted] the more it increases survival amongst the type 1 population. Therefore, within this scenario, these background costs were removed for the period of additional survival associated with nusinersen (i.e. health state costs were £0 from the point at which the mean life years for BSC was exceeded). [redacted]

When the health state costs for nusinersen were set to £0 following the discounted life years observed in the BSC cohort, the average ICER nusinersen was [redacted] because of the substantial decrease in health state costs for nusinersen patients.

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B.3.10.3.3 Later-onset (type 2 and 3) SMA

For the total population with later-onset SMA, four probabilistic scenario analyses were conducted. These scenario analyses are summarised in Table 96 and their results presented in Table 99.

The cost-effectiveness conclusion [redacted]. This scenario was using utility values elicited by experts in TA588. When compared to the utilities in the base case analysis, TA588 attributed lower utility value to the ‘not sitting’ and the ‘sitting without support’ health states and similar values were attributed to the ‘standing with support’ and ‘walking independently’ health states. Given that the cohort on BSC spent longer in the more severe health states than the cohort on nusinersen, reducing the utility for these health states increased the incremental QALYs, [redacted]

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Table 96. Scenario analyses explored

Parameter	Base case assumption	Scenarios	Rationale
HRQoL • Pre-symptomatic • Type 1 SMA • Later-onset SMA	Values as per HST24, originally from Thompson et al. 2017. (Section 3.4.5)	Based on input from clinical advisors of the nusinersen NICE appraisal (TA588) and applied in the risdiplam NICE appraisal (TA755). See Section 3.4.5, Table 58 for the utility values used in this scenario.	Some alternative health state utility values were identified in the NICE TA588 (and NICE TA755) and were tested in a scenario as described.
HRQoL • Pre-symptomatic • Type 1 SMA • Later-onset SMA	An annual utility increment (0.1) applied for people on active treatment to account for additional treatment benefit	No utility increment due to treatment effect (Section B.3.4.5)	Based on clinical advice and previous economic evaluations (US ICER assessment and in the ERG-preferred base case in HST15), it is expected that there would be some difference in quality of life in treated and untreated patients and it would be reasonable to assume additional quality of life benefit for treated patients. The impact is uncertain and therefore, a scenario whereby there is no impact of treatment on HRQoL is investigated.
Health state costs • Pre-symptomatic • Type 1 SMA • Later-onset SMA	Health state costs from HST24	Health state costs from TA588 (Wickenstones, Section B.3.5.2)	There is uncertainty over the most appropriate health state costs to utilised in the model so alternative values were explored, based on a previous NICE appraisal.
Health state costs • Type 1 SMA	Health state costs applied for the full time horizon	Health state costs for active treatments set to £0 after the BSC cohort has died	Patients in the type 1 model spend the majority of time in the 'not sitting' and 'sitting without support' health states, due to the nature of the disease. However, these health states are associated with very large background costs of £112,500 and £67,567. [redacted].
Decline	No long term decline for nusinersen	The relative risk for nusinersen is set to 0% (Section B.3.3)	The current model assumes nusinersen patients can decline from the point of nusinersen clinical trial programme ends, with no possibility of improvement from this timepoint, which is a conservative assumption. This scenario explores a more optimistic extrapolation of long-term benefits with nusinersen whereby the benefits achieved during the nusinersen trial programme are maintained in the long-term.
Decline	Halved rates of decline for BSC and nusinersen	The rate of decline for BSC is halved (Section B.3.3)	There is uncertainty over the long-term rates of decline for those patients that attain gross motor milestones. This scenario explores slower rates for both treatment arms.

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Table 97. Presymptomatic SMA scenario analysis results

Scenario	Incremental life years	Incremental QALYs	Incremental costs	ICER
Base case	0.92	5.92	[redacted]	[redacted]
Alternate utility source: TA588	0.97 (0.70 to 1.24)	6.80 (5.57 to 8.04)	[redacted]	[redacted]
Exclude caregiver utility increments	0.97 (0.70 to 1.24)	5.36 (4.37 to 6.30)	[redacted]	[redacted]
Exclude active treatment utility increments	0.97 (0.70 to 1.24)	4.80 (3.86 to 5.78)	[redacted]	[redacted]
Costs from TA588 (Wickenstones)	0.97 (0.70 to 1.24)	5.91 (4.81 to 7.03)	[redacted]	[redacted]
No long-term decline for nusinersen	2.28 (1.03 to 3.86)	9.81 (6.06 to 14.05)	[redacted]	[redacted]
Halved rates of decline for BSC and nusinersen	1.13 (0.75 to 1.55)	6.77 (5.23 to 8.37)	[redacted]	[redacted]

Table 98. Type 1 SMA scenario analysis results

Scenario	Incremental life years	Incremental QALYs	Incremental costs	ICER
Base case	5.32 (3.85 to 6.65)	4.70 (3.73 to 5.66)	[redacted]	[redacted]
Alternate utility source: TA588	5.32 (3.85 to 6.65)	3.11 (2.45 to 3.78)	[redacted]	[redacted]
Exclude caregiver utility increments	5.32 (3.85 to 6.65)	4.06 (3.27 to 4.82)	[redacted]	[redacted]
Exclude active treatment utility increments	5.32 (3.85 to 6.65)	4.00 (3.12 to 4.87)	[redacted]	[redacted]
Costs from TA588 (Wickenstones)	5.32 (3.85 to 6.65)	4.70 (3.73 to 5.66)	[redacted]	[redacted]
Background care costs remove for extended years survived	5.32 (3.85 to 6.65)	4.70 (3.73 to 5.66)	[redacted]	[redacted]
No long term decline for nusinersen	5.80 (4.23 to 7.24)	5.38 (4.27 to 6.49)	[redacted]	[redacted]
Halved rates of decline for BSC and nusinersen	5.46 (3.95 to 6.84)	4.91 (3.89 to 5.91)	[redacted]	[redacted]

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Table 99. Later-onset (types 2 and 3) SMA scenario analysis results

Scenario	Incremental life years	Incremental QALYs	Incremental costs	ICER
Base case	0.30 (0.21 to 0.41)	2.78 (2.04 to 3.54)	[redacted]	[redacted]
Alternate utility source: TA588	0.30 (0.21 to 0.41)	3.60 (2.70 to 4.52)	[redacted]	[redacted]
Exclude caregiver utility increments	0.30 (0.21 to 0.41)	2.55 (1.87 to 3.24)	[redacted]	[redacted]
Exclude active treatment utility increments	0.30 (0.21 to 0.41)	1.75 (1.10 to 2.38)	[redacted]	[redacted]
Costs from TA588 (Wickenstones)	0.30 (0.21 to 0.41)	2.78 (2.04 to 3.54)	[redacted]	[redacted]
No long term decline for nusinersen	0.75 (0.36 to 1.27)	4.30 (2.49 to 6.35)	[redacted]	[redacted]
Halved rates of decline for BSC and nusinersen	0.20 (0.12 to 0.29)	2.58 (1.76 to 3.43)	[redacted]	[redacted]

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B.3.11 Subgroup analysis

B.3.11.1 Presymptomatic subgroup analysis

The base case ICER was calculated for the total pre-symptomatic population. In acknowledgment with the final scope, deterministic, DSA, and PSA results for people with 2 and 3 copies of the SMN2 gene are presented in this section.

B.3.11.1.1 Presymptomatic SMA with 2 copies of the SNM2 gene

For the sub-population with 2 copies of the SNM2 gene, [redacted] (see Figure 59). The same conclusion is drawn in the PSA across all of the 2,000 iterations, indicating that the likelihood of cost-effectiveness was [redacted] The deterministic ICER sits centrally in the cost-effectiveness plane. The distribution of points is vertical, suggesting that health state costs are a key parameter in determining cost-effectiveness. The QALY 95% confidence interval is relatively small, thereby decreasing any uncertainty around the QALY estimates.

The DSA results give further evidence to the importance of the health state costs. An increase in the cost of the health states that are more severe (not sitting and permanent ventilation) and a decrease in the costs of the health states that are less severe (sitting without support) [redacted]. Similarly, increasing annual utility values, particularly in the less severe health states, [redacted]

Other key parameters influence the time spent in the more severe health states, and therefore the total costs in these health states. Decreasing the percentage discontinuing from nusinersen in the sitting without support health state and allowing fewer people to decline also [redacted]. [redacted]

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Table 100. Deterministic base-case results for the presymptomatic SMA sub-population with 2 copies of SMN2

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER versus baseline (£/QALY)	NHB
Nusinersen	[redacted]	20.84	14.59					
BSC	[redacted]	19.91	8.67	[redacted]	0.92	5.92	[redacted]	[redacted]

Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years

Table 101. Probabilistic base-case results for the presymptomatic SMA sub-population with 2 copies of SMN2

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER versus baseline (£/QALY)	Likelihood of cost-effectiveness at £30,000/QALY	NHB
Nusinersen	[redacted]	18.32 (17.61 to 18.93)	11.10 (9.95 to 12.20)						
BSC	[redacted]	16.61 (15.69 to 17.41)	4.50 (3.61 to 5.45)	[redacted]	1.71 (1.34 to 2.13)	6.60 (5.68 to 7.48)	[redacted]	[redacted]	[redacted]

Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years; NHB, net health benefit

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Figure 59. Cost effectiveness plane for the presymptomatic SMA sub-population with 2 copies of SMN2



Table 102. Deterministic sensitivity analysis results for the presymptomatic SMA sub-population with 2 copies of SMN2

Parameter	Base case parameter	Lower scenario		Higher scenario	
		Lower parameter	ICER	Higher parameter	ICER
Per-cycle health state costs: Not sitting (£30,000 to £45,000)	£37,500	£30,000	[redacted]	£45,000	[redacted]
Per-cycle health state costs: Permanent ventilation (£75,656 to £113,484)	£94,570	£75,656	[redacted]	£113,484	[redacted]
Per-cycle discontinuation in sitting without support (%) (2.5% to 3.8%)	3.1%	2.5%	[redacted]	3.8%	[redacted]
Relative risk of decline (Nusinersen vs BSC) (0.39 to 0.59)	0.49	0.39	[redacted]	0.59	[redacted]
Per-cycle progression to permanent ventilation (%): BSC (1.4% to 2.0%)	1.7%	1.4%	[redacted]	2.0%	[redacted]
Per-cycle discontinuation in not sitting (%) (2.5% to 3.8%)	3.2%	2.5%	[redacted]	3.8%	[redacted]
Per-cycle health state costs: Sitting without support (£18,018 to £27,027)	£22,522	£18,018	[redacted]	£27,027	[redacted]
Annual health state utilities (Percentage change (-20%) to Percentage change (+20%))	Baseline	Percentage change (-20%)	[redacted]	Percentage change (+20%)	[redacted]
Per-cycle health state costs: Standing with support (£2,222 to £3,333)	£2,778	£2,222	[redacted]	£3,333	[redacted]

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Figure 60. Tornado plot for the presymptomatic SMA sub-population with 2 copies of SMN2



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B.3.11.1.2 Presymptomatic SMA with 3 copies of the SNM2 gene

Nusinersen was [redacted] for the sub-population with 3 copies for the SMN2 gene, resulting in a deterministic ICER of [redacted] per QALY gained and a probabilistic ICER of [redacted] per QALY gained. Nusinersen was cost-effective in [redacted] of iterations for this sub-population during the PSA. The deterministic ICER sits centrally in the PSA scatter plot, indicating certainty in the overall cost-effectiveness outcomes. Incremental QALYs and costs are distributed evenly around deterministic mean, suggesting that there is equal certainty in the costs and QALY estimates. This is supported by the DSA, which found that the cost and utility estimates were the key parameters in determining the cost-effectiveness. A small increase the costs in the most severe health states, (i.e. sitting without support and not sitting) [redacted].

The utility values are bound by the population norms and the utility estimate for walking independently is assumed to be equivalent to the population norm. Population norms are not directly changed in the sensitivity analysis therefore, when the utility values are increased, the people in the higher health state (predominantly those on nusinersen) do not receive any additional benefit. However, population norms can be indirectly increased and decreased as they are weighted by age and sex. When the population norms are increased indirectly by varying the distribution of males and females, the utility estimate for walking independently increases.

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Table 103. Deterministic base-case results for the presymptomatic SMA sub-population with 3 copies of SMN2

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER versus baseline (£/QALY)	NHB
Nusinersen	[redacted]	23.90	20.65					
BSC	[redacted]	23.49	14.90	[redacted]	0.41	5.75	[redacted]	[redacted]

Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years

Table 104. Probabilistic base-case results for the presymptomatic SMA sub-population with 3 copies of SMN2

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER versus baseline (£/QALY)	Likelihood of cost-effectiveness at £30,000/QALY	NHB
Nusinersen	[redacted]	23.99 (23.67 to 24.38)	20.68 (18.56 to 22.77)						
BSC	[redacted]	23.49 (23.37 to 23.60)	14.84 (13.67 to 15.99)	£[redacted]	0.50 (0.18 to 0.89)	5.84 (3.91 to 7.85)	[redacted]	[redacted]	[redacted]

Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years; NHB, net health benefit

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Figure 61. Cost effectiveness plane for the presymptomatic SMA sub-population with 3 copies of SMN2



Table 105. Deterministic sensitivity analysis results for the presymptomatic SMA sub-population with 3 copies of SMN2

Parameter	Base case parameter	Lower scenario		Higher scenario	
		Lower parameter	ICER	Higher parameter	ICER
Per-cycle health state costs: Sitting without support (£18,018 to £27,027)	£22,522	£18,018	[redacted]	£27,027	[redacted]
Per-cycle health state costs: Not sitting (£30,000 to £45,000)	£37,500	£30,000	[redacted]	£45,000	[redacted]
Annual health state utilities (Percentage change (-20%) to Percentage change (+20%))	Baseline	Percentage change (-20%)	[redacted]	Percentage change (+20%)	[redacted]
Per-cycle health state costs: Walking independently (£2,222 to £3,333)	£2,778	£2,222	[redacted]	£3,333	[redacted]
Per-cycle discontinuation in walking independently (%) (0.8% to 1.2%)	1.0%	0.8%	[redacted]	1.2%	[redacted]
Annual utility increments for the cohort on active treatment (0.08 to 0.12)	0.10	0.08	[redacted]	0.12	[redacted]
Annual caregiver utilities (Percentage change (-20%) to Percentage change (+20%))	Baseline	Percentage change (-20%)	[redacted]	Percentage change (+20%)	[redacted]
Per-cycle health state costs: Permanent ventilation (£75,656 to £113,484)	£94,570	£75,656	[redacted]	£113,484	[redacted]
Sex (female, %) (31% to 89%)	60%	31%	[redacted]	89%	[redacted]

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Figure 62. Tornado plot for the presymptomatic SMA sub-population with 3 copies of SMN2



B.3.11.2 Later-onset (type 2 and 3) SMA subgroup analysis

B.3.11.2.1 Sub-population with type 2 SMA

For the sub-population with type 2 SMA, the deterministic and probabilistic total costs were found to be marginally higher and the total QALYs were marginally lower and closer together. This was caused by the severity of type 2 SMA compared to later onset. The population on nusinersen spend longer in more severe health states, and, therefore, the incremental cost increases and the incremental QALYs decrease resulting in [redacted] than the later-onset population. The cost-effectiveness conclusion [redacted].

The wide distribution of iterations on the scatter plot highlight that the utilities are key in determining the cost-effectiveness of nusinersen. This is supported by DSA outcomes. The top two parameters show that when the utility increment for nusinersen or annual health state utilities are increased the [redacted].

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Table 106. Deterministic base-case results for type 2 later-onset SMA sub-population

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER versus baseline (£/QALY)	NHB
Nusinersen	[redacted]	21.80	12.46					
BSC	[redacted]	21.54	10.90	[redacted]	0.26	1.55	[redacted]	[redacted]

Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years

Table 107. Probabilistic sensitivity analysis results for type 2 later-onset SMA sub-population

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER versus baseline (£/QALY)	Likelihood of cost-effectiveness at £30,000/QALY	NHB
Nusinersen	[redacted]	21.82 (21.73 to 21.92)	12.49 (10.92 to 14.07)						
BSC	[redacted]	21.54 (21.51 to 21.57)	10.91 (9.50 to 12.35)	[redacted]	0.28 (0.19 to 0.38)	1.58 (1.22 to 1.99)	[redacted]	[redacted]	[redacted]

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Figure 63. Cost effectiveness plane for the type 2 later-onset SMA sub-population



Table 108. Deterministic sensitivity analysis results for type 2 later-onset SMA sub-population

Parameter	Base case parameter	Lower scenario		Higher scenario	
		Lower parameter	ICER	Higher parameter	ICER
Annual utility increments for the cohort on active treatment (0.08 to 0.12)	0.10	0.08	[redacted]	0.12	[redacted]
Annual health state utilities (Percentage change (-20%) to Percentage change (+20%))	Baseline	Percentage change (-20%)	[redacted]	Percentage change (+20%)	[redacted]
Per-cycle discontinuation in sitting without support (%) (2.5% to 3.8%)	3.1%	2.5%	[redacted]	3.8%	[redacted]
Per-cycle health state costs: Not sitting (£30,000 to £45,000)	£37,500	£30,000	[redacted]	£45,000	[redacted]
Per-cycle discontinuation in not sitting (%) (2.5% to 3.8%)	3.2%	2.5%	[redacted]	3.8%	[redacted]
Per-cycle health state costs: Sitting without support (£18,018 to £27,027)	£22,522	£18,018	[redacted]	£27,027	[redacted]
Per-cycle discontinuation in standing with support (%) (0.8% to 1.2%)	1.0%	0.8%	[redacted]	1.2%	[redacted]
Annual caregiver utilities (Percentage change (-20%) to Percentage change (+20%))	Baseline	Percentage change (-20%)	[redacted]	Percentage change (+20%)	[redacted]
Baseline health state occupancy (Lower 95% CI to Upper 95% CI)	Baseline	Lower 95% CI	[redacted]	Upper 95% CI	[redacted]

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Figure 64. Tornado plot for the type 2 later-onset SMA sub-population



B.3.11.2.2 Sub-population with type 3 SMA

Interestingly, the ICERs for the deterministic and probabilistic results are more similar for the sub-population type 2 SMA than later-onset SMA. This is a result of the BSC population spending initiating the model in the walking independently motor milestone and, therefore, the health state costs accrued are smaller than more severe SMA types. Therefore, the costs for treatment had a large impact on the incremental costs, resulting in [redacted] compared with the total presymptomatic population.

The distribution of points cost-effectiveness plane was like that observed in the type 2 sub-population, in that the QALYs had a large impact on the ICER (Section B.3.11.2.1). This was supported by DSA results, in which annual utility estimates and utility increment for nusinersen were found to be the top 2 key parameters. The effect of utilities observed is consistent with the total later onset population. The appearance of sex in the diagram also adds weight to the importance of utility estimates. The reason for sex

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appearing in the tornado diagram is described in the sub-population results for the pre-symptomatic population with 3 copies (Section B.3.11.1.2).

Table 109. Deterministic results for type 3 later-onset SMA sub-population

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER versus baseline (£/QALY)	NHB
Nusinersen	[redacted]	25.71	24.60					
BSC	[redacted]	25.55	21.68	[redacted]	0.15	2.92	[redacted]	[redacted]

Table 110. Probabilistic sensitivity analysis results for type 3 later-onset SMA sub-population

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER versus baseline (£/QALY)	Likelihood of cost-effectiveness at £30,000/QALY	NHB
Nusinersen	[redacted]	25.74 (25.63 to 25.88)	24.17 (21.67 to 26.00)						
BSC	[redacted]	25.55 (25.53 to 25.57)	21.27 (19.36 to 22.78)	[redacted]	0.19 (0.08 to 0.33)	2.90 (1.69 to 4.24)	[redacted]	[redacted]	[redacted]

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Figure 65. Cost effectiveness plane for the type 3 later-onset SMA sub-population



Table 111. Deterministic sensitivity analysis results for type 3 later-onset SMA sub-population

Parameter	Base case parameter	Lower scenario		Higher scenario	
		Lower parameter	ICER	Higher parameter	ICER
Annual health state utilities (Percentage change (-20%) to Percentage change (+20%))	Baseline	Percentage change (-20%)	[redacted]	Percentage change (+20%)	[redacted]
Annual utility increments for the cohort on active treatment (0.08 to 0.12)	0.10	0.08	[redacted]	0.12	[redacted]
Per-cycle discontinuation in walking independently (%) (0.8% to 1.2%)	1.0%	0.8%	[redacted]	1.2%	[redacted]
Per-cycle health state costs: Sitting without support (£18,018 to £27,027)	£22,522	£18,018	[redacted]	£27,027	[redacted]
Annual caregiver utilities (Percentage change (-20%) to Percentage change (+20%))	Baseline	Percentage change (-20%)	[redacted]	Percentage change (+20%)	[redacted]
Per-cycle discontinuation in standing with support (%) (0.8% to 1.2%)	1.0%	0.8%	[redacted]	1.2%	[redacted]
Per-cycle health state costs: Walking independently (£2,222 to £3,333)	£2,778	£2,222	[redacted]	£3,333	[redacted]
Sex (female, %) (38% to 60%)	49%	38%	[redacted]	60%	[redacted]
Per-cycle health state costs: Not sitting (£30,000 to £45,000)	£37,500	£30,000	[redacted]	£45,000	[redacted]

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Figure 66. Tornado plot for the type 3 later-onset SMA sub-population



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B.3.12 Validation

B.3.12.1 Validation of cost-effectiveness analysis

A technical validation of all three models was undertaken with a primary focus of checking that the formulae with the models were correct and appropriately applied. A quality assurance checklist was used as the starting point for the technical validation exercise. This checklist included a range of tests, including sense checks, for instance, changing certain inputs to zero and confirming that the observed effect was as expected. If unexpected results were generated the cause of this was explored in detail to ensure errors did not exist within the model formulae. Alongside the application of the checklist, a series of ad hoc checks were completed to examine the elements of the model that are key to deriving the results (i.e. the main engine of the models). These were completing by reviewing the formulae that were applied to ensure these were implemented without error. This internal validation process was undertaken by a health economist who was not directly involved in the conceptualisation and development of the models.

The face validity of the models was also examined during the UK Advisory Board. This was achieved by describing the model structure and inputs to UK clinical experts and health economists to ensure the suggested approach appropriately captured costs and outcomes for UK clinical practice. Specific revisions were made to the model upon the advice received.

B.3.13 Interpretation and conclusions of economic evidence

Despite the challenges of fully capturing the benefits of nusinersen due to the floor and ceiling effect of the scales, efficacy outcomes showed long-term benefits of treatment with nusinersen that are inconsistent with the progressive decline seen in the natural history of infantile-onset and later-onset SMA. This is shown by the results of the nusinersen clinical trial programme. For example, during the ENDEAR trial the risk of death or permanent ventilation was 47% lower compared with sham control (p=0.046) for the infantile-onset population. Also, 51% of nusinersen patients achieved a motor milestone response, as measured by HINE-2, versus 0% in the sham control arm.

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For the later-onset population, clinically meaningful differences in HFMSE scores (5.9, $p<0.05$) and RULM (3.7, $p<0.05$) were shown in the CHERISH trial for nusinersen versus sham control. Due to the outcomes measure during ENDEAR and CHERISH they were terminated early to remove patients from the sham control arm. In terms of the pre-symptomatic population, data were available from the single-arm NUTURE trial and showed that 23 out of 25 nusinersen patients were able to walking independently following treatment.

The benefits generated by nusinersen are highlighted further in the cost-effectiveness outcomes, particularly when administered early. This was shown by the QALY gains in the outcomes for presymptomatic and type 1 SMA patients: 5.91 (95% CI: 4.81 to 7.03), 4.70 (95% CI: 3.73 to 5.66) respectively. Clinical experts for TA588 and the EAG in TA755 found that, for those who require permanent ventilation, their utility was the same as or worse than death. For the type 1 population, the model predicted treatment would reduce the average time spent in this state by 1.35 years and even allow patients to achieve milestones like sitting without support, standing with support and walking independently that would have otherwise been unattainable. When treatment was administered later, nusinersen was still highly effective, as shown by the 2.78 (95% CI: 2.04 to 3.54) gain in QALYs for the type 2/3 SMA results. Indeed, for the PSA undertaken for all populations and sub-populations of people with SMA, nusinersen consistently increased the HRQoL.

Thorough research was undertaken during the conceptualisation of the economic models to ensure that they adhered as closely as possible to the real-world setting. Research included extensive clinical and economic literature searches (as provided in Appendix D and Appendix G). Furthermore, previous models developed for the treatment of SMA were carefully reviewed, including the previous cost-effectiveness models submitted to NICE (TA588, TA755, HST15 and HST24). EAG and Committee critique were taken onboard, and the model structure was adapted accordingly. Economic assessments in other countries, including the model developed by ICER in the US and the model submitted to CADTH in Canada were also reviewed in SMA.

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This research was supplemented by advice from experts in health economic modelling and clinical experts specialising in SMA. Feedback from these experts allowed the model to adhere closely with a real-world setting, especially when determining the most appropriate way of modelling long-term decline and the selection of the most appropriate motor milestones. This was particularly pertinent given the data gaps that existed, which is to be expected given the fact that SMA is a rare disease. In particular, there was no long-term data to show how effective treatment will be over a person's lifetime. While the SHINE trial provided up to 8 years of efficacy data, uncertainty remains with respect to the longer-term outcomes. As per clinical advice, the models included a per-cycle probability of decline allowing decline to predict how soon patients would lose any gross motor milestones that had previously been achieved. However, the probability of decline required assumptions as, again, there was no robust long-term data to inform this for nusinersen. This approach may also have been conservative for nusinersen as it assumed that patients receiving nusinersen would be unable to attain additional gross motor milestones following the SHINE follow-up period and there is no evidence to prove that is the reality.

The model uses health states that are based on the achievement of gross motor milestones and this was again validated by experts at an advisory board. However, interim motor milestones, including head control, rolling, and crawling, and other measures of efficacy, including upper body function (as measured by RULM) were not captured as explicit health states in the model. It could be argued that the inclusion of additional, interim health states would more accurately capture the benefits of nusinersen on HRQoL and costs. However, because of the rarity of SMA and the small populations included in the clinical trials, there is a paucity of robust data to inform a more granular approach.

Overall, since most of the key approaches and assumptions in the base-case analysis of the economic evaluation are either conservative in nature, in line with UK clinical expert opinion, or based on precedent from prior economic models, it is believed that the base-case cost-effectiveness results presented are an appropriate basis for NICE decision-making.

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Based on the comprehensive economic analysis presented, nusinersen demonstrated a consistent improvement in efficacy outcomes across all populations considered in the models and all scenarios. Furthermore, it was found to not only be cost-effective but dominant compared to BSC in a subset of patients. Results from the economic model should be viewed with the consideration that SMA is a severe and rare genetic disorder and meets the criteria for a severity modifier in infantile onset (type 1) SMA. Furthermore in this specific population, nusinersen extends survival but patients remain with complex care needs and high resource use, removing disease management costs in these extended years survived, dramatically improves cost-effectiveness. Natural history studies and clinical expert opinion emphasise the large impact on the HRQoL of the infants, children and adults who are afflicted, as well as their caregivers. There is a high remaining unmet need for patients who are either not eligible to receive onasemnogene or for whom onasemnogene is not reimbursed. Nusinersen offers a valuable, efficacious, and clinically relevant additional therapeutic option for all patients across the continuum of SMA.

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NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Multiple technology appraisal

Nusinersen for treating spinal muscular atrophy. Review of TA588

Addendum

Revised Modelling of Caregiver Impact - Cost-Effectiveness Estimates

January 2025

File name	Version	Contains confidential information	Date
ID6195 Nusinersen for treating 5qSMA_Cost-effectiveness results addendum [redacted]	**V1.0**	**No**	**9th January 2025**

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Description of the issue

Following the sharing of the cost-effectiveness models and Assessment report produced by the Warwick External Assessment Group (EAG), the approach to quantifying both patient and carer QALYs in the Biogen models were reviewed to cross-check the methods that were utilised. During the process, a small number of issues were identified in the methods that had been applied in the original Biogen company submission. These issues, and the updates that have been made to rectify them, are described below.

Caregiver Mortality

Within the formula that have been used to estimate the caregiver QALYs for all health states, a statement was incorporated to adjust for caregiver mortality (i.e. the survival of caregivers was tracked over time, using general population mortality data, and QALYs stopped accumulating once the caregiver had died). However, upon reflection, it has been judged that the patient would still need caregiver support, even if one caregiver has died. Therefore, that original caregiver would be replaced by a different family member or friend. As such, the statement related to caregiver mortality was removed from all relevant formula and this removes caregiver mortality from the calculations of caregiver QALY. This, in turn, has meant the total caregiver QALYs have increased in all three models.

The updates have been made to the formula in the cells listed below (by model) on the ‘Markov trace’ sheet:

- Pre-symptomatic model: cells CT50:CX349
- Type 1 model: cells CU50:CY349
- Type 2/3 model: cells CI51:CL350

Mean Number of Caregivers

As noted in the original Biogen submission, it was assumed that people with SMA would require fewer carers once they achieved the ability to stand (and subsequently walk) and, for this reason, the number of caregivers differed by health state in all models. More specifically, 2 caregivers were assigned to the ‘permanent ventilation’, ‘not sitting’ and ‘sitting’ health states, whereas 1 caregiver was assigned to the ‘standing’ and ‘walking’ health states. However, upon review of the model, it is clear that this approach leads to QALY estimates that lack face validity. This is because the drop in caregiver numbers, when patients transition to the ‘standing’ health state, means that the total accumulated caregiver QALYs will be lower in the ‘standing’ and ‘walking’ health states. This occurs because the total number of caregivers is lower in these health states and is despite the fact that caregiver utility increases for these states. An example is provided below, to illustrate the issue.

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In the original pre-symptomatic model submitted by Biogen, the ‘sitting’ health state is associated with a mean number of caregivers of 2.00 and a caregiver utility of 0.63. Therefore, the total caregiver QALYs for a patient in this health state would be 1.26 over a one year period. Alternatively, the mean number of caregivers in the ‘standing’ health state is 1.00 with a utility of 0.77, which equates to total annual caregiver QALYs of 0.77. This means, patients in the ‘sitting’ health state accumulate an additional 0.49 caregiver QALYs per year, despite the caregivers having a lower utility whilst patients are in that health state.

To resolve this issue, all three models have been updated so that the mean number of caregivers in all health states is 1.

The updates have been made on the ‘Utilities’ sheet, to cells E45:E49 in the pre-symptomatic and type 1 models, and to cells E44:E47 in the type 2/3 model.

Caregiver utilities by health state

As stated in the original Biogen company submission: “equivalent health state caregiver utility increments have been applied to all three models, based on the assumption that it is the health state itself, and not the type of SMA, that determines the impact of the disease on patient health-related quality of life.” These caregiver utilities were based on the EAG preferences from TA755 and are presented in Table 1. However, upon review of the model, it was noted that the data from TA755 was not used consistently across all three models. More specifically, within both the type 1 model and the type 2/3 model the utility for certain health states were taken from the revised base case submitted by Biogen, following the circulation of the Appraisal Consultation Document, for the original nusinersen SMA appraisal [TA588]. All data were taken from Table 15 (p23) of Appendix 2 of the Biogen resubmission and were based on the ‘wide range’ values that were reported – see Table 2 for a summary. Therefore, the data that were applied in the original submission were misreported.

Table 1: Summary of caregiver utilities taken from TA755 and reported in the Biogen company submission

Health state	Caregiver utilities from TA755
Permanent ventilation	0.48
Not sitting	0.48
Sitting without support	0.63
Standing with support	0.77
Walking	Population norm

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Table 2: Summary of the caregiver utilities that were applied in the type 1 and type 2/3 models in the original Biogen submission

Health state	Utility in T1 model	Details about source	Utility in T2/3 model	Details about source
Permanent ventilation	0.48	Early Onset – No Milestone Achieved	N/A	N/A
Not sitting	0.59	Later Onset – Sits and Rolls Independently	0.48	Early Onset – No Milestone Achieved
Sitting without support	0.70	Early Onset – Sits Without Support	0.59	Later Onset – Sits and Rolls Independently
Standing with support	0.81	Later Onset – Stands/Walks With Assistance	0.81	Later Onset – Stands/Walks With Assistance
Walking	Population norm		Population norm	

To rectify this issue, the type 1 and type 2/3 models have been updated so that the carer utilities for all health states align with the values reported in Table 1.

Additive versus Multiplicative methods

Within all three models that were developed for the original Biogen submission, utilities were adjusted to account for aging (i.e. utilities will decline over time naturally), which is in-line with the NICE methods guide[1]. Within the same section of the NICE manual (Section 4.3.7) it is noted that, when adjusting utilities to account for age and co-morbidities, a multiplicative approach is preferred. However, upon review, it was noted that an additive approach was used in the original models submitted by Biogen. Therefore, to more closely align with the current NICE manual, the patient QALY calculations in all three models were updated to use a multiplicative approach to adjust utilities over time.

The updates were made to the formula in the cells listed below (by model) on the 'Markov trace' sheet:

- Pre-symptomatic model: cells CI50:CM349
- Type 1 model: cells CJ50:CN349
- Type 2/3 model: cells BY51:CB350

[1] NICE health technology evaluations: the manual [PMG36]. Available from: https://www.nice.org.uk/process/pmg36

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Results

The results from the original Biogen submission, and following the updates described in this addendum, are display for all three models in Table 3 to Table 8.

Table 3: Deterministic Results from the Pre-Symptomatic Model – Original Submission

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)	NHB at £30,000 / QALY
Nusinersen	[redacted]	14.59				
BSC	[redacted]	8.67	[redacted]	5.92	[redacted]	[redacted]

Table 4: Deterministic Results from the Pre-Symptomatic Model – Updated

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)	NHB at £30,000 / QALY
Nusinersen	[redacted]	16.85				
BSC	[redacted]	8.75	[redacted]	8.10	[redacted]	[redacted]

Table 5: Deterministic Results from the Type 1 Model – Original Submission

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)	NHB at £30,000 / QALY
Nusinersen	[redacted]	5.03				
BSC	[redacted]	0.25	[redacted]	4.78	[redacted]	[redacted]

Table 6: Deterministic Results from the Type 1 Model – Updated

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)	NHB at £30,000 / QALY
Nusinersen	[redacted]	4.31				
BSC	[redacted]	0.16	[redacted]	4.16	[redacted]	[redacted]

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Table 7: Deterministic Results from the Type 2/3 Model – Original Submission

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)	NHB at £30,000 / QALY
Nusinersen	[redacted]	16.56				
BSC	[redacted]	13.72	[redacted]	2.85	[redacted]	[redacted]

Table 8: Deterministic Results from the Type 2/3 Model – Updated

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)	NHB at £30,000 / QALY
Nusinersen	[redacted]	19.00				
BSC	[redacted]	15.21	[redacted]	3.79	[redacted]	[redacted]

The changes that have been implemented have led to a small increase in the total QALYs in both the pre-symptomatic and type 2/3 models. This has subsequently led to decreases in the ICER within these two models as there is a greater increase in QALYs with nusinersen, leading to a larger value for the incremental QALYs. Alternatively, for the type 1 model there has been a small decrease in total QALYs, with the decrease of a higher magnitude with nusinersen, and this has led to an increase in the ICER.

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NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Multiple Technology Appraisal

Nusinersen and risdiplam for treating spinal muscular atrophy (MA review of TA588 and TA755) [ID6195]

Document B

Company evidence submission

April 2024

File name	Version	Contains confidential information	Date
ID6195_Risdiplam for SMA_Company evidence submission [Redacted]	**1**	**No**	**19 April 2024**

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B.1 Decision problem, description of the technology and clinical care pathway

B.1.1 Decision problem

The submission covers the technology's full marketing authorisation for this indication.

Table 1: The decision problem

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
Population	People with 5q spinal muscular atrophy	As per NICE final scope and in line with NICE reference case	N/A
Intervention	Risdiplam	As per NICE final scope and in line with NICE reference case	N/A
Comparator(s)	• Established clinical management • The interventions will be compared to each other In addition, for children aged 12 months and under with a bi-allelic mutation in the *SMN1* gene and present with a clinical diagnosis of type 1 SMA or pre-symptomatically with up to 3 copies of the *SMN2* gene • Onasemnogene abeparvovec • Nusinersen • Best Supportive Care (BSC)	As per NICE final scope and in line with NICE reference case	N/A
Outcomes	The outcome measures to be considered include: • Motor function (including, where applicable, both age-appropriate gross motor milestones and fine motor skills) • Bulbar function (including, for example, swallowing and ability to communicate)	As per NICE final scope and in line with NICE reference case	N/A

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	• Frequency and duration of hospitalisation • Respiratory function • Complications of spinal muscular atrophy (including, for example, scoliosis and muscle contractures) • Need for non-invasive or invasive ventilation • Stamina and fatigue • Mortality • Adverse effects of treatment • Health-related quality of life		
Economic analysis	The reference case stipulates that the cost effectiveness of treatments should be expressed in terms of incremental cost per quality-adjusted life year. The reference case stipulates that the time horizon for estimating clinical and cost effectiveness should be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared. Costs will be considered from an NHS and Personal Social Services perspective. The availability of any commercial arrangements for the intervention, comparator and subsequent treatment technologies will be taken into account. The availability of any managed access arrangement for the intervention will be taken into account.	In the presymptomatic population, a cost-comparison has been used to compare risdiplam to Nusinersen and Onasemnogene abeparvovec	Given insufficient comparative efficacy data, equal efficacy had to be assumed
Subgroups to be considered	If the evidence allows the following subgroups will be considered: • SMA type • Number of *SMN2* gene copies • Functional status (non-sitter, sitter, walker)	As per NICE final scope and in line with NICE reference case	N/A

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	• People who have had prior active treatment for SMA		
Special considerations including issues related to equity or equality	In the current funding situation, the MAA for risdiplam excludes patients who are permanently ventilated or have a tracheostomy. The situation has developed significant in the past few years, and clinicians now report an improvement in quality of life or a slowing of the expected deterioration in motor / respiratory function.	Permanently ventilated patients have been presented as a subgroup to consider (B.2.7.5)	In the current situation, the decision to treat permanently ventilated patients must be taken to an NHSE panel, delaying treatment and potentially worsening prognosis

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B.1.2 Description of the technology being evaluated

The technology being appraised is described in Table 2. See Appendix C for details of the draft summary of product characteristics (SmPC) and European Public Assessment Report (EPAR).

Table 2: Technology being evaluated

UK approved name and brand name	**Risdiplam (Evrysdi®)**
Mechanism of action	Risdiplam is a survival of motor neuron 2 (*SMN2*) pre-mRNA splicing modifier designed to treat SMA caused by mutations in chromosome 5q that lead to SMN protein deficiency. Functional SMN protein deficiency is the pathophysiological mechanism of all SMA types. Risdiplam corrects the splicing of *SMN2* to shift the balance from exon 7 exclusion to exon 7 inclusion into the mRNA transcript, leading to an increased production in functional and stable SMN protein. Thus, risdiplam treats SMA by increasing and sustaining functional SMN protein levels (1).
Marketing authorisation/CE mark status	As of December 2023, risdiplam has been granted marketed authorisation from the MHRA in the following indication: *Risdiplam (Evrysdi, Roche) is indicated for the 'treatment of 5q spinal muscular atrophy (SMA) in patients with a clinical diagnosis of SMA Type 1, Type 2 or Type 3 or with one to four SMN2 copies'.* This was granted based on the RAINBOWFISH presymptomatic SMA (<2 months of age) patient population. Before the December 2023 licence extension, risdiplam was indicated only for people 2 months and over.
Indications and any restriction(s) as described in the summary of product characteristics (SmPC)	The indication in the UK is as per the marketing authorisation from the EMA. Please refer to the Summary of Product Characteristics for full details (1).
Method of administration and dosage	Risdiplam is taken orally once a day using the re-usable oral syringe provided, at approximately the same time each day. The recommended once daily dose of risdiplam is determined by age and body weight. • < 2months of age: 0.15mg/kg • 2 months to < 2 years of age: 0.20 mg/kg • ≥2 years of age (<20 kg): 0.25 mg/kg • ≥2 years of age (≥20 kg): 5 mg
Additional tests or investigations	No additional tests or investigations are required to identify patients eligible for risdiplam.
List price and average cost of a course of treatment	£7,900 per 60 mg/80 ml vial

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	Treatment with risdiplam is continuous as SMA is a life-long chronic disease, therefore the average cost of a course of treatment is N/A.
Patient access scheme (if applicable)	A patient access scheme (PAS) with a simple discount of [redacted] has been submitted to PASLU. The resulting net price per 60 mg/80 ml vial is [redacted]

B.1.3 Health condition and position of the technology in the treatment pathway

B.1.3.1 Disease overview

Pathophysiology

SMA is a neuromuscular disorder resulting in severe weakness of the limbs, trunk, bulbar and respiratory muscles secondary to failure to gain and maintain functional motor nerve innervation of skeletal muscles (2). SMA is characterised by the dysfunction of alpha motor neurons within the anterior horn of the spinal cord, leading to skeletal muscle weakness and atrophy (3-5). Respiratory failure accounts for the majority of deaths in people with SMA (6).

SMA is an autosomal recessive disorder secondary to loss-of-function mutations in both alleles of the survival motor neuron 1 (*SMN1*) gene with subsequent loss of SMN protein expression. In humans, there are two SMN genes, the *SMN1* gene and its paralog *SMN2*. The *SMN2* pre messenger ribonucleic acid (mRNA) undergoes alternative splicing that excludes exon 7 from 85–90% of mature *SMN2* transcripts, which produces an unstable SMNΔ7 protein that is rapidly degraded, so that full length *SMN2* mRNA is generated in only 10–15% of splicing events (7, 8). Accordingly, people with SMA lacking a functioning *SMN1* gene are dependent on their *SMN2* gene and SMA is the consequence of decreased, insufficient levels of functional SMN protein produced by the *SMN2* gene. Children born with multiple copies of the *SMN2* gene have milder phenotypes, further demonstrating that the pathophysiology of the disease is due to insufficient production of functional SMN protein (9, 10).

SMA subtypes

SMA is a disease continuum with its subtypes defined by age at onset and the most advanced motor milestone achieved during development, classified as types 0 through 4, where type 1 (infantile-onset) and types 2 and 3 (later- onset) represent approximately 99% of all patients (Table 3). Type 0 (congenital SMA) is very rare and most of these patients are unable to survive beyond 6 months of age. Type 4 SMA (adult onset) accounts for only approximately 1% of all SMA cases (11). Natural history data demonstrate that clinical decline can manifest differently for each SMA type depending on functional level, age, disease duration and clinical severity (12-17). It should be noted, however, that classifying a spectrum disorder such as SMA into discrete subtypes is problematic due to overlap in diagnostic criteria between infantile-onset and later-onset patients (18).

Table 3: SMA subtypes and clinical course

Type	Onset	Highest achieved motor function	Lifespan if untreated

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0	Prenatal/foetal	Nil	< 6 months
1	<6 months	Sit with support only	<2 years
2	≥6–<18 months	Sit independently	>2 years
3	≥18–<36 months	Stand and walk	Normal
4	Adult (2nd or 3rd decade)	Walk during adulthood	Normal

The incidence of SMA in Europe is approximately one in every 3,900 to 16,000 births, with type 1 SMA accounting for approximately 60% of cases (19-22). It is estimated that 68 children were born with SMA in the UK in 2022, with an estimated 675 – 1,350 children and adults living with SMA (21).

People with infantile onset (type 1) SMA most commonly have two *SMN2* gene copies and typically present symptomatically before the age of 6 months. At diagnosis, these infants demonstrate reduced motor function compared with age matched non-SMA infants, and will uniformly and rapidly lose motor function over time as assessed with a standard instrument for infants with SMA known as the CHOP-INTEND - Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders (23). In addition, without an effective treatment, infants with type 1 SMA never gain major motor milestones such as sitting independently (2). They also experience progressive loss of independent swallowing and respiratory function, requiring feeding tubes and chronic ventilatory support, and will face a very high risk of death. Natural history of the disease demonstrates that 50% of infants with type 1 SMA, who only have two copies of *SMN2* gene, will die or require permanent daily non-invasive ventilation support by 10.5 months of age. This statistic will reach 92% for type 1 toddlers by 20 months of age (24).

People with type 2 SMA most commonly have three *SMN2* gene copies, and typically present symptomatically between the ages of 6–18 months. Consistent with all SMA subtypes, children with type 2 SMA have proximal greater than distal limb weakness and lower limb greater than upper limb weakness. These children will likely be able to sit and possibly stand but never walk independently given the greater amount of weakness in their lower limbs (2). Natural history of SMA demonstrates that without treatment these children with type 2 SMA have a progressive decline in motor function over time, most prominently during the ages of 6 to 16 years, pertaining to maintaining an upright position while performing tasks with their upper limbs as measured by the Motor Function Measure 32-item version (MFM32) (25). People with type 2 SMA may also require noninvasive ventilator support, depending on the severity of the decline in pulmonary function. Children with type 2 SMA are at risk for hypoventilation, especially during sleep, which may be exacerbated by viral respiratory infection (26). People with type 2 SMA have a better prognosis than those with type 1 disease and often survive into adulthood but they will remain severely disabled (14, 27).

Type 3 SMA is a less severe phenotype compared to type 1 and type 2 SMA. People with type 3 SMA most commonly have three or four *SMN2* gene copies, and typically present symptomatically between the ages of 18–36 months. Consistent with all SMA subtypes, children with type 3 SMA have proximal greater than distal limb weakness and lower limb greater than upper limb weakness. These children are able to sit, stand, and walk independently (2). Natural history of SMA demonstrates that without treatment children with type 3 SMA progressively decline in motor function over time, most prominently during the

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ages of 10 to 15 years. Nearly a third of these patients will lose their ability to walk between the ages of 3 to 28 years old (25). Children and adults with type 3 SMA generally have normal lung function and rarely require noninvasive ventilatory support. However, pulmonary function declines over time and adults with type 3 SMA may need noninvasive ventilatory support as they age (26).

People with type 4 SMA represent less than 1% of the overall SMA population (11). They have four to six *SMN2* gene copies and present with mild symptoms in adulthood (2, 28).

Clinical measures used to assess people with SMA

Given the broad and clinically heterogeneous nature of the SMA patient population, the expectations for what determines clinical benefit will vary between patients based on age, prognosis and motor function. Several outcome measures are used in clinical practice and trials to assess and monitor people with SMA, but none are applicable to the whole spectrum of patients (29) (Table 4).

With regards to type 1 SMA, scales aim to capture if infants achieve developmental and motor milestones that are rarely or only ever partially achieved in the natural history of type 1 SMA patients (30). These include the BSID-III, HINE-2 and CHOP-INTEND as outlined in the table below. The CHOP-INTEND scale is the most popular scale used worldwide and therefore may be used to compare results. However, its limitations include that it can be challenging for heavier children to perform, while it may not be sensitive enough to capture small improvements in the youngest newborns and infants that are considered clinically meaningful to families (e.g. fine finger movements, or turning of the head). Indeed, changes in the CHOP-INTEND score do not always correspond with the improvements reported by families (29). As with all functional measures, there are also floor / ceiling effects, making assessment of patients over a combination of scales necessary.

The Hammersmith Functional Motor Scale Expanded (HFMSE) is widely used to measure clinically relevant items assessing functional skills in people with type 2 and type 3 SMA, such as sitting, rolling and standing/stepping. While the HFMSE does not assess fine motor function skills, other specific scales are available to assess upper limb function such as the Revised Upper Limb Module, with other measures utilised to assess other functions, such as respiratory performance, i.e. forced vital capacity. It is also becoming more common to use other outcome measures in clinical practice such as the Adapted Test of Neuromuscular Disorders (ATEND), Egen Klassifikation Scale II (EK2), Vignos scale and SMA Independence Scale - Upper Limb Module (SMAIS-ULM) but these are not routinely used by many multi-disciplinary teams (MDTs) yet and, as above, are only used for patients with appropriate motor function.

However, the different clinical features related to progressed SMA may affect patients' performance on these outcome measures, therefore the most appropriate assessment scale to use will vary by patient, depending on factors such as age, SMA subtype and symptoms experienced. For instance, the HFMSE is not sensitive to capture change in people with a baseline HFMSE score <10 (31, 32), compared with the MFM32 scale, which includes items relating to distal motor function that are primarily not assessed by the HFMSE, making it a more relevant measure in those patients severely impacted by a more advanced disease (25, 31, 33). This is an important consideration since severe complications such as contractures are associated with diminished motor ability and can impact performance on

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the HFMSE scale, thereby limiting a person's ability to attain a functional skill and therefore the ability of the scale to detect improvement in motor function (34).

Additionally, as people with SMA will be at different stages of disease, particularly those with type 2 and type 3 SMA, given the heterogeneous nature of this group individuals will have a different definition of what is considered to be a clinically meaningful outcome. It is therefore challenging to define a single clinically meaningful difference for all people with SMA for any of the motor function measures used in the trials. However, the large majority of people with SMA and their caregivers feel that disease stabilisation would represent an important and meaningful outcome (35). Moreover, a discrete choice experiment conducted by Roche identified that people with SMA placed greater value on avoiding disease progression over actual improvement of their disease (36).

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Table 4: Summary of outcome measures for SMA

Outcome	Description	Clinical meaningfulness
Infantile-onset SMA (type 1 SMA)		
BSID-III	• Validated outcome measure in infants to assess attainment of motor milestones including static positioning (e.g., head control, sitting), dynamic movement including locomotion (e.g., crawling), quality of movement (e.g., kicking), balance and motor planning • 72 items scored on a 2-point scale to measures whether or not patients are able to perform the assessed items • This scale is scored by domain; cognitive, motor, language, with two scales conducted with parent questionnaires: social-emotional and adaptive behaviour.	• The natural history of the disease is well defined: per definition, untreated type 1 SMA infants never achieve sitting without support (23, 24, 30) • The achievement of sitting unsupported is dramatically different from the natural disease course, therefore the ability to achieve a sitting position unsupported at 12 months, as measured by the BSID-III, is considered a clinically meaningful and important milestone in type 1 SMA.
HINE-2	• Tool scored on a 3–5 point scale to evaluates eight developmental motor milestones (head control, sitting, voluntary grasp, ability to kick, rolling, crawling, standing, and walking) • Previously used to evaluate motor function in SMA natural history studies and in a clinical trial in infantile-onset SMA (24, 30)	• HINE-2 motor milestones are never fully achieved or maintained in untreated infants with type 1 SMA according to natural history (30) • Achievement of important motor milestones and higher scores on the HINE-2 scale (≥ 2-point increase in the ability to kick [or maximal score] or a 1-point increase in head control, rolling, sitting, crawling, standing, or walking) are therefore considered to be a clinically relevant improvement for an infant with type 1 SMA (37)
CHOP-INTEND	• 16 item motor function measure, with a total score ranging from 0–64 to assess both active and elicited reflexive movement (16 items in total, each scored from 0–4), such as spontaneous movement of upper and lower extremity, hand grasping, rolling, head control, and others	• In type 1 SMA natural history studies, infants typically have a mean or median total CHOP-INTEND score of < 33 points; patients progressively lose motor function following onset of symptoms, which is confirmed by a decrease in CHOP-INTEND scores over time (23, 24, 30) • Any improvement in CHOP-INTEND scores, or achievement of a score of at least 40, is considered as a clinically meaningful improvement for infants with type 1 SMA (lower threshold estimate of a clinically meaningful improvement) (23, 24) • Change of ≥ 4 in CHOP-INTEND represents an estimate of a meaningful improvement in motor function (higher threshold estimate of a clinically meaningful improvement) (37)
Later-onset SMA (type 2 and type 3 SMA)		

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MFM32	• Valid and reliable assessment of different levels of motor function ability in neuromuscular diseases, including a broad range of people with SMA, validated in individuals aged 2–6 years and older (38, 39) • Contains 32 items related to everyday activities of daily living, assessing three domains of motor function: D1 (standing and transfers), D2 (axial and proximal motor function), and D3 (distal motor function) • Scored on a 0–3 scale are summed and then transformed onto a 0–100 scale to yield the MFM32 total score expressed as a percentage of the maximum score possible for the scale (the lower the total score, the more severe the functional impairment)	• Natural history data collected on patients aged 5.7 to 59 years, demonstrated that the overall slope of decline over time using the MFM32 total score is in the range of -0.9 points/year for type 2 patients and -0.6 points/year for type 3 patients (25) • SMA patients and caregivers consider stabilisation in functional ability as progress (35, 40-42), therefore a change of ≥ 0 in MFM32 total score representing stabilisation or improvement of motor is clinically meaningful in this patient population • A threshold of improvement on the MFM32 scale, such as ≥3 points, should be considered as a marked improvement for patients as it may represent either the acquisition of a new function or the improvement in performance of several functions (43)
RULM	• Validated scale in SMA to assess upper limb motor performance (44) • Consists of 19 items (scored on a 0–2 scale for 18 items and 0–1 for one item) assessing the performance of shoulder, elbow, wrist, and hand function. A total score from 0–37 is calculated with higher scores indicating greater upper limb functioning	• A Natural history data show that over 12 months, the mean change in RULM score is -0.4 points in type 2 and type 3 patients aged 2.7 to 49.7 years (45, 46) • Patients and caregivers have reported that small improvements and stabilisation on the RULM have meaningful impacts on daily life (42); a change of ≥0 in RULM total score representing stabilisation or improvement of motor function is clinically meaningful. • Change of ≥ 2 in RULM represents an estimate of a meaningful improvement in motor function (higher threshold estimate of a clinically meaningful improvement) (45)
HFMSE	• Widely used in SMA type 2 and 3 (32); includes clinically relevant items assessing sitting, rolling, transitions relating to crawling and kneeling, and standing/stepping but no items to assess the fine motor function of the hand, wrist, or elbow • Assesses gross motor function in individuals aged two years or older, with type 2 and 3 SMA (47) • 33 items to assess functional abilities, including standing, transfers, ambulation, and proximal and axial function,	• Study in type 2 and type 3 patients aged 2.5 to 55 years demonstrated that the overall slope of decline in the HFMSE total score over a 12-month period is -0.57 in non-ambulant patients (48) • Stabilisation and small improvements on the HFMSE are meaningful in daily life (42); change of ≥ 0 in HFMSE total score representing stabilisation or improvement of motor function is clinically meaningful (49)

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	each scored on a 0–2 scale by a clinical evaluator (maximum score of 66 points)	• Change of ≥3 in HFMSE represents an estimate of a meaningful improvement in motor function (higher threshold estimate of a clinically meaningful improvement) (50)
Other outcomes measures used in clinical practice		
RHS	• The RHS was developed for individuals with SMA Type 2/3 to evaluate motor function (51) • The scale was derived from the Hammersmith Functional Motor Scale Expanded using Rasch analysis to develop a revised scale that provides a more sensitive description of SMA phenotype and disease progression (47) • The RHS consists of 35 items; 33 of the items are scored from 0-2 (where 0 is inability to perform and 2 is performance without mofidication/adaptation/compensation); the remaining 3 items are scored 0 (unable) or 1 (able) • All WHO developmental milestones can be scored/derived within the RHS	• The timed elements (10m run test, 6m walk test, rise from floor) of the RHS scale can be used to measure clinical benefit in SMA type 2/3 patients who are ambulant • In SMA patients, the 10-meter running test (10MRT) appears to discriminate between older and younger ambulatory patients and correlates with both longer distance walking endurance measured by 6-meter walk test (6MWT) distance and with knee flexor and extensor strength.
ATEND	• A functional motor outcomes assessment for individuals with a neuromuscular disorder who are not able to sit or transfer out of the wheelchair (52) • This is a 14 item assessment based on testing in the wheelchair in 2 positions; 1. Semi-reclined 2. Supported sitting. The 14 items range from cervical, trunk strength to distal strength including arm and hand function based on contractures and the emerging changing phenotype from older, weaker individuals with neuromuscular disease (52)	• This assessment was developed through an iterative approach based on CHOP ATEND (a modified scale constructed from the CHOP-INTEND), whereby the 27 CHOP ATEND assessments performed in the wheelchair were reviewed. Through this researchers found items that were not feasible to administer in an older, chronic population including rolling, side lying reaching, suspended hip and knee flexion and head and pelvic extension in prone suspension (52). • Stanford are currently collaborating with other institutions to collect data to further develop this instrument (52).
EK2	• Designed to measure functional ability in non-ambulant Duchenne muscular dystrophy (DMD), examining activities and abilities such as transfers, trunk mobility, wheelchair use, bed mobility, cough and well-being (53)	• Studies have confirmed the validity of the EK2 for non-ambulant adult SMA patients without the presence of floor or ceiling effects (56, 57). • Moreover, its ability to detect improvements in non-ambulant patients receiving treatment has been shown; a risdiplam study has shown that

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	• Contains 17 items with a total possible score of 51 (54) with lower scores indicating better function • The items on the scale are scored according to the best an individual has done in the last two weeks especially if there is variation between good and bad days (55)	as a functional scale, it is helpful for setting personalized goals and measuring individual responses to treatment in non-sitter patients over 16 years of age because it can detect subtle but meaningful changes in aspects of daily life (58).
SMAIS-ULM	• A measure that can be used to assess the amount of assistance required to perform activities of daily living (ADL) in non-ambulatory patients with Type 2/3 SMA (59). • Results can indicate important improvements in patients' everyday lives with regards to increased independence when completing upper limb related activities such as writing, using a touchscreen, dressing and washing the upper body. • There are two versions of the scale; a patient-reported outcome measure for individuals ages 12 years and older; and a caregiver observer-reported outcome measure for individuals ages 2 years and older. Both versions contain 29 items, 22 of which are related to daily activities and self-care involving upper limbs, the remaining 7 items are related to chores and mobility/strength (59).	• A study using data from the Cure SMA Community Update Survey was conducted to assess the cross-sectional item- and scale-level psychometric performance of the scale. The SMAIS-ULM demonstrated acceptable cross-sectional measurement properties, including internal consistency. Fit statistics and subgroup validity findings supported the suitability of SMAIS-ULM items to form a scale and confirmed the SMAIS-ULM can distinguish between individuals with different SMA types. Overall, the findings support the further use of the SMAIS-ULM in clinical trials and research (60).

ADL, Activities of Daily Living; ATEND, Adapted Test of Neuromuscular Disorders; BSID-III, Bayley Scales of Infant and Toddler Development III; CHOP-INTEND, Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders; EK2, Egen Klassifikation Scale Version 2; HFMSE, Hammersmith Functional Motor Scale Expanded; HINE-2, Hammersmith Infant Neurological Examination Module 2; MFM32 motor function measure–32 item; RHS, Revised Hammersmith Scale; RULM, Revised Upper Limb Module; SMA, spinal muscular atrophy; SMAIS-ULM, SMA independence Scale – Upper Limb Module

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B.1.3.2 Burden of disease and impact on quality of life

When left untreated SMA is a devastating and debilitating disease, and is life threatening for individuals with the most severe types. There are a wide range of symptoms and complications that can have detrimental effects on the day-to-day lives of people with SMA and their families (61-65). For instance:

- People with type 1 SMA require repeated visits to hospital or medical providers in addition to prolonged use of home and palliative care such as diet provision via feeding tubes, frequent pneumonia treatment and chronic ventilatory support, which often place a significant emotional and social burden on patients and caregivers.
- Progressive orthopaedic deformity is a hallmark morbidity of type 2 SMA, resulting in severe scoliosis, thoracic deformity, large joint subluxations, dislocations and contractures. These deformities result in pain, impaired seating, transfers and mobility issues, and respiratory impairment due to mechanical impact of a collapsing, rotated and twisted thoracic cage. Invasive surgery is required to manage these complications and requires significant periods of recovery.
- Older children and adolescents with type 2 or 3 SMA often require extensive home services, while people with non-ambulatory forms of SMA require 24-hour care to assist with toilet use, transfers, changing and hygiene, feeding and turning in bed. These needs bring significant challenges for patients in fully accessing and maintaining continuity in educational and employment opportunities (66), and can also impact accessibility to available therapeutic options due to the severity of their deformities and the need to travel to a specialised centre, frequently far from home (36).
- Caring for people with SMA places a significant burden on caregivers, both from a detrimental impact on their own well-being and quality of life as well as from a financial perspective, for example loss of earnings. The inclusion of the impact on carers was considered appropriate in previous NICE appraisals of treatments for SMA (18, 67). Indeed, the original risdiplam submission clearly indicated that despite the modelling challenges associated with including carer perspective, it was of paramount importance that carers QoL was considered in the assessment (67).

The progressive nature of the disease with loss of function over the course of months and years requires almost constant adaptation of the environment and leads to increasing disability and handicap for people with SMA. Minor viral respiratory infections or aspiration episodes may become life threatening and require intensive care and significant pulmonary rehabilitation (40, 68, 69). Given the severity of the condition, data suggest patients will benefit greatly if treated pre-symptomatically or soon after symptoms are observed rather than months after symptom onset (70) (71).

Overall, clinicians, people living with SMA, and their parents or caregivers repeatedly cite that small improvements can make a significant difference in the ability of a person or their family to function and thrive (42). People with SMA and caregivers fear progressive loss of function, and being able to maintain those abilities (stabilisation) is a meaningful outcome. In a recent survey conducted by SMA Europe (EUPESMA-2019) covering 26 European countries (including the UK) and including over 1474 validated responses from patients and caregivers aged from 0 to 81 years, across all SMA types, almost all participants (96.5%) considered stabilisation as progress (41), even in the current clinical environment where

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some patients have access to an approved treatment. Furthermore, a discrete choice experiment conducted by Roche identified that people with SMA placed greater value on avoiding disease progression over actual improvement of their disease (72).

The inability or loss of activities of daily living (ADL) can have a major impact on individual well-being. Independence and the ability to perform basic personal tasks has been described by patients as a priority for type 2 and 3 SMA patients (73), with the preservation of or small improvements in upper extremity function being of particular importance to maintaining independence, social participation and quality of life (74). Furthermore, the importance of maintaining the ability to independently perform ADLs has been highlighted in the extensive SMA Europe survey, with patients and families expressing sadness and fear at the prospect of gradually loosing these functional abilities (66).

B.1.3.3 Current treatment practice

There are currently two other approved disease-modifying treatments for SMA in the EU.

Nusinersen (Spinraza®), a *SMN2* targeting antisense oligonucleotide drug, is approved for the treatment of 5q SMA in paediatric and adult patients. Nusinersen is intrathecally administered, thus largely limiting the effects to the central nervous system (CNS). The first 3 doses of nusinersen are administered in 2-week intervals, followed by a 4th injection after 35 days and maintenance of dosing every 4 months thereafter; hence, frequent repeats of the invasive administration (lumbar puncture) are required for this treatment. Nusinersen is available in England, Wales and Northern Ireland via a managed access agreement (MAA) as an option for people with pre-symptomatic SMA or people with type 1, type 2 and type 3 SMA, excluding those unsuitable for intrathecal administration, on permanent ventilation or requiring a tracheostomy at baseline, and have a diagnosis of severe scoliosis and/or severe contractures. Furthermore, if independent ambulation is gained before starting therapy, patients must still be independently ambulant, with the exception of paediatric patients who have lost independent ambulation in the previous 12 months (18). In Scotland, nusinersen is routinely funded for all patients within the licensed indication.

Approval of nusinersen was granted based on the clinical benefit demonstrated in the ENDEAR trial in infants with SMA (75) and the CHERISH trial in people with later-onset SMA (76). Patients up to 7 months old and between 2–12 years were eligible to enrol in ENDEAR and CHERISH respectively. However, the oldest patient enrolled in CHERISH at screening was 9 years, therefore there are no controlled clinical trials of nusinersen in patients over 9 years old or in people with type 3 SMA.

Onasemnogene abeparvovec (Zolgensma®) is an intravenously administered gene therapy to deliver a functional copy of the *SMN1* gene. In 2021, Onasemnogene abeparvovec was recommended as an option for treating babies under 12 months with genetically confirmed Type 1 5q SMA in line with the commercial agreement, unless patients are permanently ventilated or have a tracheostomy (77). In 2023, Onasemnogene abeparvovec was recommended as an option for treating presymptomatic 5q SMA with a biallelic mutation in the *SMN1* gene and up to 3 copies of the *SMN2* gene in babies aged 12 months and under in line with the commercial agreement (78).

Best supportive care (BSC) requires a multidisciplinary approach and is tailored for individual patients. This includes the monitoring and support of patients in the absence of active

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disease modifying treatment and relies on the prevention and treatment of co-morbidities such as swallowing and feeding difficulties, scoliosis and thoracic deformity, contractures, and respiratory insufficiency. In the last decade, improvements in SMA care, including guidance on ventilatory and feeding support, have enabled prolonged survival in people with type 1 SMA who did not receive disease-modifying therapies. Over time, palliative management for the most severe type 1 patients has been introduced more frequently at home with increased levels of technical supportive care such as enteral nutrition, oxygen therapy, and analgesic and sedative treatments (79). Nevertheless, these measures have very limited or no impact on motor milestone achievements, and mortality rates in this patient population are still high (23, 24, 30), and with motor function declining over time for people with type 2 and type 3 SMA receiving BSC (25), there is a need to ensure all people with SMA can access targeted therapies.

B.1.3.4 Limitations of current treatment and the unmet medical need

The approval of disease-modifying treatments has been a welcome breakthrough for people with SMA. However, physicians deem there to be a continuing unmet need for those who are ineligible for nusinersen or onasemnogene abeparvovec as well as the many individuals for whom these treatment options are less than ideal (80-83).

Nusinersen

While the results of Phase 3 studies with nusinersen in infantile-onset SMA (ENDEAR) (75) and in later-onset SMA (CHERISH) (76) overall demonstrate benefit in patients receiving active drug versus sham procedure control, there is still a proportion of patients who do not respond to the drug and, thus, for whom nusinersen may not be the best option. For instance, 49% of the treated patients in ENDEAR did not exhibit an improvement in their motor milestones and 39% did not reach event-free survival (75).

Intrathecal administration is an invasive procedure that is associated with risks and may not be feasible for all SMA patients, especially those who develop severe scoliosis, joint contractures or undergo a spinal surgery procedure (84-86). Additionally, many infants and young children with SMA require anaesthesia to undergo the lumbar puncture procedure, and sedation is known to potentiate adverse respiratory reactions, which can be extremely serious in SMA patients (87). Given these factors, the intrathecal administration procedure is likely causing anxiety for SMA patients and their families (88).

Clinical experts confirmed to Roche that lumbar puncture requires visits to specialist facilities with specific medical expertise and is therefore a burden on both patients and families and healthcare resources. Situations where external factors prevent patients visiting health care facilities can also impact on consistent therapy administration; for example, when patients require interventional radiology to deliver nusinersen it is most often delivered in a separate service where emergency cases take priority over elective, often leading to patients missing their nusinersen dose.

In addition to the logistical and emotional challenges associated with delivery of nusinersen, there are additional potential limitations associated with its efficacy. Given the method of delivery, the SMN protein delivered by nusinersen is largely limited to the CNS, while emerging evidence indicates functional SMN protein is crucial for the development for many cells where it is expressed, and that SMA is in fact a multi-organ disease that goes beyond

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just the motor neurons (89, 90) (91). A recent study also indicates that many adult patients report perceived wearing-off of nusinersen effects, primarily within the last month prior to the next administration (92).

Moreover, nusinersen is not routinely funded on the NHS and for those eligible patients, some may not receive treatment due to constrained capacity within centres that are capable of intrathecal administration; therefore, there is a need for treatment options with alternative methods of administration to increase accessibility for disease-modifying treatments for all people with SMA.

Onasemnogene abeparvovec

A recent US study aimed to describe parents' experiences with gene replacement therapy with onasemnogene abeparvovec to explore best practices for newborn screening and counselling of families. This study found that while this was a preferred treatment choice, parents struggled with uncertainty associated with the lack of knowledge of long-term outcomes and whether the therapeutic effect would eventually fade (83). Indeed, with limited clinical evidence so far, experts have acknowledged that guidance is required in terms of patient selection and other important issues surrounding use of onasemnogene abeparvovec.

A group of European neuromuscular experts developed eleven consensus statements to address this need, which capture qualification, patient selection, safety considerations and long-term monitoring for gene replacement therapy in SMA (93). On the topic of patient selection, experts agreed that: age at onset, disease duration and baseline motor function status are the most important predictors of treatment response in symptomatic patients and *SMN2* copy number is the most important consideration in presymptomatic patients. In addition, the European experts agreed that gene therapy may not reduce risk of severe disability in patients presenting symptoms at birth, treated after a long disease duration, or with already severe evolution; and patients above 13.5 kg should only be treated in specific circumstances. On the topic of structural requirements for administration of gene therapy, experts agreed that: centres performing gene therapy for SMA should have broad expertise; and inclusion of SMA in newborn screening programs is important. Finally, experts agreed that generation of effectiveness and safety evidence is vital, and should be collected systematically for all patients treated (93).

In response to these expert consensus statements, SMA Europe published an article to add perspective from 15 patient experts across Europe (66). These experts agreed with the consensus statements in principal. However, they voiced concern about additional patient selection criteria being used to exclude candidates when evidence related to their prediction of response may still be limited, and perception of response varies across different patients. They also call for collaboration between neuromuscular and patient experts for the development of treatment guidelines that focus on individual therapeutic benefits rather than cohort-specific benefits (66).

Subsequent expert recommendations for the treatment of SMA with onasemnogene abeparvovec have been published. In addition to the recommendations above they discuss the following: the importance of retesting patients with elevated anti–AAV serotype 9 antibodies to confirm eligibility for treatment; prednisolone tapering and monitoring for AEs such as hepatotoxicity and thrombotic microangiopathy (with potential long-term steroid use

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to control liver function abnormalities required in some patients); and the need for caregiver education on family-centred discussions on treatment expectations (82). The presence of pre-existing anti-AAV9 antibodies can increase the risk of immune responses, resulting in reduced transduction and limited therapeutic efficacy. Therefore, SMA patients must have AAV9 antibody titers no greater than 1:50 (94). While the prevalence of antibodies against AAVs are relatively low in infants, particularly neonates, they can result from maternal transplacental transfer or exposure during breastfeeding. Anti-AAV9 antibodies are more common in older children, where they may arise from environmental exposure. Given the current NHS newborn blood spot (NBS) screen programme does not currently test for SMA, this threshold is particularly relevant for the UK (95).

In the UK, a National panel must be sought to discuss advice before dosing any child >6 months of age or weighing >13.5kg, further indicating the need for additional disease-modifying treatments to improve accessibility for all patients with SMA. In conclusion, while the availability of gene replacement therapy has been an exciting progression in the treatment of SMA, there remains a critical need for alternative DMTs, as evidenced by the continued initiation of new patients on risdiplam and nusinersen.

B.1.3.5 Risdiplam for the treatment of SMA

SMA is caused by a deficiency in SMN protein, SMN is ubiquitiously expressed systemically and has been shown to be involved with multiple pathways beyond those directly involved with the development and maintenance of motor neurons (96-98). The need to systemically increase SMN protein is at the core of disease intervention across the continuum of SMA phenotypes. Risdiplam, an *SMN2* mRNA splicing modifier, is an efficacious small molecule disease modifying therapy (DMT) for SMA. It modulates *SMN2* splicing to include exon 7 into the mRNA transcript, thereby increasing the expression of functional SMN protein from the *SMN2* gene. Risdiplam has good distribution into both the central nervous system (CNS) and systemically throughout the body, increasing levels of functional SMN protein in both the CNS and periphery to a similar magnitude (99, 100). Risdiplam is therefore hypothesised to bring greater efficacy in people with SMA than treatments targeting increases of functional SMN protein in the CNS alone (see section B.2.12). This is particularly relevant for the respiratory complications that affect people with SMA as these are often the cause of early death. Clinical trial data of risdiplam in people with infantile-onset SMA has shown that 81% of infants were alive and not on permanent ventilation after four years of treatment, while 96% of those patients alive at this point were also able to maintain the ability to swallow, demonstrating the systemic effects of risdiplam on bulbar function.

Risdiplam is the first to market orally administered (liquid formulation) DMT. The oral route of administration and liquid formulation present a significant advantage over intrathecal injections for people with SMA. Risdiplam is a sustainable treatment option because it is administered at home daily by the patient or a caregiver orally or via feeding tube, without requiring hospital clinic visits, invasive procedures or concomitant use of additional medicines. It is less burdensome not only to patients and caregivers but also to the health care system, addressing an important unmet medical need in the SMA community. For example, a 2019 survey carried out by Cure SMA of adults living with SMA or caregivers of children with SMA treated with nusinersen found that on the day of administration, the mean time associated with treatment for all patients was 8.26 hours (standard deviation 11.29 hrs, median 5.0 hrs [77 respondents]), with longer mean administration times reported by

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caregivers of paediatric patients compared to adult patients (11.32 vs. 4.78 hours respectively) (101).

In practical terms, the availability of an orally administered drug expands the population able to receive treatment to include those for whom other routes of administration can be challenging and even contra-indicated (e.g., severe scoliosis and spine surgery for intrathecal administration or intolerance to nusinersen). Therefore, risdiplam offers a long term, sustainable treatment option for all SMA patients, across a wide range of SMA subtypes, irrespective of the patient's age, physical status, or disease severity.

Risdiplam-specific clinical data are available to support the major contribution to patient care for this efficacious, well-tolerated oral medicine compared to other invasive routes of administration. These data are from a broad range of patients in the ongoing open-label trial of risdiplam for SMA patients who had received prior experimental or standard-of-care therapy (JEWELFISH). Of the 76 patients who previously received nusinersen, the most frequent patient-reported reasons for switching were treatment related tolerability concerns (31.2% of patients), treatment response: lack of efficacy (18.2% of patients), and treatment response: loss of efficacy (10.4% of patients) (102). This demonstrates that some patients who have already had access to nusinersen are not able to receive continued nusinersen therapy for medical reasons.

In addition to the medical issues of lumbar puncture discussed above, data show that patients and caregivers would prefer an oral treatment to an intrathecal injection. Sixteen patients (21%) in the JEWELFISH study cited the inconvenience of the treatment, patient preference, or caregiver preference as the primary reason for switching from nusinersen to risdiplam (103). These data support the results of a preference study conducted in the United Kingdom in 2019, which was specifically designed to quantify caregiver and patient preferences for SMA treatment attributes. These data showed that caregivers were 2.9 times more likely to choose an oral solution administered once daily over an intrathecal injection every 4 months, with all other factors being equal, and adult patients were 2.0 times more likely to choose the oral treatment (72). The recent SMA Europe survey (EUPESMA-2019) also demonstrated that patients are more ready to accept treatment through oral administration (91.0%) compared to intrathecal (63.1%) or intravenous (84.4%) administration (66).

B.1.3.6 Proposed position of risdiplam in the treatment pathway

As an efficacious treatment in all people with SMA, risdiplam has the potential to significantly contribute towards addressing the continuing unmet need of people with SMA. Moreover, as an orally administered treatment, risdiplam provides a sustainable treatment option that can be administered at home and used for a life-long condition.

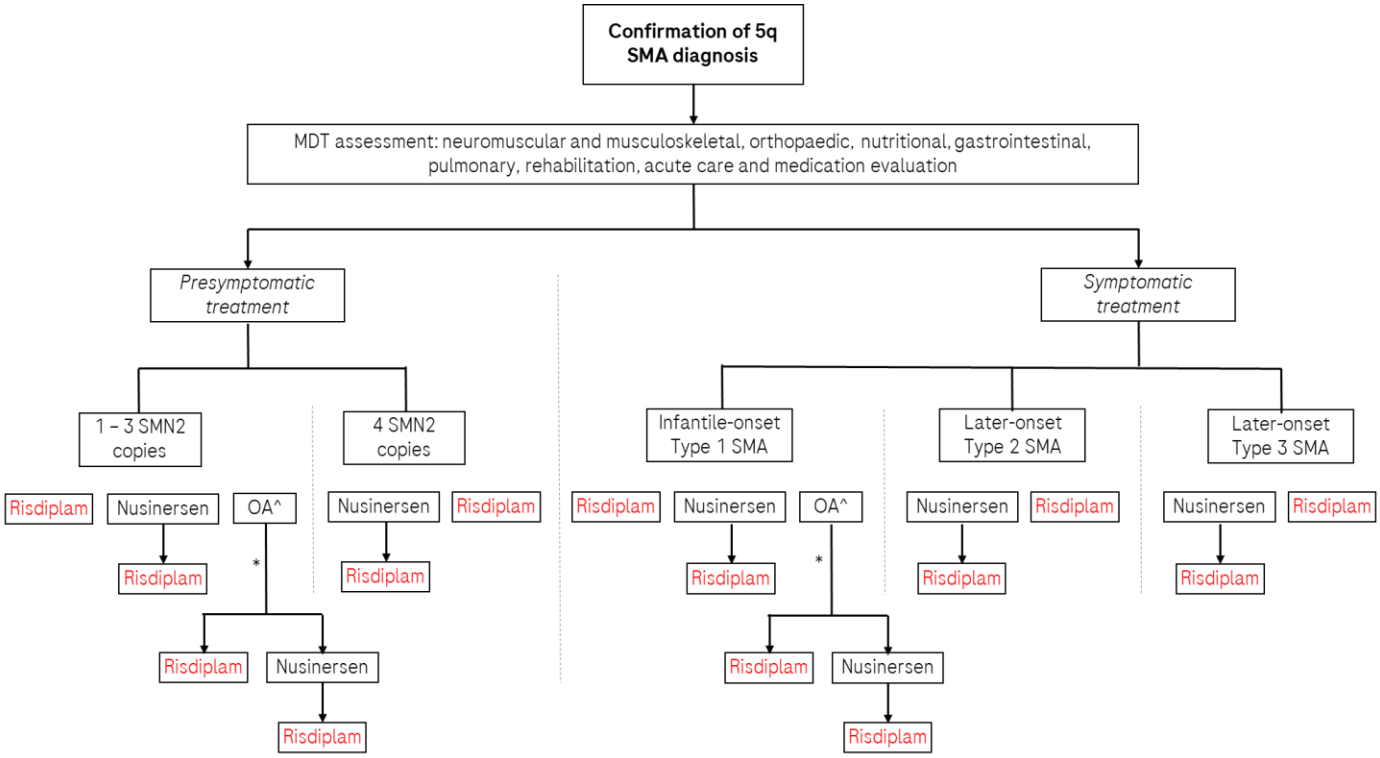
The eligibly population for risdiplam is all patients with SMA, and as an alternative treatment option for those patients who choose not to receive or are unsuitable for nusinersen or onasemnogene abeparvovec. For nusinersen, this includes patients with severe scoliosis or joint contractures, as well as those who cannot tolerate the treatment and/or respond poorly, while for onasemnogene abeparvovec this includes patients who test seropositive against AAV-9, or are classified as having failed treatment. Therefore, risdiplam is anticipated to provide an additional therapeutic option for all patients across the continuum of SMA (i.e.,

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irrespective of the patient's age, type of SMA, or physical status), and in some of those cases it will be the only available treatment option. The proposed position of risdiplam in the SMA treatment pathway is outlined below in Figure 1.

The proposed positioning of risdiplam in the clinical care pathway for SMA is supported by the broadest clinical development programme in SMA (see Section B.2.2) that has demonstrated risdiplam to be an efficacious and well tolerated treated in an SMA population as representative as possible of real-world clinical practice, ranging from infantile-onset SMA to later-onset SMA (age span: 16 days to 60 years), with varied baseline characteristics.

Figure 1: Proposed position of risdiplam in the pharmacologic treatment pathway for SMA



^Babies under 12 months of age *If OA is considered a treatment failure

B.1.4 Equality considerations

Although risdiplam will be appraised through a multiple technology appraisal (MTA), its assessment is anticipated to have several features that are commonly seen in the highly specialised technologies (HST) programme, therefore decision modifiers and flexibility in NICE's decision making should be taken into account. The application of decision modifiers for SMA was recognised by NICE in the previous appraisals of nusinersen [TA588] (18) and risdiplam [TA755] (67), where the committee acknowledged the difficulty of appraising drugs for very rare conditions. SMA is both rare and a very serious lifetime condition, and any treatment benefits are highly valued by patients and families. Therefore, the committee was mindful during its decision making of the need to consider whether any adjustments to its normal considerations were needed to take into account the rarity and severity of the disease (18, 67).

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In addition, the SMA patient population, for which risdiplam will be a treatment option, includes babies, children and young people, as well as adults with disabilities. This will be reflected in our clinical evidence and economic analyses and should also be considered in NICE's decision-making, as per the precedent set in both the nusinersen [TA588] and risdiplam [TA755] NICE appraisals (18, 67). The NICE committee discussed the need to balance the importance of improving the lives of children and their families with fairness to people of all ages. It noted NICE's social value judgements: principles for the development of NICE guidance, which emphasise the importance of considering the distribution of health resources fairly within society as a whole, as well as considering factors other than relative costs and benefits (104).

In the current funding situation, the MAA for risdiplam excludes patients who are permanently ventilated or have a tracheostomy. When this decision was made, there was little to no experience of treating permanently ventilated patients with DMTs and therefore no clearly known benefits. In the past few years the situation has developed significantly. While it can be challenging to measure clinical benefit in these individuals as it is typically based on subjective observations, clinicians do report an improvement in quality of life or a slowing of the expected deterioration in motor / respiratory function. A survey has been completed by 5 neuromuscular specialists in the UK who have been managing permanently ventilated risdiplam patients as part of a Free of Charge scheme, this is detailed in B.2.7.5 and Appendix P.

Overall, pragmatism should be taken in the interpretation of the economic case presented for this rare and very seriously debilitating condition during the decision making process, to ensure fairness of access for this population.

B.2 Clinical effectiveness

B.2.1 Identification and selection of relevant studies

See appendix D for full details of the process and methods used to identify and select the clinical evidence relevant to the technology being evaluated.

B.2.2 List of relevant clinical effectiveness evidence

Two pivotal studies deliver robust and long-term clinical evidence relevant to the decision problem of this appraisal; Study BP39056 (FIREFISH) in infants with type 1 SMA and Study BP39055 (SUNFISH) in paediatric and adult people with type 2 or 3 SMA. Both studies were conducted in two parts: a dose-finding Part 1 and a confirmatory Part 2 at the dose selected based on Part 1 data, with each part conducted in different patients of similar characteristics and with a small proportion of ambulant patients included in SUNFISH Part 1.

Results of Part 2 of each study are included in this submission, providing key data confirming the efficacy and safety of risdiplam over the course of 5-years in the treatment of SMA[1]. The results of Part 1 of each study are presented as supportive data in Appendix L.

[1] As previously agreed with NICE, the 5-year FIREFISH results will be provided during the consultation stages of this appraisal

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In addition to these two pivotal studies, BN40703 (RAINBOWFISH) is an open-label, single-arm, multicenter study to investigate the efficacy, safety, pharmacokinetics and pharmacodynamics of risdiplam in patients aged from birth to 6 weeks (at first dose) who have been genetically diagnosed with SMA (*SMN1* deletion and any *SMN2* copies) but are not yet presenting with SMA symptoms.

The pivotal FIREFISH and SUNFISH studies are also supported by BP39054 (JEWELFISH), an open-label, non-comparative study in people with type 1, 2 and 3 SMA (6 months to 60 years) previously enrolled in Roche Study BP29420 (MOONFISH) with the splicing modifier RO6885247 (development discontinued), or previously treated with nusinersen, onasemnogene abeparvovec or olesoxime (a Roche development molecule which has since been discontinued). The primary objective of JEWELFISH was to assess safety with efficacy data as exploratory endpoints only. Therefore, only safety outcomes are included in this submission, but an overview of the exploratory findings are provided in Appendix N.

Following the initial NICE appraisal [TA755], risdiplam is recommended as a treatment option for SMA only under the conditions of a managed access agreement (MAA) (67). As part of the MAA, a data collection agreement (DCA) outlined the mandated criteria to be collected to address uncertainties highlighted in the initial submission. As such, the data sources that will be utilised to address these uncertainties comprise the four risdiplam clinical trials described above (FIREFISH, SUNFISH, RAINBOWFISH and JEWELFISH), but also data collected on the use of risdiplam in clinical practice. The adult and paediatric SMA registry datasets, Adults SMA REACH and SMA REACH UK, were developed and included within the DCA to better understand how risdiplam was used within clinical practice. Analyses of these registries are included in this submission, and aim to help address the uncertainties surrounding the long-term clinical benefits and cost-effectiveness of risdiplam.

Due to the different populations and age ranges of patients included in the studies (as a consequence of the different age of onset of symptoms across the different SMA types), the studies utilise different assessment scales for motor function and, hence, efficacy data have not been pooled. Instead, the efficacy results of each study are summarised separately.

In summary, evidence for the clinical effectiveness of risdiplam is sourced from the broadest clinical development programme in SMA, which confirms that risdiplam offers a clinical benefit to a broad and heterogeneous population of people with SMA, reflective of that seen in clinical practice, without restrictions or limitations on their physical conditions.

Conducting clinical and economic comparisons to nusinersen is challenging due to the significant gaps in nusinersen clinical trial evidence concerning the benefit it offers for the real-world SMA population, considering the limited populations studied in the pivotal studies (e.g. there are no data of nusinersen in patients over 9 years old or in people with type 3 SMA) and the restrictions due to special warnings and precautions for its use. Furthermore, it is worth noting that the population of patients receiving nusinersen generally have less severe SMA disease than the risdiplam population, as neither the clinical trial nor registry data includes patients with spinal complications that affect intrathecal delivery, which could skew the population towards one with a better expected prognosis.

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Table 5 Clinical effectiveness evidence

Study	BP39056 (FIREFISH)
Study design	Open-label, two-part seamless, multicentre, single-arm study. Part 1 objectives: safety, tolerability, PK and PD, dose selection for Part 2 Part 2 objectives: efficacy, safety and tolerability, PK and PD
Population	Infants with type 1 SMA aged ≥1 month and ≤7 months at the time of enrolment
Intervention(s)	Risdiplam
Comparator(s)	None (single arm)
Indicate if study supports application for marketing authorisation	Yes
Indicate if study used in the economic model	Yes
Rationale for use/non-use in the model	FIREFISH is a Phase II/III trial providing efficacy and safety evidence for risdiplam in people with type 1 SMA. Data from Part 2 of the study were used to inform the efficacy and safety of risdiplam in the economic model
Reported outcomes specified in the decision problem	Motor function (BSID III, HINE-2, CHOP-INTEND); bulbar function; survival and ventilation-free survival; healthcare utilisation; adverse events, HRQoL
Study	BP39055 (SUNFISH)
Study design	Two-part seamless, randomised, multicentre, placebo-controlled, double-blind study. Part 1 objectives: safety, tolerability, PK and PD, dose selection for Part 2 Part 2 objectives: efficacy, safety and tolerability, PK and PD
Population	People aged 2–25 years with type 2 and non-ambulant type 3 SMA
Intervention(s)	Risdiplam
Comparator(s)	Placebo for the first 12 months Single arm OLE for the remaining 4 years
Indicate if study supports application for marketing authorisation	Yes
Indicate if study used in the economic model	Yes
Rationale for use/non-use in the model	SUNFISH is a Phase II/III trial providing efficacy and safety evidence for risdiplam in people with type 2 or 3 SMA. Data from Part 2 of the study were used to inform the efficacy and safety of risdiplam in the economic model

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Reported outcomes specified in the decision problem	Motor function (MFM32, RULM, HFMSE); adverse events; HRQoL
Study	RAINBOWFISH
Study design	Open-label, single-arm, multicentre study
Population	People aged from birth to 6 weeks (at first dose) who have been genetically diagnosed with SMA (*SMN1* deletion and any *SMN2* copies) but not yet presenting with SMA symptoms
Intervention(s)	Risdiplam
Comparator(s)	None (single arm)
Indicate if study supports application for marketing authorisation	Yes
Indicate if study used in the economic model	Yes
Rationale for use/non-use in the model	RAINBOWFISH provides efficacy and safety evidence for risdiplam for pre-symptomatic patients with a genetic diagnosis of SMA. Data from this study were used to inform the efficacy and safety of risdiplam in the economic model
Reported outcomes specified in the decision problem	Motor function (BSID-III, HINE-2, CHOP-INTEND, survival and ventilation-free survival, nutritional status (ability to swallow and feed orally)
All other reported outcomes	Development of clinically manifested SMA, growth measures (weight, length, height, head circumference, chest circumference), degree of innervation (CMAP amplitude)
Study	BP39054 (JEWELFISH)
Study design	Multicentre, open label, non-comparative, single-arm, exploratory study in SMA patients previously enrolled in BP29420 (MOONFISH) or previously treated with nusinersen, onasemnogene abeparvovec or olesoxime. 24 month treatment period plus extension phase
Population	People aged 6 months to 60 years with type 1, 2 and 3 SMA
Intervention(s)	Risdiplam
Comparator(s)	None (single arm)
Indicate if study supports application for marketing authorisation	Yes
Indicate if study used in the economic model	No
Rationale for use/non-use in the model	The primary objective was safety, all efficacy outcomes were exploratory

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Reported outcomes specified in the decision problem	Adverse events, motor function (MFM-32, HFMSE, RULM, 6MWT, BSID-III, HINE-2), HRQoL, survival and ventilation-free survival
Study	REACH registries
Study design	Adult and paediatric SMA registry datasets, collecting observational data on the use of risdiplam within the real world setting.
Population	Patients treated with risdiplam under the MAA
Intervention(s)	Risdiplam
Comparator(s)	None (observational study)
Indicate if study supports application for marketing authorisation	No
Indicate if study used in the economic model	The baseline characteristics are included as a scenario analysis.
Rationale if study not used in model	The REACH registries provide real-world efficacy evidence for risdiplam paediatric and adult SMA patients. The observational baseline data from this study were used to inform a scenarios analysis in the economic model. However, the efficacy and safety data was insufficient to be modelled.
Reported outcomes specified in the decision problem	Motor function (CHOP-INTEND, RHS, RULM, HINE, Adult registry; ATEND, EK2), survival and ventilation-free survival

BSID-III, Bayley Scales of Infant and Toddler Development Third Edition; CHOP-INTEND, Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders; HFMSE, Hammersmith Functional Motor Scale Expanded; HINE-2, Hammersmith Infant Neurological Examination Module 2; HRQoL, health-related quality of life; MFM32, Motor Function Measure – 32 items; PD, pharmacodynamics; PK, pharmacok.inetics; RULM, Revised Upper Limb Module; SMA, spinal muscular atrophy

B.2.3 Summary of methodology of the relevant clinical effectiveness evidence

Unless otherwise stated, information on the clinical trials were sourced from the clinical study reports (102, 105-110). All studies were conducted in accordance with the principles of the "Declaration of Helsinki" and Good Clinical Practice (GCP). For the pivotal studies FIREFISH and SUNFISH, information was sourced from the primary and updated clinical study reports and final clinical study reports, for data up to 12-24 months and 5 years respectively. As previously agreed with NICE, the long-term data for FIREFISH is currently provided up to 4-years but will be updated with 5-year outputs and the final clinical study report will be provided during the consultation stages of the NICE appraisal process.

B.2.3.1 FIREFISH study design (infantile-onset type 1 SMA)

FIREFISH is a two-part, multicentre study to investigate the safety, tolerability, pharmacokinetics, pharmacodynamics, and efficacy of risdiplam in infants with infantile-onset (Type 1) SMA.

The study consists of an exploratory dose-finding part (Part 1) and a confirmatory part (Part 2) to assess the safety and efficacy of risdiplam. Following the dose selection for Part 2,

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patients in Part 1 were given the possibility to continue receiving risdiplam at the dose selected for Part 2, for a total treatment period of 24 mo.nths. Part 2 had a treatment period of 24 months, with the primary analysis at month 12. For both parts, patients could then enter the open-label extension (OLE) phase of 3 years duration. In this study, both the 24-month treatment period and the OLE phase are open-label; however, the OLE has less frequent assessments than the 24-month treatment period.

B.2.3.2 SUNFISH study design (later onset type 2 and 3 SMA)

SUNFISH is a two-part, operationally seamless, multicentre, randomised, placebo-controlled, double-blind study designed to investigate the safety, tolerability, pharmacokinetics, pharmacodynamics, and efficacy of risdiplam in adult and paediatric later onset (type 2 and type 3) SMA.

Like FIREFISH, SUNFISH consisted of a dose-finding part (Part 1) and a confirmatory part (Part 2) to assess the efficacy and safety of treatment with risdiplam at the selected dose level from Part 1. The two parts of the study were independent, had their own objectives and eligibility criteria, and were analysed separately. After selection of the dose for Part 2, patients in Part 1 (i.e., those on placebo and on lower doses of risdiplam) were switched to the dose selected for Part 2 (the pivotal dose) as part of an OLE phase. Efficacy outcome measures overlapping with those collected in Part 2 were assessed throughout Part 1 including the OLE phase.

Part 2 was designed to investigate the efficacy and safety of risdiplam over a 24-month treatment period, in patients aged 2-25 years with type 2 and non-ambulant type 3 SMA. A total of 168 patients were planned to be randomized (2:1) to receive either risdiplam or placebo. Randomization was stratified by age group (2-5 years, 6-11 years, 12-17 years, 18-25 years). Patients enrolled in Part 2, who initially received placebo, were switched to active treatment at week 52, and the initial treatment assignment remained blinded to patients and clinical site staff until all patients completed the week 104 study visit. After week 104, all patients had the opportunity to join OLE for 3 years.

B.2.3.3 RAINBOWFISH study design (paediatric, pre-symptomatic patients, genetically diagnosed SMA)

RAINBOWFISH is an ongoing, open-label, single-arm, multicentre clinical study to investigate the efficacy, safety, pharmacokinetics, and pharmacodynamics of risdiplam in pre-symptomatic patients aged from birth to 6 weeks (at first dose) who have been genetically diagnosed with SMA (*SMN1* deletion and any *SMN2* copies).

The study consists of screening, treatment period, OLE phase, and a follow-up. Patients were enrolled in the study regardless of *SMN2* copy number. All patients will receive risdiplam orally once daily for 2 years at a dose selected to achieve the targeted exposure range (the dose may be adapted as patients grow and mature), following by an OLE phase of at least 36 months and a follow-up, for a total treatment duration of at least 5 years for each infant enrolled. The OLE phase (month 24 to month 60) will continue as per the main study in regards to dosing and will include regular monitoring of safety, tolerability, pharmacokinetics and efficacy (107).

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Enrolment in this ongoing study is complete with 26 patients enrolled. The primary analysis is presented in this submission, including efficacy and safety results up to the clinical cut-off date (CCOD) of 20 February 2023, corresponding to the date when the last patients enrolled had completed 12 months (52 weeks of treatment).

B.2.3.4 REACH registries design (SMA in clinical practice)

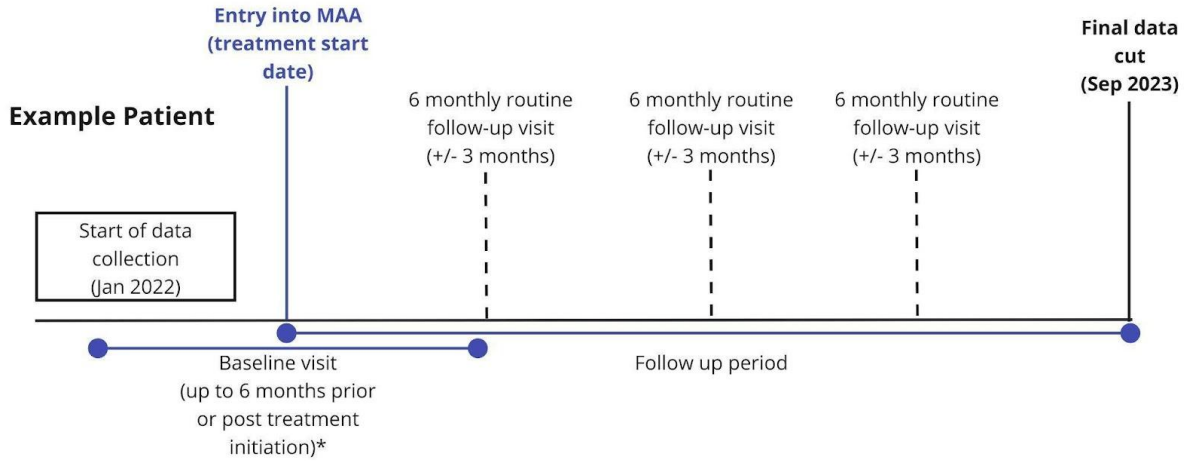
The study is designed as an analysis and description of registry data, to include (as a primary population) patients with SMA that are eligible for inclusion in the risdiplam MAA. The aim of the study is to provide additional long-term data on the use of risdiplam in clinical practice, address uncertainties highlighted in the initial NICE appraisal (TA755) and to help inform this updated NICE submission.

The proposed analyses use data from SMA REACH UK and Adult SMA REACH, which are disease-specific registries collecting data from paediatric and adult patients with SMA in the UK, respectively. These registries collect data regardless of treatment regimen, but only patients treated with risdiplam under the MAA are included in this analysis. The registries contain data on each patient's demographics, mortality, motor function, orthopaedics, respiratory function and nutritional status. Data are collected from 17 SMA REACH UK and 19 Adult SMA REACH national centres at patients' routine clinical visits and are then reported by each patient's healthcare team to the SMA REACH or Adult SMA REACH databases.

Data on the specified outcomes of interest for all patients are reported at baseline, recorded by the patient's healthcare team within six months of the date of treatment commencement (pre- or post-treatment start date). Outcomes are then assessed and reported within 3 months of every routine 6-montly follow-up clinical appointment (pre- or post-visit). Mortality data are recorded at the time of event, if applicable.

For full details please see the Statistical Analysis Plan (SAP).

Figure 2: Data collection schematic for an example risdiplam patient



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B.2.3.5 FIREFISH Part 2 patient demographics and baseline characteristics (infantile-onset, type 1 SMA)

Of the 41 patients enrolled in Part 2, 22 were female (53.7%), the median age at enrolment was 5.3 months (range: 2.2–6.9 months) and the majority of patients were White (22/41, 53.7%) or Asian (14/41, 34.1%).

The baseline characteristics of patients in Part 2 were typical of a symptomatic type 1 SMA population, with a median age of 1.5 months (range: 1.0–3.0 months) at symptom onset. The disease duration (time between onset of symptoms and first treatment) was <3 months in 27 patients (65.9%) and ≥3 months in 14 patients (34.1%), for a median disease duration of 3.4 months (range: 1.0–6.0 months).

Median baseline scores for CHOP-INTEND (22.0), BSID-III (2.0), HINE-2 (1.0), and CMAP amplitude (0.2 mV) were low, as expected for this symptomatic patient population. Patients' current levels of motor function at screening were also typical of this patient population, confirming that all patients had well-established disease by the time of study enrolment.

Table 6: FIREFISH Part 2 key demographic and baseline disease characteristics (infantile-onset, type 1 SMA)

	Risdiplam N=41
Median age at enrolment, months (range)	5.32 (2.2–6.9)
Median age at onset of symptoms, months (range)	1.45 (1.0–3.0)
Median age at diagnosis, months (range)	2.79 (0.9–6.1)
Sex, n (%)	
Male	19 (46.3)
Female	22 (53.7)
Race, n (%)	
White	22 (53.7)
Asian	14 (34.1)
Unknown	5 (12.2)
Region, n (%)	
Europe	24 (58.5)
North America	1 (2.4)
China	11 (26.8)
Japan	1 (2.4)
Rest of world	4 (9.8)
Median disease duration, months (range)	3.38 (1.0–6.0)
≤3 months, n (%)	14 (34.1)
>3 months, n (%)	27 (65.9)
SMN2 copy number, n (%)	
2	41 (100)
Tracheostomy, n (%)	
Yes	0
No	41 (100)
Median CHOP-INTEND score (range)	22.0 (8.0–37.0)
Median BSID-III gross motor scale total raw sore (range)	2.0 (0.0–8.0)
Median HINE-2 score (range)	1.0 (0.0–5.0)
Median CMAP negative peak amplitude, mV (range)	0.19 (0.0–0.8)

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Current level of motor function, n (%)	
Head control carried upright	1 (2.4)
Head control ventral	1 (2.4)
No appropriate function listed	39 (95.1)
Highest motor function achieved, n (%)	
Controls head upright	2 (4.9)
Kicking horizontally	2 (4.9)
Kicking vertically	2 (4.9)
No appropriate function listed	35 (85.4)
Baseline level of respiratory support	
Current level of respiratory support, n (%)	
No pulmonary care	29 (70.7)
BiPAP support <16 hours per day	10 (24.4)
BiPAP support ≥16 hours per day	0
Cough assist – used daily for therapy, not illness related	3 (7.3)
Cough assist – used with an illness	1 (2.4)
Ventilation provided prophylactically, n (%)	
Yes	11 (26.8)
No	20 (73.2)
Awake assisted ventilation	0
Night-time assisted ventilation	9 (22.0)
Nap-time assisted ventilation	2 (4.9)
>16 h assisted ventilation	0
Airway clearance through cough assistance	3 (7.3)
BiPAP support ≥16h per day for >21 consecutive days, n (%)	
Yes	0
No	41 (100)
Intubation for >21 consecutive days, n (%)	
Yes	0
No	41 (100)
Baseline nutritional check up	
Able to swallow, n (%)	
Yes	40 (97.6)
No	1 (2.4)
Missing	0
Median age ability to swallow lost, months (range)	n=1 1.58 (1.6–1.6)
Primary food intake type, n (%)	
Oral fluid (milk) food intake	30 (73.7)
Mixed (fluid/pureed food) oral intake	4 (9.8)
Modified oral food intake	0
Solid food	0
Nasogastric food intake	6 (14.6)
Gastrostomy tube fed	1 (2.4)
Missing	0
Feeding route, n (%)	
Fed orally	33 (80.5)
Fed via a feeding tube	4 (9.8)
Fed via a combination of oral and tube feeding	2 (4.9)
Missing	2 (4.9)

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Disease duration is the time between onset of symptoms and first treatment. Total raw score of the BSID-III gross motor scale is based on the assessment of the site clinical evaluator. Current level of motor function and highest motor function achieved reported at screening. Bi-PAP, Bilevel positive airway pressure; BSID-III, Bayley Scales of Infant Development (third edition); CHOP-INTEND, Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders; CMAP, compound muscle action potential; HINE-2, Hammersmith Infant Neuromuscular Examination section 2; SMA, spinal muscular atrophy; *SMN2* survival motor neuron 2

B.2.3.6 SUNFISH Part 2 patient demographics and baseline characteristics (later onset, type 2 and type 3 SMA)

Demographic and baseline characteristics were well balanced across treatment arms. At screening, the median patient age was 9.0 years (range: 2–25 years) in the risdiplam arm and 9.0 (range: 2–24 years) in the placebo arm. The majority of the population were White (67.2%).

Patients enrolled in SUNFISH Part 2 represent a broad range of the late-onset SMA clinical spectrum, including people with both type 2 and non-ambulant type 3 SMA, with different numbers of *SMN2* copies, and with varied baseline disease characteristics including severe scoliosis. Additionally, people with contractures were not excluded from the study.

Table 7: SUNFISH Part 2 key demographic and baseline disease characteristics (later onset, type 2 and type 3 SMA)

	Risdiplam n=120	**Placebo n=60**
Median age at screening, years (range)	9.0 (2–25)	9.0 (2–24)
Age group, years, n (%)		
2–<6	37 (30.8)	18 (30.0)
6–11	39 (32.5)	18 (30.0)
12–17	30 (25.0)	16 (26.7)
18–25	14 (11.7)	8 (13.3)
Median age of onset of initial symptoms, months (range)	12.3 (0–57)	12.8 (6–135)
Median time between onset for initial symptoms to first treatment, months (range)	106.3 (17–275)	96.6 (1–271)
Sex, n (%)		
Male	59 (49.2)	30 (50.0)
Female	61 (50.8)	30 (50.0)
Race, n (%)		
White	80 (66.7)	41 (68.3)
Asian	23 (19.2)	12 (20.0)
Black or African American	2 (1.7)	0
Multiple	1 (0.8)	0
Unknown	14 (11.7)	7 (11.7)
Region		
Europe	81 (67.5)	43 (71.7)
North America	16 (13.3)	6 (10.0)
China	11 (9.2)	5 (8.3)
Japan	10 (8.3)	5 (8.3)
Rest of world	2 (1.7)	1 (1.7)
SMN2 copy number, n (%)		
2	3 (2.5)	1 (1.7)
3	107 (89.2)	51 (85.0)
4	10 (8.3)	8 (13.3)
SMA type, n (%)		

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Type II	84 (70.0)	44 (73.3)
Type III	36 (30.0)	16 (26.7)
Patients that could or could not stand, n (%)		
Standing	13 (10.8)	6 (10.0)
Could not stand	107 (89.2)	54 (90.0)
Patients that could or could not walk, n (%)		
Walking	3 (2.5)	1 (1.7)
Could not walk	117 (97.5)	59 (98.3)
No. of fractures, n (%)		
None	94 (78.3)	53 (88.3)
1–2	20 (16.7)	7 (11.7)
3–5	5 (4.2)	0
Scoliosis, n (%)		
Yes	76 (63.3)	44 (73.3)
No	44 (36.7)	16 (26.7)
Degree of curvature due to scoliosis, n (%)		
0–10	16 (13.3)	8 (13.3)
10–40	25 (20.8)	12 (20.0)
>40	34 (28.3)	23 (38.3)
Surgery for scoliosis before screening, n (%)		
Yes	29 (24.2)	17 (28.3)
No	63 (52.5)	33 (55.0)
Hip subluxation or dislocation, n (%)		
Yes	26 (21.7)	11 (18.3)
No	94 (78.3)	49 (81.7)
Hip surgery, n (%)		
Yes	4 (3.3)	3 (5.0)
No	116 (96.7)	57 (95.0)

SMA, spinal muscular atrophy; *SMN2* survival motor neuron 2

The median motor function scores for the different scales at baseline were comparable across the risdiplam and placebo arms. The range of total scores at baseline for MFM32, RULM, and HFMSE was broad (i.e. MFM32: 17 to 72 points; RULM: 3 to 37 points; HFMSE: 0 to 48 points) reflecting the wide disease severity distribution of the patients in this study. The proportion of people with a HFMSE score below 10 at baseline (i.e. a baseline score that would be difficult for the HFMSE scale to detect a change from due to the insensitive nature of the assessment (31, 32)) was 41.1% across the study population, with a similar proportion in each treatment arm (risdiplam 40.8%; placebo 41.7%). Such wide range in baseline scores indicates that the patient population randomised to both treatment arms had a broad level of motor function, and that some patients were severely limited by a progressed disease by the time of study enrolment, as predicted given the natural history of SMA and the broad age range allowed by the inclusion criteria.

B.2.3.7 RAINBOWFISH demographics and baseline characteristics (Paediatric, pre-symptomatic, genetically diagnosed SMA)

Primary Efficacy (PE) Population

Per protocol, all patients in the PE population had two *SMN2* copes (excluding the known *SMN2* gene modifier c.859G>C) and a baseline CMAP amplitude ≥ 1.5mV. Patients ranged in age from 22-35 days at first dose. All 5 patients were white, and 3 of the 5 patients (60%)

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were female. The 5 patients were enrolled across 4 countries: Australia, Brazil, Poland and the Russian Federation.

Table 8: RAINBOWFISH Primary Efficacy Population Demographic and Baseline Characteristics

	SMN2 Copy Number
	2 (N=5)
Age at enrolment (Days)	
Mean (SD)	24.6 (4.8)
Median	23.0
25%-75%-ile	22 – 24
Min – Max	21 – 33
Age at First Dose (Days)	
Mean (SD)	25.8 (5.3)
Median	24.0
25%-75%-ile	23 – 25
Min – Max	22 – 35
Sex	
Male	2 (40.0%)
Female	3 (60.0%)
Ethnicity	
Hispanic or Latino	2 (40.0%)
Not Hispanic or Latino	3 (60.0%)
Race	
White	5 (100.0%)
Country	
Australia	1 (20.0%)
Brazil	2 (40.0%)
Poland	1 (20.0%)
Russian Federation	1 (20.0%)
Region	
Europe	2 (40.0%)
Rest of the World	3 (60.0%)
Weight (g	
Mean (SD)	4049.6 (151.6)
Median	4045.0
25%-75%-ile	3968 – 4100
Min – Max	3865 – 4270
Height / Length (cm)	
Mean (SD)	55.40 (3.78)
Median	54.0
25%-75%-ile	53.0 – 55.0
Min – Max	53.0 – 62.0
Head Circumference (cm)	
Mean (SD)	37.02 (1.10)
Median	37.00
25%-75%-ile	36.0 – 37.5
Min – Max	36.0 – 38.6
Chest Circumference (cm)	
Mean (SD)	36.20 (1.92)
Median	37.0
25%-75%-ile	36.0 – 37.0
Min – Max	33.0 – 38.0
Chest to Head Circumference Ratio	
Mean (SD)	0.9776 (0.0347)
Median	0.9870

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25%-75%-ile	0.984 – 1.000
Min – Max	0.917 – 1.000

Intention to Treat (ITT) Population

Patients in the ITT population ranged in age from 16 – 41 days at first dose. The majority (84.6%) of patients were White, and 61.5% of patients were female.

Table 9: RAINBOWFISH Intention to Treat Population Demographic and Baseline Characteristics

	SMN2 Copy Number			
	2 (N=8)	3 (N=13)	>=4 (N=5)	All Patients (N=26)
Age at enrolment (Days)				
Mean (SD)	22.8 (5.0)	28.9 (7.5)	31.2 (6.1)	27.5 (7.1)
Median	22.5	27.0	31.0	24.0
25%-75%-ile	21 – 24	23 – 36	28 – 36	22 – 36
Min – Max	15 – 33	19 – 40	23 – 38	15 – 40
Age at First Dose (Days)				
Mean (SD)	23.9 (5.3)	29.9 (7.5)	32.4 (6.3)	28.5 (7.2)
Median	23.5	28.0	32.0	25.0
25%-75%-ile	22 – 25	24 – 37	29 – 37	23 – 37
Min – Max	16 – 35	20 – 41	24 – 40	16 – 41
Sex				
Male	4 (50.0%)	4 (30.8%)	2 (40.0%)	10 (38.5%)
Female	4 (50.0%)	9 (69.2%)	3 (60.0%)	16 (61.5%)
Ethnicity				
Hispanic or Latino	3 (37.5%)	0	0	3 (11.5%)
Not Hispanic or Latino	5 (62.5%)	12 (92.3%)	5 (100%)	22 (84.6%)
Not stated	0	1 (7.7%)	0	1 (3.8%)
Race				
Asian	0	1 (7.7%)	2 (40.0%)	3 (11.5%)
White	8 (100.0%)	11 (84.6%)	3 (60.0%)	22 (84.6%)
Unknown	0	1 (7.7%)	0	1 (3.8%)
Country				
Australia	1 (25.0%)	6 (46.2%)	0	8 (30.8%)
Belgium	0	1 (7.7%)	2 (40.0%)	3 (11.5%)
Brazil	3 (37.5%)	0	0	3 (11.5%)
Poland	1 (12.5%)	1 (7.7%)	1 (20.0%)	3 (11.5%)
Russian Federation	2 (25.0%)	3 (23.1%)	0	5 (19.2%)
Taiwan	0	0	2 (40.0%)	2 (7.7%)
United States	0	2 (15.4%)	0	2 (7.7%)
Region				
Europe	3 (37.5%)	5 (38.5%)	3 (60.0%)	11 (42.3%)
Rest of the World	5 (62.5%)	6 (46.2%)	2 (40.0%)	13 (50.0%)
US	0	2 (15.4%)	0	2 (7.7%)
Weight (g)				
Mean (SD)	3820.5 (435.1)	4060.1 (647.5)	4190.0 (902.9)	4011.3 (635.6)
Median	3999.0	4000.0	4170.0	4015.0
25%-75%-ile	3538 – 4073	3560 – 4345	3585 – 4300	3560 – 4270
Min – Max	3076 – 4270	3400 – 5726	3275 – 5620	3076 – 5726
Height / Length (cm)				
Mean (SD)	53.88 (3.72)	53.46 (2.73)	54.60 (2.70)	53.81 (2.97)
Median	53.0	53.0	53.0	53.0
25%-75%-ile	52.5 – 54.5	51.0 – 55.0	53.0 – 57.0	52.0 – 55.0
Min – Max	49.0 – 62.0	50.0 – 59.0	52.0 – 58.0	49.0 – 62.0
Head Circumference (cm)				
Mean (SD)	36.26 (1.44)	36.82 (1.21)	37.00 (1.77)	36.68 (1.37)

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Median	36.00	36.80	36.50	36.50
25%-75%-ile	35.5 – 37.3	36.0 – 37.4	36.0 – 38.0	36.0 – 37.5
Min – Max	34.0 – 38.6	35.0 – 38.8	35.0 – 39.5	34.0 – 39.5
Chest Circumference (cm)				
Mean (SD)	35.10 (2.23)	36.18 (2.24)	37.22 (3.38)	36.05 (2.49)
Median	35.40	36.10	36.0	36.00
25%-75%-ile	33.0 – 37.0	35.5 – 37.8	35.0 – 40.0	33.6 – 37.8
Min – Max	32.0 – 38.0	33.0 – 40.5	33.6 – 41.5	32.0 – 41.5
Chest to Head Circumference Ratio				
Mean (SD)	0.9675 (0.0342)	0.9825 (0.0489)	1.0046 (0.0500)	0.9822 (0.0452)
Median	0.9775	0.9740	1.0000	0.9810
25%-75%-ile	0.942 – 0.994	0.963 – 1.014	0.986 – 1.051	0.963 – 1.000
Min – Max	0.914 – 1.000	0.904 – 1.066	0.933 – 1.053	0.904 – 1.066

5.2.3.8 REACH registries (SMA in clinical practice)

Nusinersen was licensed and reimbursed in the UK prior to risdiplam. As such, at the time of launch most patients starting risdiplam were ineligible for treatment with nusinersen, as those who were eliginle had already started treatment. Accordingly, patients treated with risdiplam present with more severe symptoms at baseline as compared to those treated with nusinersen, such as scoliosis. Therefore, given the differences in baseline characteristics, the resulting clinical outcomes are challenging to compare.

Paediatric Registry

Of the 126 total patients included in the paediatric registry, 25 patients had type 1 SMA, 36 patients had type 2/3 and were non-sitters, and 65 patients had type 2/3 and were able to sit or walk. Details of baseline characteristics of the full cohort are presented below, with summaries presented by pre-defined group.

It is worth noting the high presence of scoliosis in this patient cohort, with 81 patients (64.29%) overall having scoliosis, and the majority of patients with type 2/3 having scoliosis (77.78% for non-sitters and 66.15% for sitters or walkers). Scoliosis is a hallmark sign of disease progression which may render patients ineligible for nusinersen due to challenges of delivering a lumbar puncture (76). It is now well understood that the clinical disease severity of a patient is a prognostic factor for SMA (111).

Table 10: Paediatric REACH registry baseline demographics and clinical characteristics

	Cohorts			
	Type I **N=25**	**Type II/III- Non-Sitters** **N=36**	**Type II/III- Sitters/Walkers** **N=65**	**All SMA types** **N=126**
Age at Symptom Onset (months)				
Mean (SD)	3.40 (2.5)	13.47 (19)	14.32 (12)	11.80 (14)
Median	3.00	8.04	12.00	9.00
Range	0.00 – 9.96	3.96 – 20.00	6.00 – 96.36	0.00 – 120.00
Age at First Risdiplam (years)				
Mean (SD)	5.40 (5.1)	13.00 (4)	10.33 (3.7)	10.11 (4.8)
Median	4.27	13.64	10.73	10.91
Range	0.16 – 16.98	0.51 – 17.51	1.09 – 17.01	0.16 – 17.51

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Base Age (years)				
Mean (SD)	5.42 (5.1)	13.02 (4)	10.29 (3.6)	10.11 (4.8)
Median	4.36	13.76	10.73	10.95
Range	0.15 – 17.01	0.50 – 17.63	1.52 – 16.93	0.15 – 17.63
Gender				
Male N (%)	13 (52.00)	18 (50.00)	31 (47.69)	62 (49.21)
Female N (%)	12 (48.00)	18 (50.00)	34 (52.31)	64 (50.79)
Number of *SMN2* copies				
2 N (%)	16 (64.00)	3 (8.33)	4 (6.15)	23 (18.25)
3 N (%)	5 (20.00)	8 (22.22)	29 (44.62)	42 (33.33)
4 N (%)	0 (0.00)	0 (0.00)	7 (10.77)	7 (5.56)
Unknown N (%)	4 (16.00)	25 (69.44)	25 (38.46)	54 (42.86)
Scoliosis				
No N (%)	15 (60.00)	5 (13.89)	21 (32.32)	41 (32.54)
Yes N (%)	10 (40.00)	28 (77.78)	43 (66.15)	81 (64.29)
Unknown N (%)	0 (0.00)	3 (8.33)	1 (1.54)	4 (3.17)
CHOP-INTEND				
N	13	1	1	15
Mean (SD)	28.85 (19)	39.00 (0.0)	41.00 (0.0)	30.33 (18)
Median	25.00	39.00	41.00	39.00
Range	0.00 – 50.00	39.00 – 39.00	41.00 – 41.00	0.00 – 50.00
CHOP-INTEND (Rescale)				
N	12	1	1	14
Mean (SD)	32.33 (19)	42.00 (0.0)	41.00 (0.0)	33.64 (18)
Median	35.00	42.00	41.00	41.50
Range	6.00 – 57.00	42.00 – 42.00	41.00 – 41.00	6.00 – 57.00
HINE-2				
N	15	9	16	40
Mean (SD)	4.80 (4.6)	5.44 (1.7)	14.62 (7.7)	8.88 (7.3)
Median	2.00	6.00	9.50	8.00
Range	1.00 – 15.00	2.00 – 8.00	8.00 – 26.00	1.00 – 26.00
HINE-2 (Rescale)				
N	15	9	16	40
Mean (SD)	4.87 (4.6)	5.44 (1.7)	14.62 (7.7)	8.90 (7.3)
Median	3.00	6.00	9.50	8.00
Range	1.00 – 15.00	2.00 – 8.00	8.00 – 26.00	1.00 – 26.00
RHS				
N	10	10	57	77
Mean (SD)	7.20 (4.5)	2.00 (1.2)	17.60 (16)	14.22 (15)
Median	7.50	2.00	12.00	9.00
Range	1.00 – 14.00	0.00 – 4.00	2.00 – 62.00	0.00 – 62.00
RHS (Rescale)				
N	9	9	51	69
Mean (SD)	6.44 (4.1)	2.11 (1.2)	18.80 (16)	15.01 (16)
Median	6.00	2.00	13.00	9.00
Range)	1.00 – 13.00	0.00 – 4.00	2.00 – 62.00	0.00 – 62.00
RULM				
N	10	27	52	89
Mean (SD)	12.60 (7.4)	9.74 (5.1)	21.06 (8.5)	16.67 (9.1)
Median	15.50	10.00	19.00	15.00
Range	1.00 – 20.00	0.00 – 19.00	5.00 – 37.00	0.00 – 37.00
RULM (Rescale)				
N	10	24	48	82
Mean (SD)	12.60 (7.4)	10.33 (4.7)	21.52 (8.7)	17.16 (9.1)
Median	15.50	10.50	19.50	15.50
Range	1.00 – 20.00	2.00 – 19.00	5.00 – 37.00	1.00 – 37.00

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WHO Motor Achievement				
Non-sitters N (%)	20 (80.00	36 (100.00)	0 (0.00)	56 (44.44)
Sitting without support N (%)	4 (16.00)	0 (0.00)	46 (70.77)	50 (39.68)
Crawling N (%)	0 (0.00	0 (0.00)	7 (10.77)	7 (5.56)
Standing with Assistance N (%)	1 (4.00)	0 (0.00)	0 (0.00)	1 (0.79)
Walking with Assistance N (%)	0 (0.00)	0 (0.00)	2 (3.08)	2 (1.59)
Standing alone N (%)	0 (0.00)	0 (0.00)	1 (1.54)	1 (0.79)
Walking Alone N (%)	0 (0.00)	0 (0.00)	9 (13.85)	9 (7.14)
Feeding problems				
No N (%)	17 (68.00)	28 (77.78)	63 (96.62)	108 (85.71)
Yes N (%)	8 (32.00)	6 (16.67)	2 (3.08)	16 (12.70)
Unknown N (%)	0 (0.00)	2 (5.56)	0 (0.00)	2 (1.59)
TLSO Brace use				
No N (%)	13 (52.00)	17 (47.22)	25 (38.46)	55 (43.65)
Yes N (%)	4 (16.00)	2 (5.56)	10 (15.38)	16 (12.70)
Unknown N (%)	8 (32.00)	17 (47.22)	30 (46.15)	55 (43.65)
At least one fracture				
No N (%)	22 (88.00)	29 (80.56)	59 (90.77)	110 (87.30)
Yes N (%)	3 (12.00)	2 (5.56)	3 (4.62)	8 (6.35)
Unknown N (%)	0 (0.00)	5 (13.89)	3 (4.62)	8 (6.35)
Upper limb contractures				
No N (%)	7 (28.00)	4 (11.11)	34 (52.31)	45 (35.71)
Yes N (%)	12 (48.00)	27 (75.00)	23 (35.38)	62 (49.21)
Unknown N (%)	6 (24.00)	5 (13.89)	8 (12.31)	19 (15.08)
Lower limb contractures				
No N (%)	3 (12.00)	1 (2.78)	5 (7.69)	9 (7.14)
Yes N (%)	16 (64.00)	28 (77.78)	53 (81.54)	97 (76.98)
Unknown N (%)	6 (24.00)	7 (19.44)	7 (10.77)	20 (15.87)
Spinal surgery				
No N (%)	13 (52.00)	6 (16.67)	20 (30.77)	39 (30.95)
Yes N (%)	5 (20.00)	22 (61.11)	22 (33.85)	49 (38.89)
Unknown N (%)	7 (28.00)	8 (22.22)	23 (35.38)	38 (30.16)
Salbutamol Use				
No N (%)	22 (88.00)	22 (61.11)	33 (50.77)	77 (61.11)
Yes N (%)	3 (12.00)	11 (30.56)	31 (47.69)	45 (35.71)
Unknown N (%)	0 (0.00)	3 (8.33)	1 (1.54)	4 (3.17)
Other treatments				
No N (%)	9 (36.00)	7 (19.44)	10 (15.38)	26 (20.63)
Yes N (%)	8 (32.00)	14 (38.89)	24 (36.92)	46 (36.51)
Unknown N (%)	8 (32.00)	15 (41.67)	31 (47.69)	54 (42.86)

CHOP-INTEND, Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders; HINE-2, Hammersmith Infant Neurological Examination Module 2; RHS, Revised Hammersmith Scale; RULM, Revised Upper Limb Module; *SMN2*, Survival Motor Neuron 2; WHO, World Health Organisation

Adult registry

Of the 176 patients included in the adult registry, the majority of patients had type 2/3 SMA (171), with 82 non-sitters and 89 sitters / walkers. There were only 5 patients enrolled with type 1 SMA. Similarly to the paediatric registry, a high proportion of patients had scoliosis at baseline; 80% of patients with type 1 SMA, 93.90% of patients with type 2/3 non-sitters, and

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66.29% of type 2/3 sitters / walkers. As described above, this is likely indicative of patients with severe disease who were ineligible to receive nusinersen, and therefore may not perform as well as patients who receive a DMT earlier on in their disease progression.

It is also worth noting that if a patient transitioned from the paediatric dataset into the adult dataset during the data collection period, their patient data did not transfer from the paediatric SMA REACH UK dataset to the Adult SMA REACH dataset. Patients who transitioned during the data collection period have new baseline patient characteristic data collected at the first routine visit scheduled after they have turned 18 years of age. As a result, their adult dataset baseline data may not be reflective of their true baseline data prior to beginning treatment and may skew the data. However, a sensitivity analysis is planned to assess the impact of removing any patients who transition.

Table 11: Paediatric REACH registry baseline demographics and clinical characteristics

	Cohorts		
	Type I **N=5**	**Type II/III- Non-Sitters** **N=82**	**Type II/III-Sitters/Walkers** **N=89**
Age at Symptom Onset (years) Mean (SD) Median Range	 0.42 (0.12) 0.46 0.25 – 0.50	 1.37 (1.75) 1 0.08 – 14.00	 3.68 (5.08) 1.5 0.33 – 25.00
Age at First receipt of Risdiplam (years) Mean (SD) Median Range	 20.06 (2.76) 19.34 17.87 – 23.68	 32.29 (11.09) 29.23 16.17 – 58.65	 37.38 (13.53) 36.60. 16.49 – 70.35
Gender Male N (%) Female N (%)	 4 (80.00) 1 (20.00)	 50 (60.98) 32 (39.02)	 38 (42.70) 51 (57.30)
Number of *SMN2* copies 1 N (%) 2 N (%) 3 N (%) 4 N (%) Unknown N (%)	 0 (0) 0 (0) 0 (0) 0 (0) 5 (100)	 1 (1.22) 2 (2.44) 39 (47.56) 4 (4.88) 36 (43.90)	 0 (0) 1 (1.12) 33 (37.08) 17 (19.10) 38 (42.70)
Total number of comorbid medical conditions Mean (SD) Median Range	 0.25 (0.5) 0 0 – 1	 1.32 (2.15) 0 0 – 10	 1.35 (1.93) 0 0 – 8
Scoliosis No N (%) Yes N (%) Unknown N (%)	 1 (20) 4 (80) 0 (0)	 4 (4.88) 77 (93.90) 1 (1.22)	 30 (33.71) 59 (66.29) 0 (0)
Fractures No N (%) Yes N (%) Unknown N (%)	 - - -	 76 (92.68) 4 (4.88) 2 (2.44)	 83 (93.26) 4 (4.49) 2 (2.25)
RHS total baseline score Mean (SD) Median	 - -		 25.76 (22.13) 19

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Range	-	Only 5 patients have baseline RHS scores (all are either 0 or 1)	1 – 68
RULM total baseline score			
Mean (SD)	3.6 (4.62)	7.73 (6.67)	19.27 (9.78)
Median	2	7	18
Range	0.00 – 11.00	0.00 – 29.00	0.00 – 37.00
ATEND total right baseline score			
Mean (SD)	15.33 (10.02)	19.20 (8.89)	28.38 (9.25)
Median	19	18.50	31.00
Range	4.00 – 23.00	1.00 – 32.00	0.00 – 44.00
ATEND total left baseline score			
Mean (SD)	15.67 (9.45)	19.39 (9.17)	26.15 (9.6)
Median	19	21.5	28
Range	5.00 – 23.00	1.00 – 32.00	0.00 – 44.00
EK2 baseline score			
Mean (SD)	-	25.32 (7.33)	16.74 (7.85)
Median	-	24	17
Range	-	5 – 42	0 – 37
VIGNOS baseline score			
Mean (SD)	-	9.01 (0.21)	8.03 (2.25)
Median	-	9	9
Range	-	8 – 10	1 – 9
WHO baseline			
Non-sitter N (%)	5 (100)	82 (100)	-
Sitter N (%)	-	-	74 (83.15)
Walker N (%)	-	-	15 (16.85)
Concomitant therapies*			
Yes N (%)	0	9 (10.98)	7 (7.87)
No N (%)	4 (80)	53 (64.63)	56 (62.92)
Unknown N (%)	1 (20)	20 (24.39)	26 (29.21)
(Parental) perceived benefit / patient/parent/carer perception of change			
Benefit N (%)	-	29 (35.37)	14 (15.73)
No change N (%)	-	17 (20.73)	14 (15.73)
Unknown N (%)	-	20 (24.39)	61 (68.54)
Estimated hours of ventilation used			
Greater than 16h day N (%)	0 (0)	1 (1.22)	-
Less than 16h day N (%)	2 (40)	8 (9.76)	6 (6.74)
Night	2 (40)	35 (42.68)	11 (12.36)
Prophylaxis	0 (0)	5 (6.10)	2 (2.25)
Unknown or NA	1 (20)	33 (40.24)	70 (78.65)
Type of ventilator support			
None N (%)	-	30 (36.59)	69 (77.53)
Bipap N (%)	-	45 (54.88)	13 (14.61)
Cough assist N (%)	-	1 (1.22)	-
CPAP N (%)	-	-	6 (6.74)
CPAP overnight N (%)	-	-	1 (1.12)
Other N (%)	-	2 (2.44)	-
Unknown N (%)	-	4. (4.88)	-

*Concomitant therapies are salbutamol as per SAP

ATEND, Adapted Test of Neuromuscular Disorders; EK2, Egen Klassifikation Scale Version 2; RHS, Revised

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B.2.4 Statistical analysis and definition of study groups in the relevant clinical effectiveness evidence

B.2.4.1 FIREFISH (infantile-onset type 1 SMA)

B.2.4.1.1 Statistical hypothesis and planned sample size

The purpose of Part 2 of FIREFISH was to estimate the proportion of infants who were sitting without support at 12 months of treatment and to test whether this proportion was higher than the pre-defined performance criterion of 5%. This was based on the well-defined natural history of type 1 SMA, in which infants never achieve sitting without support (24, 30, 112), therefore this 5% threshold was used to define the performance criterion for success, i.e., a threshold of achievement for the risdiplam-treated infants to be assessed against within this study

The target sample size for Part 2 was 40 infants. This sample size provided at least 90% power to test the null hypothesis H_o: p≤5% versus the alternative hypothesis Ha: p>5%, if the true proportion of infants who would sit on treatment was 20%, based on an exact binomial test with a one-sided 5% significance level. With a planned sample size of 40 infants, a minimum of 5 infants sitting without support would provide a statistically significant difference from the pre-defined performance criterion (i.e., the lower limit of the two-sided 90% Clopper-Pearson [exact] confidence interval would be above 5%).

In the sample size calculations, no allowance was made for infants who withdraw early, as these infants would be classified as non-responders/non-sitters and included within the primary analysis.

Following a 24-month treatment period, patients could enter the OLE phase of the study to receive risdiplam for up to a total of 5 years. Therefore, longer-term efficacy outcomes have been included in this appraisal to investigate if the therapeutic benefits of risdiplam were sustained. However, natural history studies demonstrate that historically type 1 SMA infants never achieve major motor milestones such as rolling or sitting independently, and have a median age of death (or at least 16 hours/day of required non-invasive ventilation) of 10.5 months (23, 24, 30). Therefore, given the lack of long-term natural history data, no formal statistical comparisons to natural history data were possible.

B.2.4.1.2 Analysis populations

The intent-to-treat (ITT) population for Part 2 was defined as all patients enrolled in Part 2 of the study, regardless of whether they received treatment or not. The ITT population was the primary analysis population for all efficacy analyses, with the exception of weight-for-age and length/height-for-age percentiles, which were analysed based on the safety population.

B.2.4.1.3 Assessment of efficacy

Efficacy results from Part 2, (for the 24-month treatment period), are compared to, and put into context with, data describing the natural history of untreated infants with type 1 SMA. These natural history data were used to define thresholds of achievement, i.e. objective

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performance criteria or performance goals, against which to assess the efficacy of treatment. Full details of the available sources used as the external control are provided in Appendix D.

Key efficacy endpoints for FIREFISH are summarised below.

In addition to this, an indirect treatment comparison has been performed for risdiplam versus BSC, nusinersen and onasemnogene abeparvovec in patients with type 1 SMA, aiming to inform both the clinical and the economic section of this evidence submission. More details are provided in Section B.2.9.

Table 12: Key efficacy endpoints in FIREFISH (infantile-onset type 1 SMA)

Motor function and development milestones
• Proportion of patients sitting without support for at least 5 seconds, as assessed by Item 22 of the BSID-III gross motor scale [a] • Proportion of patients who achieve an increase of at least 4 points in their CHOP-INTEND score from baseline • Proportion of motor milestone responders as assessed by the HINE-2[b] • Proportion of patients able to support weight or stand with support as assessed by the HINE-2 • Proportion of patients able to bounce while assessing the walking item of the HINE-2
Survival and ventilation-free survival
• Proportion of patients alive without permanent ventilation (≥16 hours of noninvasive ventilation such as BiPAP per day or intubation for >21 consecutive days in the absence of, or following the resolution of, an acute reversible event or tracheostomy) • Proportion of patients alive
Nutrition
• Proportion of patients with the ability to feed orally • Proportion of patients with the ability to swallow
Healthcare utilisation
• Number of hospitalisations per patient-year • Proportion of patients with no hospitalisations
Patient/caregiver reported outcomes
• Change from baseline in the ITQOL-SF47 Questionnaire domains and single item scores

BiPAP, Bilevel Positive Airway Pressure; BSID-III, Bayley Scales of Infant and Toddler Development III; CHOP-INTEND, Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders; HINE-2, Hammersmith Infant Neurological Examination Module 2; ITQOL-SF47, Infant and Toddler Quality of Life Questionnaire (47 item short form)

[a] The BSID-III gross motor scale was administered in a modified order, starting with the assessment of sitting positions (including the primary endpoint in Part 2).

[b] An infant was classified as a motor milestone responder if more HINE-2 motor milestones showed improvement than showed worsening, as defined in the SAP. Improvement was defined as at least a 2-point increase in the ability to kick (or maximal score) or a 1-point increase in head control, rolling, sitting, crawling, standing, or walking. Worsening was defined as at least a 2-point decrease in the ability to kick (or lowest score) or a 1 point decrease in the other milestones. Voluntary grasp was excluded from the definition.

The **primary endpoint** for the confirmatory Part 2 of the study was the proportion of infants who were sitting without support after 12 months of treatment. Sitting was defined as '*sits without support for at least 5 seconds'* as assessed in Item 22 of the BSID-III Gross Motor Scale. As per the scoring manual, Item 22 was not achieved if the infant sat alone for less

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than 5 seconds before losing balance and falling over, or if the infant used his or her arms to prop him or herself up. The assessment of the independent central readers was used for the primary analysis. Both central readers had to classify the milestone as achieved for the endpoint to be confirmed. Infants were classified as non-responders (i.e., non-sitters) for the primary analysis if they did not achieve sitting, did not maintain sitting achieved earlier, were withdrawn, died, or had a missing assessment at Month 12.

The pre-defined performance criterion for the primary endpoint was 5%.

The proportion of infants who were sitting after 12 months of treatment is presented with a two-sided 90% Clopper-Pearson (exact) confidence interval. An exact binomial test was performed to test the hypothesis that the proportion of infants who sit on treatment (p) is:

Ho: p≤5% (null) versus Ha: p>5% (alternative).

If the one-sided p-value was ≤5% (Type 1 error rate), then the null hypothesis was rejected. If the lower limit of the two-sided 90% confidence interval was above the 5% threshold, then the primary objective of the study was considered achieved.

All **secondary endpoints** (except for time-to-event) were summarised by timepoint for the ITT population using descriptive statistics.

Performance criteria were derived for some of the secondary efficacy endpoints in Part 2 using data from similar cohorts of untreated infants with type 1 SMA constructed from real world data sources/natural history studies. If multiple sources of data were available for a secondary endpoint, the cohort with the baseline characteristics most similar to those targeted by the study inclusion and exclusion criteria was used. The benchmark was based on the associated upper limit of the 90% CI from the historical data. When a pre-defined benchmark could be determined for the secondary endpoint, hypothesis testing was performed.

The tested hypothesis was that the treatment response rate (p) is:

H_0: p≤pre-defined benchmark (null) versus H_a: p>benchmark (alternative).

If the one-sided p-value was ≤5% (nominal) then the null hypothesis was rejected.

To control for multiplicity across the different endpoints, a hierarchical testing approach was implemented. The first secondary efficacy endpoint, the proportion of infants who achieve a score of 40 or higher in the CHOP-INTEND at Month 12, was tested if and only if the primary endpoint had reached the 5% significance level (i.e., p-value ≤0.05). Other secondary endpoints were tested at a 5% significance level according to the following hierarchy, as long as the p-value was ≤0.05 for endpoints higher in the hierarchy:

- Proportion of infants who achieve an increase of at least 4 points in their CHOP-INTEND score from baseline at Month 12.
- Proportion of motor milestone responders as assessed by the HINE-2 at Month 12
- Proportion of infants who are alive without permanent ventilation at Month 12
- Proportion of infants sitting without support for 30 seconds (defined as ‘Sits without support for 30 seconds’ as assessed in item 26 of the BSID-III gross motor scale) at Month 24
- Proportion of infants standing at Month 24 (defined as ‘Stands alone’ as assessed in item 40 of the BSID-III gross motor scale)

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- Proportion of infants walking at Month 24 (defined as ‘Walks alone’ as assessed in item 42 of the BSID-III gross motor scale).

Any other endpoints for which hypothesis testing was performed were simultaneously tested at the 5% significance level without adjustment for multiplicity, as they were considered to provide supportive information.

As discussed above, no formal statistical comparisons to expected performance thresholds were possible for the long-term study data, given the traditionally poor outcomes and early mortality for type 1 SMA infants who did not receive a DMT in natural history studies (23, 24, 30). Please also note, the results up to 24 months are based on the assessment of the independent central readers and those in the OLE period are based on the assessment of the site clinical evaluator.

B.2.4.2 SUNFISH (later-onset type 2 and type 3 SMA)

B.2.4.2.1 Statistical hypothesis and planned sample size

The target sample size for Part 2 of SUNFISH was 168 people with 112 patients randomised to risdiplam and 56 patients randomised to placebo (2:1 randomisation).

For the primary endpoint of mean change from baseline in total MFM score at Month 12, the sample size of 168 patients (allowing for a 10% dropout rate) provided at least 80% power at a two-sided 5% significance level for testing the null hypothesis (the true treatment difference is zero) versus the alternative hypothesis (the true treatment difference is 3), and assuming that the common standard deviation will be 6. This corresponds to a hypothesised effect size of 0.5. The minimal detectable treatment difference was approximately 2.03.

Patients enrolled in Part 2 who initially received placebo were switched to active treatment at week 52. Therefore, all efficacy endpoints after month 12 were exploratory and no formal statistical analysis is available past this point.

B.2.4.2.2 Analysis populations

The ITT population, defined as all randomised patients in Part 2, was the primary analysis population for all efficacy analyses. Patients in the ITT population were reported according to the treatment to which they were randomised. Patients not randomised but received study medication were excluded from the ITT population.

B.2.4.2.3 Assessment of efficacy

Efficacy analyses presented within this submission document are from Part 2 only. The primary efficacy estimand is based on a hypothetical treatment strategy assuming no prohibited medications intended for treatment of SMA were available and patients continued on their randomised treatment until the primary analysis timepoint. This approach facilitated the exploration of the efficacy of risdiplam in the absence of other treatments. A treatment policy strategy was also applied. For any patients who discontinued study treatment but continued in the study, all data were included regardless of initialisation of prohibited medications. Efficacy endpoints in Part 1 are considered exploratory; the results of Part 1 are presented in Appendix M as supportive data as they also showed clear efficacy of risdiplam in SMA. Key efficacy endpoints are summarised below.

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Table 13: Key efficacy endpoints in SUNFISH (later onset type 2 and type 3 SMA)

Motor function and development milestones
• Change from baseline in MFM32 total score • Proportion of patients who achieved a change from baseline greater or equal to 3 points in the MFM32 total score • Proportion of patients who achieved stabilization or improvement (change from baseline greater or equal to 0 points) in the MFM32 total score • Change from baseline in RULM total score • Change from baseline in HFMSE total score
Patient/caregiver reported outcomes
• Change from baseline in the patient- and caregiver-reported SMAIS total score

HFMSE, Hammersmith Functional Motor Scale Expanded; MFM, Motor Function Measure; RULM, Revised Upper Limb Module; SMAIS, SMA Independence Scale.

Motor function was assessed by three different clinically relevant and validated scales in SUNFISH: the Motor Function Measure 32 (MFM32), the Revised Upper Limb Module (RULM), and the Hammersmith Functional Motor Scale Expanded (HFMSE). The clinical relevance of each motor function scale was taken into account when designing the study. Importantly, although both the MFM32 and HFMSE assess the concept of motor function, the items in the MFM32 capture a broader range of ability, including items relating to distal motor function that are primarily not assessed by the HFMSE, and therefore captures the entire breadth of the patient population within one scale. This broad range of functional ability is thus applicable, whatever the severity of the deficiencies, in non-ambulant and ambulant patients. For this reason, the MFM32 scale was chosen to evaluate the primary endpoint in SUNFISH Part 2. The primary analysis was the Mixed Model Repeated Measure (MMRM) analysis performed on the change from baseline in the total MFM32 score using all data collected in Part 2 up to 12 months.

Given the importance to people with type 2 and type 3 SMA of maintaining independence (see Section B.1.3.2.), the SMA Independence Scale (SMAIS) was developed specifically for SMA patients in order to assess function-related independence. The SMAIS contains items assessing the amount of assistance required from another individual to perform daily activities such as eating, or bathing. The SMAIS was completed by patients aged ≥12 years and caregivers of patients 2–25 years. The items in the two scales are identical. The SMAIS total score comprises 22 of the 29 items focused on upper limb ability, with each item scored on a 0-2 scale (0–44 total score). Higher scores indicate greater independence in completing activities.

The reliability, validity and responsiveness of the SMAIS has been confirmed via quantitative analysis using SUNFISH data and an independent US survey source (113). Anchor-based analyses indicated that meaningful change estimates on the SMAIS 22-item upper limb total score vary by age subgroup and that a range of 1–5 points may be meaningful. The mean score change for patients classified as ‘minimally improved’ on CGI-C at week 52 mean was 1.4 for the caregiver-report version (2–25 years old) and 2.8 for the patient self-report version (12-25 years old). An estimate of 2–3 points for both scales is considered a conservative meaningful change threshold in light of these data (113).

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B.2.4.2.4 Adjustment for multiple testing

To control the type I error rate due to multiple testing of risdiplam versus placebo for the primary and the five key secondary efficacy endpoints in the ITT population, a gatekeeping approach was applied to the six null hypotheses which were grouped into five families. The hypotheses to be tested were ordered hierarchically and the truncated Hochberg procedure was used in the family which contains more than one hypothesis. The following shows the six null hypotheses and the five families of the testing for Part 2.

- Family 1 includes the hypothesis for the primary endpoint on the change from baseline total MFM32 score at Month 12 comparing risdiplam versus placebo: H_{11} (MFM32)
- Family 2 includes the hypothesis for the proportion of patients who achieve a change from baseline ≥3 on the total MFM32 score at Month 12 comparing risdiplam versus placebo: H_{21} (Prop. MFM32 ≥3)
- Family 3 includes the hypothesis for the change from baseline total score of RULM at Month 12 comparing risdiplam versus placebo: H_{31} (RULM)
- Family 4 includes the hypothesis for the change from baseline total score of HFMSE at Month 12 comparing risdiplam versus placebo: H_{41} (HFMSE)
- Family 5 includes the hypothesis for the change from baseline in total score of caregiver/parent reported SMAIS at Month 12 comparing risdiplam versus placebo: H_{51} (SMAIS)

Further information on the multiple testing approach can be found in the Primary CSR (106).

B.2.4.2.5 Long-term data

Following the initial 12-month placebo-controlled period of the SUNFISH clinical trial, all patients had the opportunity to switch to risdiplam. Therefore, for long-term data collected after the primary analysis (24 – 60 months) only summary descriptive statistics were possible.

B.2.4.3 RAINBOWFISH (Paediatric, pre-symptomatic, genetically diagnosed SMA)

B.2.4.3.1 Statistical hypothesis and planned sample size

The purpose of the study is to estimate the proportion of infants with two *SMN2* copies (excluding the known *SMN2* gene modifier mutation c.859G>C) and a baseline CMAP amplitude ≥1.5 mV who are sitting without support after 12 months of treatment and to test whether this proportion is higher than a performance criterion set at 5%. The 5% threshold was chosen based on the natural history of the disease (typically patients with Type 1 SMA never achieve sitting without support by definition) and based on the assumption that there is a 97% chance that a presymptomatic infant with two *SMN2* copies develops Type 1 SMA (9).

B.2.4.3.2 Analysis population

The intend-to-treat (ITT) population is defined as all enrolled patients, regardless of whether they receive risdiplam or not. The primary efficacy (PE) analysis population is defined as all infants in the ITT population with two *SMN2* copies (excluding the known *SMN2* gene modifier mutation c.859G>C) and a baseline CMAP amplitude ≥1.5 mV. The ITT population

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will be used for all secondary and exploratory efficacy summaries; however, any hypothesis testing if performed will be limited to the primary efficacy analysis population.

B.2.4.3.3 Assessment of efficacy

The primary endpoint of the study is the proportion of infants who are sitting without support after 12 months of treatment. Infants who do not achieve sitting, or have not maintained sitting achieved earlier, have been withdrawn, or died, will be classified as non-responders (i.e., non-sitters) for the primary analysis. Sitting is defined as "sits without support for 5 seconds" as assessed in Item 22 of the BSID-III Gross Motor Scale. The assessment of the independent central readers will be used for the primary analysis.

The proportion of infants who are alive and sitting after 12 months of treatment will be presented with a two-sided 90% Clopper-Pearson (Exact) confidence interval. An exact binomial test will be performed. The hypothesis to be tested will be that the proportion of infants who sit on treatment (p) is:

Ho: $p \leq 5\%$ (null) versus Ha: $p > 5\%$ (alternative).

If the one-sided p-value is $<5\%$ (Type 1 error rate), then the null hypothesis will be rejected. If the lower limit of the two-sided 90% confidence interval is above the 5% threshold, the primary objective of the study will be considered achieved. The number and percentage of infants sitting at each timepoint will also be presented, using the same responder/non-responder definition described above.

In this open-label study, the minimum number of infants needed for a statistically significant result has been achieved and the primary objective of the study is considered achieved. The primary analysis was conducted once the last patient enrolled (irrespective of *SMN2* copy number) had reached 12 months of treatment, in order to assess the primary endpoint, and to allow the assessment of the 12 month secondary and exploratory endpoints in all patients. The study was not stopped early once the primary objective had been reached, and all infants enrolled will continue to receive treatment to provide unbiased estimates of the secondary and exploratory endpoints.

Key efficacy endpoints for RAINBOWFISH are summarised below.

Table 14: Key efficacy endpoints in RAINBOWFISH (paediatric, pre-symptomatic, genetically diagnosed SMA)

Development of clinically manifested SMA
• Proportion of patients developing clinically manifested SMA at month 12 and month 24
Survival and ventilation-free survival
• Time to death or permanent ventilation[a] (from enrolment) • Proportion of patients who are alive without permanent ventilation at month 12 and 24 • Proportion of patients who are alive at month 12 and 24
Motor function and development milestones
• Proportion of patients who achieve the attainment levels of the motor milestones as assessed in the HINE-2 (head control, sitting, voluntary grasp, ability to kick, rolling, crawling, standing, and walking) at month 12 and 24 • Proportion of patients sitting without support for 5 seconds, sitting without support for 30 seconds, standing alone, walking alone at month 24 as assessed in Item 22, 26, 40 and 42 of the BSID-III Gross Motor Scale, respectively

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• Proportion of patients demonstrating the ability to achieve a scaled score within 1.5 standard deviations of chronological reference standard at Months 24 and 42 (as assessed through the use of the BSID-III Gross Motor Scale) • Change from baseline score in the CHOP INTEND motor function scale at Month 12 • Proportion of patients who achieve a score of ≥40, ≥50, and ≥60 or higher in the CHOP INTEND motor function scale at Month 12 • Proportion of patients who [redacted] • Change from baseline (Month 24) in the HFMSE at Month 60 of treatment
Growth measures
• Number and proportion of patients within 3rd percentile of normal range for weight-for-age, length/height-for-age, weight-for-length/height, and head circumference-for-age at Month 12, 24, 36, 48 and 60 o, based on the WHO Child Growth Standards (WHO 2019) • Change from baseline percentiles for weight-for-age, length/height-for-age, weight-for-length/height, and head circumference-for-age at Month 12, 24, 36, 48, 60 • Change from baseline in chest circumference at Month 12 and 24 • Ratio[b] between chest and head circumferences at Month 12 and 24
Nutrition
• Proportion of patients with the ability to swallow at month 12, 24, 36, 48 and 60 • Proportion of patients with the ability to feed orally at month 12, 24, 36, 48 and 60
Muscle electrophysiology
• Change from baseline in CMAP amplitude at month 12 and 24

[a]Permanent ventilation is defined as >16 hours of non-invasive ventilation per day or intubation for >21 consecutive days in the absence of, or following the resolution of, an acute reversible event or tracheostomy,
[b]Head circumference will be the denominator of the ratio

Analyses of the secondary efficacy endpoints will be performed using all data available at the time of the 12-month, 24-month, and further analysis reporting events. All secondary endpoints will be summarized by timepoint (except for the time-to-event endpoints) by overall population, by *SMN2* copy number for the ITT population and the primary efficacy analysis population using descriptive statistics. The two-sided 90% confidence intervals will also be presented as appropriate.

Time-to-death or permanent ventilation and its individual components will be presented graphically using Kaplan-Meier curves. The median time to ventilation-free survival and the proportion of patients who are surviving ventilation-free at Months 12 and 24 of treatment will be estimated using Kaplan-Meier methodology, when possible. Time-to-death or permanent ventilation is defined as the time in months from the date of enrolment in the study until the date of death from any cause or date of permanent ventilation, whichever event occurs first. Patients with no event reported prior to the analysis cutoff date will be censored at the latest date before the cutoff in which they were known to be alive and ventilation free.

For the primary efficacy population only, the proportion of infants who at 12 months of treatment are alive and sitting without support for 30 seconds (as assessed in item 26 of the BSID-III Gross Motor Scale), and the proportion of patients who at 24 months of treatment are alive and 1) sitting without support for 5 seconds (as assessed in Item 22 of the BSID-III Gross Motor Scale), 2) sitting without support for 30 seconds (as assessed in Item 26 of the BSID-III Gross Motor Scale), 3) standing (as assessed in Item 40 of the BSID-III Gross Motor Scale), and 4) walking (as assessed in Item 42 of the BSID-III Gross Motor Scale) will

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be analyzed as for the primary endpoint (using the same performance criterion of 5%) testing the null hypothesis that the proportion of patients who are alive and have achieved the motor milestone $\delta 5\%$ (null) versus $p > 5\%$ (alternative).

B.2.4.4 REACH registries (SMA in clinical practice)

Please refer to the SAP and final reports for full details on the statistical analysis of the registries. Please note that Roche played no part in running the statistical analysis, this was conducted by statisticians within the registries.

B.2.4.4.1 Statistical analysis and planned sample size

All eligible patients in the SMA REACH UK and Adult SMA REACH registries will be considered for outcome analyses in the final report. These data were not originally expected to include hypothesis testing and therefore formal sample size determination was not performed. Instead, the sample size used for each analysis presented in this submission is the maximum number of patients with appropriate data available.

All data collected was observational and the associated analysis descriptive in nature. All planned analyses will be included in the final report unless it is determined that no meaningful evidence would be produced by the data collected during the managed access period. A decision on whether an analysis should be excluded will be taken with input from the registries, NICE and the Newcastle External Assessment Group, and a justification for the exclusion described in the final report.

The goal of this statistical analyses is to provide real-world data to supplement the ongoing, long-term clinical trial data for risdiplam. Real-world data analysis is not intended to replace the need for clinical trials, and typically data collected on patients receiving a drug through managed access is not expected to have a comparator group. Additionally, comparative analyses between the registry patients and clinical trial patients would not be appropriate due to differences between the two patient groups. Therefore, this supplementary registry data is not intended to be used alone for decision making and may only contain a small number of patients (after stratification), limiting statistical power. If the inferential analyses planned was not feasible then the outcomes have been analysed through differences in outcome values (for continuous measures) or the percentage of patients in each category for each outcome (for categorical and binary measures) and reported at each timepoint.

Inferential analysis

Mixed-effects modelling have been performed for two separate cohorts: those with SMA Type 1 and those with SMA Type 2 or 3. Data reporting for these analyses include the sample size, parameter estimate, and 95% CIs. Please note that these analyses are not intended to formally compare treatment effects, and so p values are not be reported. As formal statistical comparisons are not appropriate, no adjustment for multiple comparisons is included in this analysis.

Descriptive analysis

Descriptive statistics have been produced for the data items of interest and are presented for both the SMA REACH UK and Adult SMA REACH data analyses. For continuous and count variables, the mean, standard deviation (SD), 95% confidence interval (CI) of the mean,

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median and interquartile range (IQR) are summarised. For categorical variables, the number and percentage of patients for each category are reported.

Descriptive statistics are reported for outcome measures at baseline, and at every 6-month routine follow-up visit (any two entries need to be at least three months apart and a minimum of one data entry per patient per year is required to be captured after the initial assessment) through to the end of the collection period (expected Q3 2025). Based on the data collection period, the maximum amount of data would comprise 6-month, 12-month and 18-month follow-up visits. For this submission, a data cut was performed at the end of 2023 and therefore very few patients have 18-month data available. For data that is last available in between two routine follow-up timepoints due to discontinuation of treatment or reaching the end of the collection period, data from the previous visit are considered (last visit available prior to stopping treatment within the MAA period).

B.2.4.4.2 Analysis populations

Paediatric and adult data are stored in SMA REACH UK and Adult SMA REACH respectively; both are used in this analysis. The adult and paediatric datasets have been analysed separately. Both registries report data from centres in England only. The analyses are aligned for the adult and paediatric datasets. If a patient transitioned from the paediatric dataset into the adult dataset during the data collection period, their patient data did not transfer from the paediatric SMA REACH UK dataset to the Adult SMA REACH dataset. Patients who transitioned during the data collection period have new baseline patient characteristic data collected at the first routine visit scheduled after they have turned 18 years of age. As a result, their adult dataset baseline data may not be reflective of their true baseline data prior to beginning treatment. However, a sensitivity analysis is planned to assess the impact of removing any patients who transitioned.

B.2.4.4.2 Assessment of efficacy

For the key motor function outcomes of interest, only the appropriate measurement scale(s) were collected and reported for each patient, alongside the World Health Organization (WHO) Motor Achievement scale. However, the patient's healthcare team determined the most appropriate scale for each patient at each visit. It is possible that the measurement scale used at a patient's baseline visit was not measured at all follow-up visits if the scale that was most appropriate for the patient changed during the follow-up period. If a patient's healthcare team decided that the motor function scales should be switched for a patient, then the previously used and new scales should both have been measured, where possible, at that visit, but then only the new motor function scale will be measured at subsequent follow-up visits.

Table 15: Appropriate patient population for use with the mandated motor function scales of interest

Motor Function Scale	Appropriate patient population for collection
CHOP-INTEND	• Patients <2 years of age who cannot yet walk independently • Patients ≥2 years of age who have not yet achieved a score of 64 on the CHOP-INTEND
HINE	• Patients <2 years of age who cannot yet independently walk
RHS	• Patients ≥2 years of
RULM	• Non-ambulatory patients ≥30 months of age (assessment will continue if patients subsequently become ambulatory)

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WHO Motor Achievement	• All patients

CHOP-INTEND, Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders; HINE, Hammersmith Infant Neurological Exam; RHS, Revised Hammersmith Scale; RULM, Revised Upper Limb Module; WHO, World Health Organisation

In addition to the mandated data items, additional data items (EK2 scale, Vignos and ATEND) that have been captured by SMA REACH UK and Adult SMA REACH are of interest to further explore the long-term effectiveness of risdiplam. These data items are not be included in the main analysis as they are not mandated in the MAA. They are also not expected to have the same level of completeness and data cleaning performed as the mandated data items.

B.2.5 Critical appraisal of the relevant clinical effectiveness evidence

Critical appraisal of the included randomised clinical trial was performed using established risk of bias tools recommended for HTA submissions. The complete quality assessment is presented in Appendix D. A summary is presented below.

Table 16: Clinical effectiveness evidence quality assessment

Study question	BP39055 (SUNFISH)
Was randomisation carried out appropriately?	Yes
Was the concealment of treatment allocation adequate?	Yes
Were the groups similar at the outset of the study in terms of prognostic factors?	Yes
Were the care providers, participants and outcome assessors blind to treatment allocation?	Yes
Were there any unexpected imbalances in drop-outs between groups?	No
Is there any evidence to suggest that the authors measured more outcomes than they reported?	No
Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	Yes

B.2.6 Clinical effectiveness results of the relevant studies

B.2.6.1 FIREFISH Part 2 (infantile-onset, type 1 SMA)

Efficacy overview

- The primary efficacy endpoint for this study was met. After 12 months of treatment with risdiplam, 29.3% of patients in Part 2 were sitting without support, as assessed by Item 22 of the BSID-III gross motor scale. This proportion is significantly higher than the pre-defined performance criterion of 5% based on natural history data ($p<0.0001$).
- The results of the secondary and exploratory efficacy endpoints supported the primary endpoint, showing that risdiplam treatment was associated with clinically meaningful improvements in people with type 1 SMA:
  - At Month 12, 56.1% of patients achieved a CHOP-INTEND total score of 40 or higher, and 90.2% of patients achieved an increase of at least 4 points in their CHOP-INTEND score from baseline. These results are significantly higher than the

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pre-defined performance criteria of 17% based on natural history data (p<0.0001 for each of these endpoints).
    - At Month 12, 78.0% of patients were classified as motor milestone responders (defined as having more milestones that showed improvement from baseline than showed worsening) as assessed by the HINE-2. This proportion was significantly higher than the pre-defined performance criterion of 12% based on natural history data (p<0.0001).
    - At Month 12, 85.4% of patients were alive without permanent ventilation. This proportion is significantly higher than the pre-defined performance criterion of 42% based on natural history data (p<0.0001).
- The long-term efficacy data in the OLE phase of the study support the analysis results at 12 months of treatment. Risdiplam treatment for up to 4 years resulted in infants with type 1 SMA achieving major motor milestones that they would never be able to achieve without treatment. Infants treated with risdiplam maintained or continued to improve in their ability to sit without support, and one had even begun to walk alone by 48 months. The data show that long-term risdiplam treatment continues to maintain or increase the clinically meaningful improvement in patients with Type 1 SMA.
    - After 48 months of risdiplam treatment [redacted].
    - Improvements in CHOP-INTEND total score were maintained to month 48; motor function improvement, as measured by an increase of at least 4 points from baseline was achieved by [redacted].
    - At 48 months, [redacted]n.
    - At 48 months, [redacted].

B.2.6.1.1 Primary efficacy endpoint

At 12 months of treatment, 12 of 41 patients (29.3%; 90% CI: 17.8%, 43.1%) in Part 2 were sitting without support, as assessed by Item 22 of the BSID-III gross motor scale, '*sits without support for 5 seconds'*. This proportion (29.3% of patients sitting at Month 12) is significantly higher than the pre-defined performance criterion of 5% based on well-established natural history data (p<0.0001) (24, 112).

Month 24

At month 24, 25 patients (61%; 90% CI: 46.9%, 73.8%) were sitting without support for 5 seconds as assessed by Item 22 of the BSID-III gross motor scale. This is an increase in the number of patients who had achieved this milestone at month 12. All 12 patients (100%) who had the ability to sit without support at month 12 had maintained this ability at month 24.

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The proportion of patients with the ability to sit without support for 5 seconds at month 24 (61.0%) is significantly higher than the pre-defined performance criterion of 5% based on well-established natural history data (p<0.0001).

Open-label extension (Up to 48 months)

Data from the OLE phase of the study demonstrates that children treated with risdiplam maintained or continued to improve in their ability to sit without support for 5 seconds as assessed by Item 22 of the BSID-III gross motor scale [redacted]

Table 17: Patients sitting without support for 5 seconds over time (ITT Population, FIREFISH Part 2)

Endpoint	Risdiplam n=41	Performance criterion	p-value
Number / proportion (90% CI) of patients sitting without support for 5 seconds (BSID-III) at Month 12	12/41 29.3% (17.8 – 43.1%)	5%	< 0.0001
Number / proportion (90% CI) of patients sitting without support for 5 seconds (BSID-III) at Month 24	25/41 61.0% (46.94% – 73.77%)	5%	<0.0001
Number / proportion (90% CI) of patients sitting without support for 5 seconds (BSID-III) at Month 36 (OLE)	[redacted]	[redacted]	[redacted]
Number / proportion (90% CI) of patients sitting without support for 5 seconds (BSID-III) at Month 48 (OLE)	[redacted]	[redacted]	[redacted]

BSID-III, Bayley Scales of Infant and Toddler Development, third edition; CI, confidence interval

B.2.6.1.2 Secondary efficacy endpoints

Motor function and development milestones

BSID-III: Sitting without support for 30 seconds

At month 24 of treatment, 18 patients (43.9%; 90% CI: 30.6%, 57.9%) were sitting without support for 30 seconds as assessed by Item 26 of the BSID-III gross motor scale. This is more than twice as many as had the ability at month 12 (7 patients; 17.1%; 90% CI: 8.3%, 29.7%). The proportion of patients with the ability to sit without support for 30 seconds at month 24 (43.9% of patients) is significantly higher than the pre-defined performance criterion of 5% based on well-established natural history data (p<0.0001).

Data from the OLE phase of the study demonstrates that the number of children able to sit without support for 30 seconds increased over the risdiplam treatment period, with [redacted]

BSID-III: Standing Alone

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No patients in Part 2 were standing alone as assessed by Item 40 of the BSID-III gross motor scale at month 12 or month 24 of treatment. The proportion of patients standing alone at month 24 is not different from the pre-defined performance criterion of 5%.

Data from the OLE phase of the study shows that by month 48, [redacted] were able to stand alone as assessed by Item 40 of the BSID-III gross-motor scale.

BSID-III: Walking alone

No patients in Part 2 were walking alone as assessed by Item 42 of the BSID-III gross motor scale at month 12 or month 24 of treatment. The proportion of patients standing alone at month 24 is not different from the pre-defined performance criterion of 5%.

Data from the OLE phase of the study shows that by month 48, [redacted] (6). A summary of BSID-III outcomes, showing the proportion of patients with the ability to sit without support for 30 seconds, stand alone and walk alone over time up to 48 months is presented below.

Table 18: A summary of patients sitting without support for 30 seconds, standing alone, and walking alone over time as assessed by the BSID-III gross motor scale (ITT population, FIREFISH Part 2)

Endpoint and time point	Risdiplam n=41	Performance criterion	p-value
Number (proportion) and (90% CI) of patients sitting without support for 30 seconds (BSID-III)			
Month 12	7 (17.1%) 8.3% – 29.7%	NA	-
Month 24	18 (43.9%) 30.6% – 57.9%	5%	<0.0001
Month 36 (OLE)	[redacted]	[redacted]	[redacted]
Month 48 (OLE)	[redacted]	[redacted]	[redacted]
Number (proportion) and (90% CI) of patients standing alone (BSID-III)			
Month 12	0 (0%) 0% – 7.1%	NA	-
Month 24	0 (0%) 0.00% – 7.1%	5%	1.0000
Month 36 (OLE)	[redacted]	[redacted]	[redacted]
Month 48 (OLE)	[redacted]	[redacted]	[redacted]
Number (proportion) and (90% CI) of patients walking alone (BSID-III)			
Month 12	0 (0%) 0% – 7.1%	NA	-

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Month 24	0 (0%) 0.00% – 7.1%	5%	1.0000
Month 36 (OLE)	[redacted]	[redacted]	[redacted]
Month 48 (OLE)	[redacted]	[redacted]	[redacted]

BSID-III, Bayley Scales of Infant and Toddler Development, third edition; CI, confidence interval

CHOP-INTEND

At 12 months of treatment, 23 of 41 patients (56.1%; 90% CI: 42.1%, 69.4%) in Part 2 achieved a CHOP-INTEND total score of 40 or higher. This proportion is significantly higher than the pre-defined performance criterion of 17% based on natural history data (p<0.0001).

At 12 months of treatment, 37 of the 38 surviving patients in Part 2 presented motor function improvement, as measured by an increase of at least 4 points from baseline in their CHOP-INTEND score. One patient had a change of -2 at Month 12; this patient had fluctuations in the CHOP-INTEND scores during the first 12 months, with changes from baseline ranging from -2 to +3. Overall, 37 of 41 patients (90.2%; 90% CI: 79.1%, 96.6%) achieved an increase of at least 4 points from baseline, which is a significantly higher proportion than the pre-defined performance criterion of 17% based on natural history data (p<0.0001).

The improvements in CHOP-INTEND scores seen at month 12 were further enhanced at month 24 and maintained through to month 48. The proportion of patients who presented motor function improvement, as measured by an increase of at least 4 points from baseline in their CHOP-INTEND score was maintained at month 24, and remained relatively stable in the OLE phase of the study up to month 48.

Table 19: CHOP-INTEND scores over time (ITT Population, FIREFISH Part 2)

Endpoint and time point	Risdiplam n=41	Performance criterion	p-value
Number (proportion) and (90% CI) of patients who achieve a score of 40 or higher in the CHOP-INTEND			
Month 12	23 (56.1%) 42.1–69.4%	17%	<0.0001
Month 24	31 (75.6%) 62.2–86.1%	NA	-
Month 36 (OLE)	[redacted]	[redacted]	[redacted]
Month 48 (OLE)	[redacted]	[redacted]	[redacted]
Number (proportion) and (90% CI) of patients who achieve an increase of at least 4 points in their CHOP-INTEND			
Month 12	37 (90.2%) 79.1–96.6%	17%	<0.0001
Month 24	37 (90.2%) 79.1–96.6%	NA	-
Month 36 (OLE)	[redacted]	[redacted]	[redacted]
Month 48 (OLE)	[redacted]	[redacted]	[redacted]

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CHOP-INTEND, Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders; CI, confidence interval.

Data from the OLE phase of the study demonstrate that the mean change from baseline in the CHOP-INTEND score continued to improve over time (Figure 3).

Figure 3: Mean change from baseline in the CHOP-INTEND Score and 90% CI by visit, (ITT Population)



CHOP-INTEND, Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders; CI, confidence interval. CCOD 22 Nov 2022.

The proportion of patients exhibiting head control increased over time. At baseline, 2 patients (4.9%) exhibited head control as defined by Item 12 of the CHOP-INTEND (score of ≥3; "*patient maintains the head upright for more than 15 seconds while sitting with trunk erect and support at the shoulders*"). The CHOP-INTEND Item 12 score continued to improve over time; the percentage of patients who achieved head control increased to 53.7% (22/41) of patients at month 12, and 70.7% (29/41) of patients at month 24. Long-term data from the OLE phase of the study will be provided for this item once the 5-year analysis has been completed in July 2024.

HINE-2 – motor milestone responders

At 12 months of treatment, 32 of 41 patients (78.0%; 90% CI: 64.8%, 88.0%) in Part 2 were classified as motor milestone responders, as assessed by the HINE-2. This proportion is significantly higher than the pre-defined performance criterion of 12% based on natural history data (p<0.0001). This proportion of patients classified as motor milestone responders was increased or maintained over time.

Table 20: Summary of motor milestone responders as assessed by HINE-2 over time (ITT Population, FIREFISH Part 2)

Endpoint and time point	Risdiplam n=41	Performance criterion	p-value
Number (proportion) and (90% CI) of motor milestone responders[a] as assessed by the HINE-2			
Month 12	32 (78.0%) 64.8–88.0%	12%	<0.0001
Month 24	35 (85.4%) 73.2–93.4%	NA	-
Month 36 (OLE)	[redacted]	[redacted]	[redacted]
Month 48 (OLE)	[redacted]	[redacted]	[redacted]

[a] An improvement in a motor milestone was defined as at least a 2-point increase in the ability to kick (or maximal score) or a 1-point increase in head control, rolling, sitting, or walking. Worsening was defined as a 2-point decrease in ability to kick (or lowest score) or a 1-point decrease in head control, rolling, sitting, crawling, standing or walking. Voluntary grasp was excluded from the definition. An infant was classified as a responder if more motor milestones showed improvement than showed worsening.
CI, confidence interval; HINE-2, Hammersmith Infant Neurological Examination Module 2.

HINE-2 – motor milestones

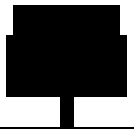
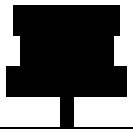
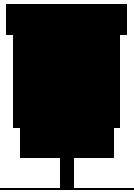
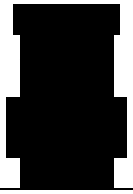
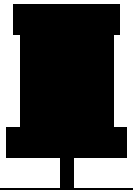
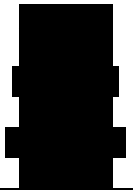
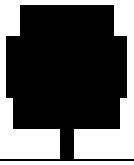
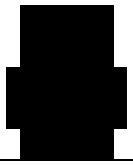
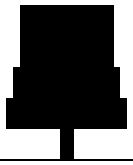
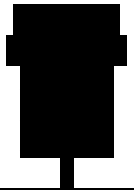
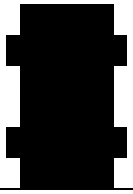
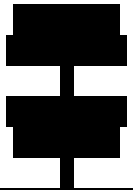
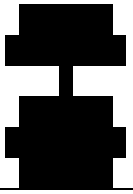
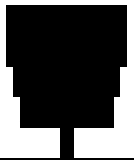
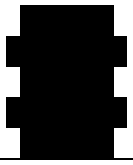
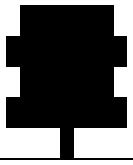
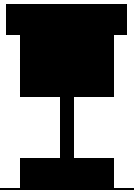
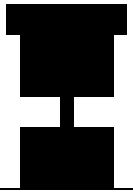
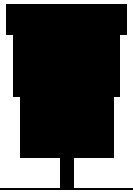
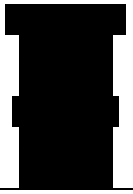
The percentage of infants within the higher attainment response categories of the HINE-2 increased over time; data up to month 48 are presented below. For instance, at baseline no patients could sit. At month 12, most of the patients (61.0%) achieved some level of sitting,

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which increased to 70.7% at month 24. Data from the OLE phase demonstrated that children treated with risdiplam maintained or continued to achieve HINE-2 motor milestones.

Natural history data demonstrates that at 12 months, infants achieved no motor milestones in voluntary grasping, kicking or rolling, and achieve no level of crawling, standing or walking at any time point (114). Therefore, the fact that after long-term treatment with risdiplam, a large proportion of infants achieved motor milestones with regards to grasping, kicking and rolling and some patients had even begun to crawl and show signs of standing shows clinically meaningful developments for these patients and their families.

Table 21: Summary of the infants within each attainment response category of the HINE-2 over time (ITT Population, FIREFISH Part 2)

n, (%)	Time point (risdiplam n=41)			
	Month 12	Month 24	Month 36 (OLE)	Month 48 (OLE)
Head control Unable to maintain head upright Wobbles All the time maintained upright Not done				
Sitting Cannot sit Sits with support at hips Props Stable sit Pivots (rotates) Not done				
Voluntary grasp No grasp Uses whole hand Index finger and thumb but immature grip Pincer grip Not done				
Ability to kick (in supine) No kicking Kicks horizontally, legs do not lift Upward (vertically) Touches leg Touches toes Not done				
Rolling No rolling Rolling to side Prone to supine Supine to prone Not done				
Crawling Does not lift head On elbow On outstretched hand Crawling flat on abdomen Crawling on hands and knees Not done				
Standing Does not support weight Supports weight				

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Stands with support Stands unaided Cannot test Not done	[redacted]			
Walking Bouncing Cruising (walks holding on) Walking independently Cannot test Not done	[redacted]			
Withdrawal			[redacted]	
Death	[redacted]		[redacted]	
Missing			[redacted]	

Patients who reached the target date for a visit but did not perform the assessment by the clinical cutoff date are counted as missing.

Survival and ventilation-free survival

Time to death or permanent ventilation

The proportion of infants alive without permanent ventilation at month 12 was 85.4% (35/41; 90% CI: 73.4%, 92.2%) Three infants died within the first 3 months following study enrolment, and 3 infants met the endpoint of permanent ventilation. The proportion of infants alive without permanent ventilation (85.4%) is significantly higher than the pre-defined performance criterion of 42% based on natural history data (p<0.0001).

[redacted]

The median time to death or permanent ventilation was not estimable as few patients had an event. However, when compared with natural history, where the median age (IQR) for reaching death or permanent ventilation for infants with two *SMN2* copies is 10.5 (8.1–13.6) months (24), risdiplam treatment greatly improved event-free survival.

Table 22: Time to death or permanent ventilation (ITT population, FIREFISH Part 2)

	Risdiplam n=41			
	Month 12	**Month 24**	**Month 36 (OLE)**	**Month 48 (OLE)**
People with event, n (%)	6 (14.6)	7 (17.1)	[redacted]	
Earliest contributing event, n Death Permanent ventilation	3 3	3 4		
Median time to event, months (90% CI)	NE (NE, NE)	NE (NE, NE)		
Patients remaining at risk Proportion event-free, % (90% CI)	35 85.37 (73.35, 92.24)	34 82.93 (70.54, 90.44)		
Performance criterion	42%	NA		
p-value (z-test)	<0.0001	-		

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*There were no events between 24 and 36 months – the change in the number of patients at risk is due to an discontinuation (this patient is censored in the analysis and the Kaplan-Meier estimate remains constant over this interval)

Nutrition

At month 12, 34 patients (82.9%; 90% CI: 70.3%, 91.7%) had the ability to feed orally. Of these 34 patients, 28 (68.3%) were fed exclusively by mouth, and 6 (14.6%) were fed via a combination of oral and tube feeding. Four patients (9.8%) were fed exclusively by feeding tube at month 12, including 2 patients who were fed via feeding tube at baseline, 1 patient who was fed orally at baseline, and 1 patient whose feeding route at baseline was missing. At month 24, infants' ability to feed orally had remained relatively stable from baseline and month 12, with 35 patients (85.4%; 90% CI: 73.2%, 93.4%) able to feed orally; 29 patients (70.7%) fed exclusively by mouth, 6 patients (14.6%) fed via a combination of oral and tube feeding, and 3 patients (7.3%) fed exclusively via feeding tube. Feeding and swallowing abilities were maintained by the majority of infants in the OLE phase of the study as shown in the table below.

Table 23: Summary of patients' ability to feed over time (ITT population, FIREFISH Part 2)

	Risdiplam n=41			
	Month 12	Month 24	Month 36* (OLE)	Month 48 (OLE)
Able to feed orally, n (%) (90% CI)	34 (82.9) (70.3, 91.7)	35 (85.4) (73.2, 93.4)	[redacted]	[redacted]

*There was some missing data at month 36 as this data was initially not collected during the OLE period

Healthcare utilisation

The rate of hospitalisations decreased over time. There were a total of 50 hospitalisations by month 12, resulting in a rate of 1.30 (90% CI: 1.02, 1.65) hospitalisations per patient-year. [redacted] These numbers include planned / elective hospital admissions.

Table 24: Summary of hospitalisations over time; number of hospitalisations per patient-year and number of nights admitted to hospital per infant (ITT population, FIREFISH Part 2)

	Risdiplam n=41			
	Month 12	Month 24	Month 36 (OLE)	Month 48 (OLE)
Number of hospitalisations Number of hospitalisations per patient-year 90% CI	50 1.30 1.02, 1.65	72 0.94 0.76, 1.14	[redacted]	[redacted]
Number of nights per infant Median Min – Max	 17.00 2.0 – 151.0	 15.00 2.0 – 164.0	[redacted]	[redacted]

B.2.6.2 SUNFISH Part 2 (later onset, type 2 and type 3 SMA)

Efficacy Overview

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Final Part 2 efficacy data up to the CCOD of 2 October 2023, corresponding to the last patient last visit (LPLV), is provided below. Results are presented for patients originally randomised to risdiplam who continued to receive risdiplam for 5 years.

12-month placebo-controlled period

The primary analysis was performed at the point at which the last patient in Part 2 completed 12 months of treatment. To adjust for multiple testing in the comparison of risdiplam versus placebo for the primary and the six key secondary efficacy endpoints, a gatekeeping approach was applied and a hierarchical testing was performed (see section B.2.4.2.4). The primary and the following key secondary endpoints were met, indicating improvement or stabilisation in this broad SMA population:

- Family 1- Primary endpoint: Improvement in the MMRM analysis of the change from baseline in the MFM32 total score at Month 12 with risdiplam compared to placebo was both clinically meaningful and statistically significant for the ITT population (treatment difference: 1.55; p=0.0156).
- Family 2- Secondary endpoint: A greater proportion of patients in the risdiplam arm (38.3%) than in the placebo arm (23.7%) had a clinically meaningful and statistically significant improvement in MFM32 total score ≥3 points (odds ratio [95% CI]: 2.35 [1.01, 5.44]; unadjusted p=0.0469; adjusted p=0.0469).
- Family 3- Secondary endpoint: Improvement in the MMRM analysis of the change from baseline in the RULM total score at Month 12 with risdiplam compared to placebo was both clinically meaningful and statistically significant (treatment difference: 1.59; unadjusted p=0.0028; adjusted p=0.0469).

In the next family of endpoints in the hierarchy (Family 4 - HFMSE scale), although a numerical improvement was demonstrated, in most cases statistical significance was not achieved, therefore, these and other subsequent secondary endpoints in the rest of the families of the hierarchy (SMAIS) are considered exploratory.

- Improvement in the MMRM analysis of the change from baseline in the HFMSE total score at Month 12 was numerically greater with risdiplam compared to placebo (treatment difference: 0.58; unadjusted p=0.3015; adjusted p=0.3902), despite low median HFMSE scores at baseline in this patient population.
- A numerically greater improvement in the MMRM analysis of the change from baseline in both caregiver-reported SMAIS (treatment difference: 2.55; unadjusted p=0.0022; adjusted p=0.3902) and patient-reported SMAIS (treatment difference: 1.45; p=0.1778) at Month 12 was observed with risdiplam compared to placebo.
- A greater proportion of patients in the risdiplam arm (69.6%) than in the placebo arm (54.2%) had an improvement in the exploratory secondary endpoint of change from baseline in MFM32 total score ≥0 points, demonstrating improvement or stabilization of disease with risdiplam treatment.

Long-term outcomes: Open-label extension

[redacted]

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[redacted]

B.2.6.2.1 Primary efficacy endpoint

In the MMRM analysis of the MFM32 total score, the least square means (SE) change from baseline at Month 12 was 1.36 (0.38) in patients receiving risdiplam and -0.19 (0.52) in patients receiving placebo. This improvement in MFM32 total score with risdiplam treatment when compared to placebo was statistically significant and clinically meaningful (the least square difference in mean [95% CI] change from baseline in MFM32 at Month 12: 1.55 [0.30, 2.81]; p=0.0156).

Table 25: MMRM analysis on the change from baseline in MFM32 total score at Month 12 (SUNFISH Part 2; ITT Population)

	Risdiplam n=120	**Placebo n=60**
Baseline mean MFM32 score, (SD)	n=115 45.48 (12.09)	n=59 47.35 (10.12)
LS Means change from baseline at week 52 (SE) (95% CI)	1.36 (0.38) (0.61, 2.11)	-0.19 (0.52) (-1.22, 0.84)
MMRM difference from placebo, (SE) 95% CI Unadjusted p value Adjusted p value	1.55 (0.64) (0.30, 2.81) 0.0156 0.0156	

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CI, confidence interval; LS, least-squares; MFM-32, Motor Function Measure, 32-Item version; SD, standard deviation; SE, standard error

B.2.6.2.1 Secondary and exploratory efficacy endpoint

Functional Motor Assessments

MFM32 responder analysis

Placebo-controlled period

There was a greater proportion of responders (MFM32 total score ≥3) in the risdiplam arm (38.3%) than in the placebo arm (23.7%) at Month 12; the difference between the risdiplam arm and the placebo arm was statistically significant (odds ratio [95% CI]: 2.35 [1.01, 5.44]; unadjusted p=0.0469; adjusted p=0.0469).

The proportion of patients with changes in MFM32 total score ≥0 was 69.6% in patients receiving risdiplam and 54.2% in those receiving placebo at Month 12 (odds ratio [95% CI]: 2.00 [1.02, 3.93]; p=0.0430) (Table 26). The proportion of people with a change from baseline in MFM32 of any threshold ≥0 (i.e., ≥0, ≥1, ≥2, ≥3, or ≥4), representing stabilisation or improvement in this measure, was greater in those receiving risdiplam than in those receiving placebo at all post-baseline scheduled assessment visits. The proportion of people with a change from baseline <0, representing decline in MFM32 total score, was greater in the placebo arm than in the risdiplam arm at all scheduled assessment visits.

Table 26: Change from baseline in MFM32 total score at month 12 (SUNFISH Part 2; ITT Population)

	Risdiplam n=120	**Placebo n=60**
Change in MFM32 total score at month 12 ≥3		
Responders, n (%) (95% CI)	44/115 (38.3) (28.94, 47.58)	14/59 (23.7) (12.03, 35.43)
Odds ratio for overall response (95% CI) p-value Adjusted p-value	2.35 (1.01, 5.44) 0.0469 0.0469	
Change in MFM32 total score at month 12 ≥0		
Responders, n (%) (95% CI)	80/115 (69.6) (60.72, 78.41)	32/59 (54.2) (40.68, 67.80)
Odds ratio for overall response (95% CI) p-value	2.00 (1.02, 3.93) 0.0430	

CI, confidence interval; MFM-32, Motor Function Measure, 32-Item version

Long-term outcomes

In patients treated with risdiplam from the start of the study, the mean (SD) change from baseline in MFM32 total score was [redacted]. Of these patients, [redacted] achieved a change from baseline in MFM32 total score of ≥0, representing stabilisation or improvement in motor function, and [redacted] achieved an improvement of ≥3 in MFM32 total score from baseline. Percentages were calculated at each time point using the total number of patients with a valid baseline total score as the denominator.

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Table 27: Summary of MFM32 total score and change from baseline total scores at each yearly time point (all exposure to risdiplam treatment period) (SUNFISH Part 2; ITT Population)

Visit	Risdiplam (N=120)	
	Value at visit	Change from baseline
Week 104		
n	103	103
Mean (SD)	47.47 (12.71)	1.83 (5.59)
Median	48.96	1.04
Min – Max	13.5 – 71.9	-9.4 – 20.8
95% CI for Mean	(44.99, 49.96)	(0.74, 2.92)
Week 156		
n		
Mean (SD)		
Median		
Min – Max		
95% CI for Mean		
Week 208		
n		
Mean (SD)		
Median		
Min – Max		
95% CI for Mean		
Week 260		
n		
Mean (SD)		
Median		
Min – Max		
95% CI for Mean		

MFM-32, Motor Function Measure, 32-Item version; SD, standard deviation

Sensitivity analysis was conducted using the total number of patients with a valid total score at each corresponding study visit as a denominator. When considering only the patients who contributed data at a given time point, in patients treated with risdiplam from the start of the study, a higher percentage of patients achieved stabilization or improvement in motor function (change of ≥0 in MFM32 total score from baseline) in this sensitivity analysis compared with the original analysis ( ) at week 260. The percentage of patients who achieved an improvement in MFM32 total score of ≥3 was in the sensitivity analysis compared with in the original analysis.

MFM32 domain score analysis

The MFM32 domain scores for D1 (standing and transfer), D2 (axial and proximal function), and D3 (distal function) and the combined score of D1+ D2 and D2 + D3 were summed and transformed onto a 0–100 scale (i.e., sum of all items scores within each individual domain divided by the maximum score of the corresponding domain and multiplied by 100) to yield the MFM32 domain scores, expressed as a percentage of the maximum score possible for the scale.

Placebo-controlled period

In the MMRM analysis of the change from baseline in the individual MFM32 domains, the MMRM difference (95% CI) from placebo with risdiplam treatment was 0.64 (-0.20, 1.47) for D1, 1.97 (-0.40, 4.34) for D2, and 2.34 (0.05, 4.62) for D3. When looking at the combined

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domain scores, the MMRM difference (95% CI) from placebo with risdiplam treatment was 1.28 (0.65) for D1 + D2 and 2.16 (1.00) for D2 + D3. These individual MFM32 domain results are reflective of this broad, non-ambulant population, with a high degree of disability and disease progression.

Table 28: MMRM analysis of the change from baseline in MFM32 Domains (D1, D2, D3, D1+D2 and D2+D3) score up to month 12 (SUNFISH Part 2; ITT Population)

	Risdiplam n=120	Placebo n=60
MFM32 – D1 domain total score		
Baseline mean MFM32 score, (SD)	n=118 5.74 (6.29)	n=60 6.20 (6.25)
LS Means change from baseline at week 52 (SE) (95% CI)	0.37 (0.25) (-0.12, 0.87)	-0.26 (0.35) (-0.94, 0.42)
MMRM difference from placebo, (SE) 95% CI p value	0.64 (0.42) (-0.20, 1.47) 0.1328	
MFM32 – D2 domain total score		
Baseline mean MFM32 score, (SD)	n=118 69.66 (20.51)	n=60 72.18 (18.99)
LS Means change from baseline at week 52 (SE) (95% CI)	1.04 (0.72) (-0.38, 2.46)	-0.93 (0.99) (-2.87, 1.02)
MMRM difference from placebo, (SE) 95% CI p value	1.97 (1.20) (-0.40, 4.34) 0.1030	
MFM32 – D3 domain total score		
Baseline mean MFM32 score, (SD)	n=115 77.72 (18.00)	n=59 81.44 (13.55)
LS Means change from baseline at week 52 (SE) (95% CI)	3.68 (0.69) (2.31, 5.04)	1.34 (0.95) (-0.54, 3.22)
MMRM difference from placebo, (SE) 95% CI p value	2.34 (1.16) (0.05, 4.62) 0.0451	
MFM32 – D1 + D2 domain total score		
Baseline mean MFM32 score, (SD)	n=118 36.42 (12.15)	n=60 37.87 (11.19)
LS Means change from baseline at week 52 (SE) (95% CI)	0.69 (0.39) (-0.07, 1.45)	-0.59 (0.53) (-1.64, 0.45)
MMRM difference from placebo, (SE) 95% CI p value	1.28 (0.65) (0.01, 2.56) 0.0489	
MFM32 – D2 + D3 domain total score		
Baseline mean MFM32 score, (SD)	n=115 72.63 (17.59)	n=59 75.53 (14.50)
LS Means change from baseline at week 52 (SE) (95% CI)	2.02 (0.60) (0.84, 3.20)	-0.14 (0.82) (-1.76, 1.48)
MMRM difference from placebo, (SE) 95% CI p value	2.16 (1.00) (0.18, 4.14) 0.0326	

CI, confidence interval; LS, least-squares; MFM-32, Motor Function Measure, 32-item version; SD, standard deviation; SE, standard error

Long-term outcomes

In patients treated with risdiplam from the start of the study, the mean (SD) change from baseline in MFM32 domain score at week 260 was [redacted] for D1 [redacted] for

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D2 and [redacted] for D3. In MFM32 combined domain scores, the mean (SD) change from baseline was [redacted].

Revised Upper Limb Module (RULM)

Placebo-controlled period

In the MMRM analysis of the RULM total score, the least-squares mean (SE) change from baseline at Month 12 was 1.61 (0.31) in patients receiving risdiplam and 0.02 (0.43) in patients receiving placebo. This improvement in RULM total score with risdiplam treatment when compared to placebo was statistically significant and clinically meaningful (least-square difference from placebo in mean [95% CI] change from baseline in RULM at Month 12: 1.59 [0.55, 2.62]; unadjusted p=0.0028; adjusted p=0.0469).

Table 29: MMRM analysis on the change from baseline in RULM total score at month 12 (SUNFISH Part 2; ITT Population)

	Risdiplam n=120	**Placebo n=60**
Baseline mean score, (SD)	n=119 19.65 (7.22)	n=58 20.91 (6.41)
LS Means change from baseline at week 52 (SE) (95% CI)	1.61 (0.31) (1.00, 2.22)	0.02 (0.43) (-0.83, 0.87)
MMRM difference from placebo, (SE) 95% CI Unadjusted p value Adjusted p value	1.59 (0.52) (0.55, 2.62) 0.0028 0.0469	

CI, confidence interval; LS, least-squares; SD, standard deviation; SE, standard error

The proportion of people with a change from baseline in RULM of any threshold ≥0, representing stabilisation or improvement in this measure, was greater in those receiving risdiplam than in those receiving placebo at all timepoints. The proportion of people with a change from baseline <0, representing decline in RULM total score, was greater in the placebo arm than in the risdiplam arm at all timepoints.

There was a greater proportion of people with RULM total score ≥2 in the risdiplam arm (47.9%) than in the placebo arm (31.0%) at Month 12 (odds ratio [95% CI]: 2.18 [1.05, 4.54]; p=0.0369). The proportion of people with changes in RULM total score ≥0 was 72.3% in patients receiving risdiplam and 56.9% in those receiving placebo at Month 12 (odds ratio [95% CI]: 1.93 [0.98, 3.79]; p=0.0555).

Table 30: Change from baseline in RULM total score at month 12 (SUNFISH Part 2; ITT Population)

	Risdiplam n=120	**Placebo n=60**
Change in RULM total score ≥2 at Month 12		
Responders, n (%) (95% CI)	57/119 (47.9) (38.50, 57.29)	18/58 (31.0) (18.27, 43.80)
Odds ratio for overall response (95% CI) p-value	2.18 (1.05, 4.54) 0.0369	
Change in RULM total score ≥0 at Month 12		
Responders, n (%) (95% CI)	86/119 (72.3) (63.81, 80.73)	33/58 (56.9) (43.29, 70.50)

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Odds ratio for overall response (95% CI) p-value	1.93 (0.98, 3.79) 0.0555

CI, confidence interval; RULM, Revised Upper Limb Module

Long-term outcomes

In patients treated with risdiplam from the start of the study, the mean (SD) change from baseline in RULM total score was [redacted] at week 260. Of these, [redacted] of patients achieved a change from baseline in RULM total score of ≥0, representing stabilisation or improvement in upper-limb function, and [redacted] of patients achieved an improvement of ≥2 in RULM total score from baseline. Percentages were calculated at each time point using the total number of patients with a valid baseline total score as the denominator.

Visit	Risdiplam (N=120)	
	Value at visit	Change from baseline
Week 104 n Mean (SD) Median Min – Max 95% CI for Mean	 105 22.39 (8.00) 22.00 7.0 – 37.0 (20.84, 23.94))	 105 2.79 (4.38) 2.00 -6.0 – 20.0 (1.94, 3.64)
Week 156 n Mean (SD) Median Min – Max 95% CI for Mean		
Week 208 n Mean (SD) Median Min – Max 95% CI for Mean		
Week 260 n Mean (SD) Median Min – Max 95% CI for Mean		

CI, confidence interval; RULM, Revised Upper Limb Module; SD, standard deviation

When considering only the patients who contributed data at a given time point, in patients treated with risdiplam from the start of the study, a higher percentage of patients achieved a stabilisation or improvement in upper-limb function (change of ≥0 in RULM total score from baseline) in this sensitivity analysis compared with the original analysis ([redacted] at week 260. The percentage of patients who achieved an improvement in the RULM total score of ≥2 was [redacted] at week 260 in the sensitivity analysis compared with [redacted] in the original analysis.

Hammersmith Functional Motor Scale Expanded (HFMSE)

Placebo-controlled period

In the MMRM analysis of the HFMSE total score, the mean (SE) change from baseline at Month 12 was 0.95 (0.33) in patients receiving risdiplam and 0.37 (0.46) in patients receiving

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placebo. This improvement in HFMSE total score with risdiplam treatment when compared to placebo was not statistically significant (least squares difference from placebo in mean [95% CI] change from baseline in HFMSE at Month 12: 0.58 [-0.53, 1.69]; unadjusted p=0.3015; adjusted p=0.3902). Of note, the median HFMSE total score at baseline was 14.0 points (min–max: 0.0–48.0) in patients receiving risdiplam and 13.0 points (min–max: 2.0–43.0) in those receiving placebo, with 41.1% of patients having a HFMSE score below 10 at baseline (risdiplam: 40.8%; placebo: 41.7%). This illustrates the advanced SMA disease in the studied patient population, and is significant because the HFMSE scale is not sensitive enough to detect a change in people with a baseline score <10 (31, 32).

Table 31: MMRM analysis on the change from baseline in HFSME total score in month 12 (SUNFISH Part 2; ITT Population)

	Risdiplam n=120	Placebo n=60
Baseline mean score, (SD)	16.10 (12.46)	16.62 (12.09)
LS Means change from baseline at week 52 (SE) (95% CI)	0.95 (0.33) (0.29, 1.61)	0.37 (0.46) (-0.54, 1.28)
MMRM difference from placebo, (SE) 95% CI Unadjusted p value Adjusted p value	0.58 (0.56) (-0.53, 1.69) 0.3015 0.3902	

CI, confidence interval; LS, least-squares; SD, standard deviation; SE, standard error

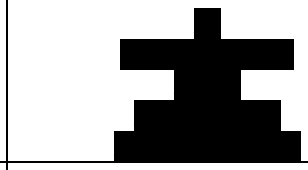
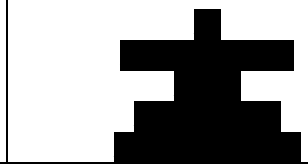
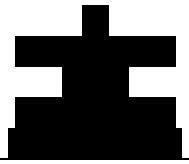
Long-term outcomes

In patients treated with risdiplam from the start of the study, the mean (SD) change from baseline in HFSME total score was [redacted] at week 260. Of these patients, [redacted] of patients achieved a change from baseline in HFMSE total score of ≥0, representing stabilisation or improvement in motor function, [redacted] achieved an improvement of ≥2 in HFMSE total score at week 260. Percentages were calculated at each time point using the total number of patients with a valid baseline total score as the denominator. As mentioned above, a substantial proportion of patients had an HFMSE score <10 at baseline, indicating they had advanced disease and that this scale would not be sensitive enough to detect any change, which could potentially be skewing the data.

Table 32: Summary of HFMSE total score and change from baseline score over time (SUNFISH Part 2; ITT Population)

Visit	Risdiplam (N=120)	
	Value at visit	Change from baseline
Week 104		
n	106	106
Mean (SD)	18.76 (14.11)	2.15 (5.28)
Median	16.00	2.00
Min – Max	0.0 – 66.0	-13.0 – 29.0
95% CI for Mean	(16.05, 21.48)	(1.13, 3.17)
Week 156		
n	[redacted]	[redacted]
Mean (SD)		
Median		
Min – Max		
95% CI for Mean		

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Week 208 n Mean (SD) Median Min – Max 95% CI for Mean		
Week 260 n Mean (SD) Median Min – Max 95% CI for Mean		

CI, confidence interval; HFMSE, Hammersmith Functional Motor Scale Expanded; SD, standard deviation

When considering only the patients who contributed data at a given time point, in patients treated with risdiplam from the start of the study, a higher percentage of patients achieved stabilisation or improvement in motor function (change of ≥0 in HFMSE total score from baseline) in this sensitivity analysis compared with the original analysis ( ). The percentage of patients who achieved an improvement in HFMSE total score of ≥2 was in the sensitivity analysis at week 260 compared with in the original analysis.

Patient/caregiver and clinician-reported outcomes

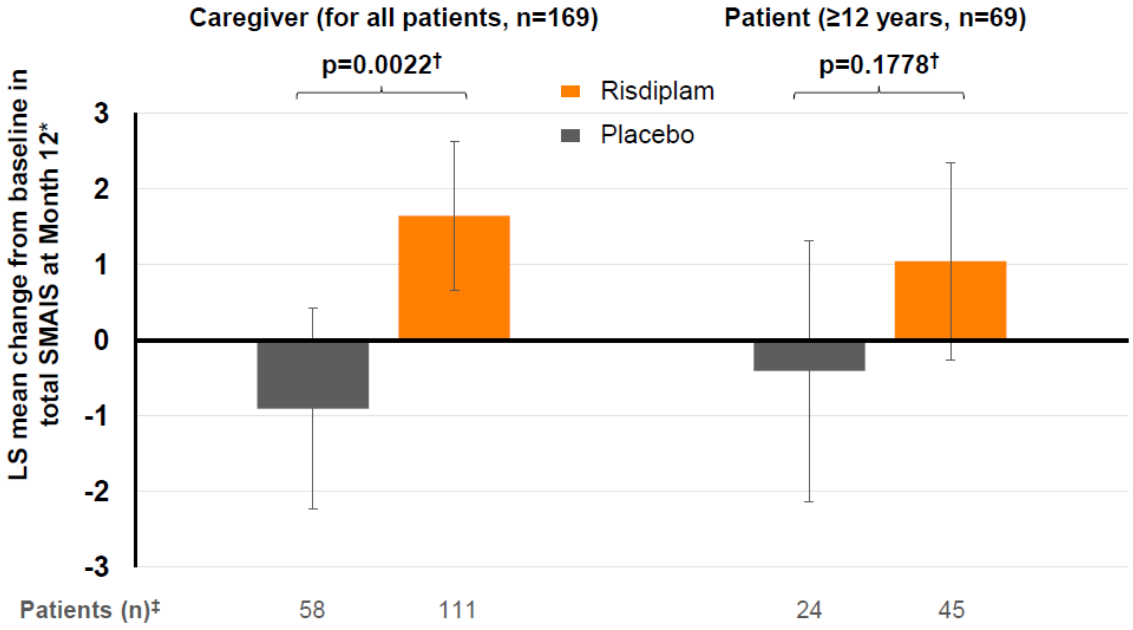
SMA Independence Scale (SMAIS)

Placebo-controlled period

The MMRM analyses of the change from baseline in SMAIS total score at Month 12 as reported by caregivers (n=176) and by patients (aged 12 or above) (n=66) are presented below. Caregivers and patients both reported gains in independence with risdiplam but losses in independence with placebo; the difference from placebo with risdiplam treatment was 2.55 (95% CI: 0.93, 4.17; unadjusted p=0.0022; adjusted p=0.3902) in the caregiver-reported assessment and 1.45 (95% CI: -0.68, 3.57; p=0.1778) in the patient-reported assessment.

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Figure 4: MMRM analysis of the change from baseline in caregiver and patient-reported SMAIS total score at month 12 (SUNFISH Part 2: ITT Population)



* +/-95% confidence interval. †Mixed Model Repeated Measure, unadjusted p-value at 5% significance level. ‡Number of patients with valid results = number of patients with an available total score (result) at respective time points.
LS, least squares; SMAIS, SMA Independence Scale.

Long-term outcomes

In patients treated with risdiplam from the start of the study, the mean (SD) change from baseline in the caregiver-reported SMAIS-ULM total score was [redacted] at week 260. In the patient-reported (≥12 years old) SMAIS-ULM total score, the mean (SD) change from baseline was [redacted] at week 260.

Table 33: Summary of SMAIS-ULM caregiver and patient reported total score and change from baseline total score at each yearly time point (SUNFISH: ITT population Part 2)

Visit	Risdiplam (N=120)			
	SMAIS Caregiver Report Total Score		SMAIS Patient Report Total Score	
	Value at visit	Change from baseline	Value at visit	Change from baseline
Week 104				
n	106	103	40	39
Mean (SD)	28.75 (9.08)	2.73 (5.16)	31.53 (9.31)	0.82 (4.83)
Median	27.00	2.00	30.50	0.00
Min – Max	7.0 – 44.0	-10.0 – 16.0	11.0 – 44.0	-7.0 – 18.0
95% CI for Mean	(26.22, 29.43)	(1.72, 3.74)	(28.55, 34.50)	(-0.75, 2.39)
Week 156				
n	[redacted]	[redacted]	[redacted]	[redacted]
Mean (SD)				
Median				
Min – Max				
95% CI for Mean				

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Week 208 n Mean (SD) Median Min – Max 95% CI for Mean	[redacted]	[redacted]	[redacted]	[redacted]
Week 260 n Mean (SD) Median Min – Max 95% CI for Mean	[redacted]	[redacted]	[redacted]	[redacted]

CI, confidence interval; SMAIS, SMA Independence Scale

B.2.6.3 RAINBOWFISH (Paediatric, pre-symptomatic, genetically diagnosed SMA)

Efficacy overview

The primary endpoint of sitting without support for 5 seconds (as assessed by Item 22 of the BSID-III Gross Motor Scale; assessed by two independent central readers) at month 12 was met with a statistically significant and clinically meaningful proportion of patients in the PE population achieving this milestone compared with the predefined performance criterion of 5%. The efficacy data from the 26 patients in the ITT population who completed at least 12 months of risdiplam treatment show that, overall, patients achieved important motor milestones and high levels of motor function (as assessed by BSID-III, HINE-2 and CHOP-INTEND). All patients were alive without the need for permanent ventilation during the first year of treatment. Additionally, all patients were able to feed orally and swallow.

B.2.6.3.1 Primary efficacy endpoint

The primary endpoint of sitting without support for 5 seconds (as assessed by Item 22 of the BSID-III Gross Motor Scale; assessed by two independent central readers) at month 12 was met with a statistically significant and clinically meaningful proportion of patients in the PE population achieving this milestone compared with the predefined performance criterion of 5%. 80.0% of patients (4/5; 90% CI 34.3, 99.0) in the PE population were sitting without support for 5 seconds at the month 12 visit. The proportion is significantly higher than the predefined performance criterion of 5% based on the natural history of disease (p<0.0001). [redacted]

Table 34: Patients sitting without support for 5 seconds as assessed by Item 22 of the BSID-III Gross Motor Scale at month 12 (RAINBOWFISH, Primary Efficacy Population)

Endpoint	2 *SMN2* copies N=5	Performance criterion	p-value
Number / proportion (90% CI) of patients sitting without support for 5 seconds (BSID-III) at week 52	4/5 80.0% (34.26 – 98.98%)	5%	< 0.0001

BSID-III, Bayley Scales of Infant and Toddler Development, third edition; CI, confidence interval

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B.2.6.3.2 Secondary efficacy endpoints

Motor Function and Development Milestones

BSID-III Gross Motor Scale

Patients treated with risdiplam for 12 months achieved clinically meaningful motor milestones as assessed by the BSID-III Gross Motor Scale. Patients were not only sitting independently, but were acquiring more complex functions and motor abilities, such as standing and walking. The improvement was seen for both the ITT and PE populations and was also evidenced by an increase in the median raw score of the BSID-III Gross Motor Scale.

A summary of the motor milestones achieved across the ITT population, as measured on the BSID-III scale, is presented below in Table 36, stratified by *SMN2* copy number.

BSID-III: Sitting without support for 5 seconds

In the ITT population [redacted] were able to sit without support for 5 seconds (as assessed by Item 22 of the BSID-III Gross Motor Scale) at month 12 as assessed by two independent central readers.
[redacted]. [redacted].
[redacted] Of patients with 2 *SMN2* copies in the ITT population, [redacted] were able to sit without support for 5 seconds at 12 months as assessed by two independent central readers.

BSID-III: Sitting without support for 30 seconds

In the ITT population [redacted] and in the PE population [redacted] were able to sit without support for 30 seconds (as assessed by Item 26 of the BSID-III Gross Motor Scale) at month 12 as assessed by two independent central readers.
[redacted]The age range for first demonstrating this milestone at a study visit was [redacted].

In the PE population sitting without support for 30 seconds was at the [redacted]. The age range for first demonstrating this milestone at a study visit was [redacted]

Table 35: Patients sitting without support for 30 seconds as assessed by Item 26 of the BSID-III Gross Motor Scale at month 12 (RAINBOWFISH, Primary Efficacy Population)

Endpoint	2 *SMN2* copies N=5	Performance criterion	p-value
Number / proportion (90% CI) of patients sitting without support for 30 seconds (BSID-III) at week 52	[redacted]	[redacted]	[redacted]

BSID-III, Bayley Scales of Infant and Toddler Development, third edition; CI, confidence interval

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BSID-III: Standing alone

In the ITT population [redacted] were able to stand alone (as assessed by Item 40 of the BSID-III Gross Motor Scale) at month 12 as assessed by two independent central readers.

[redacted] The age range for first demonstrating this milestone at a study visit was [redacted].

BSID-III: Walking alone

In the ITT population [redacted] were able to walk alone (as assessed by Item 42 of the BSID-III Gross Motor Scale) at month 12 as assessed by two independent central readers.

[redacted] The age range for first achieving this milestone at a study visit was [redacted]

A summary of BSID-III outputs, showing the proportion of patients with the ability to sit without support for 30 seconds, stand alone and walk alone over time up to 12 months is presented below.

Table 36: A summary of patients sitting without support for 5 seconds, sitting without support for 30 seconds, standing alone, and walking alone at 12 months as assessed by the BSID-III gross motor scale (ITT population, RAINBOWFISH)

	***SMN2* copy number**			
Endpoint	**2** **N=8**	**3** **N=13**	**≥4** **N=5**	**All patients** **N=26**
Number / proportion (90% CI) of patients sitting without support for 5 seconds (BSID-III) at week 52	[redacted]	[redacted]	[redacted]	[redacted]
Number / proportion (90% CI) of patients sitting without support for 30 seconds (BSID-III) at week 52	[redacted]	[redacted]	[redacted]	[redacted]
Number / proportion (90% CI) of patients standing alone (BSID-III) at week 52	[redacted]	[redacted]	[redacted]	[redacted]
Number / proportion (90% CI) of patients walking alone (BSID-III) at week 52	[redacted]	[redacted]	[redacted]	[redacted]

BSID-III, Bayley Scales of Infant and Toddler Development, third edition; CI, confidence interval

Comparison of BSID-III Gross Motor Milestone achievement vs WHO windows for healthy children

[redacted]

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[redacted]

Figure 5: BSID-III motor milestones vs age (in months) at time of assessment (RAINBOWFISH; ITT Population)

[redacted]

HINE-2

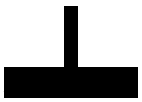
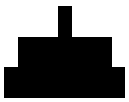
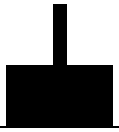
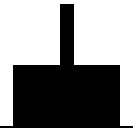
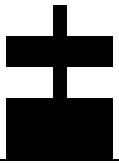
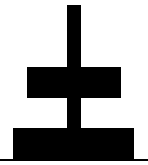
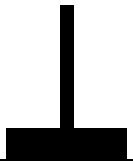
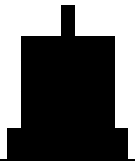
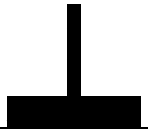
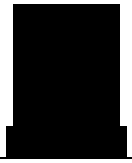
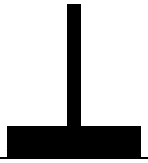
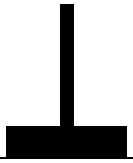
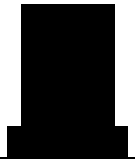
Patients in the ITT population treated with risdiplam for 12 months developed complex motor abilities, including sitting, standing and walking independently. Of the patients who were assessed at month 12 (n=25), all patients except one were sitting without support at month 12, as assessed by the HINE-2 categories of “stable sit” and “pivots (rotates)”.

At month 12, 25/26 patients were assessed using HINE-2 (one patient with ≥4 *SMN2* copies could not be assessed as they were crying). Achievements for each milestone at month 12 are as follows:

- [redacted]. Out of those 25 patients, [redacted] could maintain their head upright all the time; the remaining [redacted] with 2 *SMN2* copies could hold their head upright intermittently (wobbles) [redacted]
- All except one of the assessed patients (24 patients, 96%) were sitting without support. Out of those 24 patients, 23 (92%) achieved the highest level of sitting (pivot/rotate); 1 patient (4%) with 2 *SMN2* copies (non-PE patients) achieved stable sit, 1 patient (4%) with 2 *SMN2* copes (PE patient) could not sit.
- All assessed patients [redacted] achieved voluntary grasping, [redacted] were able to use a pincer grasp, [redacted] achieved an immature grasp (with index finger and thumb)
- [redacted] achieved the highest level of kicking in supine (touching toes), [redacted] achieved kicks upwards vertically and [redacted] achieved touches leg, [redacted] achieved the lowest level of kicking (kicks horizontally [legs do not lift])
- [redacted] achieved the highest level of rolling (supine to prone); [redacted] with 2 *SMN2* copies [redacted] achieved prone to supine rolling and [redacted]
- 13 patients (52%) could stand unaided and 8 patients (32%) could stand with support; the other 4 patients (12%) with 2 *SMN2* copies did not support weight
- 12 patients (48%) were walking independently, 4 patients (16%; 3 patients with 3 *SMN2* copies; 1 patient with ≥4 *SMN2* copies) were cruising, and 2 patients (8%; both with 2 *SMN2* copies [both PE patients]) were able to bounce. 7 patients (28%) could not be tested or testing was not done (5 patients with 2 *SMN2* copies; 1 patient with 3 *SMN2* copes and 1 patient with ≥4 *SMN2* copies)

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Table 37: Summary of HINE-2 motor milestones at month 12 (RAINBOWFISH: ITT Population)

n, (%)	*SMN2* copy number			
	2 (N=8)	3 (N=13)	≥4 (N=5)*	All patients (N=26)
Head control				
Unable to maintain head upright				
Wobbles				
All the time maintained upright				
Sitting				
Cannot sit	1 (12.5)	0	0	1 (4.0)
Sits with support at hips	0	0	0	0
Props	0	0	0	0
Stable sit	1 (12.5)	0	0	1 (4.0)
Pivots (rotates)	6 (75.0)	13 (100.0)	4 (100.0)	23 (92.0)
Voluntary grasp				
No grasp				
Uses whole hand				
Index finger and thumb but immature grip				
Pincer grip				
Ability to kick (in supine)				
No kicking				
Kicks horizontally, legs do not lift				
Upward (vertically)				
Touches leg				
Touches toes				
Rolling				
No rolling				
Rolling to side				
Prone to supine				
Supine to prone				
Crawling				
Does not lift head				
On elbow				
On outstretched hand				
Crawling flat on abdomen				
Crawling on hands and knees				
Standing				
Does not support weight	4 (50.0)	0	0	4 (16.0)
Supports weight	0	0	0	0
Stands with support	3 (37.5)	3 (23.1)	2 (50.0)	8 (32.0)
Stands unaided	1 (12.5)	10 (76.9)	2 (50.0)	13 (52.0)
Walking				
Bouncing	2 (25.0)	0 (2.4)	0	2 (8.0)
Cruising (walks holding on)	0	3 (23.1)	1 (25.0)	4 (16.0)
Walking independently	1 (12.5)	9 (69.2)	2 (50.0)	12 (48.0)
Cannot test	4 (50.0)	1 (7.7)	1 (25.0)	6 (24.0)
Not done	1 (12.5)	0	0	1 (4.0)

*One patient could not be assessed as they were crying

CHOP-INTEND

Patients who were treated with risdiplam for 12 months achieved high levels of motor function with a median CHOP-INTEND score near the maximum score of the assessment. At month 12, 25/26 patients were assessed using CHOP-INTEND (one patient with ≥4 *SMN2* copies could not be assessed as they were crying). In the ITT population,

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[redacted] achieved a score of ≥60 at month 12; furthermore, [redacted] achieved the maximum score of 64 at month 12. Patients had already achieved high levels of motor function prior to month 12, with [redacted] achieving scores of ≥60 at week 28.

[redacted]. Of the patients with 2 *SMN2* copies, [redacted] had a total CHOP-INTEND score of ≥50 at month 12. The median score at month 12 was [redacted] and the range extended from [redacted].

[redacted]

Table 38: Patients who achieve a CHOP-INTEND score of ≥40/50/60 at month 12 (RAINBOWFISH: ITT Population)

Endpoint	*SMN2* copy number			
	2 (N=8)	3 (N=13)	≥4 (N=5)*	All patients (N=26)
Proportion of patients who achieved a CHOP-INTEND score of ≥40 n (%) 90% CI	[redacted]	[redacted]	[redacted]	[redacted]
Proportion of patients who achieved a CHOP-INTEND score of ≥50 n (%) 90% CI	[redacted]	[redacted]	[redacted]	[redacted]
Proportion of patients who achieved a CHOP-INTEND score of ≥60 n (%) 90% CI	[redacted]	[redacted]	[redacted]	[redacted]

*One patient could not be assessed as they were crying

Survival and ventilation-free survival

By the time of the CCOD, no patient enrolled in this study required permanent ventilation. The proportion of patients alive and without permanent ventilation at month 12 was 100% (no patients died, and no patients met the definition of permanent ventilation).

Development of clinically manifested SMA

One patient met the criteria of development of clinically manifested SMA at month 12. This patient (3.8%; 90% CI: 0.2, 17.0) with 2 *SMN2* copies (PE patient) was considered to have developed clinically manifested SMA, having met two separate criteria for this endpoint; 1) they failed to achieve sitting without support at month 12 as assessed by both the HINE-2 and Item 22 of the BSID-III Gross Motor Scale, and 2) they withdrew from the study in order to switch to an alternative treatment for SMA. The patient, who is in the PE population, was withdrawn from the study at the request of the parent/caregiver, in order to switch to onasemnogene abeparvovec. According to the SAP, if a patient withdraws from treatment to

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start an alternative medication intended for the treatment of SMA, the withdrawal is classified as “related to study drug or disease related progression” and thus meets the criteria for development of clinically manifested SMA.

Nutrition

Patients who were treated with risdiplam for 12 months maintained their abilities to feed orally and to swallow. No patients required nasogastric or gastrostomy tube feeding. At month 12, all 26 patients (100%; 90% CI: 89.1, 100.0) had the ability to swallow. At month 12, 25/26 patients (96.2%; 90% CI: 83.0, 99.8) in the ITT population had the ability to feed orally. Furthermore, these 25 patients (96.2%) were fed exclusively by mouth. For the remaining patient (who withdrew from the study), only partial information regarding feeding/swallowing at month 12 is available.

Growth measures

The majority of patients treated with risdiplam for 12 months showed consistent growth, as expected for their age, in all evaluated growth and development parameters from baseline to month 12 of treatment, as summarised below.

Table 39: Growth measurements at baseline and month 12 (RAINBOWFISH: ITT Population)

	Baseline	Month 12	
	Value at visit	Value at visit	Change from baseline
Weight-for-age percentile			
n Mean (SD) Median (range) Patients in ≤ 3rd percentile, n (%)	[redacted]	[redacted]	[redacted]
Length/height for age percentile			
n Mean (SD) Median (range) Patients in ≤ 3rd percentile, n (%)	[redacted]	[redacted]	[redacted]
Weight for length / height percentile			
n Mean (SD) Median (range) Patients in ≤ 3rd percentile, n (%)	[redacted]	[redacted]	[redacted]
Head circumference-for age percentile			
n Mean (SD) Median (range) Patients in ≤ 3rd percentile, n (%)	[redacted]	[redacted]	[redacted]

Patients in ≤ 3rd percentile based on the number of patients with data at that visit

Respiratory

[redacted] who were treated with risdiplam for 12 months did not require any respiratory support; [redacted]. [redacted]. At baseline,

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[redacted]. At month 12, [redacted] did not require any pulmonary care.

[redacted]. At month 12, [redacted] in the PE population did not require any pulmonary care.

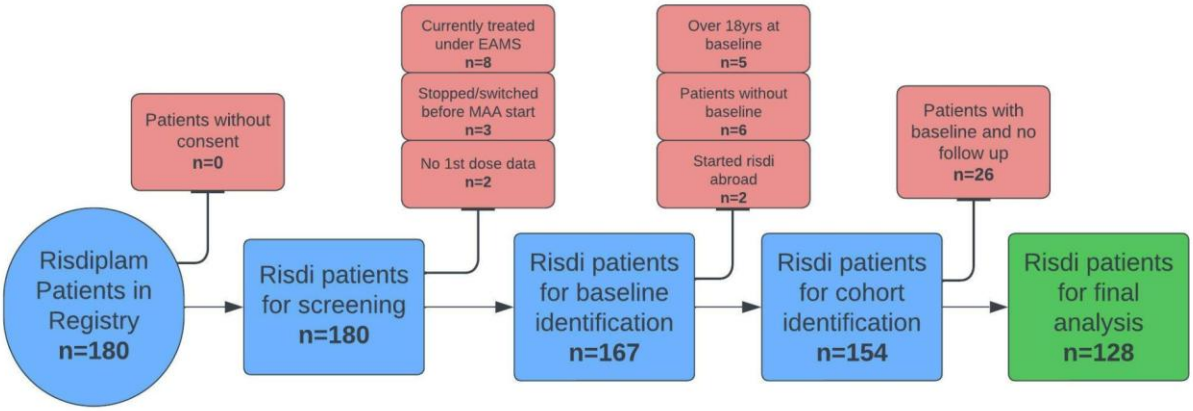
B.2.6.4 REACH registries (SMA in clinical practice)

B.2.6.4.1 Paediatric REACH registry

Risdiplam treated patients

Details of patients who received risdiplam treatment and were included in the analysis is provided in the flow chart below. The final paediatric cohort included 25 type 1 patients, 36 type 2/3 non-sitters, 65 type 2/3 sitters/walkers, and 2 pre-symptomatic patients who were not included in the analysis.

Figure 6: Patient flow for the paediatric REACH UK registry



Treatment details for the patients included in the final analysis are provided below. Fifty-three patients had previously received other treatments; of the type 1 patients 14 were on nusinersen and 1 was on zolgensma, of the type 2/3 non-sitters 2 were previously on nusinersen, of the type 2/3 sitters/walkers, 31 were on nusinersen, 4 were enrolled in the SUNFISH trial and 1 in the SHINE trial.

One SMA type 1 patient stopped risdiplam treatment at 6 months and went onto zolgensma. One SMA type 2/3 sitter/walker stopped treatment after 6 months due to side effects of nausea, stomach pain and itching. Four patients transitioned to adult care; 1 type 1 patient after 6 months, 2 type 2/3 non sitters after 6 months and 18 months respectively, and 1 type 2/3 sitter/walker after 18 months from initiating reatment. No other patients were lost to follow-up.

A large proportion of patients were enrolled on the EAMS, particularly in type 2/3 non-sitters with 75% of patients enrolled on the EAMS, meaning they had previously received risdiplam before the start of the MAA data collection period. To be eligible for the EAMS, patients had

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to be ineligible for nusinersen, which was most often due to scoliosis, spinal fusion or contractures, all of which are markers of disease severity. It is important to take the large number of pre-treated and EAMS patients into account in this study, as this can skew the data and mean the registry will not capture the initial improvement we tend to see in SMA patients when they first receive treatment. SMA clinical trials clearly indicate that with DMTs the most substantial improvement in motor functions scores is seen in the first 6-12 months before stabilisation.

The low discontinuation rate observed across SMA groups reflects in the real world what has been observed in clinical trials; that risdiplam is well tolerated with a consistent safety profile (See B.2.10).

Table 40: Patient treatment information (at last visit)

	Cohorts		
	Type 1	**Type 2/3 non-sitters**	**Type 2/3 sitters/walkers**
Number of patients, n	25	36	65
Patients enrolled on the EAMS, n (%)	8 (32.00)	27 (75.00)	24 (36.92)
Patients previously receiving treatment, n (%)	15 (60.00)	2 (5.56)	36 (55.38)
Time on risdiplam at last visit (months)			
Mean (SD)	9.43 (5.5)	13.54 (4.8)	14.59 (5)
Median	6.97	13.93	14.80
Range	3.12 – 21.58	4.38 – 21.41	4.38 – 25.16
Patient discontinued risdiplam treatment, n (%)	1 (4.00)	0	1 (1.54)

The risdiplam MAA started at the beginning of 2022, therefore there has been a relatively short follow-up period so far, and very few patients have 12 or 18 month follow-up outcomes at the time of this data cut, particularly when the data is broken down by SMA type (Table 41). It is also likely that the majority of patients with the longer 12-24 month follow up are patients who originally received risdiplam through the EAMS, as this was initiated before the MAA, meaning these patients were already receiving treatment when their baseline was captured in January 2022. Most other patients were recruited after January 2022. As discussed above, EAMS patients would be expected to be on the severe end of the disease spectrum given the EAMS was set up to accept patients ineligible for nusinersen (e.g. unable to receive a lumbar puncture due to spinal complexities). Therefore, given the likely skew effect it would have on the data for the majority of patients with long-term follow to be severe EAMS patients, accurate interpretation is challenging and any conclusions should be taken with extreme caution.

Table 41: Number of follow up visits (Paediatric SMA REACH UK)

	Cohorts			
	Type 1	**Type 2/3 non-sitters**	**Type 2/3 sitters/walkers**	**All SMA types**
Baseline	25	36	65	126
6 months	23	27	57	107
1 year	6	22	44	72
18 months	6	14	32	52
2 years	1	1	2	4

SMA type 1 patients: motor function and development milestones

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For all of the motor function scales, there was insufficient data to run a full MMRM in this patient cohort, but observed cross-sectional summaries and changes from baseline are shown in the table below. For the small number of patients presented below there are signs of motor function improvement as shown by the positive change from baseline across scales. However, it should be noted that the small sample size makes interpretation difficult, so these should be considered with extreme caution. Longer follow-up would allow a more robust inspection of this data, including exploration of distributions.

Table 42: Observed cross-sectional summaries and changes from baseline across motor function scales (REACH paediatric registry)

Visit	Number of patients with a score per visit	Score (Mean, SD)	Change from baseline (Mean, SD)
CHOP-INTEND			
Baseline	8	24.5 (18.9)	-
6 months	5	43.0 (10.6)	10.6 (17.9)
1 year	1	34.0 (0)	9.0 (0)
18 months	2	47.0 (1.4)	30.5 (13.4)
RHS			
Baseline	9	6.4 (4.1)	-
6 months	5	7.2 (2.0)	0 (1.2)
1 year	1	5.0 (0)	3.0 (0)
18 months	2	8.5 (3.5)	3.0 (1.4)
RULM			
Baseline	9	11.8 (7.4)	-
6 months	7	9.1 (6.9)	-0.7 (2.0)
1 year	1	1.0 (0)	-1.0 (0)
18 months	1	20.0 (0)	3.0 (0)
HINE			
Baseline	10	3.8 (3.5)	-
6 months	7	5.9 (3.7)	0.9 (1.5)
1 year	2	2.0 (0)	0.5 (0.7)
18 months	1	6.0 (0)	4.0 (0)

SMA type 2/3 patients: motor function and development milestones

For the type 2/3 cohort, mixed effect modelling was performed for the Revised Hammersmith Scale (RHS), and Revised Upper Limb Module (RULM), including 128 observations from 48 patients and 173 observations from 66 patients, respectively. From the small patient numbers shown below the analysis of both scales indicates an improvement in motor function, relative stabilisation at 12 months and a slight decline at 18 months. However, this analysis should be interpreted with caution given the small number of patients with long-term follow-up scores, and the likely skew of the data due to the high proportion of pre-treated and EAMS patients as discussed above.

Table 43: Mixed-effects repeated measures results: RHS and RULM for SMA Type 2/3 patients

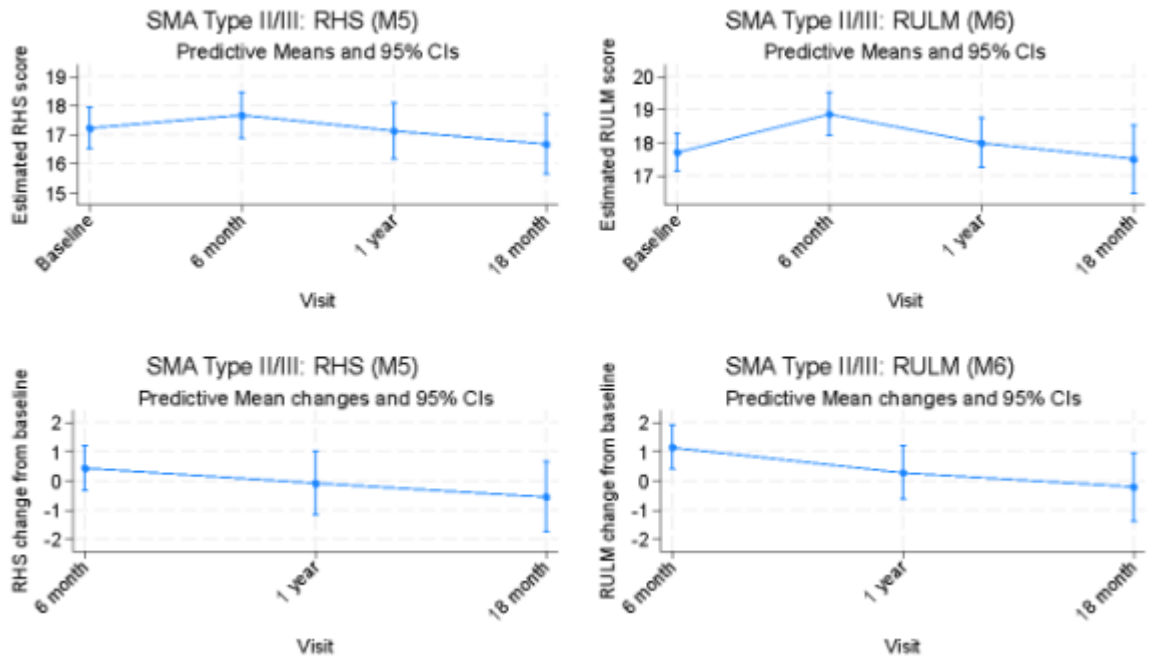
Visit	Number of patients with score per visit	Estimated score* (SE)	Predicted change from baseline	95% CI
RHS				
Baseline	48	17.22 (0.36)	-	-
6 months	37	17.66 (0.40)	0.44	-0.34, 1.22
1 year	22	17.13 (0.49)	-0.09	-1.17, 1.00

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18 months	21	16.68 (0.53)	-0.54	-1.75, 0.66
RULM				
Baseline	66	17.71 (0.29)	-	-
6 months	50	18.87 (0.33)	1.15	0.39, 1.92
1 year	37	18.00 (0.38)	0.29	-0.63, 1.20
18 months	20	17.51 (0.52)	-0.21	-1.37, 0.96

*Estimates are derived at the average value of each of the covariates
RHS, Revised Hammersmith Scale; RULM, Revised Upper Limb Module

Figure 7: Plot of estimated changes from baseline and predicted means based on MMRM



Time to event analysis

None of the events covered in this section provide sufficient data to run a formal analysis or produce a Kaplan-Meier curve, as detailed in the SAP.

In terms of mortality, one type 1 patient enrolled into the MAA died before any follow-up visits and was not included in the final analysis cohort (the primary cause of death was an hypoxic head injury). One patient from the SMA type 2/3 non-sitter group died after 2 years of follow-up (no cause of death was reported by the clinical team). No patients have been recorded as being on permanent ventilation, either at baseline or at the most recent visit.

Two patients stopped taking risdiplam as detailed above.

During the MAA, six patients are known to have had spinal surgery; 3 type 1 patients, of which 2 had surgery at 6 months and 1 at 18 months follow-up, and 3 type 2/3 sitters/walkers, who all had spinal surgery at 18 months post treatment initiation.

Patient reported outcomes measures (PROMs)

PROMs were not included in the original MAA, but were included in a pilot study aiming to recruit 50 paediatric patients from two centres (GOSH and Leeds). There was insufficient data to look at groups separately or carry out any formal analysis, due to these limitations

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there is no interpretation of the results. However, a crude summary of the data is presented in Appendix O

B.2.6.4.2 Adult REACH registry

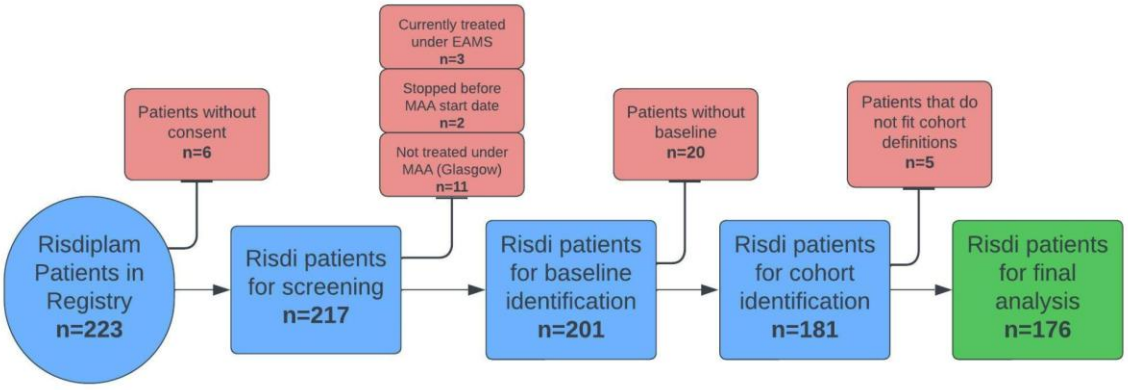
Risdiplam treated patients

The objective was for the analytic population to be comprised of patients for whom baseline data had been collected upon entry into Adult SMA Reach UK and at least one post-entry visit. However, due to the limited patient numbers at the time of the data cut, the Adult REACH statistician also included patients with just a baseline visit in order to strengthen the MMRM model.

Details of patients who received risdiplam treatment and were included in the analysis is provided in the flow chart below; the final adult cohort included 5 type 1 patients, 82 type 2/3 non-sitters, and 89 type 2/3 sitters/walkers.

As discussed in B.2.3.8, patients transitioning between paediatric and adult services have a new baseline assessment collected at the first routine visit scheduled in an adult centre after they have turned 16-18 years of age (due to a lack of data sharing agreement). Consequently, this baseline data would not be reflective of their true baseline prior to treatment initiation. Sensitivity analyses have been conducted excluding any transition patient in the mixed model analyses for mean score and change from baseline.

Figure 8: Patient flow for patients included in the adult REACH registry



Of the 176 total SMA patients included in the adult registry, 90 patients were pre-treated; 4/5 with type 1, 58/82 type 2 non-sitters, and 28/89 type 2 sitters / walkers. Furthermore, a large proportion (128/176) of these patients were enrolled in the EAMS (of the 150 adults enrolled in the EAMS (115), 128 moved onto commercial risdiplam through the MAA). As discussed above for the paediatric registry, both of these factors are likely to skew the data. Firstly, for the patients pre-treated the baseline will not be a true reflection of their baseline status without treatment and the results will likely miss the initial improvement in motor function observed when patients initially receive a DMT for SMA. Secondly, patients with the longest follow up are likely to be EAMS patients who have more severe disease, given their ineligibility to receive nusinersen, which is a well understood prognostic factor (111).

Motor function and development milestones

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As outlined in the SAP, MMRM modelling has been performed for two separate cohorts; those with SMA type 1 and those with SMA type 2/3. The MMRM models were fitted to provide summary statistical estimates of longitudinal mean scores and changes from baseline for RHS and RULM. For full details please see the Adult SMA Reach Report.

Revised Upper Limb Module (RULM)

There was insufficient data due to the low patient numbers to fit MMRM models for the type 1 cohort. For the type 2/3 patient cohort, MMRM modelling shows an overall increase in RULM score over time when compared to baseline. For the small type 2/3 patient population shown below, at all time points the change from baseline in RULM score of is ≥0, representing stabilization or improvement in upper limb function. However, given the low patient numbers for follow-up scores, this should be interpreted with extreme caution.

Table 44: Change from baseline and mean score on the RULM motor function assessment

	Cohort	
RULM Motor Function Assessment	**SMA type 1 (n=3)**	**SMA type 2/3 (n=114)**
Baseline		
n	3	105
Mean score (SE)	*	13.50 (0.78)
6 months		
n	2	86
Mean score (SE)	*	14.01 (0.78)
Change from baseline (95% CI)	*	0.51 (-0.14 – 1.16)
12 months		
n	1	66
Mean score (SE)	*	13.95 (0.79)
Change from baseline (95% CI)	*	0.46 (-1.53 – 1.06)
18 months		
n	1	35
Mean score (SE)	*	13.89 (0.83)
Change from baseline (95% CI)	*	0.39 (-0.42 – 1.21)

*no results displayed due to high collinearity or insufficient observations

Revised Hammersmith Scale (RHS)

There was insufficient data due to the low patient numbers to fit MMRM models for the type 1 cohort. For the type 2/3 patient cohort, MMRM modelling shows an increase in scores at month 6 and 12 versus baseline, but a slight decline at 18 months. However, extreme caution should be taken when interpreting this data, especially given the very low patient numbers even at baseline (baseline measurements are available for only 26/114 patients due to incomplete data), meaning the findings are not necessarily representative of the entire type 2/3 subgroup.

Table 45: Change from baseline and mean score on the RHS motor function assessment

	Cohort	
RHS Motor Function Assessment	**SMA type 1 (n=3)**	**SMA type 2/3 (n=114)**
Baseline		
n	0	26
Mean score (SE)	*	20.98 (3.00)

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6 months		
n	0	26
Mean score (SE)	*	22.44 (3.00)
Change from baseline (95% CI)	*	1.46 (0.11 – 2.82)
12 months		
n	0	15
Mean score (SE)	*	21.90 (3.04)
Change from baseline (95% CI)	*	0.92 (-0.64 – 2.49)
18 months		
n	0	2
Mean score (SE)	*	20.62 (3.56)
Change from baseline (95% CI)	*	-0.36 (-4.33 – 3.62)

*no results displayed due to high collinearity or insufficient observations

Additional outcome measures

It was not mandatory to collect data across any of the scales presented below (see the SAP), but descriptive analysis for the data available is presented for type 2/3 patients. There is no data available for type 1 SMA across these outcomes from the registry data, likely due to the very small patient numbers, the outcomes not being mandatory, and these measures being better suited to capture changes in the type 2/3 population.

Adult Test of Neuromuscular Disorders (ATEND)

ATEND was designed to capture changes in the older, chronic, wheelchair-bound population of people living with neuromuscular disorders. Again, these results should be interpreted with caution due to the substantial decrease in patient numbers over time. However, the data available from the small patient numbers indicate that while the non-sitter group deteriorated slightly, the change from baseline in the sitter/walker group was largely positive and very pronounced at 18 months. This could suggest a potentially huge increase in independence based on what the scale measures (see Table 4).

Table 46: Change from baseline over time in SMA Type 2/3 patients in the ATEND motor function scale

Time point	Cohorts			
	Type 2/3 non-sitters (n=82)		Type 2/3 sitters/walkers (n=89)	
	Total right	Total left	Total right	Total left
Baseline				
n (missing)*	44 (38)	44 (38)	52 (37)	52 (37)
Mean (SD)	19.20 (8.89)	19.39 (9.17)	28.38 (9.25)	26.15 (9.60)
6 months				
n (missing)*	43 (19)	43 (19)	32 (35)	32 (35)
Mean (SD)	21.21 (9.62)	21.63 (9.30)	27.94 (8.95)	25.78 (9.13)
Change from baseline				
n (missing)**	30 (32)	30 (32)	30 (37)	30 (37)
Mean (SD)	-1.7 (4.94)	-1.83 (6.31)	0.27 (4.2)	0.6 (4.82)
12 months				
n (missing)*	44 (13)	44 (13)	23 (17)	23 (17)
Mean (SD)	20.86 (9.42)	21.14 (9.08)	29.00 (7.23)	29.91 (6.32)
Change from baseline				
n (missing)**	28 (29)	28 (29)	17 (23)	17 (23)
Mean (SD)	-0.75 (5.11)	0.68 (4.20)	-0.12 (3.76)	2.12 (3.44)
18 months				
n (missing)*	31 (5)	31 (5)	13 (1)	13 (1)
Mean (SD)	24.10 (9.57)	22.19 (10.57)	26.15 (6.97)	26.23 (6.80)

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Change from baseline n (missing)** Mean (SD)	 18 (18) -0.28 (4.75)	 18 (18) -2.56 (6.19)	 8 (6) 4.13 (8.11)	 8 (6) 5.00 (7.48)

*Patient records are blank
**Patients do not have a baseline and/or time point recorded
ATEND, Adult Test of Neuromuscular Disorder

Egen Klassification 2 (EK2)

EK2 is designed to assess change in non-ambulant patients with neuromuscular disorders, focusing on the preservation of function and independence. As such, this scale may capture smaller motor functional milestones that others miss due to a lack of sensitivity. While caution is advised due to the reduction in subject number over time, the results show benefits in the non-sitter group that increase over time and stabilisation in the sitter/walker group. Please note a decrease in EK2 score demonstrates a positive benefit for patients.

Table 47: Change from baseline over time in SMA Type 2/3 patients in the EK2 motor function scale

Time point	Cohorts	
	Type 2/3 non-sitters (n=82)	Type 2/3 sitters/walkers (n=89)
Baseline n (missing)* Mean (SD)	 71 (11) 25.32 (7.33)	 68 (21) 16.74 (7.85)
6 months n (missing)* Mean (SD) **Change from baseline** n (missing)** Mean (SD)	 55 (7) 25.02 (7.57) 49 (13) -0.49 (4.69)	 51 (16) 16.08 (7.92) 45 (22) 0.16 (5.33)
12 months n (missing)* Mean (SD) **Change from baseline** n (missing)** Mean (SD)	 49 (8) 23.82 (6.89) 47 (10) -1.11 (3.24)	 26 (14) 17.00 (5.57) 23 (17) -0.43 (1.97)
18 months n (missing)* Mean (SD) **Change from baseline** n (missing)** Mean (SD)	 33 (3) 22.61 (6.51) 32 (4) -1.38 (3.95)	 14 (0) 19.93 (5.23) 13 (1) -0.31 (2.25)

*Patient records are blank
**Patients do not have a baseline and/or time point recorded
EK2, Egen Klasification 2

Time to event analysis

There were no patients with an event (death, permanent ventilation, or spinal surgery) occurring after the initiation of risdiplam treatment. However, the final report includes analysis of events occurring before the start of treatment. For full details please see the final report and Appendix O.

Patient reported outcome measures (PROMs)

The adult patient registry collected data across the following measures; EQ-5DL, SMAIS, patient-reported Global Impression of Change (P-GIC) – severity, P-GIC – improvement and

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adult patient comments. The baseline score (defined as the first data entry into the patient registry post risdiplam initiation), and score at the patients final observation (reporting window +/- 8 weeks either side of the patient's clinic visit) were summarised for each PROM. For full details please see Appendix O.

B.2.7 Subgroup analysis

B.2.7.1 FIREFISH Part 2 (infantile-onset, type 1 SMA)

Subgroup analyses were performed for the primary efficacy endpoint (proportion of patients sitting without support for 5 seconds at Month 12) and for two of the secondary efficacy endpoints (proportion of patients who achieve a CHOP-INTEND score of 40 or higher at Month 12 and time to death or permanent ventilation). Each of these endpoints was analysed by age at enrolment, sex, race, region, disease duration (i.e., time between first treatment and onset of symptoms), and baseline CHOP-INTEND score. Please refer to Appendix E for full details.

- Overall, the proportion of patients sitting without support for 5 seconds, achieving a CHOP-INTEND total score of 40 or higher, and who were alive without permanent ventilation at Month 12 was consistent among the subgroups investigated
    - Some differences were observed with subgroups based on disease duration and sex, but the numbers of patients in each subgroup are small, so the results should be interpreted with caution.

Subgroup analyses for outcomes will be provided when the final 5-year CSR becomes available.

B.2.7.2 SUNFISH Part 2 (later-onset, type 2 and type 3 SMA)

The consistency of the primary efficacy endpoint and key efficacy endpoints (all secondary endpoints up to Family 4 in the hierarchical testing) were explored for the following subgroups below (the SUNFISH study was not powered to demonstrate efficacy in these subgroups and the study was stratified by age only).

- Age group (2–5, 6–11, 12–17, and 18–25 years at randomisation)
- Disease severity (patient with MFM32 baseline total score ≤25th percentile, >25th percentile and ≤75th percentile, and >75th percentile)
- SMA type (type 2, type 3)
- *SMN2* copy number (<2, 2, 3, ≥4 copies, unknown) from genotype analysis.

Subgroup analysis showed that the greatest response in the MFM32 with risdiplam compared to placebo was observed in the youngest patients (aged 2–5 years). Importantly, improvements in RULM and disease stabilisation by the MFM32 were also achieved in the oldest patients (aged 18–25 years), an important goal of treatment in older SMA patients with more advanced disease. These results confirm the effect of risdiplam treatment on motor function, which is clinically meaningful to confer benefit for patients' daily function. Please see Appendix E for full details.

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Longer-term results (up to 5 years) from SUNFISH Part 2 for MFM32, RULM, HFMSE and SMAIS-ULM were analysed by age, SMA type, *SMN2* copy number, region, disease severity and baseline HFMSE score.

[redacted] Overall, the results of the other subgroup analyses are consistent with the overall study results. Please see Appendix E for full details.

An additional subgroup analysis was performed for the economic analysis of this submission, excluding patients enrolled to SUNFISH from Asia as they appear to have reported differently to patients enrolled from elsewhere (primarily Europe and North America).

B.2.7.3 RAINBOWFISH (Paediatric, pre-symptomatic, genetically diagnosed SMA)

Two endpoints (sitting without support for 5 seconds at month 12 and sitting without support for 30 seconds at month 12) were analysed for patients with 2 *SMN2* copies, according to predefined subgroups based on demographic and baseline characteristics (age at enrolment, sex, baseline CHOP-INTEND score, baseline CMAP amplitude). The analysis of the predefined subgroups yielded consistent results with that of the overall population of patients with 2 *SMN2* copies. It should be noted that patient numbers are small in each of the subgroups, and the study was not powered to demonstrate efficacy within subgroups thus, results should be interpreted with caution. Please see Appendix E for full details.

B.2.7.4 REACH registries (SMA in clinical practice)

B.2.7.4.1 Paediatric REACH registry

The SAP outlined the following subgroups for analysis:

- Pre-treated patients (including previous EAMS)
- Treatment naïve patients (no treatment prior to the start of the MAA)
- Patients who chose to stop treatment for any reason
- Patients meeting criteria for stopping risdiplam treatment
- EAMS patients not eligible for MAA

At the point of the data cut, the sample size up to 18 months is too small and there are too many outcomes considered for a formal comparative analysis. Therefore, the data has been described in the form of baseline clinical characteristics to provide an estimate of variability. At the time of the data cut, only 2 patients had stopped risdiplam treatment, and therefore there is insufficient numbers for form subgroup 3 or 4. For a description of the pre-treatment, treatment-naïve patients, and patients included in EAMS and not eligible for the MAA (compassionate use) please see Appendix E.

B.2.7.4.2 Adult REACH registry

To assess the potential variation of results across different patient subgroups, sensitivity analysis was conducted across the following subgroups:

- Treatment naïve, pre-treated, and stopped treatment subgroups

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- Excluding patients who have transitioned from the paediatric to the adult dataset (n=14) during the data collection period. The exclusion of transition patients for sensitivity analysis did not result in a significant change in the analysis results
- Excluding patients had who baseline data collected on a date after the treatment initiation date. The exclusion of these patients did not results in any significant change in the analysis results.

All the results obtained from these analyses are similar and consistent with the baseline demographic and clinical characteristics for the whole population.

For descriptive statistic tables showing the distribution of baseline measurements across these subgroups please see Appendix E.

Tables are provided in the full report that explore patient baseline demographics per subgroup, to understand how the patients differed before receiving treatment. However, the number of patients remaining for follow-up over 18 months became too small to conduct any form of analysis to understand the impact of these differences on the overall results.

B.2.7.5 Permanently ventilated patients

Currently under the MAA, SMA patients who require permanent ventilation (≥16 hours / day for 21 consecutive days in the absence of acute reversible infection / tracheostomy) are not eligible to receive risdiplam, and the decision to treat must be taken to an NHS England Clinical Panel. However, anecdotally, we hear that clinicians see value in treating these patients and therefore sent a survey to five neuromuscular specialists in the UK, who manage 6 permanently ventilated risdiplam patients under a free of charge scheme, to understand the potential clinical benefit. The specialists reported observing clinical benefits in this patient cohort, across motor, respiratory and bulbar function (116). In addition, the specialists reported that providing risdiplam to these patients could also potentially reduce hospital admissions, give patients more energy and mean they could maintain employment. Overall, all of the neuromuscular specialists confirmed they would recommend that this patient population receive a DMT.

For further details of the survey responses see Appendix P.

B.2.8 Meta-analysis

There is no head-to-head trial data available for risdiplam in the presymptomatic population (RAINBOWFISH is a single arm study) or for the Type 1 population (FIREFISH is a single arm study), and for Types 2-3 SMA patients no longer term head-to-head data exists. For all populations under consideration, a meta-analysis is not appropriate or feasible as an approach, therefore other indirect treatment comparison (ITC) methods were explored.

B.2.9 Indirect and mixed treatment comparisons

B.2.9.1 Systematic literature review

For presymptomatic and types 1-3 SMA, an SLR of all published and ongoing trials was performed to identify available evidence for comparators of interest (searches run until 29th February 2023). This SLR was an update of the SLR run in 2020 (117). The search strategy

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was pre-specified in terms of population, interventions, comparisons, outcomes and study design and is outlined in Appendix D. Although the clinical SLR was not conduced within 6 months of the company evidence submission, since then no further significant data has been published. Moreover, following the SLR for the ITC feasibility assessment, hand searching of HTA documentation and grey literature was conducted to identify further recent evidence or additional publically available data in October 2023, see Section B.2.9.2 Network meta-analysis (NMA) feasibility assessment.

Comparators of interest

The comparators of interest considered in the decision problem for this NICE evidence submission are risdiplam, nusinersen, onasemnogene abeparvovec (OA) and best supportive care (please note the comparators vary depending on the patient population in consideration). Within the SLR, a broader patient population and additional interventions were included in the eligibility criteria to account for all available interventions and clinical studies in SMA for the purpose of informing reimbursement activities in other countries; not all of these interventions are within scope of this appraisal.

Criteria used in trial selection

The inclusion and exclusion criteria for the SLR and the study selection process are described in Appendix D.

B.2.9.2 Network meta-analysis (NMA) feasibility assessment

As a result of the clinical SLR update (an update from the SLR conducted in 2020 (117), there were 230 primary studies (37 clinical trials and 193 observational studies) identified, including three studies for pre-symptomatic SMA, 47 for Type 1 SMA, 68 for Type 2/3 SMA and 112 for patients with a mix of SMA types (i.e., studies comprising patients across several SMA types, including Type 1/2, Type 1/2/3, Type 2/3/4, Type 1/2/3/4 and unclear SMA type). These are outlined according to their status (completed/ongoing) and according to SMA type in Appendix D. This SLR was used to inform all three SMA cohorts (presymptomatic, type 1 and type 2/3) under consideration for this appraisal.

Presymptomatic SMA patients

Based on the results of the literature review, the feasibility assessment conclude that a naïve comparison could be conducted. A matched adjusted indirect comparison (MAIC) or a simulated treatment comparison (STC) were found to not be feasible due to the small sample sizes and substantial differences at baseline. Where possible, comparisons would be quantitative, however it would also consist of qualitatively describing differences in results, as not all endpoints are comparable.

Three relevant studies were identified for the presymptomatic cohort: SPR1NT, NUTURE and RAINBOWFISH. All three trials are non-comparative (i.e. single arm) trials. SPR1NT is a completed trial with results published in 2021 (118), whilst NURTURE and RAINBOWFISH are ongoing studies. NURTURE has already published results, reporting on several efficacy and safety outcomes including HFMSE, time to death/respiratory intervention/permanent ventilation, and growth measurements (119). RAINBOWFISH is a single arm trial evaluating risdiplam in infants with genetically diagnosed and pre-symptomatic SMA (120). There are no studies assessing BSC in presymptomatic patients.

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Type 1 SMA patients

The evidence base for SMA type 1 consists mostly of single arm, dose comparison or dose escalating studies. Of the 12 clinical trials, 11 had a primary publication available that assessed the comparators of interest (risdiplam, BSC, nusinersen and OA).

The ITC analysis provided for risdiplam versus nusinersen comparison is an update to the previously performed analysis of FIREFISH vs ENDEAR-SHINE (121); the 4-year FIREFISH data is presented alongside up to 5-year ENDEAR-SHINE data. The updated indirect comparison to OA is a new comparison provided in this submission and has been informed by STR1VE EU data (122), which is a similar study to STR1VE US but only includes a European cohort, is a larger study (n=33 v n=22) and allowed patients requiring non-invasive ventilatory support (for less than 12 hours daily) or feeding support to enrol. However, as both studies are notably different from FIREFISH, the comparison to both STR1VE-US and –EU will be provided. The results for the EU comparison are from the 2022 ITC (117), as the 2023 updated SLR (see Appendix D) did not indicate any new data sources that could be used in order to perform the ITC between type 1 risdiplam and OA patients for longer treatment durations (123). The follow-up time compared between FIREFISH to STR1VE-US and STR1VE-EU is 12 months and between 12-18 months, respectively.

Type 2 and 3 SMA patients

The ITC analysis for type 2/3 population is a new comparison provided in this submission versus TA755. SUNFISH provides head-to-head comparative data for risdiplam versus BSC up to 12 months, there is a lack of longer term comparative data and data versus other treatments. Three RCTs were identified for the evaluation of nusinersen: CHERISH-SHINE, DEVOTE (single arm) and EMBRACE. It is worth noting that both EMBRACE and DEVOTE are across SMA mixed types 1-3 and report small sample sizes, with no reporting specifically for Type 2/3. Therefore, only CHERISH-SHINE is taken forward to provide the evidence for the nusinersen comparator.

SHINE has been identified as relevant for both type 1 and type 2/3 populations; SHINE is an open-label extension study for nusinersen, with patients being rolled over as separate cohorts from various studies.

Criteria used in trial selection

This section provides a summary of the comparison of the studies of interest for the ITC in each SMA cohort.

Study design and enrolment criteria

Presymptomatic SMA patients

RAINBOWFISH is an ongoing, open-label, single-arm study where participants receive risdiplam oral treatment daily for two years followed by an open label extension phase of at least three years. SPR1NT is a phase 3, open-label, single arm study evaluating patients receiving a one-time intravenous infusion of OA and has been extended by an additional three years to assess longer term outcomes of OA. NURTURE is a phase 2, open-label, single-arm study evaluating multiple doses of nusinersen over the course of 2.5 years. All studies were conducted globally.

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All participants involved in the above clinical trials are infants, genetically diagnosed with SMA who did not show any symptoms prior to their enrolment, therefore they could not be attributed a phenotypical SMA type and were labelled as pre-symptomatic. The inclusion criteria and study design of each trial are noted within the report provided on file (124). Overall, RAINBOWFISH included a wider population than NUTURE and SPR1NT as the study had no limitations on CMAP amplitude or SMN2 copy number at enrolment.

All three trials observe small sample sizes with RAINBOWFISH having the smallest sample size n=18 (with n=4 including ≥4 SMN2 copies) versus n=25 and n=29 in the NUTURE and SPR1NT trials, respectively. The limited sample size significantly hinders the ability to effectively compare the populations of these three trials. This issue becomes more apparent when comparing the distributions of SMN2 copies across trials, given that SMN2 copy number is a strong predictor of SMA type (10). RAINBOWFISH also has the shortest follow-up time (8.72 months versus 34.8 and 14.8 months for NUTURE and SPR1NT), respectively, creating a further limitation when applying the MAIC methodology. Moreover, the differences in inclusion criteria add further complexity, i.e. CMAP.

All 3 studies had different eligibility criteria for CMAP amplitude. RAINBOWFISH permitted any value, but limited the primary analysis population to those pts with baseline CMAP amplitude >=1.5mV (and 2 SMN2 copies). SPR1NT excluded from the study patients with amp < 2mV and NURTURE excluded patients with <1mV. Furthermore, RAINBOWFISH and NURTURE measured CMAP amplitude via the ulnar nerve, whilst SPR1NT used the peroneal nerve, which has different normal values.

These differences in inclusion criteria contribute to the heterogeneity of the trial populations, which present a significant challenge when implementing MAIC. Historically, MAICs are effective when there is substantial overlap between populations; however, when this overlap is limited, the effective sample size can decrease significantly, diminishing the utility of MAICs.

On the subject of exclusion criteria, it is worth noting that there appears to be some harmonization across all three trials. They all exclude patients who would otherwise exhibit severe respiratory difficulties or a heavy burden of disease, which can be identified through haematological examinations. This alignment in exclusion criteria helps ensure that patients with these severe conditions are consistently excluded from the analysis, contributing to a more meaningful comparison.

Type 1 SMA patients

FIREFISH is an open-label, two-part, phase II/III dose-escalation/single-arm study. Part 1 is a dose-escalation study, while Part 2 is confirmatory as the dose selected is based on the results from Part 1. ENDEAR is a double-blind phase III RCT. The enrolment criteria and study design between the included studies is provided within the report on file (121). Both studies are in infants with SMA type 1. The study designs are different; most notably, FIREFISH is an open-label single arm trial, whereas ENDEAR-SHINE is a randomized, double-blinded controlled trial. The study eligibility criteria are similar, although FIREFISH participants should be <3 months at onset of SMA, whereas ENDEAR participants are <6 months of age.

When considering the evidence for risdiplam versus OA, for STR1VE-US versus FIREFISH (117) and STR1VE-EU to FIREFISH (123) – all studies are evaluating treatment efficacy in

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infants with SMA type 1. For both STR1VE trials, infants could only have one or two copies of the SMN2 gene, whilst FIREFISH determines this based on confirmed diagnosis of 5q-autosomal recessive SMA and 2 SMN2 copies. For STR1VE-US/EU, it is specified that patients had be younger than 6 months of age at first dose while FIREFISH patients had to be ≤7 months old at enrolment (and could be older at first dose). STR1VE-US/EU excluded patients with previous, planned or expected scoliosis repair surgery, while no such restrictions were applied to FIREFISH.

Type 2-3 SMA patients

The enrolment criteria and study design between the included studies is provided in the report on file (125).

Although SUNFISH and CHERISH trials have a similar study design, there are important differences regarding the eligibility criteria between both trials. It has been established that age at screening is a predictive factor in a recently conducted literature review (111). Within the trials, CHERISH only allowed for patients to enter the study between the ages of 6 months and 12 years old inclusive, whereas SUNFISH allowed for patients between the ages of 2 to 25 inclusive. Therefore, by design, CHERISH has a younger cohort of patients versus the SUNFISH population.

Both studies allow for patients who can sit independently but limited ability to walk independently, however the motor function ability of participants are assessed by different tools, i.e. SUNFISH uses the MFM 32 while CHERISH utilises the HFMSE score. Furthermore, CHERISH has a more stringent criteria on respiratory insufficiency at screening (including invasive or noninvasive ventilation for >6 hours during a 24 hour period), whereas SUNFISH excluded patients requiring invasive ventilation or tracheostomy. Finally, patients who have severe contractures or scoliosis and medical need for gastric feeding tube are excluded from CHERISH, but were included in SUNFISH.

Patient characteristics

Presymptomatic SMA patients

Summary descriptive statistics at baseline derived from the 1-year RAINBOWFISH clinical study report (CSR), along with findings from NURTURE (De Vivo 2019), and SPR1NT (Strauss 2022) populations can be seen in Table 48 and Table 49, for patients with 2 SMN2 and 3 SMN2 copies, respectively.

Table 48. Baseline characteristics for patients with 2 SMN2 copies in RAINBOWFISH, NURTURE and SPR1NT

Baseline characteristics for patients with 2 SMN2 copies	RAINBOWFISH (N=8*)	NURTURE (N=15)	SPR1NT (N= 14)
Mean (SD) [range] age at first dose, days	23.9 (5.3) [16.0 – 35.0]	19.5 (9.3) [8.0 – 41.0]	20.6 (7.9) [9.0 – 43.0]
Mean (SD) [range] weight, kg	3.8 (0.4) [3.1 – 4.3]	NA	3.6 (0.4) [3.0 – 4.3]
Sex (% Female)	50.0%	47.0%	71.0%

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Race (%)	White	100.0%	NA	50.0%
	Other	-	NA	21.0%
	Black or African American	-	NA	14.0%
	Asian	-	NA	14.0%
	American Indian or Alaska Native	-	NA	0.0%
Ulnar CMAP amplitude, mean [range[		2.0 [0.5 – 3.8]	2.7 [1.0 - 6.7]	NA
Mean CHOP INTEND (SD)		44.9 (6.6)	47.0 (10.0)	46.0 (8.8)
Mean HINE-2 (SD)		2.1 (1.5)	2.7 (1.6)	NA

*1 patient withdrew early from the analysis in order to enroll for gene therapy treatment, before completing 12 months of treatment with risdiplam and will not be included in the analysis.

Table 49. Baseline characteristics for patients with 3 SMN2 copies in RAINBOWFISH, NURTURE and SPR1NT

Baseline characteristics for patients with 3 SMN2 copies		**RAINBOWFISH (N=13)**	**NURTURE (N=10)**	**SPR1NT (N= 15)**
Mean (SD) [range] age at first dose, days		29.9 (7.5) [20.0 – 41.0]	22.3 (12.5) [3.0 – 42.0]	28.7 (11.7)
Mean (SD) weight, kg		4.6 (0.6) [3.4 – 5.7]	NA-	4.1 (0.5) [3.1 – 5.2]
Sex (% Female)		69.2%	60.0%	60.0%
Race (%)	White	84.6%	NA	66.7%
	Other	7.7%	NA	13.3%
	Black or African American	-	NA	0.0%
	Asian	7.7%	NA	13.3%
	American Indian or Alaska Native	-	NA	6.7%
Ulnar CMAP amplitude, mean (range)		4.4 [2.1 – 6.7]	3.1 [1.8 – 4.9]	NA
Mean CHOP INTEND (SD)		53.8 (5.8)	51.9 (6.1)	NA
Mean HINE-2 (SD)		3.0 (1.4)	3.2(-)	NA

CHOP-INTEND: Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders; CMAP: Compound muscle action potential; HINE-2: Hammersmith Infant Neurological Examination Module 2; NA: Not Available; SD: standard deviation; SMN gene: survival motor neuron gene.

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Specifically, regarding patients with 2 SMN2 copies, age at first dose and CHOP INTEND score exhibited overlapping distributions across all three trials. Notably, RAINBOWFISH displayed the highest mean value and lowest standard deviation in this regard. Regarding gender distribution, RAINBOWFISH and NURTURE shared similar proportions, with 50% and 47% females, respectively, while SPR1NT had a higher percentage of female patients (71%). Furthermore, SPR1NT had a more diverse racial background when compared to RAINBOWFISH, where all patients were of white racial background, while information on race could not be obtained for NURTURE. CMAP amplitude data was available for RAINBOWFISH and NURTURE, and although their distributions overlapped, NURTURE exhibited the widest range. As for HINE-2 assessments, data was accessible for RAINBOWFISH and NURTURE, showing a minor point estimate difference of 0.5 between the two, although the standard deviation was not reported for NURTURE. Ulnar CMAP and HINE-2 are not available for SPR1NT.

Regarding patients with 3 SMN2 copies, the distribution of age at the first dose exhibited overlapping patterns across the trials, with RAINBOWFISH again reporting the highest mean age at the first dose, and the lowest standard deviation. Patients' weights were comparable between RAINBOWFISH and SPR1NT, although this information was missing for NURTURE. The proportion of females was equal between NURTURE and SPR1NT, standing at 60%, and slightly higher for RAINBOWFISH at 69.2%. In terms of racial background, there was diversity among patients in RAINBOWFISH and SPR1NT, but NURTURE did not provide data on race for this group. At baseline, CMAP amplitude and CHOP-INTEND mean scores were higher for RAINBOWFISH compared to NURTURE, with similar ranges and standard deviations. As for HINE-2 assessments, NURTURE reported slightly higher scores, but unfortunately, no standard deviation information was available. Notably, SPR1NT did not report data on CMAP, CHOP-INTEND, and HINE-2 for patients with 3 SMN2 copies.

Type 1 SMA patients

Table 50 compares the baseline characteristics between the included studies. As mean baseline characteristics are not reported for the overall ENDEAR-SHINE population (which includes 1 additional patient), weighting is conducted on the baseline characteristics of the original ENDEAR population in (75). Patient populations are similar in terms of age and disease duration, however severity of disease at baseline differs: mean CHOP INTEND score (4.1 points higher for ENDEAR patients) and mean HINE-2 score (0.36 points higher for ENDEAR patients). Although 9% more participants in ENDEAR received ventilatory support, it is highly uncertain whether this is comparable to FIREFISH, where patients use noninvasive and invasive ventilation.

The gaps in baseline characteristics evidence identified from the primary study sources will be supplemented by the identified G-BA dossier for the matching process (126).

Table 50. Baseline characteristics for FIREFISH and ENDEAR.

Baseline characteristic	Risdiplam (FIREFISH)	Nusinersen (ENDEAR)
N	58†	80
Female gender	57%†	54%
White race	53%†	NR
Mean age at first dose, months (SD) [range]	5.3	5.4

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	(1.5) [2.2 – 7.0]	(NR) [1.4 – 8.0]
Mean age at symptom onset, months (SD) [range]	1.7 (0.7) [0.9 – 3.0]	2.0 (NR) [0.5-4.5]
Mean disease duration at screening, weeks (SD) [range]	16.0 (5.8) [4.3 - 26]	13.2 (NR) [0 – 25.9]
Mean age at diagnosis, days (SD) [range]	88.9 (42.3) [28-185]	88.2 (NR) [0 – 203]
Patients with ventilatory support	16.7% *	26%
Patients with nutritional support: Gastrointestinal tube feeding	3.5% **	9%
Mean total CHOP INTEND score (SD) [range]	22.5 (6.8) [8 – 37]	26.6 (8.13) [NR]
Mean HINE-2 score (SD) [range]	0.93 (0.95) [0 – 5]	1.29 (1.07) [NR]
2 SMN2 copies	100%	100%
* 6/36 required BiPAP Support For Less Than 16 Hours Per Day. Data is not available for all 58 patients; ** 2/57 were unable to swallow, data is not available on whether gastrointestinal tube feeding was received. Data was not available for all 58 patients.		

Table 51 compares the baseline characteristics between the included studies. Patients in FIREFISH were on average 49 days (range: 32-53) older at first dose and 1 week older at diagnosis compared to STR1VE-US patients. The severity of disease at baseline was worse in FIREFISH patients, as illustrated by the differences in the baseline CHOP-INTEND score (risdiplam vs OA -9.5) and the higher proportion of patients with ventilator and feeding support (no patients with non-oral feeding support and ventilatory support were enrolled in STR1VE-US). There are also clear imbalances between FIREFISH and STR1VE-EU which limit the feasibility of the matching, such as age at initiation of treatment (127). The remaining characteristics are either not defined in a common way across trials, such as patients requiring gastrointestinal support, or are not reported in both studies, such as mean disease duration at screening and HINE-2 scores.

Table 51. Baseline characteristics for FIREFISH, STR1VE-US and STR1VE-EU.

Baseline characteristic	Risdiplam (FIREFISH)	Onasemnogene abeparvovec (STR1VE-US	Onasemnogene abeparvovec (STR1VE-EU)
N	62†	22	33
Female gender	60%†	55%	58%
White race	56%†	50%	Not reported
Mean weight (sd, [range])	6.8 (1.2 [4.1–10.6])‡	5.8 (1.1, [3.9-7.5])	5.8 (1 [4.2-8.4])
Mean age at first dose, months (sd, [range])	5.4 (1.5 [2.2–7.0])†	3.73 (1.61,[0.5-5.9])	4.1 (1.3 [1.8-6.0])
Mean age at symptom onset, months (sd, [range])	1.6 (0.9) [0-4]‡	1.9 (NR,[0-4.0])	1.7 (0.7 [0.9–3])
Mean disease duration at screening, weeks (SD) [range]	13.0 (5.9) [1–23.3]‡	Not reported	Not reported
Patients with clinical support: ventilatory	29%‡	0%	27%

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Patients with nutritional support: Gastrointestinal tube feeding	9%‡*	0%	27%
Mean total CHOP INTEND score (SD) [range]	22.3 (6.8) [8–37]†	32.0 (9.9, [17-52])	27.9 (8.3) [14-55]
Mean HINE-2 score (SD) [range]	0.93 (0.95, [0–5])	Not reported	Not reported
2 SMN2 copies	100%	100%	100%

SD: standard deviation
HINE-2 score not reported for onasemnogene abeparvovec
† Calculated from IPD; ‡ Not available from IPD,
* Patients with nutritional support: Unable to swallow/Gastrointestinal tube feeding

Type 2/3 SMA patients

Table 52 compares the baseline characteristics between the included studies. Since SUNFISH Part 2 enrolled a much broader patient population, the patient characteristics at baseline of SUNFISH are very different to those of the CHERISH trial. There is clear heterogeneity between SUNFISH and CHERISH-SHINE studies with respect to factors that are considered to be predictive of outcomes, such as the number of SMN2 copies, age, ambulatory status and motor function at baseline (111). For example, the median age at screening was 9 years old for SUNFISH and 4 years old for CHERISH-SHINE; disease duration was also longer for risdiplam patients versus nusinersen (95.8 months versus 39.3 months) and HFMSE baseline scores were also lower for risdiplam patients compared to nusinersen (16.1 and 22.4, respectively). Finally, CHERISH excluded patients with severe scoliosis, severe contractures and non-invasive ventilation, while such restrictions were not applied in SUNFISH. Sex, RULM score and SMN2 copy number were fairly similar.

The gaps in baseline characteristics evidence identified from the primary study sources will be supplemented by the identified G-BA dossier for the matching process (126).

Table 52. Baseline characteristics for SUNFISH Part 2 and CHERISH-SHINE.

Baseline characteristic	SUNFISH OLE Part 2		CHERISH-SHINE	
	Risdiplam	**Placebo**	**Nusinersen**	**Sham**
Sample size (ESS)	120	60	83*	42
Gender (female, %)	51	50	55	50
Median age at screening, years (range)	9.0 (2–25)	9.0 (2–24)	4.0‡ (2–9)	3.0‡ (2–7)
Median age at symptom onset, months (range)	12.3 (0–57)	12.8 (6–135)	10.0 (6–20)	11.0 (6–20)
Median disease duration, months (range)	95.8 (5–273)	92.2 (0–266)	39.3‡ (8–94)	30.2‡ (10–80)
Mean HFMSE baseline score (SD)	16.1 (12.5)	16.6 (12.1)	22.4‡ (8.3)	19.9‡ (7.2)
Mean RULM baseline score (SD)	19.6‡ (7.2)	20.5‡ (6.6)	19.4‡ (6.2)	18.4‡ (5.7)
SMN2 copy number (%)				
– Two copies	3%	2%	7%	10%
– Three copies	89%	83%	88%	88%
– Four copies	8%	13%	2%	2%

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– Unknown	0%	2%	2%	0%
Severe scoliosis (%)	28%	38%	0%§	0%§

† n = 119; ‡ n = 58; ǂ n = 84; § CHERISH exclusion criterion;
* One patient in the CHERISH trial opted not to participate to the CHERISH OLE study;
ESS: Effective sample size; HFMSE: Hammersmith Functional Motor Scale – Expanded; RULM: Revised Upper Limb Module; SD: Standard deviation.

Endpoints of interest

Endpoints of interest are those that are common across studies. For each outcome of interest, the publication must report Kaplan-Meier curves for time to event outcomes, mean/median for continuous outcomes, or the proportion of individuals for binary outcomes as per NICE DSU guidance (127, 128). The networks of evidence for each outcome include all studies reporting on outcome measure of interest, irrespective of the assessment time points.

Presymptomatic SMA patients

Whilst all three studies assessed efficacy, differences in the patient populations, outcome measures and timepoints of assessments make a direct comparison challenging. Similarities in the eligibility criteria for the 3 presymptomatic studies include age at first dose, requirement for clinical diagnosis, and exclusion of patients with SMA symptoms. A key difference was the CMAP amplitude.

Whilst both RAINBOWFISH and SPR1NT have BSID-III as their primary endpoint, there are several notable differences. RF assessed item 22 (sitting without support for >=5 seconds), in only patients with 2 SMN2 copies and baseline CMAP amplitude >=1.5mV, and the endpoint was assessed only at month 12. For SPR1NT, there were two different endpoints, depending on SMN2 copy number. Item 26 (sitting independently for >=30 seconds) was assessed in patients with 2 SMN2 copies (note: patients were allowed to use their upper extremities), and the endpoint could be achieved up to 18 months of age (at any visit) rather than at a single timepoint. Item 40 was assessed in patients with 3 SMN2 copies, timepoint up to 18 months.

Lastly, independent assessment was required – 2 Central Readers for RAINBOWFISH (who both needed to agree for the result to be confirmed), and 1 Central Reader for SPR1NT (less strict). For both studies, the age at first achievement may have been underestimated - if a patient reached a milestone prior to the visit, it could not be considered achieved until demonstrated at the site visit and confirmed as achieved by Central Reader(s). NURTURE assessed the WHO Motor Milestones, but as a secondary endpoint, and at no particular time point. Independent assessment was not required (no Central Reader) and caregiver reported achievement of milestones was permitted, which allowed items to be considered achieved outside of study visits (potentially earlier than RAINBOWFISH and SPR1NT).

The outcomes of interest for the analysis between RAINBOWFISH, NURTURE and SPR1NT are BSID-III, HINE-2, CHOP-INTEND, ventilation-free survival, overall survival and safety. Full details of the outcomes of interest for the analysis, and which are reported in each of the studies in patients with presymptomatic SMA, can be found in the statistical analysis plan (SAP) for the ITC (124).

Type 1 SMA patients

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Outcomes from 4-year FIREFISH were derived from individual patient data of Part 1 (including patients from the 'High-dose' cohort on pivotal dose) and Part 2. The SLR did not identify any new data that has been published for ENDEAR-SHINE, and therefore the G-BA documents were identified as the best available long-term evidence for nusinersen in this population. The dossier has been used to complete the nusinersen arm data for close to 5 years (the time points have been provided for each outcome within the tables below, but are approximate as they have been computed through the digitisation of graphs) (126). For the risdiplam and OA comparison, FIREFISH has been compared to both STR1VE-US and -EU data, although there are clear differences between the inclusion criteria and imbalances in baseline characteristics, which limits the feasibility of matching (see Study design and enrolment criteria).

The outcomes of interest for the analysis between FIREFISH and ENDEAR-SHINE cover HINE-2, CHOP-INTEND, event-free and overall survival. For FIREFISH to STR1VE, CHOP-INTEND, BSID-III, survival and safety outcomes have been identified. Full details of the outcomes of interest for the analysis, and which are reported in each of the studies in patients with type 1 SMA can be found in the methods write-up and SAP (117, 121).

Type 2-3 SMA patients

In CHERISH, the primary study endpoint was the change from baseline in HFMSE score at month 15. The proportion of children who achieved an increase from baseline of 3 points or more in HFMSE score at month 15, and change from baseline in the RULM score at month 15 were secondary endpoints, among others. In SUNFISH Part 2, the primary study endpoint was the change from baseline in the MFM 32 score at month 12 and secondary endpoints included HFMSE and RULM. The MFM 32 scale was not assessed in CHERISH.

For type 2-3 patients, in CHERISH, the HFMSE improvement of ≥3 points, age and baseline score adjusted odds ratios were only reported at 15 months. These were compared against SUNFISH Part 2 12-month data. For the RULM improvement of ≥2 points, unadjusted proportions derived from non-imputed chart data was used for nusinersen in the absence of adjusted proportions or odds ratios from the imputed dataset being reported.

Only severe adverse events were included as a safety outcome in the ITC analysis to compare against CHERISH. Occurrence of any adverse event were not included in this comparison, as all or almost all patients in the control arms of CHERISH and SUNFISH Part 2 had an adverse event, leading to uninformative results. There are no survival endpoints compared due to minimal to no events occurring within the trials. Full details of the outcomes of interest for the analysis, and which are reported in each of the studies in patients with type 2/3 SMA can be found in the SAP (125).

Endpoints and definitions

Where relevant, the differing definitions of endpoints used within the included studies has been provided below, by SMA type.

Presymptomatic SMA patients

For the presymptomatic study comparison, the motor milestone metrics are all standardised definitions however the difference identified was in the assessment schedules between studies. RAINBOWFISH entails more frequent visits, while SPR1NT reports outcomes based on patients' increasing age rather than visit intervals. Consequently, adjustments are

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necessary to synchronize the timing of outcomes. To address the issue of more frequent visits, assessment schedule matching (Kapetanakis et al. 2019) was employed. However, when comparing RAINBOWFISH to SPR1NT, the outcomes in RAINBOWFISH will be presented and matched based on the progression of patients' age. The outcomes related to oral feeding and respiratory support at baseline are not relevant matching factors as it is only when the symptoms evolve later that they become important to consider, therefore for the purpose of the analysis they have not been considered in the matching process.

Type 1 SMA patients

For the comparative analysis between FIREFISH and ENDEAR-SHINE, the included endpoints and respective study definitions has been provided in Table 53, alongside the maximum follow-up time for each endpoint from ENDEAR-SHINE (4 and 5 year data will be used for FIREFISH). Overall, the endpoint definitions are comparable between studies.

Table 53. Endpoint definitions between FIREFISH and ENDEAR-SHINE.

Endpoint	FIREFISH definition	ENDEAR-SHINE definition
Time to death	• Time to death	• Time to death • Kaplan Meier plot reporting up to day 1,800
Time to death or permanent ventilation	• Death or permanent ventilation, where permanent ventilation was defined as ≥16 hours of non-invasive ventilation per day or intubation for >21 consecutive days in the absence of, or following the resolution of, an acute reversible death or tracheostomy	• Death or permanent ventilation, where permanent ventilation was defined as either tracheostomy or ≥ 16 hours ventilation/day continuously for > 21 days • Kaplan Meier plot reporting up to day 1,800
Time to HINE-2 motor milestone response	• At least a 2-point increase in ability to kick (or maximal score) or a 1-point increase in head control, rolling, sitting, crawling, standing, or walking. Worsening is similarly defined as a 2-point decrease in ability to kick (or lowest score) or a 1-point decrease in head control, rolling, sitting, crawling, standing, or walking. • An infant is classified as a responder if more motor milestones showed improvement than showed worsening; infants who die or withdraw will be classified as non-responders. • Patients are censored at latest recorded visit • Deaths are censored (recorded as 0, rather than as an event)	• (i) subject demonstrates ≥ 2-point increase in the motor milestones category of ability to kick or achievement of maximal score on that category (touching toes), or a 1-point increase in the motor milestones category of head control, rolling, sitting, crawling, standing, or walking, and (ii) among the motor milestone categories, with the exclusion of voluntary grasp, there are more categories where there is improvement as defined in (i) than worsening. (For the category of ability to kick, worsening is defined as ≥ 2-point decrease or decrease to the lowest possible score of no kicking. For the other categories, worsening is defined as ≥ 1-point decrease.) • Cumulative density plot reporting up to ~day 990
Time to ≥ 4-point improvement in CHOP-INTEND	• Improvement of CHOP-INTEND from baseline of ≥4 • Patients are censored at latest recorded visit	• A participants was considered a CHOP-INTEND responder if the change from baseline in CHOP-INTEND total score is ≥ 4 points

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change from baseline	• Deaths are censored (recorded as 0, rather than as an event)	• Cumulative density plot reporting up to day 1,650
Time to first SAE	• Time to first serious adverse event • Patients are censored at earliest date from: CCOD, death date, study withdrawal date, and last treatment dose + 30 days	• Time to first serious adverse event • Kaplan Meier plot reporting up to day 1,500

For the comparison between FIREFISH to STR1VE-US and STR1VE-EU, due to the STR1VE motor milestone endpoints being assessed at any visit where the patient is up to and at 18 months of age, the most similar study visit to this for patients in FIREFISH would fall between the 12 and 13 month visit mark, as patients in FIREFISH had a mean age at first dose of 5.4 months. The motor milestone comparison was made to the closest assessment time point to week 52 (12 month) for FIREFISH and 18 months for STR1VE:

- BSID-III and CHOP-INTEND:
    - STR1VE time point: any study visit where the patient is aged $\leq$ 18 months
    - FIREFISH time point: study week 52 (12 month), as BSID-III and CHOP-INTEND motor function outcomes were not evaluated at study month 13.
    - STR1VE also reports mean CHOP-INTEND values over time by study month. Mean values are reported up to study visit month 16, but there are very few patients at this time point. For example in STR1VE-EU at this time point there are n=4 patients; therefore, mean change from baseline at visit month 14 has been used as there are more than 10 patients at this time point in both study arms.

The studies report event free survival data (death or permanent ventilation) and data on the proportion of participants requiring ventilatory support. However, there are differences in definition of permanent ventilation:

- STR1VE: tracheostomy or the requirement of ≥16 hours daily non-invasive ventilatory support for >14 consecutive days in the absence of acute reversible illness (excluding perioperative ventilation).
- FIREFISH: ≥16 hours of non-invasive ventilation per day or intubation for >21 consecutive days in the absence of, or following the resolution of, an acute reversible event or tracheostomy.

There are also differences in the definitions of survival:

- In STR1VE, survival was defined as time from birth date to death or permanent ventilation.
- In FIREFISH, the corresponding endpoints is ventilation-free survival, defined as time from enrolment to death or permanent ventilation.
- For the purpose of these analyses, ventilation-free survival in FIREFISH was re-calculated as time from birth date to be consistent with STR1VE.

It is not possible to adjust for these differences in any analysis. The event free survival endpoint will be included in the analysis with differences in the outcome definitions

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highlighted in any reporting of the results. Permanent ventilation will also be included in the analysis, with the proportion requiring permanent ventilation at study month 12 in FIREFISH vs. age 18 months from STR1VE-US/EU being assessed.

Similarly, there are differences in the definition of the nutritional support endpoint. FIREFISH only collects information on the patients' ability to swallow, whereas STR1VE-US/EU reports on whether feeding support was received. These will be compared in the analysis with differences in the outcome definitions highlighted in any reporting of the results.

STR1VE-US/EU reports a range of safety outcomes. For consistency with the previous ITC analyses conducted, the proportions of patients experiencing any serious adverse event will be compared and "any adverse event" will also be included.

Type 2/3 SMA patients

Definition of endpoints were similar between the two studies, except for time points (15 months for CHERISH and 12 months for SUNFISH Part 2). Results at 12 months were extracted from published CHERISH data, where available. Responder analysis for HFMSE change from baseline were based on a cut-off of 2 points in SUNFISH Part 2. In order to align with the CHERISH definition of a HFMSE responder, SUNFISH data was re-analysed using a responder cut-off of a change from baseline of at least 3 points.

Target population

NICE DSU technical support document 18 stipulates that the target population must reflect the real-world population (128). In the MAICs for presymptomatic and T1, the IPD data from RAINBOWFISH and FIREFISH will be matched to that of NUTURE and SPR1NT separately or ENDEAR-SHINE, respectively. For the analysis, it is assumed that this population reflect the real-world SMA population relevant for the decision problem.

For the type 2/3 patients, the IPD data from SUNFISH will be matched to CHERISH, however as CHERISH investigated a very selective population, inferences generated from this MAIC approach are valid only in CHERISH-like populations.

Network of evidence

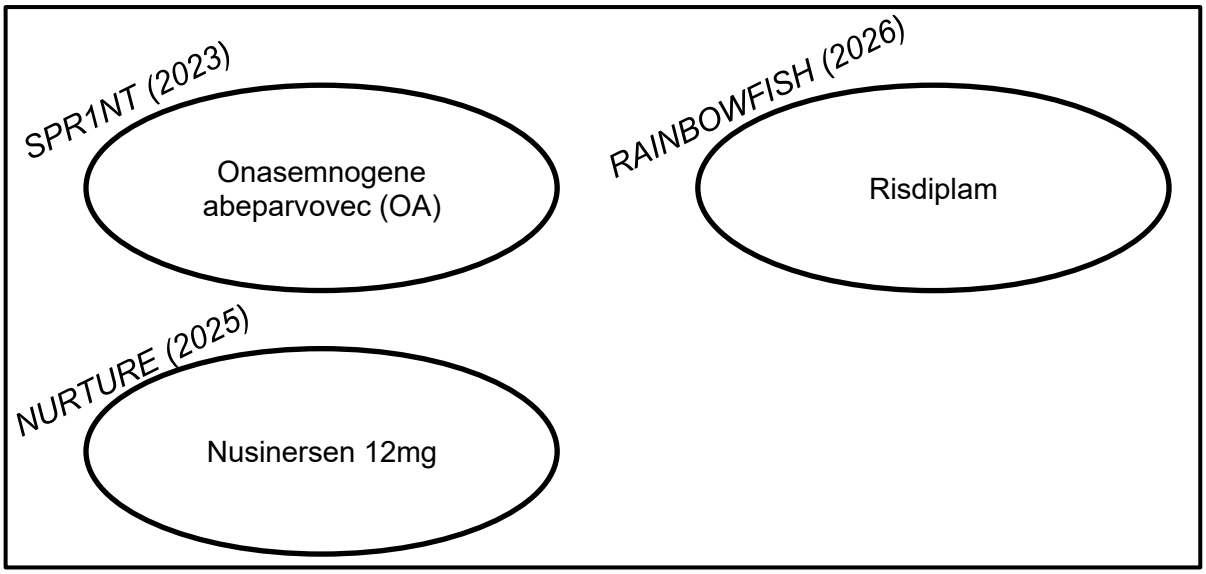
Presymptomatic SMA patients

The network of evidence for presymptomatic SMA is illustrated in

Figure ***9***. The network is disconnected; hence a network meta-analysis based on a comparison of relative treatment effects is not possible. A naïve or unanchored indirect comparison of risdiplam with nusinersen and OA may be confounded by systematic variation in both prognostic and predictive factors among the different trial populations (111). Following completion of the feasibility assessment, the most appropriate analysis would be a naïve comparison as both a MAIC and simulated treatment comparison (STC) are not feasible primarily due to the small sample sizes and substantial differences at baseline.

Figure 9. Network in presymptomatic SMA

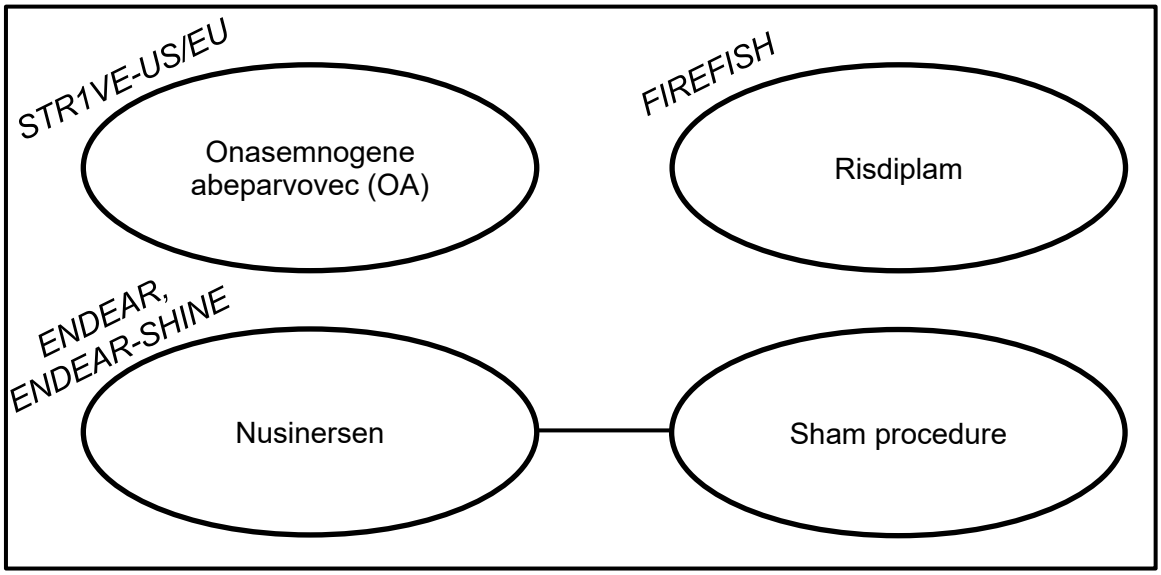
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Type 1 SMA patients

The network consists of one two-arm study and three single arm studies, and is disconnected (Figure 10). A network meta-analysis based on a comparison of relative treatment effects is therefore not possible. A naïve or unanchored indirect comparison of risdiplam with nusinersen or OA may be confounded by systematic variation in prognostic factors. Therefore, a population matching technique (unanchored MAIC) to adjust for differences between trial characteristics was conducted to compare risdiplam to nusinersen and to OA. This is to account for the fact that in disconnected networks, analyses based on non-comparative trials could potentially be confounded by prognostic factors. The approach of implementing both a naïve and adjusted comparison is in line with NICE DSU guidance (127, 128).

Figure 10. Network in type 1 SMA

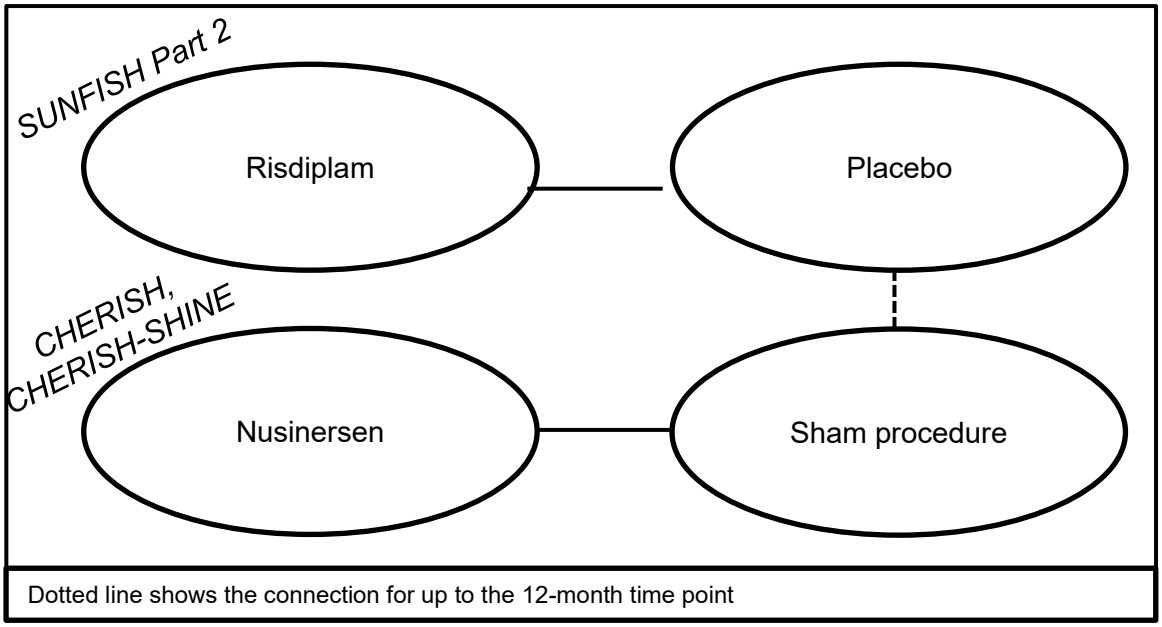


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Type 2/3 SMA patients

The network consists of two two-arm studies, and is disconnected (Figure 11). For the data available up to 12 months, based on the assumption that sham in CHERISH is comparable with placebo in SUNFISH, an anchored MAIC can be performed up to this point. However, past the 12 month point SUNFISH and CHERISH-SHINE OLE studies lack common comparators due to placebo/sham patients switching onto active treatment for the remainder of the study. As a result, past the 12 month time point an anchored MAIC is not viable as a disconnected network is formed and only an unanchored MAIC analysis is feasible given the available evidence. An unanchored MAIC approach allows indirect comparisons whilst taking into account the heterogeneity between studies.

Figure 11. Network in type 2/3 SMA



B.2.9.3 Methods

The methods applied in the ITC to perform the comparisons for risdiplam versus the relevant comparators in each SMA population are described here.

Adjustment of prognostic factors

Presymptomatic SMA patients

At baseline, the patients included in this analysis are in the pre-symptomatic stage of SMA and a specific phenotypical trait such as SMA type could not be assigned to them. However, it is well-established that there is an inverse correlation between disease severity and the SMN2 copy number (10). Thus, the ITC for this population will utilise the SMN2 copy number as a factor in the matching algorithm in order to balance the populations with an unknown SMA type at baseline. Patients with 4 or more SMN2 copies in RAINBOWFISH will be excluded from the analysis to align with the comparator trials.

Furthermore, published data in type 1 demonstrates that other baseline factors have also demonstrated their significance as strong prognostic or treatment-modifying factors, namely

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age at first dose and baseline motor function (total CHOP-INTEND score) (129, 130) . Taking into account that if left untreated SMA patients will experience rapid neuromuscular degeneration, both of these factors are also considered to be important matching covariates for presymptomatic patients and are included in all analyses involving survival, motor milestone and CHOP-INTEND assessments. Age at first dose has been confirmed through review and expert medical opinion as an important predictor of motor functional outcomes (131, 132). Total CHOP-INTEND score was further identified by medical experts as a useful criterion to classify the severity of disease progression in SMA patients.

Lower CMAP values at baseline might indicate higher disease severity as CMAP is a potential biomarker for reaching motor milestones (133). In the comparison of RAINBOWFISH vs NURTURE where CMAP is available for both studies, scenario analyses including CMAP as a matching factor will be performed.

Considering the data available, the baseline characteristics that were considered as matching factors for the comparative analyses in presymptomatic SMA patients, along with rationale for inclusion or exclusion are presented in Table 54.

Table 54. Covariates inclusion and exclusion in presymptomatic SMA comparative analyses

Characteristic	Included/Excluded	Justification
SMN2 copy number	Included	• SMN2 copy number was shown to be linked with disease severity/phenotype (SMA type) and will be used to match the pre-symptomatic patient population.
Mean age at first dose	Included	• Age characteristics are most commonly reported as prognostic • Age of symptom onset and age of treatment onset specifically are highlighted by the prognostic review, age of at first dose is the most reliable measure in clinical trials.
Mean baseline total CHOP INTEND score	Included	• Motor milestones (e.g. head and/or trunk control) flagged in the prognostic review • CHOP INTEND is seen as a stronger indicator than HINE-2 as it was developed based on infants with SMA type 1 (134) and is more granular than HINE-2 (131).
Mean weight	Excluded	• Percentile of growth curve would be a good factor, but this was not reported for NURTURE
Gender	Excluded	• Prognostic review did not found it to be a statistically significant predictor of outcomes
Race	Excluded	• Not flagged by prognostic review or medical experts
Mean HINE-2 score	Excluded	• CHOP INTEND already included as seen as a stronger indicator of motor function compared to HINE-2
Ulnar CMAP amplitude	Excluded	• CHOP INTEND already included as seen as a strong indicator of motor function • Prognostic review showed uncertainty about whether CMAP is a prognostic factor
Peroneal CMAP amplitude	Excluded	• Not reported in SPR1NT

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In the comparison between RAINBOWFISH and NURTURE, matching on CMAP, CHOP-INTEND, and HINE-2 can be viable options based on available data. For the comparison between RAINBOWFISH and SPR1NT, matching on weight and CHOP-INTEND is feasible only for patients with 2 SMN2 copies. Lastly, assessment schedules between the studies are different. RAINBOWFISH (1-year CSR) has more study visits in a shorter period of time, while SPR1NT (Strauss 2022) does not provide results by study visit but by patient age an approach to help align the two studies (as described above in "Endpoints and definitions – presymptomatic SMA patients").

Type 1 SMA patients

A review of prognostic factors and treatment-effect modifiers in SMA identified SMN2 copy number, disease severity (baseline motor function, respiratory function), age of symptom onset, age at study enrolment, clinical severity and extent of supportive care as prognostic factors in SMA (111). This complies with TSD 18 recommendations which advise showing evidence that included variables are effect modifiers or prognostic factors (127). For the comparison between FIREFISH and ENDEAR-SHINE, the following matching factors are included: age at first dose, baseline motor function (baseline total CHOP-INTEND score) and disease duration at baseline. For the comparison between FIREFISH and STR1VE-US/EU, the following matching factors are included: age at first dose and baseline motor function (baseline total CHOP-INTEND score). The former two covariates have been selected for the same reasons as listed for the presymptomatic cohort (see above). The duration of symptoms was indicated by medical experts to be a very strong predictor of treatment efficacy, as the earlier patients receive treatment in the course of their disease, the better the outcomes. Duration of symptoms is not reported in STR1VE-US/EU and therefore cannot be included within matching covariates.

Considering the data available, the baseline characteristics that were considered as matching factors for the MAIC analyses in type 1 SMA patients, along with rationale for inclusion or exclusion are presented in Table 55.

Table 55. Covariates inclusion and exclusion in type 1 SMA MAIC analyses

Characteristic	Included/Excluded	Justification
Mean age at first dose	Included	• Age characteristics are most commonly reported as prognostic • Age of symptom onset and age of treatment onset specifically are highlighted by the published prognostic review, age of at first dose is the most reliable measure in clinical trials
Mean baseline total CHOP INTEND score	Included	• Motor milestones (e.g. head and/or trunk control) flagged in the published prognostic review • CHOP INTEND is seen as a stronger indicator than HINE-2 as was developed specifically for infants with SMA type 1
Mean disease duration at baseline	Included for ENDEAR Excluded for SPR1NT	• Identified as a treatment effect modifier in ENDEAR • Not reported in STR1VE-US/EU
Mean age at symptom onset	Excluded	• Correlated with age at first dose, age at first dose previously selected in base case
Mean age at diagnosis	Excluded	• Correlated with age at first dose, age at first dose previously selected in base case

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		• Age at diagnosis was not specifically identified by the published review and is subject to local accessibility of genetic analyses, hence highly variable across centres
Mean weight	Excluded	• Percentile of growth curve would be a good factor, but this was not reported in either trial
Gender	Excluded	• The published prognostic review did not find it to be a statistically significant predictor of outcomes
Race	Excluded	• Not identified by the published prognostic review nor medical experts
Mean HINE-2 score	Excluded	• CHOP INTEND already included as an indicator of motor function • Not reported in STR1VE-US/EU
Ventilatory and/or nutritional support	Excluded	• Nutritional status and respiratory function have been identified as important predictors of survival; nevertheless medical experts emphasized that differences in protocols across centres and over the course of the years make this variable not useful for the purpose of matching across the identified studies (130, 131, 135)

Type 2/3 SMA patients

For the type 2/3 SMA population age at screening, SMN2 copy number and motor function (specifically ambulatory status) are considered to be prognostic factors (111). However, it is unclear whether prognostic factors of outcome could also be predictive of treatment efficacy. There is also no clear evidence that baseline functional score is predictive of treatment efficacy once age has been taken into consideration. Previous clinical trials in type 2/3 SMA have adjusted for both age and baseline functional score (76). Considering the lack of conclusive evidence on the role of the aforementioned factors in predicting treatment efficacy, the following criteria are considered for matching: age at screening, SMN2 copy, baseline HFMSE functional score, baseline RULM score and severe scoliosis/contractures at baseline (considering their impact on the HFMSE assessment), see Table 56.

Table 56. Covariates inclusion and exclusion in type 2/3 SMA unanchored MAIC analyses

Covariate	Included/Excluded	Justification
Age at screening	Included	• Age at baseline was identified as prognostic and predictive of motor function in the review (111) • Previous RTCs in type 2/3 SMA have adjusted for both age and baseline functional score at screening (76)
SMN2 copy number	Included	• Flagged as a prognostic factor in the review (111) • A predictive effect of patients treated with DMTs is unclear
HFMSE score at baseline	Included	• Baseline motor function was identified as a prognostic factor in

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RULM score at baseline	Included	the review (111), although there is no clear evidence if it is predictive once age has been taken into account • Previous RTCs in type 2/3 SMA have adjusted for both age and baseline functional score (76)
Age at symptom onset	Excluded	• Age at screening already included • Age at symptom onset is considered less reliable in a clinical trial setting of Type 2/3 patients due to a higher chance of recall bias.
Age at diagnosis	Excluded	• Not reported in SUNFISH
Disease duration	Excluded	• Not reliable in SUNFISH, as it had to be calculated from age at screening and age at symptom onset, which resulted in negative disease durations for some patients.
Severe contractures	Excluded	• Impacts assessment of motor function scales. However, contracture data collected in SUNFISH was considered unreliable and severity was not recorded
Gender	Excluded	• Review did not find it to be a statistically significant predictor of outcomes in patients treated with DMTs (111)
Race	Excluded	• Not flagged by literature review or medical experts
Motor milestones achieved	Excluded	• Baseline motor function already included • Unclear how this was measured in CHERISH
WHO motor milestones ever achieved	Excluded	• WHO motor milestones were not collected in SUNFISH
Geographical location	Excluded	• No clear evidence of it being a prognostic or predictive factor (111)

Analyses

Presymptomatic SMA patients

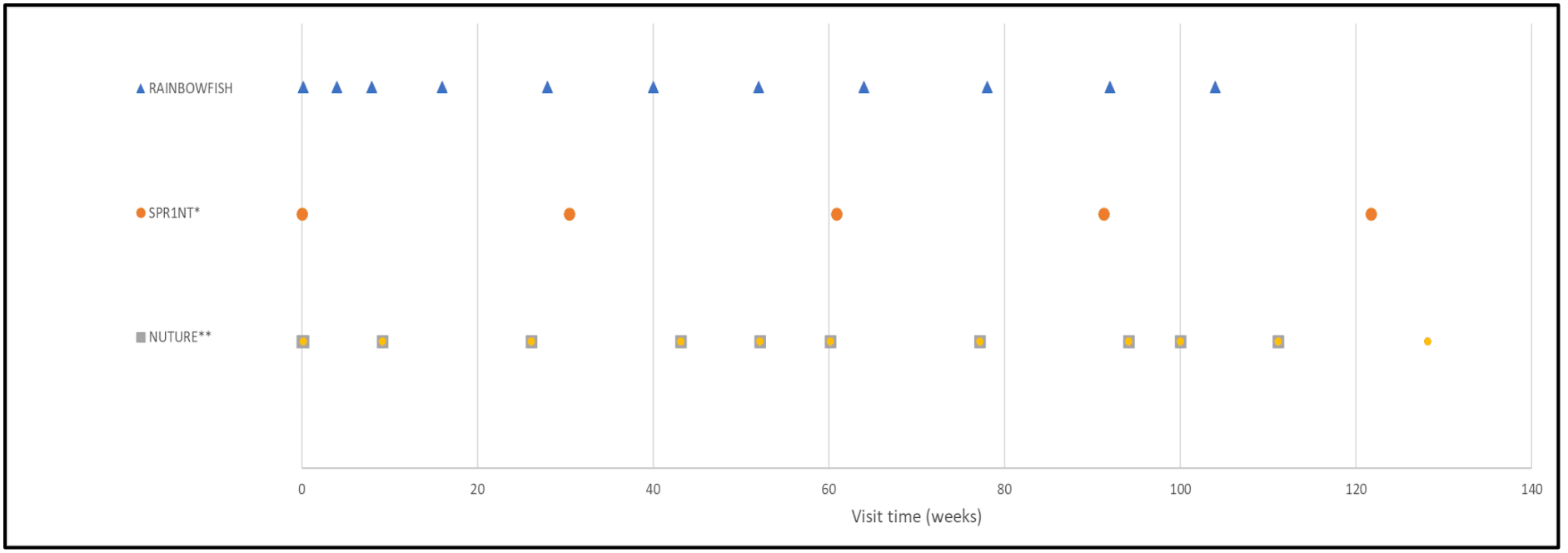
As mentioned in earlier sections, the assessment schedules related to HINE-2, CHOP-INTEND and motor milestones are not consistent across studies, as per Figure 12. The assessment schedules in SPR1NT are held according to patient's age, whereas

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RAINBOWFISH and NURTURE use time from baseline, therefore RAINBOWFISH and NURTURE have more study visits in a shorter period of time.

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Figure 12. Schematic diagram showing the trial assessment time points versus number of weeks.



*Patients will return at regularly scheduled intervals for efficacy and safety assessments, these have been assumed to be monthly;

** Grey squares indicate assessment schedule for HINE-2, yellow circles indicate assessment schedule for CHOP INTEND and motor milestones.

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Type 1 SMA patients

Table 57 and

Table ***58*** shows the list of analyses conducted for risdiplam versus nusinersen, and OA in Type 1 SMA.

Table 57. List of analyses for risdiplam vs. nusinersen in type 1 SMA

Outcomes	Effect size	Time point	Approach	Matching factors
Event-free survival (death or permanent ventilation)	HR	- FIREFISH 4 year data cut - ENDEAR-SHINE 4.9 year data (KM plot reporting up to day 1,800)	Unanchored MAIC	- Age at first dose - Duration of symptoms in weeks - Total CHOP-INTEND score at baseline
Overall survival	HR			
HINE-2, proportion of patients with motor milestone response	OR	- FIREFISH 4 year data cut - ENDEAR-SHINE 2.7 year data (KM plot reporting up to day 990)		
HINE-2, proportion of patients with full head control	OR			
HINE-2, proportion of patients achieving sitting without support	OR			
HINE-2, proportion of patients achieving sitting with or without support	OR			
HINE-2, proportion of patients achieving rolling	OR			
HINE-2, proportion of patients achieving standing	OR			
CHOP-INTEND, proportion of patients with ≥4 point improvement from baseline	OR	- FIREFISH 4 year data cut - ENDEAR-SHINE 4.5 year data (KM plot reporting up to day 1650)		
CHOP-INTEND, proportion of patients with score of ≥40	OR			
Adverse Events	OR	- FIREFISH 4 year data cut - ENDEAR-SHINE 4.1 year data (KM plot reporting up to day 1500)	Unanchored MAIC	
Adverse Events leading to discontinuation	OR			
Serious Adverse Events	OR			

Table 58. List of analyses for risdiplam vs. OA in type 1 SMA

Outcomes	Effect size	Time point	Approach	Matching factors
Event-free survival (death or permanent ventilation)	HR	- STR1VE-US/EU: All data up to data cut - FIREFISH: All data up to data cut	Unanchored MAIC	- Age at first dose in days - Total CHOP-INTEND score at baseline

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Percentage of infants sitting without support for >=30 seconds, as classified by item 26 of BSID-III	OR	- STR1VE-US/EU: At 18-months of age visit - FIREFISH: At 12-months		
Percentage of infants with head control (classified by BSID-III)	OR	- STR1VE-US/EU: By the 31 Dec 2019 data cut - FIREFISH: At 12-months		
Percentage of infants that can roll over (classified by BSID-III)	OR			
Percentage of infants that can stand with assistance (classified by BSID-III)	OR			
Percentage of infants sitting without support for >=5 seconds, as classified by item 22 of BSID-III	OR			
CHOP-INTEND, proportion of patients with ≥4 point improvement from baseline	OR	- STR1VE-EU: At latest recorded visit before 31 Dec 2019 data cut - FIREFISH: At 12-months		
CHOP-INTEND, proportion of patients with score of ≥40	OR	- STR1VE-US/EU: At latest recorded visit before 31 Dec 2019 data cut - FIREFISH: At 12-months		
Adverse Events	OR	- STR1VE-US/EU: At data cut - FIREFISH: At data cut		
Adverse Events leading to discontinuation	OR			
Serious Adverse Events	OR			

Type 2/3 SMA patients

Table 59 shows the list of analyses conducted for risdiplam versus nusinersen in type 2/3 SMA.

Table 59. List of analyses for risdiplam versus nusinersen in Type 2/3 SMA

Endpoint	Effect size	Time point	Approach	Matching factors	Model adjustments
HFMSE, change from baseline	Mean Difference	- CHERISH: At 12 months	Base case: Anchored MAIC	- Age at screening	Adjusting for age and

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		- SUNFISH: At 12 months		- Baseline HFMSE score - SMN2 copy number	HFMSE score at baseline
			Sensitivity: Restricted NMA	Not applicable	
HFMSE, proportion of patients with ≥3 point improvement	OR	- CHERISH Scenario 1: At 15 months (adjusted OR) - CHERISH Scenario 2: At 12 months (unadjusted OR) - SUNFISH: At 12 months	Base case: Anchored MAIC	- Age at screening - Baseline HFMSE score - SMN2 copy number	
			Sensitivity: Restricted NMA	Not applicable	
RULM, change from baseline	Mean Difference	- CHERISH: At 12, 24 and 36 months - SUNFISH: At 12, 24, 36 months	Base case: Anchored MAIC for 12 months Unanchored MAIC data up to 36 months	- Age at screening - Baseline RULM score - SMN2 copy number	Adjusting for age and RULM score at baseline
			Sensitivity: Restricted NMA	Not applicable	
RULM, proportion of patients with ≥2 point improvement	OR	- CHERISH: At 12 months (unadjusted OR) - SUNFISH: At 12 months	Base case: Anchored MAIC	- Age at screening - Baseline RULM score - SMN2 copy number	No adjustment
			Sensitivity: Restricted NMA	Not applicable	
Any adverse event	OR	Up to data cut	Base case: Restricted NMA	Not applicable	No adjustment
			Sensitivity: Anchored MAIC	- Age at screening - Baseline RULM score - SMN2 copy number	
Serious Adverse Events	OR	For the controlled period, matching after this point was unsuccessful	Base case: Restricted NMA	Not applicable	No adjustment
			Sensitivity: Anchored MAIC	- Age at screening - Baseline RULM score - SMN2 copy number	

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B.2.9.4 Results

Challenges faced in the indirect treatment comparisons

Whilst efforts were made to provide comparisons through exploration of different methodologies, many of these were unsuccessful. The initial challenge in all comparisons are the disconnected networks.

In the presymptomatic population, the very small sample sizes (5-15 per arm) by default leads to high uncertainty in any comparison and limits the ability of MAICs/STCs being performed. The significant differences between the populations at baseline, different assessment schedules and differences in motor milestone reporting, all contribute to why the comparisons are uninformative and irrelevant.

For type 1 SMA, the ITC between risdiplam and OA, even with the comparison to the two different STR1VE studies, does not provide sufficient evidence to draw concrete conclusions on the relative efficacy or safety between the two treatments. Similar to presymptomatic patients, this is due to limited overlap in baseline characteristics between the two populations. Whilst the comparative estimates have been produced, the uncertainty in the point estimates is high, meaning that the comparisons are not robust enough to draw conclusions from.

Finally, for the type 2/3 comparison, whilst it was possible to conduct an ITC up to 12 months, only an unanchored MAIC was possible for the comparison between RULM endpoints post 12 months. However, again due to difficulties in matching the differences across populations, there was a significantly reduced effective sample size leading to substantial uncertainty in the effect estimates, and so no conclusions can be drawn on the relative efficacy between risdiplam and nusinersen in the RULM score.

Presymptomatic SMA patients

An adjustment using MAIC or STC for indirect treatment comparisons between the RAINBOWFISH, SPR1NT, and NURTURE study populations was not feasible due to disparities in patient baseline characteristics, outcome metrics and assessment timelines (see Table 60 and Table 61). Any attempt to adjust for these differences resulted in a significant reduction in effective sample size (above 50% loss) limiting even further the already small initial sample size (N = 8 for 2 SMN copy patients and N = 13 for 3 SMN2 copy patients in RAINBOWFISH). Given the differences in baseline characteristics primarily in CHOP-INTEND and CMAP scores, the above populations differ significantly, essentially representing distinct population groups. Overall, RAINBOWFISH included a wider population than SPR1NT and NURTURE as it had no eligibility limitations on CMAP amplitude or SMN2 copy number at enrolment.

A naïve comparison was performed on the available outcomes across studies by overlaying and comparing the published outcomes to the nearest available time point separately for the patient group with 2 SMN2 copies and 3 SMN2 copies.

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Table 60. RAINBOWFISH baseline characteristics post matching, for 2 SMN2 copy patients

	Pre-matching			Post-matching	
2 SMN2 copies	**RAINBOWFISH**	**NURTURE**	**SPR1NT**	**RAINBOWFISH - NURTURE**	**RAINBOWFISH - SPR1NT**
N	8	15	14	-7	-5
Age at first dose (Days)	23.9	19.5	20.6	4.4	3.3
Weight at baseline (Kg)	3.8	NR	3.6	NR	0.2
Number of female patients (%)	4 (50)	7 (47)	10 (71)	-3 (3)	-6 (-21)
Mean CMAP score at baseline	2	2.7	3.7	-0.7	-1.7
Mean CHOP-INTEND score at baseline	44.9	47	46	-2.1	-1.1
Mean HINE-2 score at baseline	2.1	2.7	-0.6	NR	NR

Table 61. RAINBOWFISH baseline characteristics post matching, for 3 SMN2 copy patients

	Pre-matching			Post-matching	
2 SMN2 copies	**RAINBOWFISH**	**NURTURE**	**SPR1NT**	**RAINBOWFISH - NURTURE**	**RAINBOWFISH - SPR1NT**
N	13	15	10	-2	3
Age at first dose (Days)	29.9	22.3	28.7	7.6	1.2
Weight at baseline (Kg)	4.6	NR	4.1	0.5	NR
Number of female patients (%)	10 (70)	6 (60)	9 (60)	4 (10)	1 (10)
Mean CMAP score at baseline	4.4	3.1	4.3	1.3	0.1
Mean CHOP-INTEND score at baseline	53.8	51.9	NR	1.9	NR
Mean HINE-2 score at baseline	3	3.2	NR	-0.2	NR

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Risdiplam vs nusinersen

The naïve comparisons demonstrated similar outcome progression trajectories for the patient groups with 2 and 3 SMN2 copies when evaluating the mean change from baseline in CHOP-INTEND and HINE-2 scores at each visit. Moreover, t-tests conducted to assess mean differences at each timepoint between the two populations indicated no statistically significant differences, as evidenced by the 95% confidence intervals. Additionally, Exact Fisher tests for BSID motor milestones assessing odds ratios (OR) at the 12-month visit did not show any statistical differences within the 95% confidence interval across all categories, including sitting without support, standing alone, standing with assistance, and walking unaided.

CHOP-INTEND

CHOP-INTEND mean change from baseline was compared in patients with 2 and 3 SMN2 copies across RAINBOWFISH and NURTURE, as shown in Figure 13.

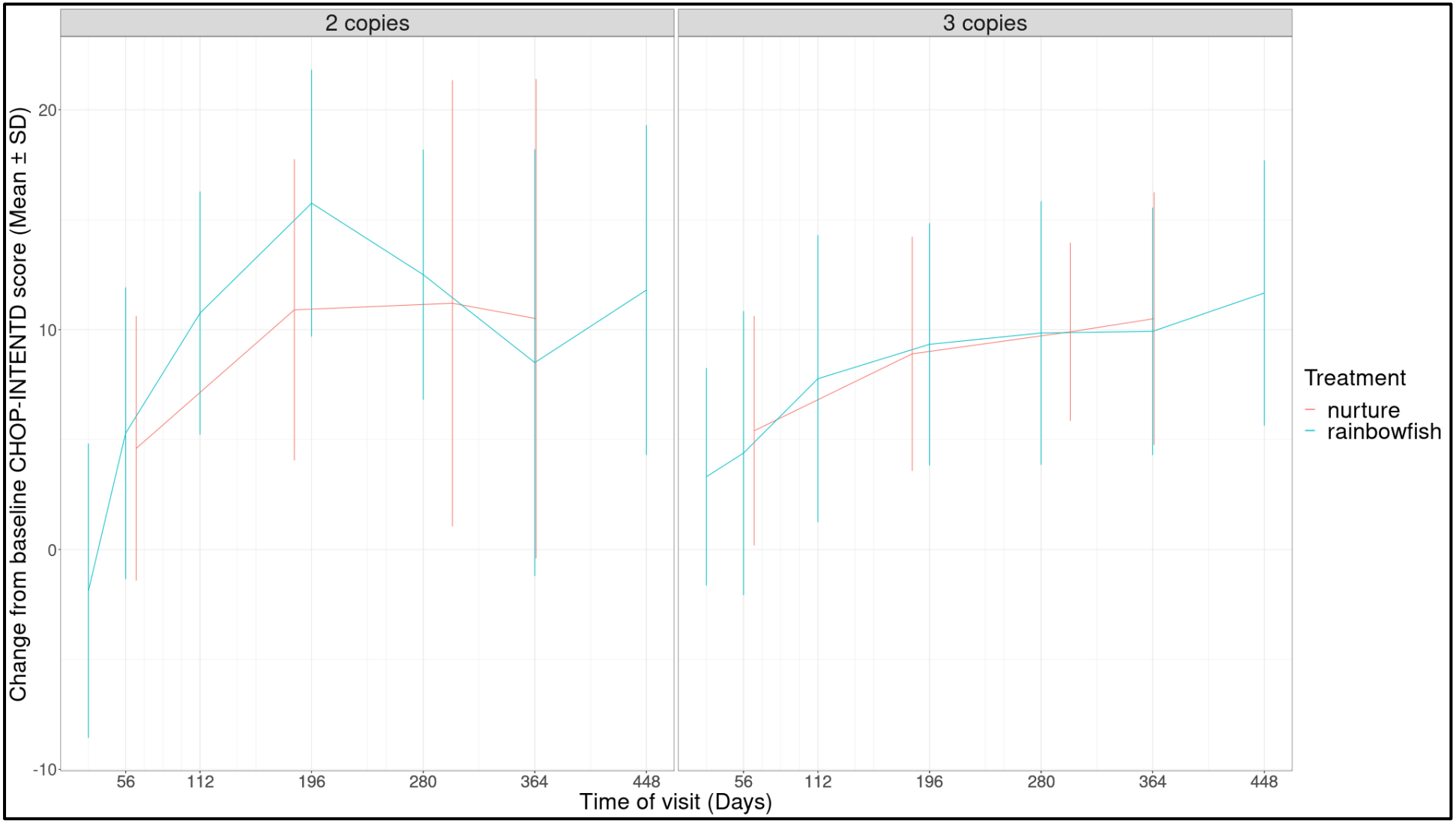
The figure presents the mean and SD for both studies at the time of visit (in days). The results of the naïve comparison show a similar trajectory for total CHOP-INTEND mean change from baseline. Confidence intervals in Table 62 show no evidence of differences for mean change from baseline for total CHOP-INTEND. Subdomains of CHOP-INTEND were not available publicly and so only the total scores over time have been presented.

Table 62. Total CHOP-INTEND mean scores by SMN2 copy number at each time point, with confidence intervals

		RAINBOWFISH		NURTURE			
SMN2 copy number	**Time**	**N**	**Mean score**	**N**	**Mean score**	**CI (95%)**	**P Value**
2 copies	Baseline	8	44.88	15	47.00	-51.59 – 43.19	0.817
2 copies	64 days	7	5.29	15	4.60	-11.39 – 6.93	0.535
2 copies	183 days	8	15.75	15	10.90	-11.48 – 9.53	0.809
2 copies	302 days	8	12.50	15	11.20	-10.29 – 3.52	0.244
2 copies	365 days	8	8.50	15	10.50	-7.63 – 0.84	0.090
3 copies	Baseline	13	53.77	10	51.90	-56.61 – 59.63	0.946
3 copies	64 days	13	4.39	10	5.40	-7.34 – 9.49	0.741
3 copies	183 days	12	9.33	10	8.90	-5.67 – 7.41	0.730
3 copies	302 days	13	9.85	10	9.90	-6.22 – 9.48	0.595
3 copies	365 days	13	9.92	10	10.50	-6.51 – 8.04	0.784

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Figure 13. Total CHOP-INTEND scores for 2 and 3 SMN2 copy patients, comparing RAINBOWFISH and NURTURE



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HINE-2

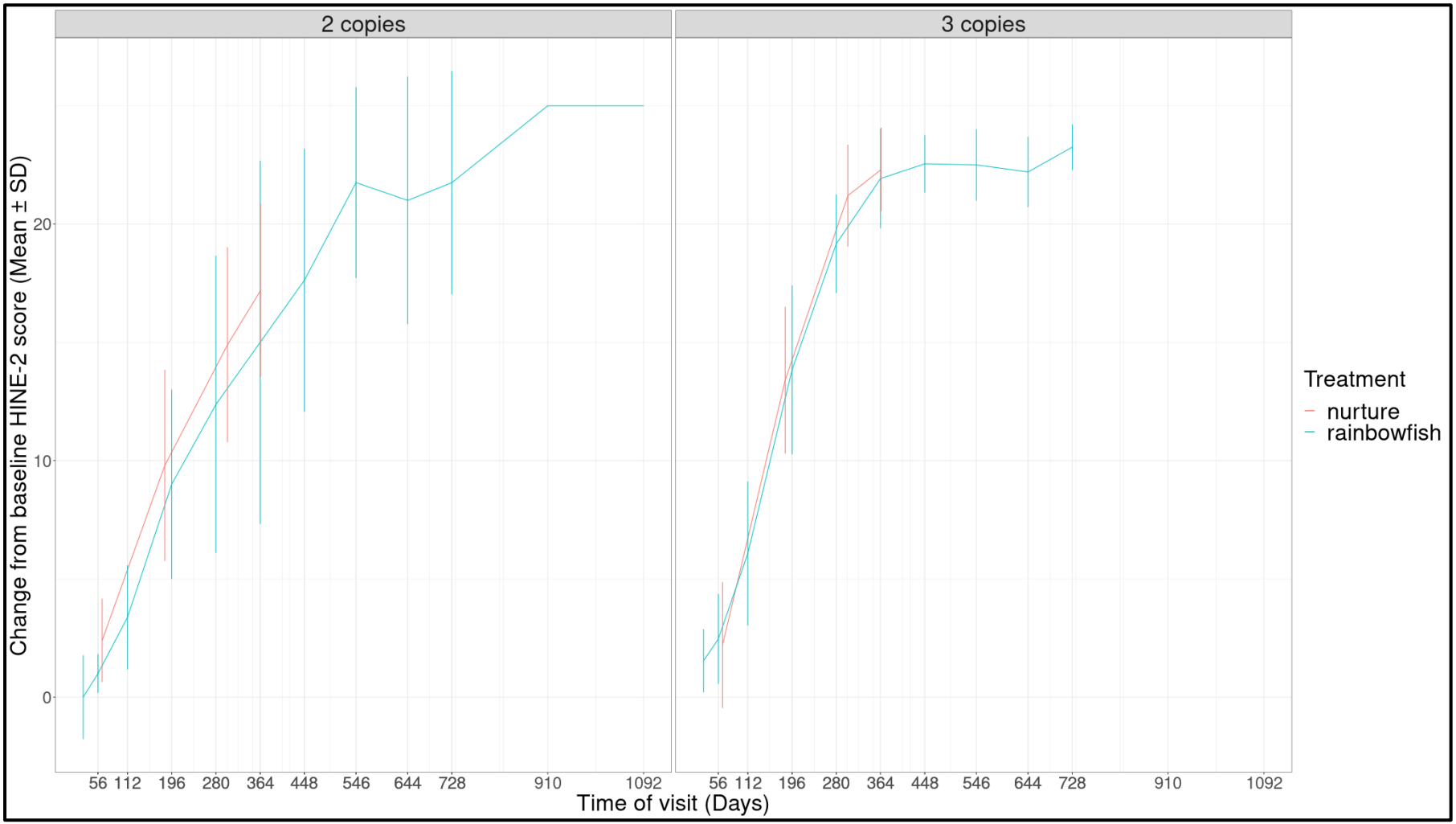
The mean change from baseline in the HINE-2 total score was compared in patients with 2 and 3 SMN2 copies across RAINBOWFISH and NURTURE, as shown in Figure 14. The figure presents the mean and SD for both studies at the time of visit (in days). The results of the naïve comparison show a similar trajectory for HINE-2 scores mean change from baseline. Confidence intervals in Table 63 show no evidence of differences for mean change from baseline for total HINE-2 scores. Subdomains for HINE-2 were not available publicly for NURTURE, and so only the total score has been presented over time.

Table 63. Total HINE-2 mean scores by SMN2 copy number at each time point, with confidence intervals

		RAINBOWFISH		NURTURE			
SMN2 copy number	**Time**	**N**	**Mean score**	**N**	**Mean score**	**CI (95%)**	**P Value**
2 copies	Baseline	8	2.13	15	2.7	-15.82 – 10.68	0.62
2 copies	183 days	8	9.00	15	9.8	-12.37 – 7.15	0.50
2 copies	302 days	8	12.38	15	14.9	-13.67 – 8.76	0.58
2 copies	365 days	8	15.00	15	17.2	-15.13 – 11.69	0.74
2 copies	64 days	7	1.00	15	2.4	-16.67 – 9.78	0.51
3 copies	Baseline	13	3.00	10	3.2	-11.48 – 13.04	0.87
3 copies	183 days	12	13.83	10	13.4	-11.20 – 13.14	0.84
3 copies	302 days	12	19.17	10	21.2	-20.64 – 20.57	1.0
3 copies	365 days	13	21.92	10	22.3	-21.98 – 23.95	0.91
3 copies	64 days	13	2.46	10	2.2	-11.40 – 13.07	0.86

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Figure 14. Total HINE-2 scores for 2 and 3 SMN2 copy patients, comparing RAINBOWFISH and NURTURE



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BSID-III

Results for the comparison on BSID-III motor milestones can be seen at Table 64. The data shows that there is no evidence of difference for BSID-III motor milestones reached at 12 months between RAINBOWFISH versus NURTURE.

Table 64. BSID-III motor milestones accomplished in RAINBOWFISH versus NURTURE at 12 months visit

		RAINBOWFISH		NURUTRE				
SMN2 copy number	**BSID-III milestone**	**N**	**Events**	**N**	**Events**	**OR**	**CI (95%)**	**Pvalue**
2 copies	Sitting without support	8	7	15	15	0.00	0 – 20.8	0.35
3 copies	Sitting without support	13	13	10	10	0.00	-	1.00
2 copies	Standing alone	8	1	15	1	1.94	0.02 – 167.76	1.00
3 copies	Standing alone	13	10	10	6	2.14	0.26 – 20.25	0.65
2 copies	Standing with assistance	8	4	15	9	0.69	0.09 – 5.26	0.69
3 copies	Standing with assistance	13	13	10	10	0.00	-	1.00
2 copies	Walking alone	8	1	15	0	-	0.05 - /	0.35
3 copies	Walking alone	13	9	10	5	2.17	0.30 – 17.21	0.42

Safety

A comparison between RAINBOWFISH and NURUTRE on safety outcomes was unable to be performed due to missing adverse event information reported for NURTURE. Moreover, in the published literature adverse events appear to be similar items with specific labels, but it is unclear if they were reported in a similar manner. For example, toxicity grade specific adverse events were not presented and it is unclear how “serious” and “severe” adverse events are defined.

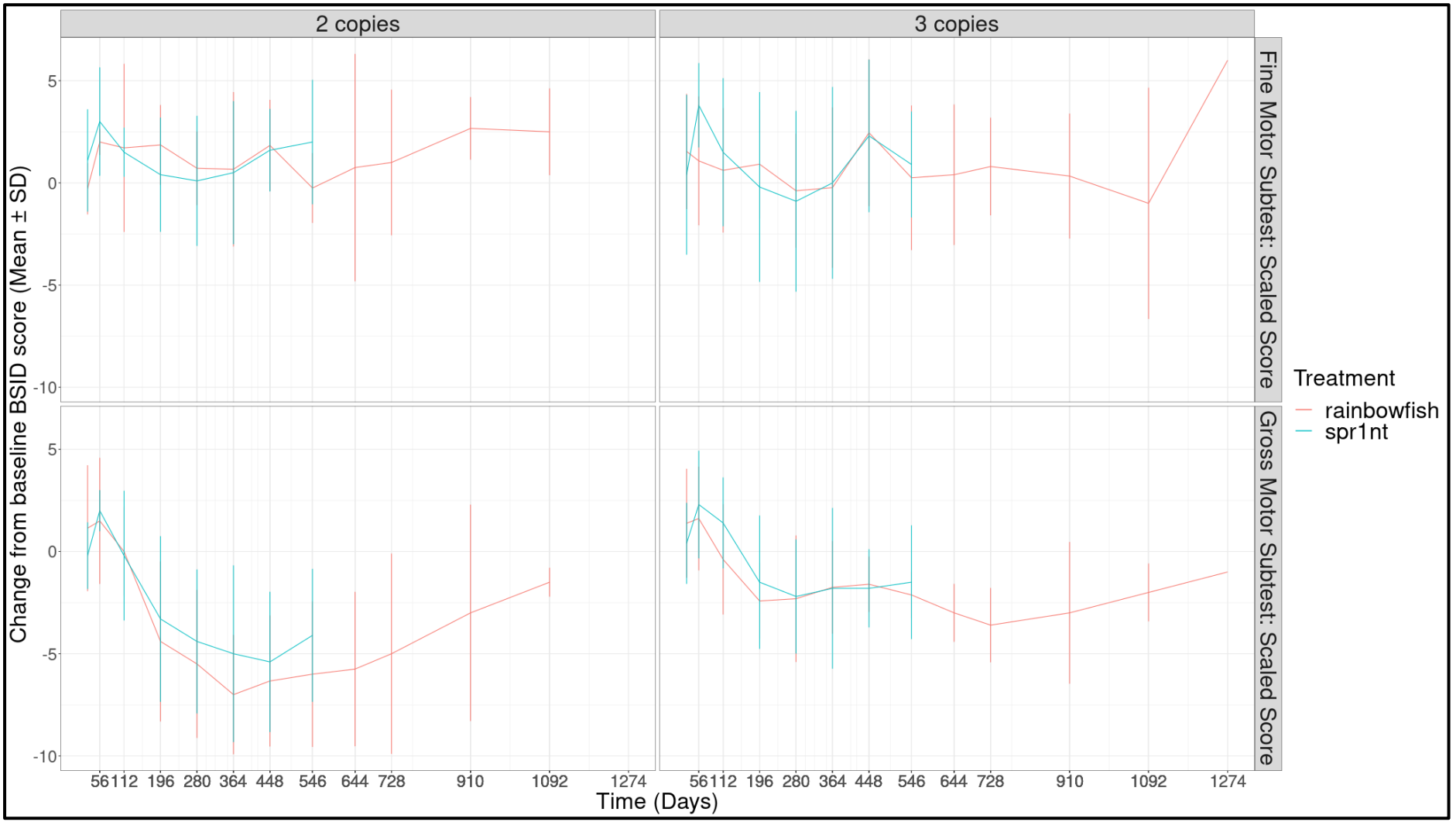
Risdiplam vs OA

BSID-III

The only published data that could be identified (118) allowed for comparisons on the gross and fine BSID-III motor scores. The naïve comparison of fine and gross scaled motor scores of BSID-III did not reveal any significant differences in treatment efficacy, see Figure 15. When aligning the BSID-III scores to the closest matching timepoints in the RAINBOWFISH and SPR1NT studies, the outcome progression trajectories within the patient groups of 2 and 3 copies of the SMN2 gene were similar, as observed in the mean change from baseline at each timepoint. Additionally, t-tests used to evaluate the mean differences at each timepoint between the two study populations showed no statistically significant differences, which is supported by the 95% confidence intervals. It’s important to note that there was greater variability in the group with 2 copies of the SMN2 gene, which could be attributed to the smaller sample size (N=8 for 2 SMN2 copies versus N=13 for 3 SMN2 copies) or potential unaccounted confounding variables.

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Figure 15. Fine and gross BSID-III mean change from baseline scores for 2 and 3 SMN2 copy patients, comparing RAINBOWFISH and SPR1NT



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Type 1 SMA patients

An unanchored MAIC was conducted for the comparison of risdiplam to nusinersen and for the comparison of risdiplam to onasemnogene abeparvovec in type 1 SMA as the studies do not have a common comparator. It was not feasible to conduct an updated comparison to BSC (versus what was presented in TA755) as patients in the sham arm of ENDEAR switched to nusinersen after 12 months.

Risdiplam vs nusinersen

As noted earlier, enrolment criteria were similar between the two trials (FIREFISH and ENDEAR) and the populations are broadly comparable. However, a population-adjusted comparison was also performed for methodological completeness and for assessing the impact on results. Table 65 provides an overview over key baseline characteristics of risdiplam before and after matching, compared to the ENDEAR baseline characteristics (mean of both arms). The risdiplam baseline characteristics show that matching to the ENDEAR trial characteristics was successful. For all three selected matching factors (age at first dose, disease duration at screening and CHOP-INTEND score at baseline), risdiplam baseline characteristics post-matching were equal to the ENDEAR baseline characteristics (mean of both arms). The ESS was reduced to 40.6 from a total sample size of 58 FIREFISH patients.

The MAIC analyses showed that after four years of treatment, the children treated with risdiplam (FIREFISH) had a 79% reduction in the rate of death (95% confidence interval [CI] 53–98%), a 79% reduction in the rate of death or permanent ventilation (95% CI 63–90%), and a 66% reduction in the rate of SAEs (95% CI 48–81%) compared to children treated with nusinersen (ENDEAR). Furthermore, children treated with risdiplam also had a 43% (95% CI 20–74%) higher rate of achieving a HINE-2 motor milestone response and a 172% (95% CI 100–210%) higher rate of achieving a ≥4-point improvement on the CHOP-INTEND scale. While adjustments were made for known prognostic factors, as in any non-randomised comparison, results may be confounded by unobserved baseline differences between groups. These results are consistent with previous findings from indirect treatment comparisons conducted using 1, 2, and 3 years of follow-up data.

Table 65. FIREFISH baseline characteristics post ENDEAR-matching

	Pre-matching			Post-matching	
	ENDEAR[b]	**FIREFISH[c]**	**Difference (ENDEAR vs FIREFISH)**	**FIREFISH**	**Difference (ENDEAR vs FIREFISH)**
Sample size (†ESS)	80[a]	58	22	40.6	39.4
Mean age at first dose, months (SD [range])	5.4 (NR [1.4–8.0])	5.3 (1.5 [2.2–7.0])	0.1	5.4	0
Gender (female)	53.8%	56.9%	3.0%	66.7%	13.0%
Mean age at symptom onset, months (SD [range])	2.0 (NR [0.5–4.5])	1.7 (0.7 [0.9–3.0])	0.3	1.7	0.3

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Mean disease duration, weeks (SD [range])	13.2 (NR [0–25.9])	13.0 (5.9 [1.0–23.3])	0.2	13.2	0
Mean age at diagnosis, days (SD [range])	88.2 (NR [0–203.0])	88.9 (42.3 [28.0–185.0])	0.7	94.9	6.7
Mean CHOP-INTEND score (SD [range])	26.6 (8.1 [NR])	22.5 (6.8 [8.0–37.0])	4.1	26.6	0
Mean HINE-2 score (SD [range])	1.3 (1.1 [NR])	0.9 (1.0 [0–5.0])	0.4	1.2	0.1
Patients with invasive ventilation or NIV[d]	26.0%	29.3%	3.3%	19.6%	6.4%
Patients with nutritional support[e]	9.0%	8.6%	0.4%	6.1%	2.9%

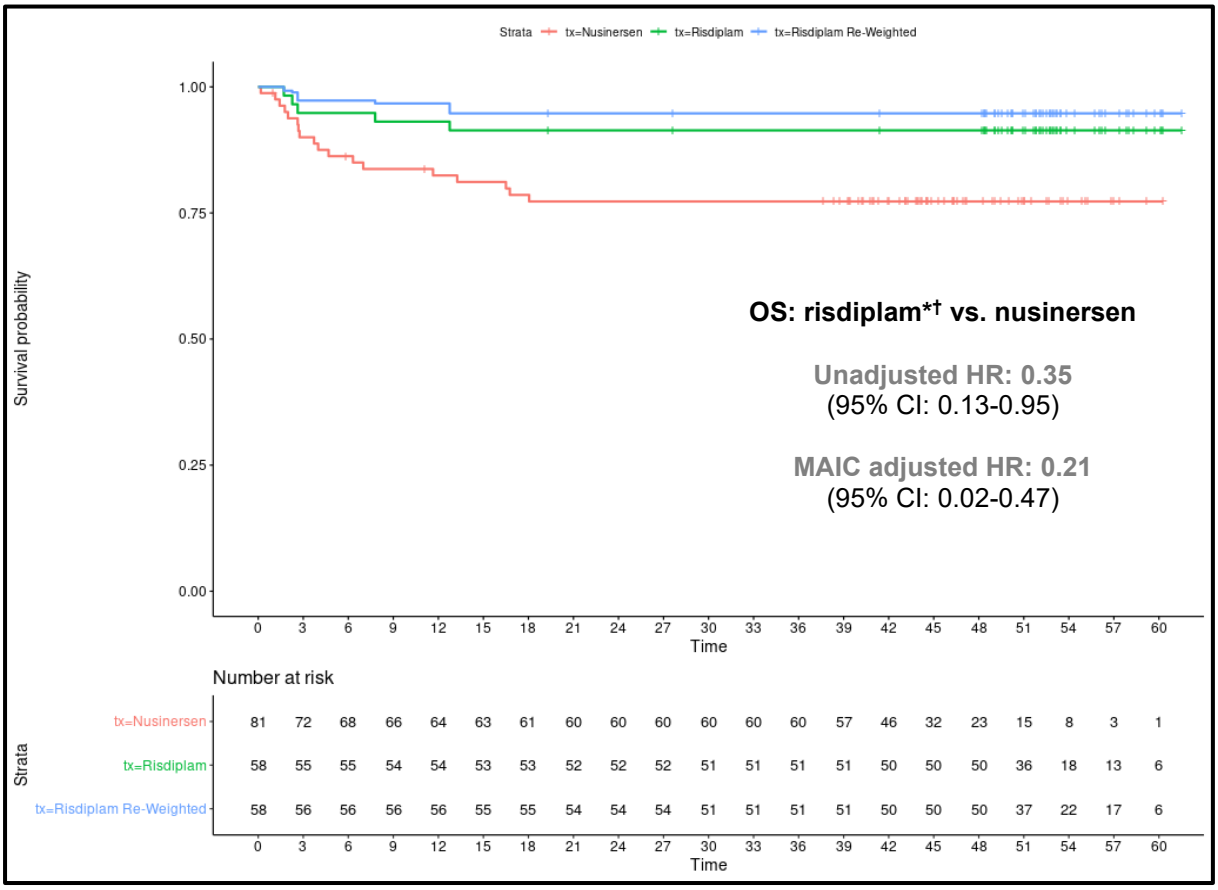
[†]ESS is an estimate of the sample size of a weighted population.
[a]Matching was conducted using MAIC methodology with the following adjustment factors: age at first dose, baseline CHOP-INTEND score and disease duration.
[b]Matching involved weighting the baseline characteristics of 80 patients who were enrolled in SHINE-ENDEAR; one additional patient received their first dose of nusinersen in the SHINE trial, but baseline characteristics for this patient were not available.
[c]Includes patients from the 'high-dose' (pivotal dose) cohort of Part 1 (*n* = 17) and all patients from FIREFISH Part 2 (*n* = 41).
[d]SHINE-ENDEAR: undefined. FIREFISH: airway clearance or BiPAP support for <16 hours/day.
[e]SHINE-ENDEAR: the use of a GI tube. FIREFISH: the ability to swallow/GI tube feeding. Baseline data on GI tube feeding were not available for most patients in Part 1, as the questionnaire was only introduced 6 months after the start of the study. Ability to swallow was used as a proxy for tube feeding for these patients.
CHOP-INTEND, Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders; ESS, effective sample size; HINE-2, Hammersmith Infant Neurological Examination, Section 2.

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Overall survival

Survival outcomes were assessed using data from the 4-year FIREFISH data cuts and approximately 5-year (4.9 years) ENDEAR-SHINE data (see Table 53) (from the G-BA dossier (126). The performed MAIC suggests children with type 1 SMA treated with risdiplam may have a 79% reduction in the rate of death compared with children treated with nusinersen, see Figure 16.

Figure 16. Overall survival Kaplan-Meier curves



*HRs of risdiplam versus nusinersen were calculated using Cox proportional-hazards models. An HR <1 favours risdiplam over comparator. 95% CIs that do not span 1 indicate a statistically significant difference.

There is no exact count data for comparator events publicly available and therefore a comparison between odds ratios for interventions was not possible. As data has been extracted from the G-BA dossier, only the Kaplan-Meier curves were available to provide direct time-to-event analyses and hazard ratios have been used.

Event-free survival

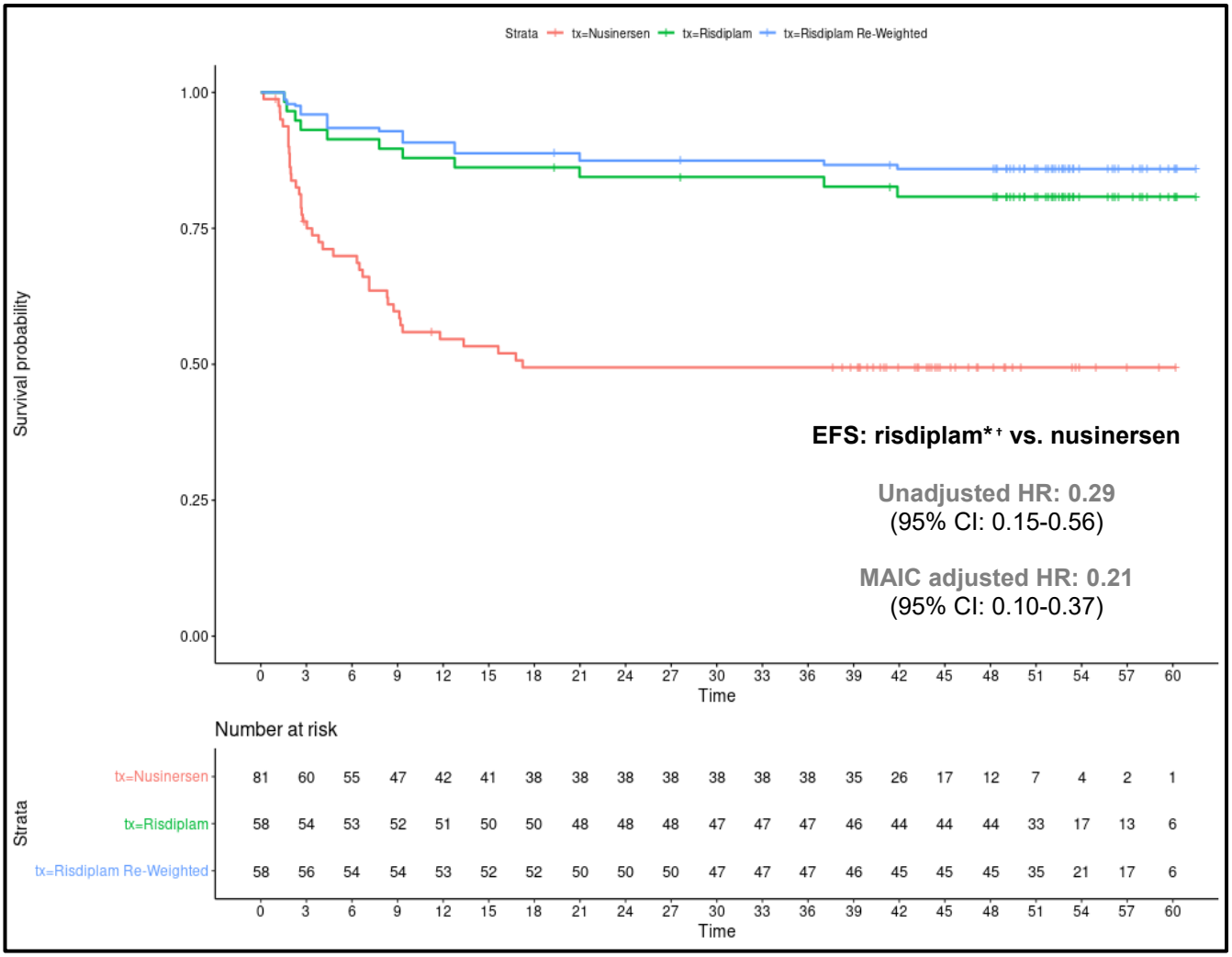
Same as overall survival, time to event analyses were conducted for the time to death or need for permanent ventilation survival endpoints (whichever occurred first) and hazard ratios were calculated based on a Cox proportional hazards model. Analyses were conducted using the 4 year FIREFISH data cut off and approximately 5 year (4.9 years) ENDEAR-SHINE data (see Table 53). Differences in follow-up duration are less relevant for survival analyses as information over all time points is taken into account, unlike in analyses of binary outcomes.

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The analysis results of event-free survival are provided in

Figure 17. The results of both the unadjusted (naïve) and MAIC are similar suggesting that risdiplam is more effective than nusinersen. The hazard ratio of risdiplam versus nusinersen is 0.29 (95% CI: 0.15-0.56) in naïve analysis and 0.21 (95% CI: 0.10-0.37) in the MAIC analysis.

Figure 17. Event free survival Kaplan-Meier curves



*Event free is defined as time to death or need for permanent ventilation, whichever occurred first. In FIREFISH, permanent ventilation was defined as ≥16 hours of NIV/day or intubation for >21 consecutive days in the absence of, or following the resolution of, an acute reversible event or tracheostomy. In SHINE-ENDEAR, permanent ventilation was defined as either tracheostomy or ≥16 hours of ventilation/day continuously for >21 days in the absence of an acute reversible event. †HRs of risdiplam versus nusinersen were calculated using Cox proportional-hazards models. An HR <1 favours risdiplam over comparator. 95% CIs that do not span 1 indicate a statistically significant difference.

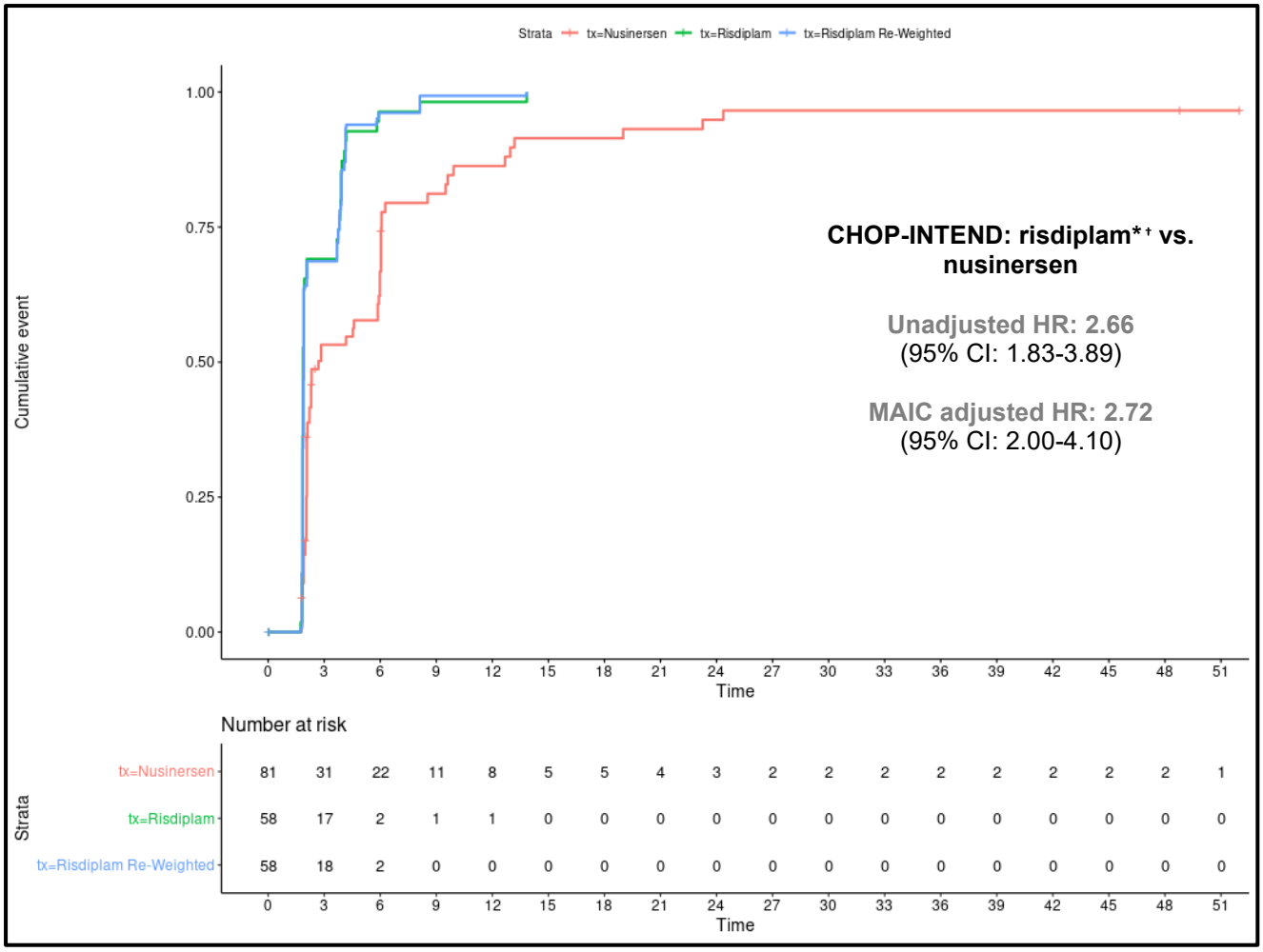
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CHOP-INTEND

ITC analyses were conducted for the CHOP-INTEND score improvement of at least 4 points. Analyses were conducted using FIREFISH 4 year data cut off and ENDEAR-SHINE 4.5 year as reported from the cumulative density plot (see Table 53).

Figure 18 displays the results from the MAIC, which suggests that type 1 SMA children treated with risdiplam may be more likely to see an earlier CHOP-INTEND response compared to those treated with nusinersen.

Figure 18. CHOP-INTEND response improvement of ≥4 points in score from baseline



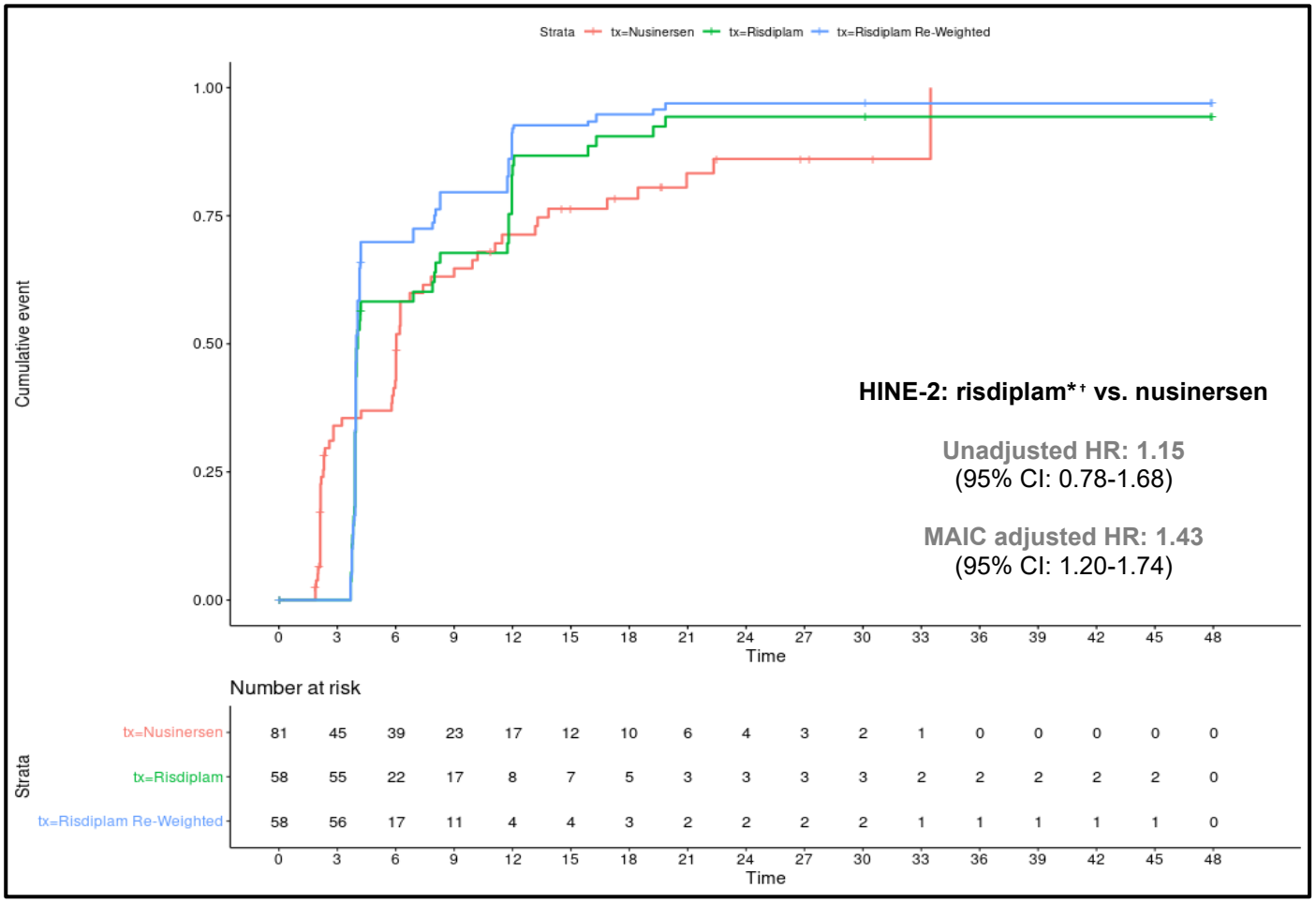
*A CHOP-INTEND response is defined as an improvement of ≥4 points in CHOP-INTEND score from baseline. †HRs of risdiplam versus nusinersen were calculated using Cox proportional-hazards models. Patients were censored at the last recorded visit. Three patients in FIREFISH died before any post-baseline visit and were therefore censored at time 0. An HR >1 favours risdiplam over comparator.
95% CIs that do not span 1 indicate a statistically significant difference.

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HINE-2

ITC analyses were conducted for the HINE-2, where a participant was considered as a responder if a higher number of motor milestones show improvement than show worsening. An improvement in domains is defined as a ≥2-point increase in the ability to kick (or maximal score) or a ≥1-point increase in head control, rolling, sitting, crawling, standing or walking. Whereas, worsening is defined as a ≥2-point decrease in the ability to kick (or lowest score) or a ≥1-point decrease in head control, rolling, sitting, crawling, standing or walking. Analyses were conducted using FIREFISH 4 year data cut off and ENDEAR-SHINE 2.7 year data as reported from the cumulative density plot (see Table 53). Figure 19 displays the results from the MAIC suggesting that children with type 1 SMA treated with risdiplam may be more likely to have a HINE-2 motor milestone response compared with those treated with nusinersen.

Figure 19.HINE-2 responder improvement from baseline.



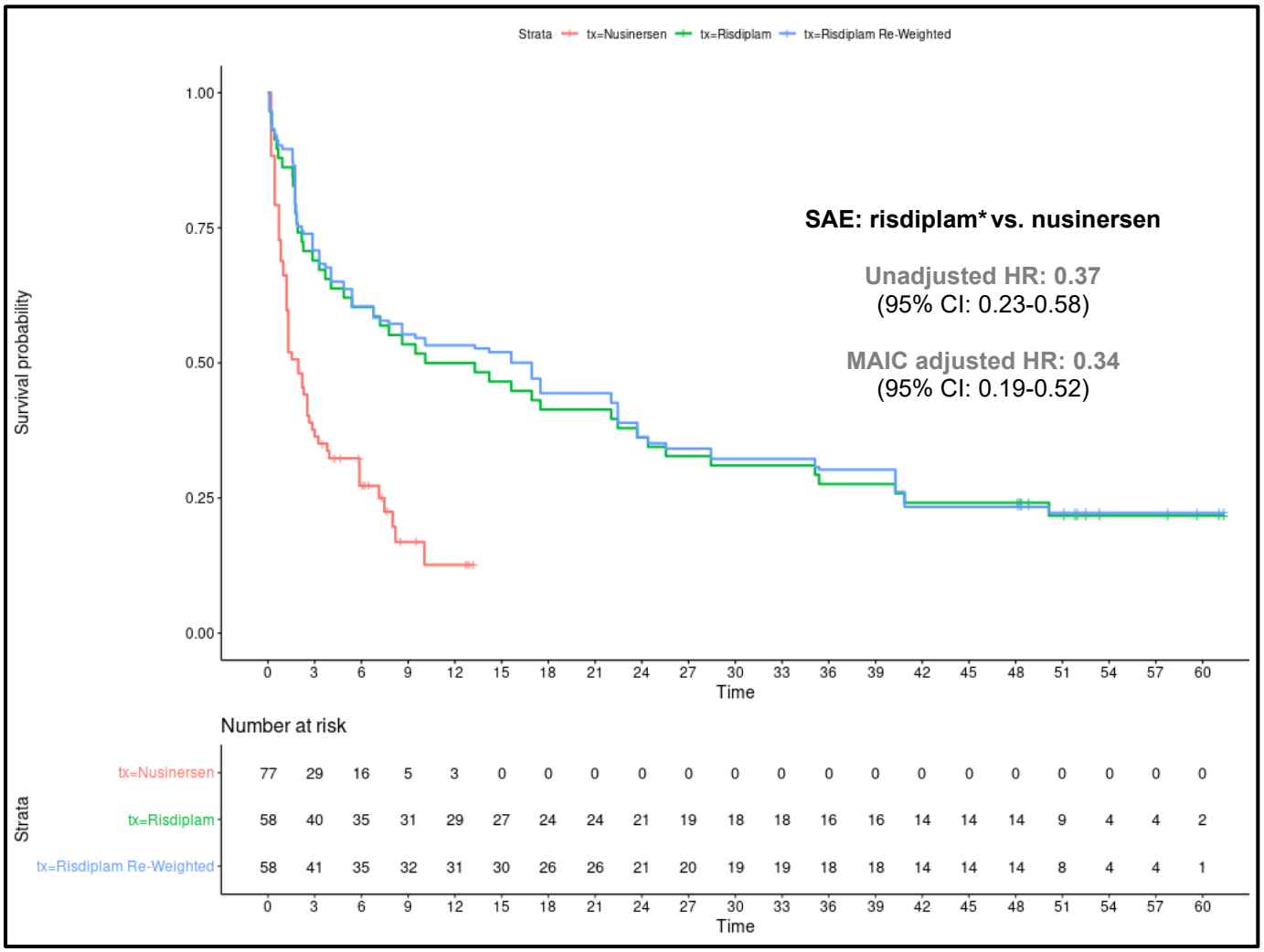
*A child is classed as a HINE-2 responder if more motor milestones show improvement than show worsening.
†HRs of risdiplam versus nusinersen were calculated using Cox proportional-hazards models. Children were censored at the last recorded visit. Three children in FIREFISH died before any post-baseline visit and were therefore censored at time 0. An HR >1 favours risdiplam over comparator. 95% CIs that do not span 1 indicate a statistically significant difference.

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Adverse events

ITC analyses were conducted in the absence of head-to-head data to compare risdiplam to nusinersen. The severe adverse events (SAE) between trials can be seen in Figure 20. The data from the naïve comparison and MAIC both suggest the type 1 SMA patients treated with risdiplam may have a longer time to experiencing any SAE compared with children treated with nusinersen.

Figure 20. Time to experiencing SAEs between risdiplam and nusinersen.



*HRs of risdiplam versus nusinersen were calculated using Cox proportional-hazards models. Patients were censored at the earliest date from: CCOD, death date, study withdrawal date and last treatment dose +30 days. An HR <1 favors risdiplam over nusinersen. 95% CIs that do not span 1 indicate a statistically significant difference.

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Risdiplam vs onasemogene aberparvovec

Table 66 provides an overview of the key baseline characteristics of risdiplam before and after matching compared to the STR1VE-US baseline characteristics (mean of both arms). The risdiplam baseline characteristics show that matching to the STR1VE-US trial characteristics was not feasible. After the matching-adjustment using the three selected matching factors (age at first dose, age at symptom onset and CHOP-INTEND score at baseline), the ESS was reduced to only 2.1 patients. This is due to the age restriction of <6 months at first dose in the enrolment criteria of STR1VE-US, and the differences in CHOP-INTEND score at baseline (FIREFISH range: 8-37; STR1VE-US range: 17-52). Imbalances remained between the re-weighted FIREFISH and STR1VE-US baseline characteristics. Patients were still on average 27 days older at first dose. This difference is important, given that early initiation of treatment was identified to be one of the key effect modifiers for survival and motor function development in Type 1 SMA (111).

Table 66. FIREFISH baseline characteristics post STR1VE-US matching

Baseline characteristic	Pre-Matching: Risdiplam (Pooled FIREFISH)	Post-matching: Risdiplam (Pooled FIREFISH matching-adjusted to STR1VE-US)	OA (STR1VE-US)
Sample size (ESS)	58	58 (2.1)	22
Mean age at first dose in days	163	141	114
Female gender	57%	100%	55%
Mean age at symptom onset in days	51	73	60
Mean age at diagnosis in days	89	104	64
Mean score on CHOP-INTEND	22.47	31.01	32.00
Patients with ventilatory support	29%	0%	0%

There are also clear imbalances between FIREFISH and STR1VE-EU, such as age at first dose, see Table 67, which provides an overview over key baseline characteristics of risdiplam before and after matching, compared to the STR1VE-EU baseline characteristics (mean of both arms). Following matching, the FIREFISH sample size was reduced to 15.32 patients (resulting in approximately a 75% reduction) rendering the MAIC unfeasible. Furthermore, even post matching, differences in baseline values for the remaining characteristics were still evident.

Table 67. FIREFISH baseline characteristics post STR1VE-EU matching

	Pre-Matching: Risdiplam (Pooled FIREFISH)[b]	Post-matching: Risdiplam (Pooled FIREFISH matching-adjusted to STR1VE-EU)	OA (STR1VE-EU)
Sample size ([†]ESS)	62	15.32	33[a]

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Mean age at first dose, months (SD [range])	5.4 (1.5 [2.2–7.0])	4.1 (1.0)	4.1 (1.3 [1.8–6.0])
Gender (female)	60%	62%	58%
Mean age at symptom onset, months (SD [range])	1.7 (0.7 [0.9–3.0])	1.53 (0.6)	1.6 (0.9 [0.0–4.0])
Mean age at diagnosis, days (SD [range])	90.1 (41.9 [28.0–185.0])	75.57 (34.6)	81.3 (36.4 [26.0–156.0])
Mean CHOP-INTEND score (SD [range])	22.3 (6.8 [8.0–37.0])	27.9 (4.7)	27.9 (8.3 [14.0-55.0])
Patients with intact swallowing	97% (n=61)	99%	97%
Reported ventilatory support	21%	13%	27%

Outcome of the indirect comparison of FIREFISH versus STR1VE-US/EU

For the planned outcomes: event-free survival, BSID-III domains, CHOP-INTEND (proportion achieving scores and change from baseline score), requirement for permanent ventilation, nutritional support and safety events, none of these showed any statistical differences post-matching between risdiplam and OA at the 12 month time point. Results have been provided below.

For comparison to STR1VE-US, since a MAIC was not feasible owing to the small overlap in baseline characteristics between the patient populations, ITC analyses were conducted using the STC methodology to estimate relative effect estimates of risdiplam versus OA. For STR1VE-EU, simulated treatment comparison (STC) was originally listed as an alternative comparative method should the unanchored MAIC not be successful, however given the large differences between baseline characteristics, the regression modelling of STC could lead to biased conclusions, and so it was not performed.

Event-free survival

Time-to-event analyses were conducted on the ventilation-free survival endpoint and hazard ratios were calculated by fitting exponential models separately to the risdiplam and OA data. Since time-to-event data OA in STR1VE-US was defined as time from birth, risdiplam data was also re-calculated as time from birth for the purpose of these analyses.

For STR1VE-US data, the analysis results of ventilation-free survival are provided in

Figure ***21*** and Table 68. The naïve analysis yielded a hazard ratio of 1.53 (95%CI: 0.72; 2.66) which decreased to 0.94 (95%CI 0.03; 4.06) in a “STR1VE-US-like” population using STC. The 14-months survival probability, one of the co-primary endpoints in STR1VE-US, was 91% for OA, 90% for risdiplam in the naïve analysis, and 93% for risdiplam in the STC.

Figure 21. Ventilation-free survival Kaplan-Meier curves (STC vs STR1VE-US)

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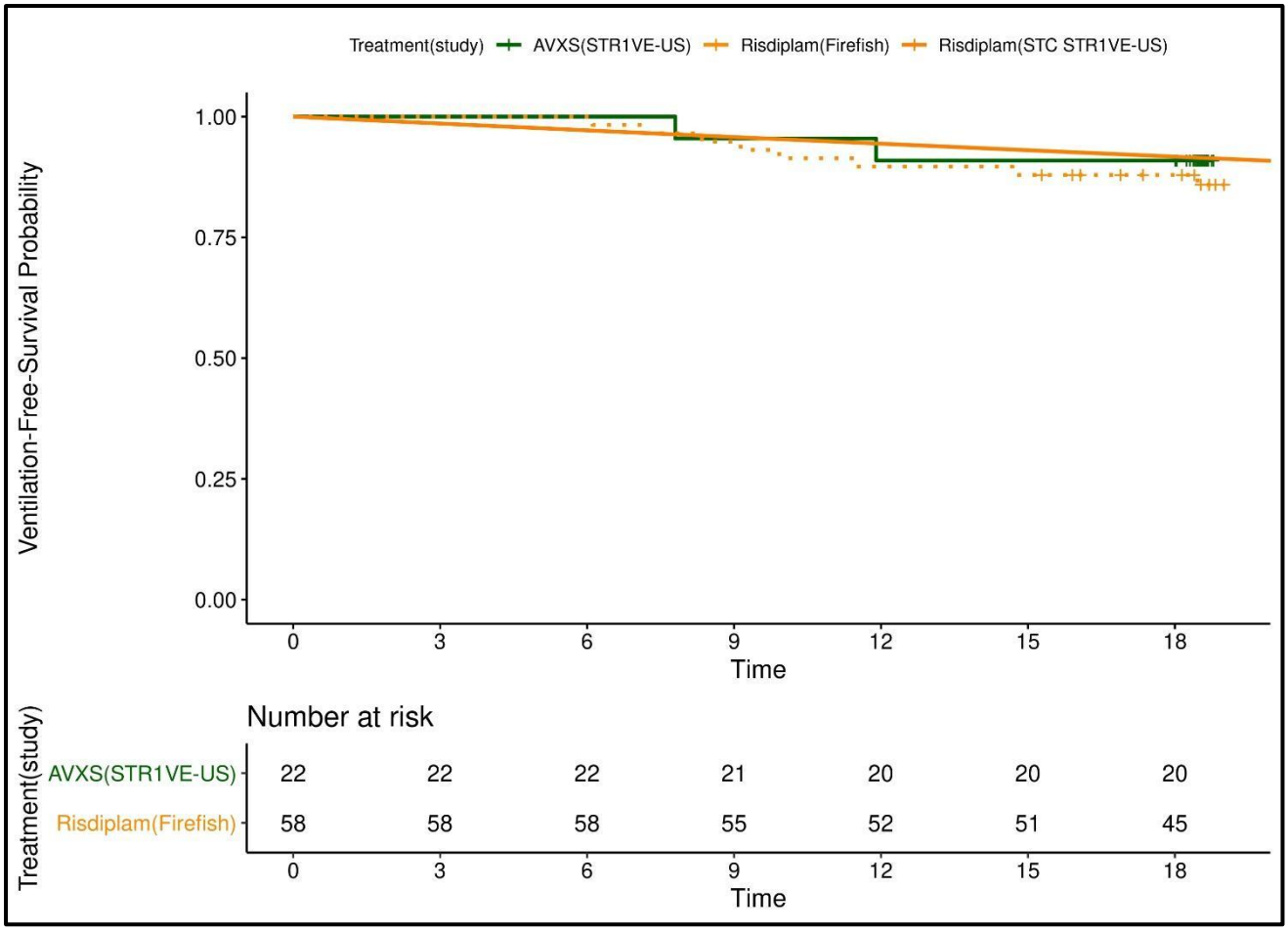


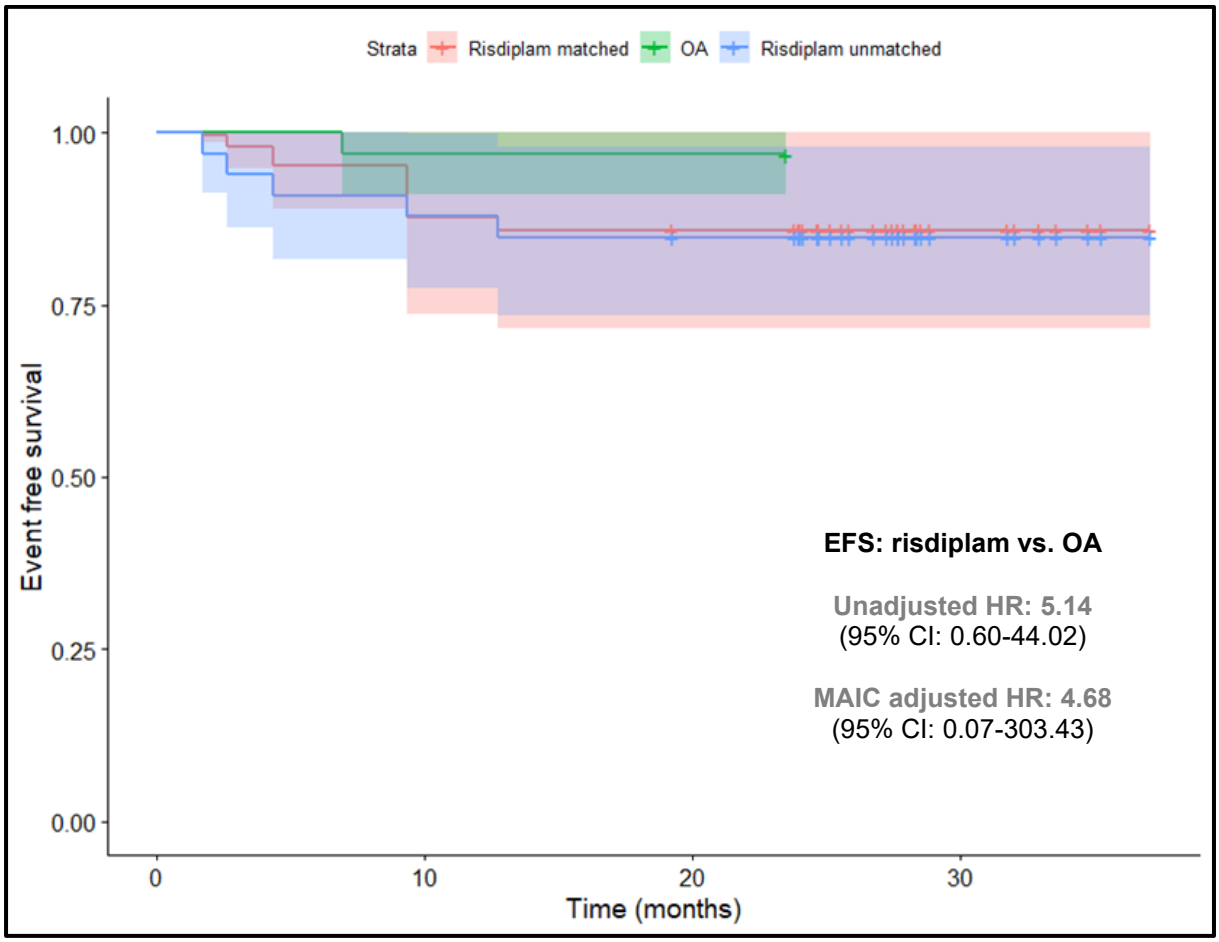
Table 68. Ventilation-free survival hazard ratios (STC vs STR1VE-US)

Comparator (STUDY)	STC		
	Sample size	Survival probability at 14-months of age	Hazard Ratio for Risdiplam against Comparator (95%CI)
Risdiplam (FIREFISH)	58	93%	-
OA (STR1VE-US)	22	91%	0.936 (0.033; 4.064)

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For comparison to STR1VE-EU, the unanchored MAIC showed no detectable difference in event-free survival between risdiplam and OA (Figure 22). The unadjusted point estimate HR was 5.14 comparing risdiplam with OA treated patients, however this result is not statistically significant and highly unstable due to the very large uncertainty as shown in the 95% confidence interval (0.6 – 44.02). The difference between the treatments shrunk after matching (i.e., treatments perform more similarly), and the confidence intervals became much wider. There were very few events with both treatments, and these estimates are highly uncertain and not statistically significant.

Figure 22. Event-free survival Kaplan-Meier curves (vs STR1VE-EU)



BSID-III

For STR1VE-US, there were slight differences in the time points and definitions of outcomes which may bias results in favour of OA. Achievement of the sitting without support over 30 second milestone was assessed at the 12-months from baseline visit for risdiplam and at the 18-months of age visit for OA. As mean age at first dose in STR1VE-US was 3.7 months, the 18-months of age visit corresponds to approximately 14 months (range: 12-18) from baseline. Hence, assessment of this endpoint was conducted earlier for risdiplam compared to OA. Similarly, for the other BSID-III endpoints, OA outcomes are defined as achievements by the 31 Dec 2019 cut off, while risdiplam outcomes are at the 12-months visit. It is unclear if achievement of these milestones for OA were also confirmed at the 18-months of age visit.

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Results of the STC analyses are presented in Table 69. On the sitting without support and head control endpoints, the STC corresponding ORs increased to 0.75 (95%CI 0.15; 5.26) and 0.65 (95%CI 0.07; 5.38) with confidence intervals including ORs >1. On the rolling back to sides endpoint, the analysis resulted in an OR of 2.09 (95%CI 0.42; 13.73) in the STC. On the standing with assistance endpoint, ORs were 5.24 (0.35; 1677.00) in the STC.

Table 69. BSID-III motor milestones results (STC vs STR1VE-US)

Milestone	Comparator (STUDY)	STC			
		Number of responders / Sample size (% Responders [95%CI])	Number of responders / Sample size (% Responders [95%CI])	Odds Ratio for Risdiplam against Comparator (95%CI)	Risk Ratio for Risdiplam against Comparator (95%CI)
Sitting without support over 30 seconds (Item 26)	Risdiplam* (FIREFISH)	11/58 (19% [10;29])	30.17/58 (52%% [21;88])	-	-
	OA† (STR1VE-US)	13/22 (59% [36;79]°)	13/22 (59% [36;79]°)	0.750 (0.149; 5.264)	0.880 (0.355; 1.682)
Head control for 3 seconds (Item 4)	Risdiplam* (FIREFISH)	33/58 (57% [45;69])	46.60/58 (80% [55;97])	-	-
	OA‡ (STR1VE-US)	19/22 (86% [65;97]°)	19/22 (86% [65;97]°)	0.645 (0.067; 5.375)	0.930 (0.623; 1.261)
Rolling back to sides (Item 20)	Risdiplam* (FIREFISH)	27/58 (47% [34;60]°)	43.57/58 (75% [46;94]°)	-	-
	OA‡ (STR1VE-US)	13/22 (59% [36;79]°)	13/22 (59% [36;79]°)	2.091 (0.425; 13.725)	1.271 (0.718; 2.088)
Standing with assistance (Item 33)	Risdiplam* (FIREFISH)	3/58 (5% [0;12])	11.59/58 (20% [0;100])	-	-
	OA‡ (STR1VE-US)	1/22 (5% [0;23]°)	1/22 (5% [0;23]°)	5.244 (0.352; 1677.00)	4.396 (0.130; 36.036)

Key: CI, Confidence Intervals (Bootstrap; N=1,000 Samples)
* Achievement at the 12 months from baseline visit
† Achievement at the 18 months of age visit (12-15 months from baseline)
‡ Achievement by the 31 Dec 2019 cut off
° Clopper-Pearson Cis

For STR1VE-EU, no statistical differences (at 95% CI) were observed post matching for BSID-III between risdiplam and OA at month 12 (the 12-month visit for FIREFISH was the closest point in time to compare to the endpoints at age 18 months in STR1VE-EU). Results of the unanchored MAIC can be seen in Table 70.

For walking with assistance, standing alone, crawling, and pulls to stand, no FIREFISH patients had an event, thus OR could not be calculated, either before or after matching. It should also be noted that for ability to roll, only one patient in each study attained this and so this result is also highly uncertain.

For other endpoints, before matching, patients treated with risdiplam were less likely to achieve motor milestones compared with OA by study month 12, although this was only significant for sitting without support, as all other confidence intervals overlap unity. After matching, the difference in the odds of achieving these endpoints shrunk between

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treatments, except for standing with assistance. Patients treated with risdiplam were more likely to achieve standing with assistance and the ability to roll, and less likely than OA to achieve sitting without support and head control, although none of these results are statistically significant.

Table 70. BSID-III motor milestones results (vs STR1VE-EU)

Analysis, proportion:	N events (risdiplam pre-matching)	N events (OA)	Pre-matching OR (95%CI)	Post-matching OR (95%CI)
Sitting Without Support	11/58 (19%)	16/33 (48%)	0.25 (0.10, 0.65)	0.77 (0.20, 2.94)
Head Control	34/58 (59%)	23/33 (70%)	0.62 (0.25, 1.55)	0.79 (0.05, 13.43)
Standing With Assistance	3/58 (5%)	2/33 (6%)	0.85 (0.13, 5.46)	2.43 (0, 0) †
Rolls	1/58 (2%)	1/33 (3%)	0.53 (0.22, 1.30)	1.20 (,)†
Walking with Assistance	0/58	1/33 (3%)	0.00 (,)†	0.00 (,)†
Standing Alone	0/58	1/33 (3%)	0.00 (,)†	0.00 (,)†
Crawling	0/58	1/33 (3%)	0.00 (,)†	0.00 (,)†
Pulls to Stand	0/58	1/33 (3%)	0.00 (,)†	0.00 (,)†
†Confidence intervals are not stable due to lack of or absence of number of events.				

CHOP-INTEND

STC analyses were conducted for two CHOP-INTEND endpoints: CHOP-INTEND score improvement of at least 4 points and CHOP-INTEND score achievement of at least 40 points.

Results of the STC analyses are presented in Table 71. On the CHOP-INTEND score improvement ≥4 points endpoint, the analysis yielded an OR of 15.04 (95%CI 0.70; 18366.51) in the STC. On the CHOP-INTEND score achievement ≥40 points endpoint, ORs were 2.30 (0.23; 54.09) in the STC.

Table 71. CHOP-INTEND results (STC vs STR1VE-US)

Endpoint	Comparator (STUDY)	STC		
		Number of responders / Sample size (% Responders [95%CI])	Odds Ratio for Risdiplam against Comparator (95%CI)	Risk Ratio for Risdiplam against Comparator (95%CI)
CHOP-INTEND score	Risdiplam* (FIREFISH)	57.40/58 (99% [90;100])	-	-

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improvement ≥4 points	OA† (STR1VE-US)	19/22 (86% [65;97]°)	15.038 (0.697; 18366.512)	1.146 (0.981; 1.435)
CHOP-INTEND score achievement ≥40 points	Risdiplam* (FIREFISH)	54.28/58 (94% [77;100])	-	
	OA† (STR1VE-US)	19/22 (86% [65;97]°)	2.304 (0.233; 54.091)	1.084 (0.872; 1.360)

For STR1VE-EU, no statistical differences (at 95% CI) were observed post matching for CHOP-INTEND between risdiplam and OA at month 12 (the 12-month visit for FIREFISH was the closest point in time to compare to the endpoints at age 18 months in STR1VE-EU). Results of the unanchored MAIC can be seen in Table 72.

For the proportion achieving a CHOP-INTEND score of 40 and 50, before matching, patients treated with risdiplam were less likely to achieve both compared to OA, although this was only significant for CHOP 50. Mean positive change from baseline at month 14 was higher for patients treated with risdiplam compared to OA, although this was not statistically significant.

After matching, the difference in the odds of achieving CHOP 40 or CHOP 50 did not change significantly, but shrunk slightly between treatments. None of these results are statistically significant, and the confidence intervals became noticeably wider for the proportion achieving CHOP 40 and CHOP 50. The difference in mean change from baseline also shrunk between treatment arms.

Table 72. CHOP-INTEND results (vs STR1VE-EU)

Analysis	Type of endpoint	N events (risdiplam pre-matching)	N events (OA)	Pre-matching (95%CI)	Post-matching (95%CI)
Proportion achieving CHOP 40	Log odds ratio calculated at study month 12	35/58 (60%)	24/33 (73%)	0.57 (0.22, 1.46)	1.48 (0.02, 96.54)
Proportion achieving CHOP 50		9/58 (16%)	14/33 (42%)	0.25(0.09, 0.68)	0.3 (0.02, 175.91)
Proportion achieving CHOP 58		0/58	3/33 (9%)	0.00 (,)†	0.00 (,)†
Change from baseline in CHOP at month 14	Mean change from baseline	Mean change from baseline: +20.2	Mean change from baseline: +18.3	1.98 (-3.89, 7.86)	0.33 (-6.6 , 7.27)
†Confidence intervals are not stable due to lack of or absence of number of events.					

Safety

Indirect treatment comparison analyses were conducted for three safety outcomes: Any AE, any AE leading to discontinuation and any serious AE.

Results of the STC analyses are presented in Table 73. On the any AE and any AE leading to discontinuation endpoints, the STC corresponding ORs decreased to 0.29 (95%CI 0.04; 2.60) and 0.13 (95%CI 0.00; 3.28). On the any serious AE endpoint, ORs were 1.02 (95%CI 0.22; 5.08) in the STC.

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Table 73. Safety results (STC vs STR1VE-US)

Endpoint	Comparator (STUDY)	STC		
		Number of events / Sample size (% with AE [95%CI])	Odds Ratio for Risdiplam against Comparator (95%CI)	Risk Ratio for Risdiplam against Comparator (95%CI)
Any adverse event	Risdiplam (FIREFISH)	54.35/58 (94% [64;100])	-	-
	OA (STR1VE-US)	22/22 (100% [85;100]°)	0.293* (0.039; 2.600)	0.950* (0.652; 1.014)
Any adverse event leading to discontinuation	Risdiplam† (FIREFISH)	0.73/58 (1% [0,11])	-	-
	OA (STR1VE-US)	2/22 (9% [1;29]°)	0.128 (0.000; 3.283)	0.139 (0.000; 2.435)
Any serious adverse event	Risdiplam (FIREFISH)	26.58/58 (46% [19,75])	-	-
	OA (STR1VE-US)	10/22 (45% [24;68]°)	1.015 (0.225; 5.075)	1.008 (0.392; 2.199)

For STR1VE-EU, no statistical differences (at 95% CI) were observed post matching for safety outcomes between risdiplam and OA at month 12 (the 12-month visit for FIREFISH was the closest point in time to compare to the endpoints at age 18 months in STR1VE-EU). Results of the unanchored MAIC can be seen in Table 74.

There was no difference in the 'any AE' endpoint before and after matching for patients treated with risdiplam because everyone experienced at least one AE. Patients treated with risdiplam are more likely to experience any serious AE compared with those treated with OA both before and after matching, although this is not statistically significantly different between treatments, and the difference shrinks after matching.

Table 74.Safety results (vs STR1VE-EU)

Analysis, proportion:	N events (risdiplam pre-matching)	N events (OA)	Pre-matching OR (95% CI)	Post-matching OR (95% CI)
Any adverse event	62/62 (100%)	32/33 (97%)	Non-calculable (,)†	Non-calculable (,)†
Any serious adverse event	44/62 (71%)	19/33 (58%)	1.80 (0.74, 4.40)	1.17 (0.12, 11.71)
†Confidence intervals are not stable due to lack of or absence of number of events.				

For both STR1VE comparisons, the results from the ITC analyses did not provide sufficient evidence to draw concrete conclusions on the relative efficacy between the two treatments with regards to survival outcomes, motor function, achievement of motor milestones and the incidence of SAEs, following adjustment for difference in age and baseline motor function scores. As can be seen in Table 67, there is limited overlap between the two populations due to the differences observed in the baseline characteristics, specifically for the mean age at first dose and the mean CHOP-INTEND score. Once the matching was performed, the

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numerical differences were reduced, however the estimation uncertainty for most outcomes either remains large or increases further. Based on the above results presented, the comparison between risdiplam and OA was deemed to not be feasible or plausible to draw robust conclusions from. Even with the STC performed vs STR1VE-US (129), there was still a lack of sufficient evidence to draw concrete conclusions on the relative efficacy between the two treatments with regards to survival outcomes, motor function, achievement of motor milestones and the incidence of SAEs after adjusting for differences in age and baseline motor function score.

Type 2/3 SMA patients

For the initial 1-year follow-up for SUNFISH and CHERISH, both trials have a common comparator in placebo and sham arms (assuming that these are similar), therefore an anchored MAIC has been conducted for this 12 month period. However, from year 2 onwards as patients assigned to the respective placebo and sham arms switch to receive active treatment (either risdiplam or nusinersen) there is no longer a control arm to use for an indirect comparison. In the absence of common comparators from year 2 onwards, an unanchored MAIC was the appropriate comparison method to indirectly assess the relative efficacy of risdiplam versus nusinersen. No longer term comparison could be provided to BSC (compared to what was presented in TA755) as patients in SUNFISH and CHERISH switched to active treatment after 12 months.

Comparison up to month 12

(i) Base Case Analysis: Results from the anchored MAIC

Table 75 provides an overview of key baseline characteristics of the SUNFISH subset before and after matching to the CHERISH means of the three matching factors, age at screening, RULM baseline score and SMN2 copy number.

Table 75. SUNFISH subset baseline characteristics pre and post CHERISH-matching

Baseline characteristic	Pre-Matching (SUNFISH subset°)		Post-matching (SUNFISH subset° matching-adjusted to CHERISH)		Nusinersen & Sham (CHERISH)
	Risdiplam	Placebo	Risdiplam	Placebo	
Sample size (ESS)	43	25		25 (8.8)	121
Female gender	53%	44%	61%	43%	53%
Mean age at screening (years)	5.0	5.3	3.7	3.7	3.7*
Mean age at symptom onset (months)	13.7	16.6	12.7	13.4	10.3*
Mean symptoms duration (months)	46.3	46.8	31.6	30.7	36.0*
Mean HFMSE baseline score	24.21	23.12	21.99	22.36	21.57
Mean RULM baseline score	21.65	22.28	19.11	19.07	19.07
Mean SMN2 copy number	3.09	3.08	3.00	2.94	2.94
% 2 copies	0%	4%	0%	7%	8%
% 3 copies	91%	84%	100%	91%	88%
% 4 copies	9%	12%	0%	1%	2%

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% Unknown	0%	0%	0%	0%	2%
*In the absence of reported means, means for the overall CHERISH population were calculated as a weighted average of the medians for the purpose of these analyses. °Patients from SUNFISH Part 2 aged ≤9 years at screening, with a HFMSE score ≥10 at baseline, and without severe scoliosis.					

In the placebo arm, matching factors were perfectly matched to the means of CHERISH. However, the matching was at the expense of the ESS which was reduced to <10 patients from 25 patients in the placebo arm. In the risdiplam arm, matching to CHERISH baseline characteristics resulted in similar means, with small differences in the decimal points of mean RULM baseline score and mean SMN2 copy number. Differences to CHERISH were also reduced in other characteristics that were not directly matched for, such as age at symptom onset, symptoms duration and HFMSE baseline score.

The ESS after matching was reduced to 28.3 from 43 patients in the risdiplam arm of the SUNFISH subset. The total ESS of both arms was estimated to be 37.1, a reduction of 45% from the total sample size of the SUNFISH subset (N=68).

Stepwise exclusion of SMN2 copy number and baseline score as matching factors was tested in order to determine if the ESS could be increased. However, the reduction in the ESS was mainly driven by differences in age and removing matching factors impacted ESS minimally.

RULM

MAIC and NMA analyses were conducted on two RULM endpoints: Change from baseline at 12 months and change from baseline ≥ 2 points at 12 months.

In CHERISH, RULM change from baseline was calculated using an ANCOVA model adjusted for age and baseline score. The same method was applied to calculate results for SUNFISH. ORs for RULM change ≥2 points were not reported from CHERISH, but were calculated from non-imputed data of RULM change from baseline at 12 months. The ORs were not adjusted for age or baseline score, as individual patient data was unavailable from CHERISH. ORs derived from the SUNFISH data were also not adjusted for age and baseline score.

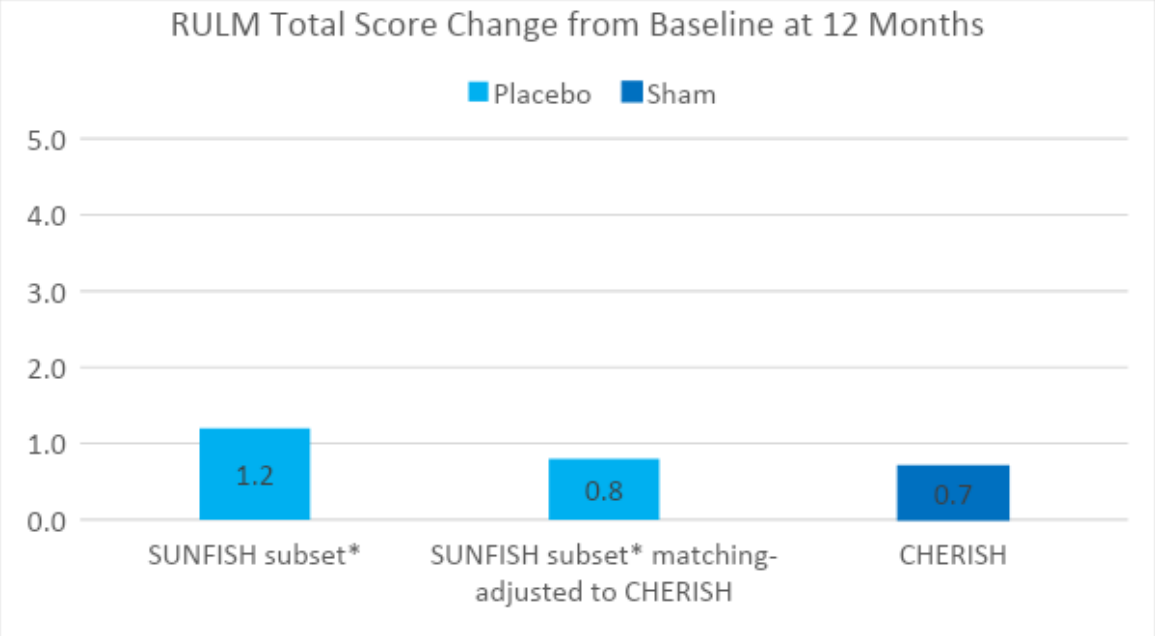
The MAIC analyses are the base case analyses, as they reduce differences in patient characteristics between the SUNFISH subset and CHERISH. Notably, median age at screening was 5 years in the SUNFISH subset and 3-4 years in CHERISH. Given the differences in motor function development and treatment effects in patients younger versus older than 5 years (111), further adjusting for age at screening in the MAIC could reduce bias.

Comparison of control arms is recommended by Signorovitch et al (136) in order to assess the potential for confounding due to differences in trials. Results of the control arms between the two studies showed similar responses between placebo and sham (

Figure ***23*** and Figure 24). The difference in the mean change from baseline at 12 months between the placebo arm outcome in the SUNFISH subset and the sham arm outcome in CHERISH was 0.5 points. This difference decreased to only 0.1 points after matching-adjusting to CHERISH, resulting in very similar control arm outcomes. The difference in proportion of RULM change from baseline ≥2 points between control arms was ±8%-points before and after matching-adjustment.

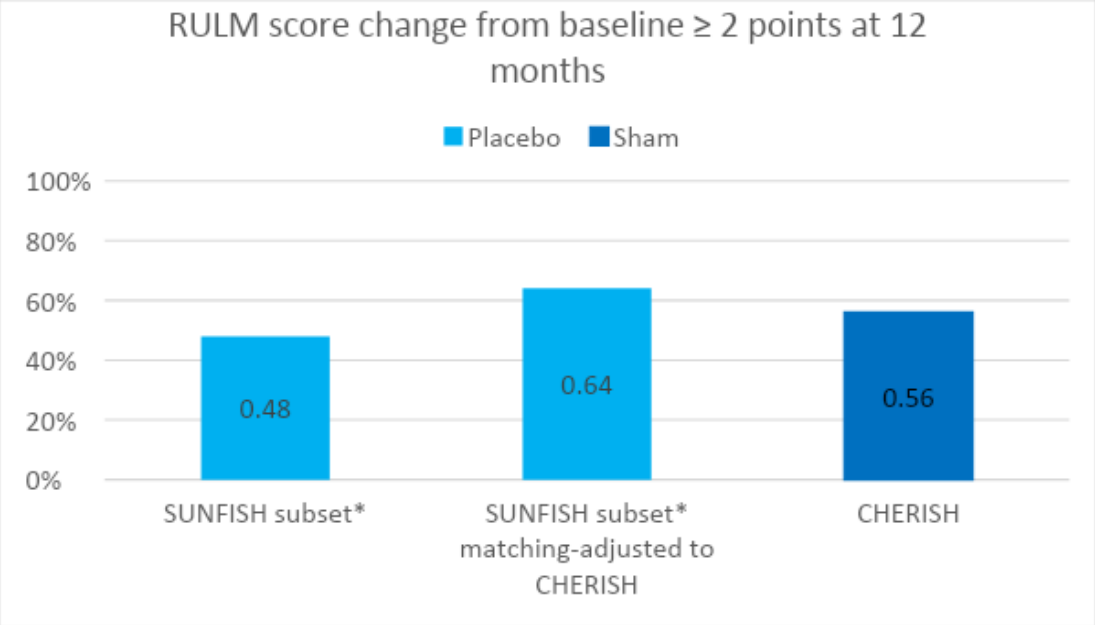
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Figure 23. Control arm outcomes of RULM score change from baseline at 12 months



*Patients from SUNFISH Part 2 aged ≤9 years at screening, with a HFMSE score ≥10 at baseline, and without severe scoliosis.

Figure 24. Control arm outcomes of RULM response (change from baseline ≥2 points) at 12 months



*Patients from SUNFISH Part 2 aged ≤9 years at screening, with a HFMSE score ≥10 at baseline, and without severe scoliosis.

RULM endpoint results from the anchored MAIC are presented in Table 76 and Table 77 for the change from baseline and RULM responder endpoints at 12 months, respectively. The analyses could not differentiate between treatment effects of risdiplam and nusinersen on these endpoints. Confidence intervals included 0 for the mean difference in RULM change

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from baseline and 1 for the odds ratios of being a RULM responder. The point estimates of RULM change from baseline indicated a numerical improvement for nusinersen compared to risdiplam. Given that we could not reliably identify and remove patients with severe contractures from the SUNFISH subset, this mean difference may be a conservative estimate. The point estimate of the odds ratio for being a RULM responder favoured risdiplam over nusinersen; however, the confidence interval was very wide.

Table 76. Anchored MAIC RULM change from baseline at 12 months

Comparator (STUDY)	Anchored MAIC in SUNFISH subset°				
	ESS/N	Change from baseline		Difference against control	Mean difference against comparator (95% CI)
		Intervention	Control		
Risdiplam (SUNFISH subset°)	37.1/68	3.3	0.8	2.5	-0.49 (-3.33; 2.53)*
Nusinersen (CHERISH)	126	3.7	0.7	3.0	-
*N=989/1000 successful bootstrap samples °Patients from SUNFISH Part 2 aged ≤9 years at screening, with a HFMSE score ≥10 at baseline, and without severe scoliosis.					

Table 77. Anchored MAIC RULM responders (score change ≥2 points) at 12 months

Comparator (STUDY)	Anchored MAIC in SUNFISH subset°				
	ESS/N	Proportion responders		OR against control	OR against comparator (95% CI)
		Intervention	Control		
Risdiplam (SUNFISH subset°)	37.1/68	88%	64%	4.1	2.64 (0; 117.94)*
Nusinersen (CHERISH)	118	66%	56%	1.5	-
*N=989/1000 successful bootstrap samples °Patients from SUNFISH Part 2 aged ≤9 years at screening, with a HFMSE score ≥10 at baseline, and without severe scoliosis.					

(ii) Sensitivity Analysis: Results from the NMA

Sensitivity analyses were conducted using Bucher ITC and Bayesian NMA approaches. Bayesian NMAs were conducted using both a fixed effects and a random effects model. The best fit according to DIC was the random effects model (Appendix Section 8.5.3). Bucher ITC results using data from the total SUNFISH Part 2 population were included for comparison purposes.

Table 78 and Table 79 present results from the NMA analyses for RULM change from baseline and RULM responders (change ≥2 points) at 12 months, respectively. In the change from baseline analysis, risdiplam was associated with a significantly smaller change from baseline in the total SUNFISH Part 2 population compared to nusinersen. This is expected given the weaker population enrolled in SUNFISH Part 2. In the SUNFISH subset that met some of CHERISH's enrolment criteria (age ≤9 years, baseline HFMSE score ≥10, no severe scoliosis), RULM outcomes increased, and the difference between risdiplam and

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nusinersen decreased. Point estimates across all methods showed comparable efficacy of risdiplam and nusinersen, with a numerically smaller improvement for risdiplam. Confidence and credibility intervals encompassed a mean difference of 0, i.e the model could not differentiate between treatment effects. The probability of being better than nusinersen was estimated to be 24% with the fixed effects model and 26% with the random effects models.

In terms of RULM responders, results from the total SUNFISH Part 2 population showed higher efficacy of risdiplam compared to nusinersen, driven by the small proportion of responders in the placebo arm. The proportion of responders increased in the SUNFISH subset. The point estimates of the Bucher and the Bayesian methods suggested a higher efficacy of risdiplam, however confidence and credibility intervals were wide and included ORs <1. The probability of risdiplam being better than nusinersen was estimated to be 92% using the fixed effects model and 87% using the random effects model.

Results of this sensitivity analysis are in line with those of the MAIC analysis.

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Table 78. Restricted NMA RULM change from baseline at 12 months

Comparator (STUDY)	N	Change from baseline		Difference against control	Bucher ITC	Bayesian NMA			
						Fixed Effects		Random Effects	
		Intervention	Control		Mean difference (95% CI)	Mean difference (95% CrI)	Probability of being better	Mean difference (95% CrI)	Probability of being better
Risdiplam (SUNFISH Part 2)	173	1.8	0.3	1.5	-1.48 (-2.99;-0.03)*	-			
Risdiplam (SUNFISH subset°)	68	3.6	1.2	2.4	-0.60 (-2.24;1.22)*	-0.60 (-2.26;1.07)	24%	-0.63 (-2.76;1.47)	26%
Nusinersen (CHERISH)	126	3.7	0.7	3.0	-				

CI, Confidence Interval; CrI, Credible Interval
*N=1000 successful bootstrap samples
°Patients from SUNFISH Part 2 aged ≤9 years at screening, with a HFMSE score ≥10 at baseline, and without severe scoliosis.

Table 79. Restricted NMA RULM responder (change ≥2 points) at 12 months

Comparator (STUDY)	N	Proportion responders		OR against control	Bucher ITC	Bayesian NMA			
						Fixed Effects		Random Effects	
		Intervention	Control		OR (95% CI)	OR (95% CI)	Probability of being better	OR (95% CI)	Probability of being better
Risdiplam (SUNFISH Part 2)	173	50%	32%	2.2	1.41 (0.48; 4.19)*	-			
Risdiplam (SUNFISH subset°)	68	79%	48%	4.1	2.66 (0.76; 12.74)*	2.65 (0.67;10.60)*	92%	2.59 (0.39;17.25)*	87%
Nusinersen (CHERISH)	118	66%	56%	1.5	-				

CI, Confidence Interval; CrI, Credible Interval
*N=1000 successful bootstrap samples
°Patients from SUNFISH Part 2 aged ≤9 years at screening, with a HFMSE score ≥10 at baseline, and without severe scoliosis.

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HFMSE

MAIC and NMA analyses were conducted on two HFMSE endpoints: Change from baseline at 12 months, and change from baseline ≥3 points. In CHERISH, HFMSE change from baseline was calculated using an ANCOVA model adjusted for age and baseline score. The same method was used to calculate results for SUNFISH. Age and baseline score adjusted OR for HFMSE change ≥3 points was reported in CHERISH at 15-months only. Age and baseline score adjusted OR at 12 months were calculated for the SUNFISH, as later data was not available.

Differences in placebo response between SUNFISH and CHERISH were observed that raise the question if the HFMSE data is comparable between the two trials. In the total SUNFISH Part 2 population, mean change from baseline at 12 months was 0.6 points in the placebo arm. In natural history, the mean 12-month change from baseline was reported to be -0.84 in non-ambulant Type 2 and 3 patients (Mercuri et al. 2016), a difference of 1.4 points compared to SUNFISH. The same pattern was observed in the SUNFISH subset (patients from SUNFISH Part 2 aged ≤9 years at screening, with a HFMSE score ≥10 at baseline, and without severe scoliosis). As shown in

Figure 25, the mean change from baseline at 12 months was 1.7 in the placebo arm of the SUNFISH subset (before matching-adjustment), 2.1 in the placebo arm of the SUNFISH subset matching-adjusted to CHERISH and 0.2 in the sham arm of CHERISH. This is a difference between control arm of 1.5 points before matching-adjustment, which is increasing to 1.9 points after matching-adjustment. Similarly, the proportion of HFMSE responders at 12 months was 48% and 49% in the placebo arm of the pre and post matching-adjusted SUNFISH subset, twice as high as in the sham arm at 12 months with 24% responders (Figure 26). It is surprising that matching-adjustment of the SUNFISH subset to CHERISH did not reduce differences in placebo response; despite successful matching of the three selected matching factors (age, baseline score, SMN2 copy number) in the placebo arm.

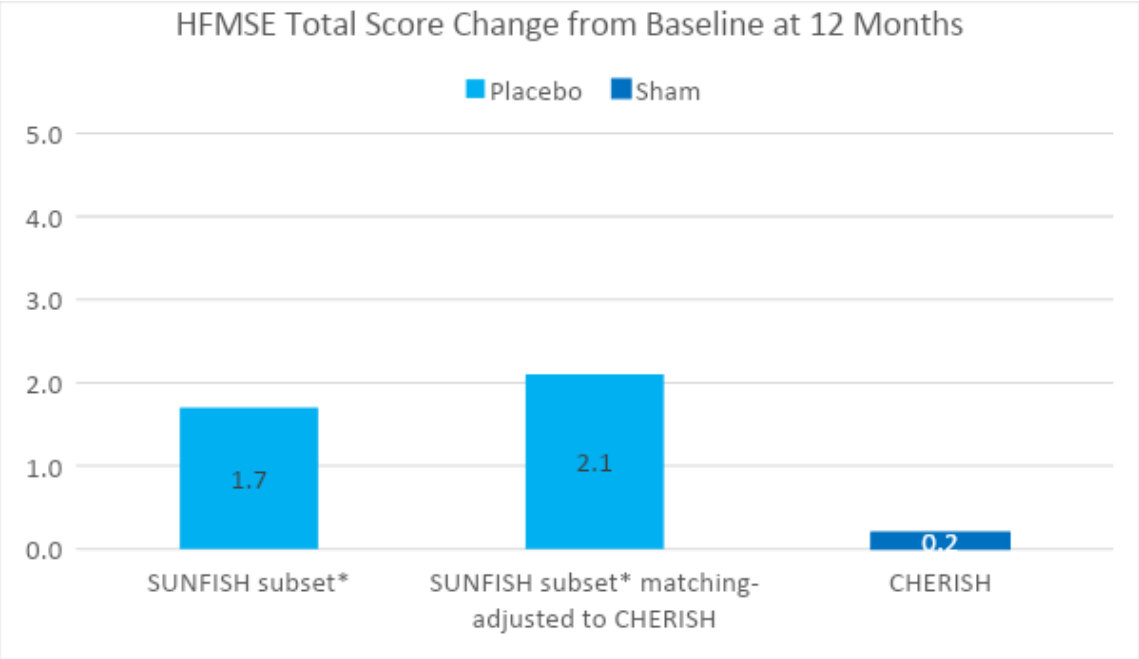
Unusually high placebo responses were not observed on other motor function scales collected in SUNFISH. In RULM, differences in placebo response between the SUNFISH subset and CHERISH were small and were almost completely removed after matching-adjustment of the SUNFISH subset to CHERISH. Difference in change from baseline was 0.5 before and 0.1 after matching-adjustment (see

Figure ***23***). Placebo response on the MFM 32 could only be compared to natural history, as the scale was not assessed in the CHERISH trial. In natural history, the MFM 32 score was estimated to decline by -0.86 and -0.55 per year in patients with Type 2 and 3 SMA, respectively (25). In the placebo arm of SUNFISH Part 2, comprising both Type 2 and 3 patients, 12-month change from baseline was -0.19 (106). This makes a difference in response of 0.36-0.67 points. Considering that the maximum achievable score in MFM 32 is 72 (versus 66 in HFMSE), this difference is small.

These differences in placebo response on the HFMSE scale suggest potential for confounding due to trial differences that were unobserved or that could not be adjusted (117).

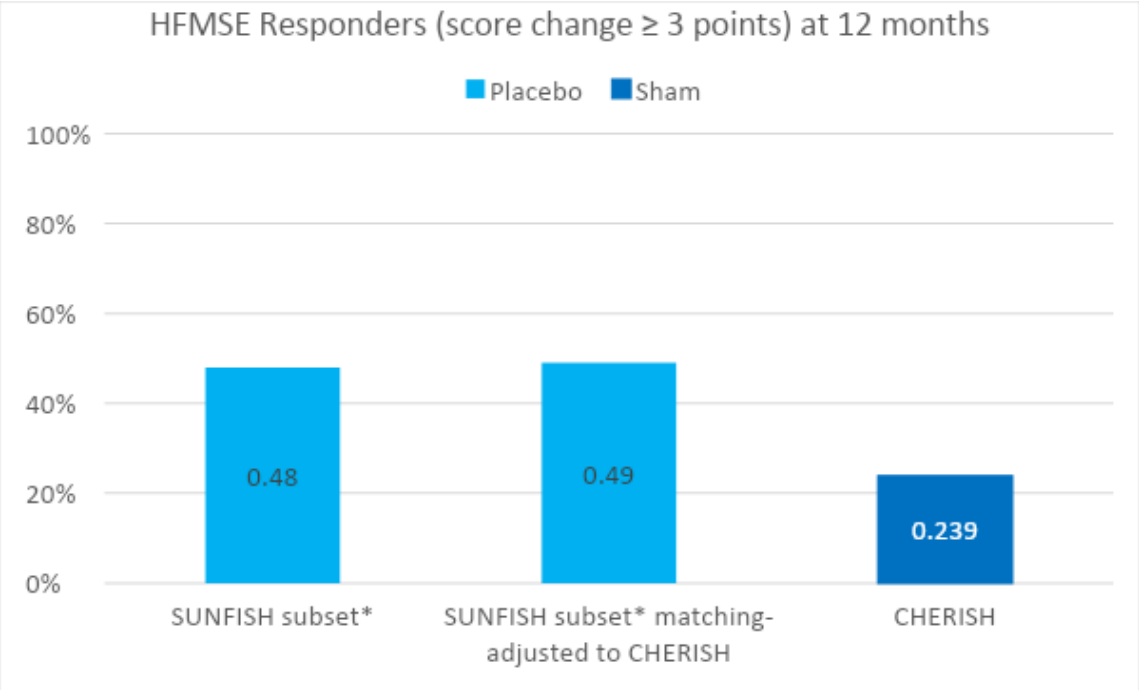
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Figure 25. Control arm outcomes of HFMSE score change from baseline at 12 months



*Patients from SUNFISH Part 2 aged ≤9 years at screening, with a HFMSE score ≥10 at baseline, and without severe scoliosis.

Figure 26. Control arm outcomes of HFMSE response (change ≥3 points) at 12 months



*Patients from SUNFISH Part 2 aged ≤9 years at screening, with a HFMSE score ≥10 at baseline, and without severe scoliosis.

Safety

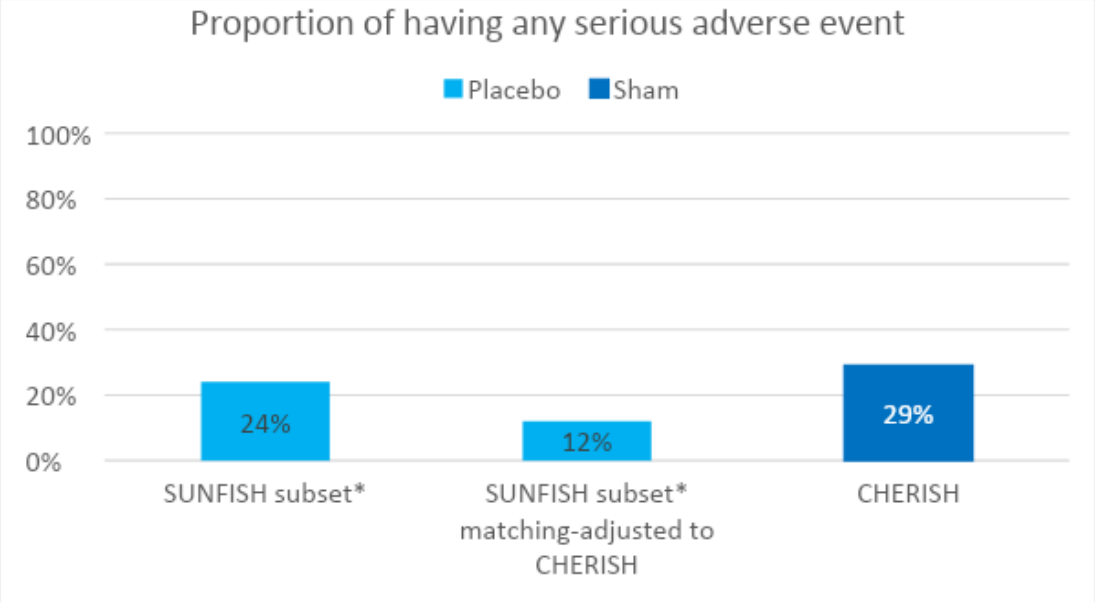
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MAIC and NMA analyses were conducted on the safety endpoint of any serious AE. Analyses on the any AE endpoint was not conducted, as CHERISH reported that all patients in the sham arm had an AE, resulting in uninformative relative effect estimates.

No prognostic or predictive factor identified in the literature review was studied in their relationship with adverse events (111). However, adverse events in patients with SMA are often related to respiratory function. Respiratory function tends to decline with time in patients with SMA. The decline was found to occur earlier in those with type 2 than with type 3 SMA, although the rate of decline was similar (137). Association of decline in forced vital capacity (FVC), a measure of respiratory function, with SMN2 copy number, SMA type (type 2 vs 3), ambulatory status and baseline HFMSE score (<20 vs ≥ 20) was also studied in natural history (111); however, none were found to be significant. Further, there is no evidence of any of those factors being predictive of treatment effect in adverse events (111).

A comparison of control arm outcomes in Figure 27 shows a smaller difference in proportion of any serious AE between CHERISH and the SUNFISH subset before (difference of 5%-points) compared to after matching-adjustment (difference of 17%-points). Hence, NMA analyses may provide less biased results for safety endpoints. Based on the control arm comparison and the uncertainty around treatment-effect modification on adverse events, the NMA analyses on the SUNFISH subset were considered to be the base case. MAIC was conducted as a sensitivity analysis. These results provided justification as to why it was not appropriate to perform an unanchored MAIC for this endpoint past 12 months.

Figure 27. Control arm outcomes of proportion with any serious adverse event



*Patients from SUNFISH Part 2 aged ≤9 years at screening, with a HFMSE score ≥10 at baseline, and without severe scoliosis.

(i) Base Case Analysis: Results from the NMA

Analyses on the safety endpoint was conducted using Bucher ITC and Bayesian NMA approaches. The Bayesian NMA was conducted both with a fixed and random effects model. The best fit according to DIC was the random effects model (117). Bucher ITC results using data from the total SUNFISH Part 2 population were included for comparison purposes.

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Table 80 presents results from the restricted NMA analyses on the any serious adverse event endpoint. In the total SUNFISH Part 2 populations, reporting of any serious adverse event was similar between risdiplam and placebo. The OR against nusinersen suggested a higher reporting of AEs for risdiplam.

In the SUNFISH subset that met some of CHERISH's enrolment criteria (age ≤9 years, baseline HFMSE score ≥10, no severe scoliosis), the proportion of patients that were reported to have any serious AE was higher in the placebo arm compared to risdiplam; similar to what was observed in CHERISH. ORs suggest comparable reporting of any serious adverse events of risdiplam and nusinersen, although point estimates across all methods provide a slightly higher OR for risdiplam. However, the analyses were not able to differentiate between the two treatments as confidence and credibility intervals contained ORs above and below 1. The probability of being better than nusinersen on this safety endpoint was 43% with the fixed effects model and 45% with the random effects models. Note that the follow-up in CHERISH (minimum 15 months) was longer than in SUNFISH (minimum 12 months), therefore ORs may be biased in favour of risdiplam.

(ii) Sensitivity Analysis: Results from the anchored MAIC

An ITC using an anchored MAIC approach was conducted as a sensitivity analyses. The same matching factors as for the RULM endpoints were used (age at screening, SMN2 copy number, baseline RULM score).

Table 81 presents results from the MAIC analyses on the any serious adverse event endpoint. The proportion of patients that were reported to have any serious AE was higher for risdiplam (24%) in the SUNFISH subset matching-adjusted to CHERISH compared to nusinersen (17%), while it was the opposite direction in the control arm. Proportion of patients with any serious AE was more than twice as high in the CHERISH sham control arm compared to placebo in the SUNFISH subset. The analysis suggests that risdiplam is associated with a higher reporting of any serious AE (OR: 4.32; 95%CI 0.88-37615888.28). However, results appear to be unstable as the upper limit of the confidence interval is very high.

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Table 80. NMA results on any serious AE

Comparator (STUDY)	N	Proportion with any serious AE		OR against control	Bucher ITC	Bayesian NMA			
						Fixed Effects		Random Effects	
		Intervention	Control		OR (95% CI)	OR (95% CrI)	Probability of being better	OR (95% CrI)	Probability of being better
Risdiplam (SUNFISH Part 2)	173	20%	18%	1.11	2.23 (0.72;8.35)*	-			
Risdiplam (SUNFISH subset°)	68	16%	24%	0.62	1.23 (0.25;5.76)*	1.24 (0.13;11.85)*	43%	1.17 (0.08;20.50)*	45%
Nusinersen (CHERISH)	126	17%	29%	0.50	Ref				

CI, Confidence Interval; CrI, Credible Interval
*N=988/1000 successful bootstrap samples
°Patients from SUNFISH Part 2 aged ≤9 years at screening, with a HFMSE score ≥10 at baseline, and without severe scoliosis.

Table 81. Anchored MAIC results on any serious AE

Comparator (STUDY)	Anchored MAIC in the SUNFISH subset°				
	ESS /N	Proportion with any serious AE		OR against control	OR against comparator (95% CI)
		Intervention	Control		
Risdiplam (SUNFISH subset°)	34.2/68	24%	12%	2.2	4.32 (0.88; 37615888.28)*
Nusinersen (CHERISH)	126	17%	29%	0.5	Ref

CI, Confidence Interval
*N=988/1000 successful bootstrap samples
°Patients from SUNFISH Part 2 aged ≤9 years at screening, with a HFMSE score ≥10 at baseline, and without severe scoliosis.

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Comparison post month 12

For the indirect comparison of data after 12 months, where there is an absence of common comparators between SUNFISH and CHERISH/SHINE, an unanchored MAIC was performed to assess the relative efficacy of risdiplam versus nusinersen. However, unanchored matching was not performed for the HFMSE and SAEs. This because the anchored MAIC analysis was not successful on the HFMSE and SAEs as illustrated by differences in responses in the control arms

Table 82 provides an overview over key baseline characteristics of the SUNFISH risdiplam subset before and after matching to the CHERISH nusinersen population by means of the three matching factors age at screening, RULM baseline score and SMN2 copy number. This matching differs from Table 75 as the anchored analysis assumed SUNFISH and CHERISH have similar comparators (placebo and sham, respectively). For the unanchored analysis, all patients switched to receive active treatments after 1 year in both trials, therefore with the absence of common comparator arms the matching was conducted only for the patients in the risdiplam and nusinersen arms, respectively. As a consequence, the baseline characteristics of the restricted population of patients in SUNFISH also differs after matching compared to the baseline results presented at Table 75. For the ITC, a CHERISH-like population was identified within SUNFISH Part 2, reducing the risdiplam population to n=43, however after matching on the identified factors the unanchored MAIC further reduced the risdiplam sample size.

Table 82. SUNFISH risdiplam subset baseline characteristics pre and post CHERISH-nusinersen subset matching

	Before matching SUNFISH Part 2 subset	After matching SUNFISH Part 2 subset	CHERISH, SHINE/CHERISH
	Risdiplam	risdiplam	nusinersen
Sample size/ESS*	43.0	29.8*	83.0
Mean age at screening, years	5.00	3.76	4.00†
Mean age at symptom onset, months	13.70	12.75	10.00†
Mean symptoms duration, months	46.30	32.40	39.30†
Mean HFMSE score	24.21	22.56	22.40
Mean RULM baseline	21.65	19.65	19.40
Mean *SMN2* copy number‡	3.090	3.00	2.95
Severe scoliosis, %	0	0	0

*ESS is an estimate of the sample size of a weighted population. †Means were not reported for these values. The average of the medians was used as a proxy for the purpose of these analyses. ‡Mean *SMN2* copy numbers were calculated to facilitate the matching.

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ESS, effective sample size; HFMSE, Hammersmith Function Motor Scale – Expanded; ITC, indirect treatment comparison; MAIC, matching-adjusted indirect comparison; RULM, Revised Upper Limb Module; *SMN2*, survival of motor neuron-2.

HFMSE and Safety endpoints

For the HFMSE and safety endpoints, unanchored matching was not feasible to be performed, as the results from the 12-month anchored matching analysis was not successful due to results showing differences in responses between the control arms (see

Figure ***25***, Figure 26 and Figure 27).

RULM

In CHERISH-SHINE, changes in RULM scores from baseline were reported at various time points, however for the purposes of the comparison only scores closer to 12, 24, 36 and 48 months were considered for the unanchored MAIC; see Table 83 for the sample size and RULM score by time point.

Table 83. RULM scores by time point from CHERISH-SHINE OLE data

	12-Month (350 days) CHERISH- SHINE OLE study	24-month (690 days) CHERISH- SHINE OLE study	36-month (1170 days) CHERISH- SHINE OLE study	48-month (1410 days) CHERISH- SHINE OLE study
	Nusinersen	Nusinersen	Nusinersen	Nusinersen
Sample size	83	83	80	61
Mean (SD) RULM score	3.58 (4.21)	4.69 (5.17)	5.16 (5.76)	6.61 (5.26)
LS Mean (SE) RULM score	3.81 (0.32)	4.98 (0.37)	5.53 (0.4)	6.96 (0.47)

OLE, Open Label Extension; ITC, indirect treatment comparison; LS, Least Square; SD, Standard Deviation; SE, Standard Error; RULM, Revised Upper Limb Module.

It is worth noting that the sample size reduces for the 48-month time points that report RULM data as reported for CHERISH-SHINE; however, the patient baseline characteristics were not reported over time making it difficult to ascertain whether the occurrence of missing data on RULM scores in patients was random. Therefore, the unanchored MAIC was performed only for the time points with a smaller number of missing patient data (namely, 12, 24 and 36 months). At 48 months, there was a notably higher number of patients with no recorded RULM score (n=22) and so it was deemed inappropriate to perform the comparison using this time point as study populations may not be comparable.

Table 84. SUNFISH Part 2 patient characteristics over 12, 24 and 36 months, including the RULM scores

	12-Month SUNFISH Part 2 subset	24-month SUNFISH Part 2 subset	36-month SUNFISH Part 2 subset

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	Risdiplam	Risdiplam	Risdiplam
Sample size	43	40	39
Mean age at screening, years	5.0	5.05	4.95
Mean age at symptom onset, months	13.7	13.72	14.06
Mean symptoms duration, months	46.3	46.88	45.32
Mean HFMSE score	24.21	24.62	23.95
Mean RULM baseline	21.65	21.70	21.28
Mean SMN2 copy number	3.09	3.10	3.10
Severe scoliosis, %	0	0	0

As seen in Table 82, the ITC had to be limited to a subset of 43 patients from SUNFISH Part 2 that resembled the CHERISH enrolled population. Table 83 reports the SUNFISH Part 2 patient summary characteristics over time, including the RULM scores used in the analysis. While the number of patients with recorded RULM scores slightly decreases over time, the baseline characteristics remain unchanged; suggesting that in the SUNFISH trial, missing data for the RULM scores occurs at random.

(i) Base Case Analysis: Results from the unanchored MAIC

Table 85 presents the unanchored MAIC for RULM data mean change from baseline at 12, 24 and 36 months. Overall, the MAIC does not provide sufficient evidence to draw conclusions on the relative efficacy of risdiplam and nusinersen using the RULM change from baseline as an endpoint. At 12 and 36 months, the confidence interval does not include the MCID value (defined as a RULM change of at >2 from baseline), suggesting the efficacy may be equivalent between risdiplam and nusinsersen at this time points. Similarly, at 24 months, whilst the point estimate indicates a numerical improvement of nusinersen compared to risdiplam, the confidence interval also suggests that the efficacy may be equivalent between the two technologies.

(ii) Sensitivity Analysis: Results from the unanchored MAIC

Table 86 presents the sensitivity analysis where risdiplam patients have been matched to the full baseline characteristics of patients in CHERISH and HFMSE score at baseline has been added as a covariate in the unanchored MAIC analyses. Whilst the confidence intervals do include the MCID value and suggest the difference is favourable to risdiplam, the data still does not provide sufficient evidence to draw conclusions on the relative efficacy of risdiplam versus nusinersen.

In summary, for the RULM endpoint the unanchored MAIC performed did not provide sufficient evidence to draw conclusions on risdiplam versus nusinersen in type 2/3 SMA over at least 3 years of follow-up. The main challenges arose from the difficulty in matching the differences across populations, as SUNFISH enrolled a broader population compared with

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CHERISH in terms of age and disease severity. The population differences led to a large reduction of the effective sample size, which resulted in substantial uncertainty of the relative effects. Therefore, no conclusions can be drawn on the relative efficacy of risdiplam versus nusinersen in the RULM score in type 2/3 SMA patients between 12 and 36 month time points. The performed sensitivity analysis matching for HFMSE score at baseline along with age, SMN2 copy number and RULM score at baseline suggested that risdiplam may be non-inferior to nusinersen over the analysed period of up to 3 years for type 2/3 SMA patients.

No long-term comparison could be made for the RULM responder (change ≥2 points) as the data is not reported from CHERISH-SHINE.

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Table 85. RULM mean change from baseline at 12, 24 and 36 months between SUNFISH and CHERISH/SHINE

	RULM change[1]: unanchored MAIC in SUNFISH subset[2]								
	12 months			24 months			36 months		
	Risdiplam[3]	Nusinersen	Difference	Risdiplam[3]	Nusinersen	Difference	Risdiplam[3]	Nusinersen	Difference
Sample size, n	29.77	83	53.23	29.67	83	53.33	28.77	80	51.23
Mean	3.92	3.81	0.11	4.47	4.98	-0.51	5.34	5.53	-0.19
95% CI			-1.20 to 1.17			-1.72 to 0.94			-1.65 to 1.35

[1]The MCID is defined as a RULM change of at least two (≥2) from baseline. Re-weighted to CHERISH, SHINE/CHERISH based on matching using age at screening, SMN2 copy number and baseline RULM scores as matching factors; [2]The SUNFISH subset excluded patients with a baseline HFMSE score <10; patients aged >9 years and those with severe contractures or scoliosis; [3]re-weighted sample.
CI, confidence interval; MAIC, matching-adjusted indirect comparison; RULM, Revised Upper Limb Module; SMA, spinal muscular atrophy; *SMN2*, survival of motor neuron-2; LSM, Least Square Mean; MCID, Minimal Clinically Important Change.

Table 86. RULM mean change from baseline at 12, 24 and 36 months between SUNFISH and CHERISH/SHINE; sensitivity analysis using risdiplam patients matched to the full baseline characteristics of CHERISH and HFMSE score as a matching covariate in the uMAIC

	RULM change[1]: unanchored MAIC in SUNFISH subset[2]								
	12 months			24 months			36 months		
	Risdiplam[3]	Nusinersen	Difference	Risdiplam[3]	Nusinersen	Difference	Risdiplam[3]	Nusinersen	Difference
Sample size, n	25.1	83	57.9	21.48	83	61.52	28.3	80	51.7
Mean	4.44	3.81	0.63	5.58	4.98	0.6	5.62	5.53	0.09
95% CI			-0.79 to 2.14			-1.08 to 2.07			-1.08 to 2.08

[1]The MCID is defined as a RULM change of at least two (≥2) from baseline. Re-weighted to CHERISH, SHINE/CHERISH based on matching using age at screening, SMN2 copy number and baseline RULM scores as matching factors; [2]The SUNFISH subset excluded patients with a baseline HFMSE score <10; patients aged >9 years and those with severe contractures or scoliosis; [3]re-weighted sample.
CI, confidence interval; MAIC, matching-adjusted indirect comparison; RULM, Revised Upper Limb Module; SMA, spinal muscular atrophy; *SMN2*, survival of motor neuron-2; LSM, Least Square Mean; MCID, Minimal Clinically Important Change; uMAIC: unanchored MAIC

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B.2.9.5 Uncertainties in the indirect and mixed treatment comparisons

Presymptomatic SMA

All identified studies are single arm (risdiplam (RAINBOWFISH), nusinersen (NURTURE), and OA (SPR1NT)) and formed a disconnected network. The sample sizes of all studies included in this analysis are very small (between 5-15 per arm), resulting in high uncertainty with any comparison (quantitative and qualitative) of these treatments. Therefore population-adjustment methods such as MAIC/STC were not feasible due to the very small sample sizes of the trials and only a naïve comparison could be conducted.

The two sample t-tests presented in the analysis comparing mean changes from baseline over time are purely exploratory and were only conducted on the absolute mean value at each time point, and so does not account for any differences in the studies (including baseline score). Moreover, the standard deviations for nusinersen were estimated from the figures in the G-BA dossier material (126). It is also not known if the populations are normally distributed, therefore this assumption was made in order to conduct the two sample t-test.

Assessing the differences in motor milestones achieved between studies is challenging due to the differences in assessment schedules and also the inability to match the populations at baseline in order to obtain an unbiased estimation of patient's progression at later time points. Motor milestones were not reported using the same measurements. Specifically, RAINBOWFISH and NURTURE used the ulnar nerve for CMAP amplitude measurement, while SPR1NT used the peroneal nerve. RAINBOWFISH Assessed item 22 in patients with 2 SMN2 copies and baseline CMAP >=1.5mV at Month 12 while SPR1NT had two endpoints based on SMN2 copy number: item 26 for patients with 2 SMN2 copies, achievable up to 18 months and item 40 for patients with 3 SMN2 copies, also up to 18 months. RAINBOWFISH required agreement from 2 Central Readers while SPR1NT required only 1 Central Reader. Both studies (RAINBOWFISH and SPR1NT) may have underestimated the age at first achievement, as milestones reached before visits were not counted until confirmed at a site visit. Lastly, NURTURE assessed WHO Motor Milestones as a secondary endpoint without a specific time point and did not require independent assessment, allowing for caregiver-reported achievements.

Type 1 SMA

The disconnected evidence network in Type 1 SMA limited the choice of ITC methodologies, as standard NMA methods require common comparators (127). Population adjustment methods were used to attempt to reduce biases resulting from study differences. However, studies available for the comparison had small sample sizes, reflecting the rare disease setting. Only a limited number of prognostic and predictive factors were included in order to avoid overfitting. Inclusion of more factors would result in a smaller ESS and higher uncertainty of results. Despite only including three matching factors in the comparison of FIREFISH and STR1VE-US/EU, a MAIC was not feasible due to limited overlap in age and baseline CHOP-INTEND score. Hence, for the STR1VE comparison, STC was explored as an alternative method to derive relative effect estimates.

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In the comparison of FIREFISH and ENDEAR, study populations appeared to be less heterogeneous, resulting in smaller uncertainty. Relative effect estimates of several outcomes were significant both in the naïve and in the MAIC analysis.

Although FIREFISH was successfully matched to ENDEAR, results could still be confounded by unadjusted characteristics or unreported study differences. Improvements in survival, as observed in the results of the MAIC analyses in Type 1 SMA, could be a result of changes in standard of care around respiratory support (130, 138) and not purely an effect of treatment with risdiplam. However, the proportion of patients on ventilatory support at baseline in the ENDEAR re-weighted FIREFISH population was similar (even slightly lower) to that of ENDEAR. Further, improvements with risdiplam were also seen consistently across motor function outcomes (CHOP-INTEND and HINE-2), which would not be impacted by proactive ventilatory support.

It is also possible that the effect sizes of risdiplam are overestimated due to the open label design of the FIREFISH trial. However, this would not affect objective measures, such as survival. Further, CHOP-INTEND and HINE-2 outcomes were calculated using a more conservative analysis set in FIREFISH compared to ENDEAR. In ENDEAR results for HINE-2 and CHOP-INTEND were calculated with an efficacy set that excluded patients that died or had less than 6 months of treatment. These restrictions were not applied to the FIREFISH analysis set; deaths were counted as non-responders and patients with less than 6 months of treatment were included in the analyses.

The comparison of risdiplam to OA was limited by the short follow-up data publicly available for STR1VE studies.

It was not feasible to conduct an updated comparison to BSC (versus what was presented in TA755) as patients in the sham arm of ENDEAR switched to nusinersen after 12 months.

Type 2/3 SMA

Comparison of risdiplam to nusinersen in Type 2/3 SMA was limited by the small overlap between the SUNFISH and CHERISH study populations. SUNFISH enrolled a much broader patient population than CHERISH, including adults, patients with a longer disease duration, patients with severe scoliosis and contractures, and patients with a lower HFMSE score at baseline. Age was found to be predictive of treatment effect (111). Younger patients (<5-6 years) may still gain motor function, while during puberty (5-15) patients often experience a decline in motor function as contractures and scoliosis develop. In older patients (>16 years), motor function tends to plateau. Many patients will experience floor effects in functional scales, likely due to severe scoliosis and contractures which limit the range of motion during the assessment of motor function scales (“Hammersmith Functional Motor Scale Expanded for SMA (HFMSE)” 2019; “Revised Upper Limb Module for SMA (RULM FOR SMA)” 2014; (139)). Resultantly, the SUNFISH patient population is significantly worse from baseline and therefore the likelihood of capturing improvements in motor milestones is going to be more challenging compared to the CHERISH population, due to the breadth in enrolment criteria. Attempts to align the two populations were made by defining a subset of patients that would be more similar to the CHERISH population (age ≤9 years, HFMSE score ≥10, no scoliosis). However, this subset constituted less than 40% of the total SUNFISH Part 2 population. Imbalances between risdiplam and placebo may have been introduced with the subset, although none were identified from the reported patient

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characteristics. Further, not all differences could be accounted for; some weaker patients that would not have been enrolled in CHERISH may still be included in the SUNFISH subset. For example, patients with severe contractures could not be reliably identified in SUNFISH and were therefore not excluded from the dataset.

The MAIC methodology was used to further adjust for remaining differences in mean patient characteristics (e.g, age, HFMSE baseline score) between the SUNFISH subset and the CHERISH population. However, the ESS was greatly reduced after the matching-adjustment, particularly in the placebo arm. This resulted in wide confidence intervals around the relative effect estimates.

Assumptions of equivalency of sham control and placebo had to be made in order to connect SUNFISH and CHERISH in the evidence network. It is well known that not all placebos have equal effects and that modality can impact outcomes (140-142) (Benedetti and Dogue 2015; Bannuru et al. 2015; Kong et al. 2013). In CHERISH, sham procedure was used as a control arm. The procedure consisted of a small needle prick, breaking the skin, but without inserting the needle or lumbar puncture injection (76). In SUNFISH, placebo oral solution was administered, matching the active drug in color and excipients (except for ascorbic acid and disodium edetate). Given the differences in drug delivery methods between nusinersen (intrathecal) and risdiplam (oral), making this assumption of equivalency was the only option to compare relative effectiveness. It is possible that the differences in modality between sham and oral placebo caused the differences in control arm response on the HFMSE scale. However, if that was the case, similar differences would have also been observed on the other motor function scales (RULM and MFM 32). As illustrated before, differences in placebo response to sham or natural history were small on the other scales.

Matching-adjustment to the comparator trial is expected to reduce differences in placebo response if baseline characteristics are similar post-matching (136). This was the case for RULM, where the difference between control arms was reduced from 0.5 points pre matching-adjustment to 0.1 points post matching-adjustment. However, on the HFMSE scale, matching-adjustment to CHERISH further increased the difference in control arms. It is unclear why this happened. Study populations in SUNFISH and CHERISH may differ in (unreported) characteristics that affect HFMSE more than RULM. This also limited the ability to update the comparison for longer-term endpoints.

Of note, SUNFISH Part 2 patients were recruited to the study while many regions have already obtained regulatory approval for nusinersen at that time. As such, the availability of this treatment option may have contributed to generate an unquantifiable selection bias.

For the longer-term comparison post 12-months, similar to the 12-month analysis, a comparison for risdiplam versus nusinersen was only feasible for the outcome of RULM. However, once again, the MAIC did not provide sufficient evidence to draw definite conclusions on the comparison at year 1, 2 or 3. Due to the significant drop in patients at year 4 for nusinersen patients, it is unknown whether the patient populations are still comparable and so the comparison was not conducted for this time point. A key limitation to this comparison is that the population differences between SUNFISH and CHERISH/SHINE led to a large reduction in the effective sample size, which resulted in substantial uncertainty of the relative effects. Moreover, there are also differences and imbalances between the study populations that the analyses could not account for.

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Finally, a general limitation of the MAIC approach is that by matching to the comparator trial, the target population is assumed to be the one of the comparator trial. This is expected to be less of a limitation in the comparison against nusinersen in Type 1 SMA, where study populations were fairly similar. However, in Type 2/3 SMA, the majority of SUNFISH patients would not have been enrolled in CHERISH. The implication is that no inference of relative efficacy of risdiplam versus nusinersen can be made in patients that were excluded from CHERISH, such as adolescents and adults, patients with scoliosis and patients with weaker motor functions.

B.2.10 Adverse reactions

B.2.10.1 FIREFISH (infantile-onset, type 1 SMA)

Exposure to study treatment

In Part 2 of the FIREFISH study up to the CCOD of 22 November 2022, the median duration of exposure to risdiplam was [redacted]). All patients had received at least [redacted] of the total number of prescribed doses (dose intensity).

Table 87: Exposure to risdiplam (FIREFISH Part 2)

	Risdiplam (n=41)
Treatment duration (months) Mean (SD) Median Min – Max	[redacted]
Treatment duration category (months) 0 - ≤ 6 months >6 - ≤ 12 months >12 - ≤ 18 months >18 - ≤ 24 months >24 - ≤ 30 months >36 - ≤ 42 months >42 - ≤ 48 months >48 - ≤ 54 months >54 - ≤ 60 months >60 months	[redacted]
Total number of doses Mean (SD) Median Min – Max	[redacted]
Missed doses n Mean (SD) Median Min – Max	[redacted]
Partial doses n Mean (SD) Median Min – Max	[redacted]
Overdoses n Mean (SD) Median	[redacted]

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Min – Max	[redacted]
Dose intensity, (%) Mean (SD) Median Min – Max	[redacted]

Treatment duration is the date of the last study drug administration minus the date of the first study drug administration plus one day. Dose intensity is the number of doses actually received divided by the expected number of doses. Partial dose: actual dose administered <90% of planned dose. Overdose: actual dose administered >110% of planned dose.

Overview of adverse events

In Part 2 of the FIREFISH study up to the CCOD of 22 November 2022, risdiplam has been well tolerated, and the current safety profile is in keeping with that observed previously. An overview of the safety is as follows:

[redacted]

The overall AE profile for risdiplam by frequency is summarised below.

Table 88: Overview of adverse events by frequency

n, (%)	Risdiplam (n=41)
Total number of people with at least one AE	[redacted]
Total number of AEs, n	[redacted]
Total number of deaths	[redacted]
Total number of people withdrawn from study due to an AE	[redacted]
Total number of people with at least one AE with fatal outcome Serious AE Serious AE leading to withdrawal from treatment Serious AE leading to dose modification/treatment interruption Related serious AE AE leading to withdrawal from treatment AE leading to dose modification/interruption Related AE Related AE leading to withdrawal from treatment Related AE leading to dose modification/interruption Grade 3–5 AE	[redacted]

Multiple occurrences of the same AE in one individual are counted only once except for “total number of AEs” row in which multiple occurrences of the same AE are counted separately.

Common adverse events

A summary of AEs by preferred term reported in more than 5% of the patients are summarised below.

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Table 89: Adverse events reported in >5% of patients (FIREFISH Part 2)

Adverse event (n, %)	Risdiplam n=41
Pyrexia	[redacted]
Upper respiratory tract infection	[redacted]
Pneumonia	[redacted]
Constipation	[redacted]
Nasopharyngitis	[redacted]
Diarrhoea	[redacted]
Rhinitis	[redacted]
Vomiting	[redacted]
Bronchitis	[redacted]
COVID-19	[redacted]
Respiratory tract infection	[redacted]
Teething	[redacted]
Urinary tract infection	[redacted]
Influenza	[redacted]
Gastroesophageal reflux disease	[redacted]
Respiratory distress	[redacted]
Respiratory failure	[redacted]
Cryptochism	[redacted]
Joint dislocation	[redacted]
Pharyngitis	[redacted]
Pneumonia viral	[redacted]
Rash	[redacted]
Rash maculo-papular	[redacted]
Bronchiolitis	[redacted]
Dehydration	[redacted]
Haematuria	[redacted]
Malnutrition	[redacted]
Miliaria	[redacted]
Urticaria	[redacted]

Serious adverse events

Overall, [redacted] experienced at least one SAE; a summary of the types of SAEs are outlined below.

Table 90: Serious adverse events (FIREFISH Part 2)

Serious adverse events (n, %)	Risdiplam (n=41)
Total number of patients with at least one adverse event	[redacted]
Overall total number of events	[redacted]
Infections and infestations Total number of patients with at least one adverse event Total number of events	[redacted]
Respiratory, thoracic and mediastinal disorders Total number of patients with at least one adverse event Total number of events	[redacted]
Gastrointestinal disorders Total number of patients with at least one adverse event Total number of events	[redacted]
Metabolism and nutrition disorders Total number of patients with at least one adverse event Total number of events	[redacted]
Cardiac disorders Total number of patients with at least one adverse event Total number of events	[redacted]

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Injury, poisoning and procedural complications Total number of patients with at least one adverse event Total number of events	[redacted]
Nervous system disorders Total number of patients with at least one adverse event Total number of events	[redacted]
Congenital, familial and genetic disorders Total number of patients with at least one adverse event Total number of events	[redacted]
Investigations Total number of patients with at least one adverse event Total number of events	[redacted]

B.2.10.2 SUNFISH (later-onset, type 2 and type 3 SMA)

Exposure to study treatment

In the all exposure to risdiplam treatment period, the median duration of exposure to risdiplam was [redacted] for all patients. Cumulative exposure to risdiplam was [redacted]. Median dose intensity in the all exposure to risdiplam treatment period was [redacted] and all patients had a dose intensity [redacted] of the planned dose and [redacted] (defined as partial dose) on at least one occasion. A total of [redacted] patients missed one or more risdiplam dose(s) with a median of [redacted].

[redacted]

	Risdiplam (n=179)
Treatment duration (months) Mean (SD) Median Min – Max	[redacted]
Treatment duration category (months) 0 - ≤ 6 months >6 - ≤ 12 months >12 - ≤ 18 months >18 - ≤ 24 months >24 - ≤ 30 months >30 - ≤ 36 months >36 - ≤ 42 months >42 - ≤ 48 months >48 - ≤ 54 months >54 - ≤ 60 months >60 - ≤ 66 months	[redacted]
No of doses taken Mean (SD) Median Min – Max	[redacted]
Missed doses n Mean (SD) Median Min – Max	[redacted]
Partial doses n Mean (SD)	[redacted]

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Median Min – Max	[redacted]
Overdoses n Mean (SD) Median Min – Max	[redacted]
Dose intensity, (%) Mean (SD) Median Min – Max	[redacted]

Safety summary

The summary of AEs for SUNFISH Part 2 focuses on all patients exposed to risdiplam (n=179) unless otherwise stated, up to the LPLV of 02 October 2023.

Up to 5 years of treatment, risdiplam continued to be well tolerated and safety remained consistent with the known safety profile. No new safety signals were identified. [redacted].

- As of the LPLV, risdiplam was well tolerated.
- During the all exposure to risdiplam period, [redacted]
- [redacted] reported [redacted] AEs which were assessed as related to study treatment by the investigator. [redacted] reported for [redacted] from the same site were considered related to study treatment by the investigator.
- Adverse events resolved for most patients [redacted] Most AEs resolved without change to the study medication. [redacted]. [redacted] for which outcome was reported as unknown. [redacted]
- The majority [redacted] of patients reported AEs that were Grade 1-2 in severity, [redacted]
- [redacted] reported a total of [redacted]. All but [redacted] SAEs had resolved/improved.
- No AEs led to withdrawal or treatment discontinuation.
- Overall, [redacted] that led to study medication dose interruption were reported in [redacted] during the all exposure to risdiplam treatment period.
- There were no AESIs reported.
- [redacted] in the system organ class (SOC) eye disorders and [redacted] in the SOC neoplasms, were reported in [redacted] All except [redacted] resolved without change of risdiplam treatment and all except [redacted] were unrelated to risdiplam treatment ([redacted]).

A summary of AEs for SUNFISH Part 2 in all patients exposed to risdiplam is presented below:

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Table 91: Overview of adverse events (SUNFISH Part 2, Safety Evaluable Patients, All exposure to risdiplam period)

n, (%)	Risdiplam (n=179)
Total number of people with at least one AE	[redacted]
Total number of AEs, n	[redacted]
Total number of deaths	[redacted]
Total number of people withdrawn from study due to an AE	[redacted]
Total number of people with at least one AE with fatal outcome Serious AE Serious AE leading to withdrawal from treatment Serious AE leading to dose modification/treatment interruption Treatment related serious AE AE leading to withdrawal from treatment AE leading to dose modification/interruption Treatment related AE Related AE leading to withdrawal from treatment Related AE leading to dose modification/interruption Grade 3–5 AE	[redacted]

Multiple occurrences of the same AE in one individual are counted only once except for "total number of AEs" row in which multiple occurrences of the same AE are counted separately.

Common adverse events

The most commonly reported AEs (≥20% of patients) were in the [redacted].

Within the SOC infections and infestations, the most common AEs were in the lower and upper respiratory tract infections baskets. Overall, [redacted]

The most commonly reported AEs that occurred in ≥15% of all patients is provided below:

Adverse event (n, %)	Risdiplam n=179
Upper respiratory tract infection	[redacted]
Nasopharyngitis	
Pyrexia	
COVID-19	
Headache	
Vomiting	
Diarrhoea	
Cough	
Gastroenteritis	
Pneumonia	

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Adverse events related to treatment

In the all exposure to risdiplam treatment period, [redacted] that were considered related to study treatment by the investigator. The most common treatment-related AEs were [redacted]. All AEs reported as related to study medication by the investigator resolved except for [redacted] AEs. [redacted].

Serious adverse events

In the all exposure to risdiplam treatment period, [redacted] reported a total of [redacted]. The most frequently reported (≥2%) SAEs [redacted] patients from the same site were considered related to the study treatment by the investigator. [redacted] let to study drug dose interruption.

All but [redacted] SAEs had resolved / resolved with sequelae or improved by the end of the study. [redacted].

The overall rate of SAEs during the all exposure to risdiplam treatment period ([redacted] remained relatively consistent over time with a decrease in Year 3 coinciding with COVID-19 lockdown. The rates by 12-month treatment period were: [redacted]

Table 92: Serious adverse events (SUNFISH Part 2; Safety evaluable population)

Serious adverse events (n, %)	Risdiplam (n=179)
Total number of patients with at least one adverse event	[redacted]
Overall total number of events	[redacted]
Infections and infestations Total number of patients with at least one adverse event Total number of events	[redacted]
Respiratory, thoracic and mediastinal disorders Total number of patients with at least one adverse event Total number of events	[redacted]

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Injury, poisoning and procedural complications Total number of patients with at least one adverse event Total number of events	[redacted]
Gastrointestinal disorders Total number of patients with at least one adverse event Total number of events	[redacted]
Metabolism and nutrition disorders Total number of patients with at least one adverse event Total number of events	[redacted]
General disorders and administration site conditions Total number of patients with at least one adverse event Total number of events	[redacted]
Musculoskeletal and connective tissue disorders Total number of patients with at least one adverse event Total number of events	[redacted]
Renal and urinary disorders Total number of patients with at least one adverse event Total number of events	[redacted]
Nervous system disorders Total number of patients with at least one adverse event Total number of events	[redacted]
Psychiatric disorders Total number of patients with at least one adverse event Total number of events	[redacted]
Vascular disorders Total number of patients with at least one adverse event Total number of events	[redacted]
Blood and lymphatic disorders Total number of patients with at least one adverse event Total number of events	[redacted]
Congenital, familial and genetic disorders Total number of patients with at least one adverse event Total number of events	[redacted]
Hepatobiliary disorders Total number of patients with at least one adverse event Total number of events	[redacted]
Product issues Total number of patients with at least one adverse event Total number of events	[redacted]

B.2.10.3 RAINBOWFISH (Paediatric, pre-symptomatic, genetically diagnosed SMA)

Exposure to study treatment

Based on PK data, the selected dose of risdiplam during the study was 0.2mg/kg. Treatment compliance was high as reflected by dose intensity and the low number of missed/partial doses and overdoses.

A total of 26 patients received at least one dose of study treatment. The median duration of treatment exposure was [redacted]. The median dose intensity (i.e., the number of doses actually received divided by the expected number of doses) was [redacted] At the time of the CCOD, [redacted] were reported to have received ≥10% above the planned dose (defined as an overdose), and these were reported as AEs of overdose [redacted] or accidental overdose [redacted] In all [redacted], the overdoses were single occurrences and no additional

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AEs were associated with the overdose. For [redacted] of these patients, treatment was interrupted for 1 day following the overdose.

[redacted] received ≤10% below the planned dose (defined as partial dose) on at least one occasion. In [redacted] patients, the partial doses were deemed major protocol deviations because of the prolonged duration of the partial dosing ([redacted]). [redacted] missed one or more ([redacted]) risdiplam doses. [redacted] had one dose adjustment and [redacted] had two dose adjustments.

For all 26 patients (100%), the route of administration was oral (i.e., without the need of a feeding tube).

Safety summary

The observed safety profile up to the CCOD was reflective of the age of the patients.

- The proportion of patients with at least 1 AE was 92.3% (24 patients). Overall, there were 203 AEs reported. The AEs reported were as would be expected for infants of this age.
- The majority of AEs (194/203) were not considered by the investigatory to be related to study treatment and the majority of related AEs (7/9) resolved despite ongoing treatment with risdiplam.
- Eight SAEs were reported in 4 patients. Of these, none were considered by the investigator as related to study treatment and all resolved without change to risdiplam treatment.
- No deaths, and no AEs of Grade ≥4 were reported.
- No adverse events of special interest (AESIs) were reported.
- AEs leading to dose modifications were accidental overdose in 2 patients; both events led to a dose interruption. One further patient experienced an AE leading to dose modification prior to the CCOD, which was confirmed by the site after the CCOD.
- Up to the CCOD, no AEs led to withdrawal or treatment discontinuation.
- There were no events or findings suggestive or risdiplam-induced effects on the retina, epithelial tissues or haematological parameters.

Adverse events

An overview of adverse events is presented below

Table 93: Summary of adverse events (RAINBOWISH, Safety-evaluable population)

	***SMN2* copy number**			
n, (%)	**2 (n=8)**	**3 (n=13)**	**≥4 (n=5)**	**All patients (n=26)**
Total number of people with at least one AE	[redacted]	[redacted]	[redacted]	24 (92.3)
Total number of AEs, n	[redacted]	[redacted]	[redacted]	203
Total number of deaths	[redacted]	[redacted]	[redacted]	0
Total number of people withdrawn from study due to an AE	[redacted]	[redacted]	[redacted]	0
Total number of people with at least one AE with fatal outcome Serious AE Serious AE leading to withdrawal from treatment Serious AE leading to dose modification/treatment interruption	[redacted]	[redacted]	[redacted]	 0 4 (15.4) 0 0

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Related serious AE	[redacted]	[redacted]	[redacted]	0
AE leading to withdrawal from treatment				0
AE leading to dose modification/interruption				2 (7.7)
Related AE				7 (26.9)
Related AE leading to withdrawal from treatment				0
Related AE leading to dose modification/interruption				0
Grade 3–5 AE				5 (19.2)
Total number of adverse events with are	[redacted]	[redacted]	[redacted]	
Serious				8
Related				9
Grade 1				132
Grade 2				59
Grade 3				6
Grade 4				0
Grade 5				0
AEs with missing grade				6

Multiple occurrences of the same AE in one individual are counted only once except for “total number of AEs”

The most frequent AEs (≥5 patients) by preferred term (PT) were: teething (38.5% [10 patients]); COVID-19 (34.6% [9 patients]); gastroenteritis (26.9% [7 patients]); pyrexia (26.9% [7 patients]); constipation (23.1% [6 patients]), diarrhoea (23.1% [6 patients]), eczema (23.1% [6 patients]); nasal congestion (19.2% [5 patients]); nasopharyngitis (19.2% [5 patients]); rhinitis (19.2% [5 patients]) and vomiting (19.2% [5 patients]).

The majority of AEs ([redacted]) had resolved and [redacted] were unresolved at the time of the CCOD.

[redacted]

Upper respiratory tract infections (basket of terms) were reported in 18 patients (69.2%) who experienced a total of 39 AEs. The most common AE within this basket of terms was COVID-19 (34.6% [9 patients]). Lower respiratory tract infections (basket of terms) were reported in 4 patients (15.4%) who experienced a total of 5 AEs. The most common AE within this basket of terms was bronchitis (7.7% [2 patients]).

When adjusted for patient-years at risk, the overall AE rate at the time of the CCOD was [redacted] The trend of decreasing AEs over time was observed during the first year

[redacted]

The majority of AEs [redacted] were not considered by the investigator to be related to study treatment and the majority of related AEs [redacted] resolved despite ongoing treatment with risdiplam. The proportion of patients experiencing AEs considered related to study treatment was [redacted] None of the related AEs were serious. The most frequent related AEs by SOC were:

[redacted]

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[redacted]

Up to the CCOD, no AEs of Grade ≥4 were reported. Of the 5 patients who reported 6 Grade 3 AEs, all the events were assessed by the investigator as unrelated to study drug and resolved by the CCOD without a change to study medication.

Up to the CCOD, no AEs led to study withdrawal or discontinuation of treatment. AEs leading to dose modifications were accidental overdose in 2 patients (7.7%); both events led to dose interruption whereby risdiplam was interrupted for 1 days. Neither case had additional AEs associated with the accidental overdose. Both events resolved after 1 day, and study treatment recommenced.

Serious adverse events

As of the CCOD, 8 SAEs were reported in 4 patients. Of these, none were considered by the investigator as related to study treatment and all resolved without change to risdiplam treatment.

Table 94: Summary of serious adverse events (safety-evaluable population)

	***SMN2* copy number**			
Serious adverse events (n, %)	**2 (n=8)**	**3 (n=13)**	**≥4 (n=5)**	**All patients (n=26)**
Total number of patients with at least one adverse event	[redacted]	[redacted]	[redacted]	4 (15.4)
Overall total number of events	[redacted]	[redacted]	[redacted]	8
Infections and infestations Total number of patients with at least one adverse event Total number of events Gastroenteritis Urinary tract infection	[redacted]	[redacted]	[redacted]	[redacted]
Gastrointestinal disorders Total number of patients with at least one adverse event Total number of events Constipation	[redacted]	[redacted]	[redacted]	[redacted]
Injury, poisoning and procedural complications Total number of patients with at least one adverse event Total number of events Femur fracture Soft tissue injury	[redacted]	[redacted]	[redacted]	[redacted]
Pregnancy, puerperium and perinatal conditions Total number of patients with at least one adverse event Total number of events Jaundice neonatal	[redacted]	[redacted]	[redacted]	[redacted]

For frequency counts by preferrer term, multiple occurrences of the same AE in an individual are counted only once. For frequency counts of "total number of events", multiple occurences of the same AE in an individial are counted separately.

B.2.10.3 JEWELFISH (Previously treated SMA patients)

Exposure to study treatment

Overall, [redacted] had received at least 24 months of treatment with risdiplam at the CCOD (according to patients' dosing diaries) and the longest exposure was [redacted]. Treatment compliance was high as reflected by dose intensity and the low number of partial doses and overdoses.

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Overall, [redacted] received at least one dose of risdiplam, and thus were included in the safety population.

[redacted]

The median total duration of risdiplam in all patients was [redacted]. In the individual treatment groups:

- [redacted] in the previous nusinersen group
- [redacted] in the previous AVXS-101 group
- [redacted] in the previous olesoxime group
- [redacted] in the previous BP29420 group

The median dose intensity of risdiplam in all patients was [redacted] In the individual treatment groups:

- [redacted] in the previous nusinersen group
- [redacted] in the previous AVXS-101 group
- [redacted] in the previous olesoxime group
- [redacted] in the previous study BP29420 group

The number of patients who received >10% above the planned dose (defined as an overdose) on at least one occasion was [redacted] across all patients; [redacted] and [redacted] patients from the previous nusinersen and AVXS-101 group, respectively. Of the [redacted]. The number of patients who received <10% below the planned dose (defined as partial dose) on at least one occasion was [redacted] across all patients; [redacted] from the nusinersen, AVXS-101 and olesoxime groups, respectively. Of the

[redacted]

The number of patients who missed doses was [redacted]; the number of missed doses ranged between [redacted]. In the individual treatment groups:

[redacted]

Safety summary

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Up to the CCOD of 31 January 2022, risdiplam has been well tolerated, and the current safety profile is in keeping with the known safety profile of risdiplam irrespective of previous treatment.

An overview of the all patients safety population at the CCOD is presented below. An overview of safety results for each separate previous treatment group is provided in Appendix F.

- Most patients (96.0%) reported at least 1 AE. The majority of AEs were mild to moderate in intensity, resolved without change to study treatment, and were reflective of the underlying disease.
- Thirty-eight patients (22.0%) experience a total of 77 AEs that were considered by the investigator as related to study medication.
- [redacted]The majority of events [redacted] were maximum intensity Grade 1 or 2. [redacted]
- No deaths or Grade 5 events were reported.
- AEs leading to dose modification or interruption were reported in [redacted]
- There was a trend toward decreasing rates of overall AEs and SAEs per 100PY over time, with the rate of AEs and the rate of SAEs decreasing by over half between the first and second years of treatment. [redacted]

A review of all available safety laboratory results, vital signs, ECGs, and ophthalmological assessments did not show any clinically significant adverse findings as compared with baseline. As of the CCOD, there have been no safety findings in patients reflective of potential risks previously identified from nonclinical toxicology studies (effects on epithelial tissue, retinal toxicity or haematological effects).

Table 95: Overview of adverse events, treatment emergent adverse events (0 – 24 months) (JEWELFISH; safety evaluable patients)

n, (%)	RO6885247 (n=13)	Nusinersen (n=76)	Olesoxime (n=70)	AVXS-101 (n=14)	All patients (n=173)
Total number of people with at least one AE	12 (92.3)	73 (96.1)	67 (95.7)	14 (100)	166 (96.0)
Total number of AEs, n	84	641	508	96	1329
Total number of deaths	0	0	0	0	0
Total number of people withdrawn from study due to an AE	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total number of people with at least one AE with fatal outcome	0	0	0	0	0

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Serious AE	3 (23.1)	16 (21.1)	12 (17.1)	4 (28.6)	35 (20.2)
Serious AE leading to withdrawal from treatment	1 (7.7)	4 (5.3)	4 (5.7)	1 (7.1)	10 (5.8)
Serious AE leading to dose modification/treatment interruption	0	0	1 (1.4)	0	1 (0.6)
Related serious AE	0	1 (1.3)	0	0	1 (0.6)
AE leading to withdrawal from treatment	6 (46.2)	20 (26.3)	12 (17.1)	0	38 (22.0)
AE leading to dose modification/interruption	0	0	0	0	0
Related AE					
Related AE leading to withdrawal from treatment					
Related AE leading to dose modification/interruption					
Grade 3–5 AE					

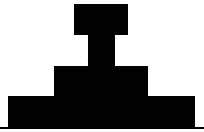
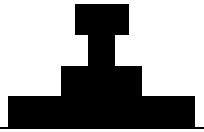
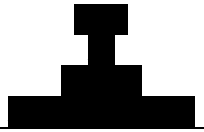
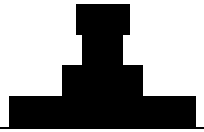
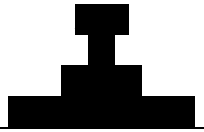
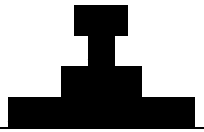
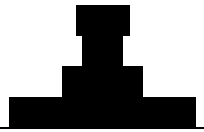
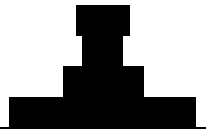
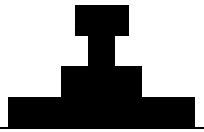
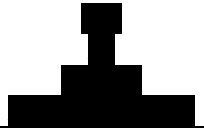
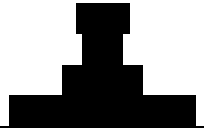
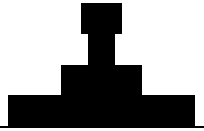
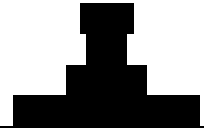
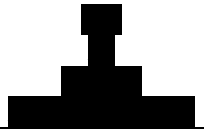
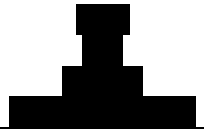
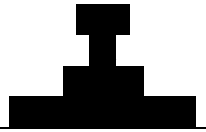
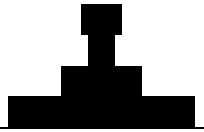
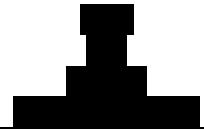
Only treatment emergent AEs are displayed. Multiple occurrences of the same AE in one individual are counted only once except for total number of AEs in which multiple occurrences of the same AE are counted separately.

Adverse events

When adjusted for PY at risk, the overall AE rate for all patients (at the time of CCOD) was [redacted].

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Table 96: Adverse event rate adjusted for patient-years at risk by six month period and overall (JEWELFISH, Safety-Evaluable Patients)

	RO6885247 (n=13)	Nusinersen (n=76)	Olesoxime (n=70)	AVXS-101 (n=14)	All patients (n=173)
Total treatment period Total patient-years at risk Number of adverse events Number of adverse events per 100 patient-years 95% CI					
0 - ≤12 months Total patient-years at risk Number of adverse events Number of adverse events per 100 patient-years 95% CI					
>12 - ≤24 months Total patient-years at risk Number of adverse events Number of adverse events per 100 patient-years 95% CI					
>0 - ≤6 months Total patient-years at risk Number of adverse events Number of adverse events per 100 patient-years 95% CI					
>6 - ≤12 months Total patient-years at risk Number of adverse events Number of adverse events per 100 patient-years 95% CI					

Total patient-years at risk is the sum over all patients of the time intervals (in years) from the start of study treatment to the earliest date of study withdrawal, last treatment date or the clinical cut-off date. Only treatment emergent AEs are counted.

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The proportion of patients with at least one AE in the all patient population was [redacted] Overall, there were [redacted].

The most frequent AEs by SOC (≥10% of patients in the all patients population) were:

[redacted]

The most frequent AEs by PT (≥10% of patients in the all patients population) were:

[redacted]

The most frequent SAEs by PE (≥3% of patients in the all patients population) were:

[redacted]

The majority of AEs [redacted] had resolved or were resolving at the time of the CCOD.

[redacted]

Adverse events related to treatment

[redacted]

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[redacted]

Adverse events by intensity

The proportion of patients with Grade 3 – 5 AEs in the all patients population was [redacted]. [redacted]. Grade 3 AEs were reported in [redacted] Grade 4 AEs were reported in [redacted] none of which were considered by the investigator to be related to study medication and resolved with no change to study medication.

Serious adverse events

Of the SAEs reported, the majority did not require dose interruption and none led to treatment discontinuation. All SAEs had resolved at the time of the CCOD and [redacted] The proportion of patients with at least one SAE in the all patients population was [redacted]. When adjusted for PY at risk, the overall SAE rate (at the time of the CCOD) was [redacted]

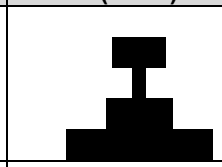
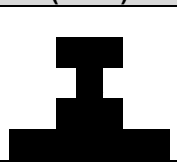
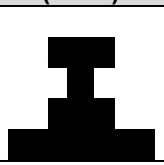
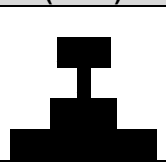
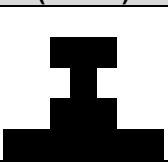
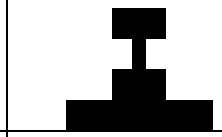
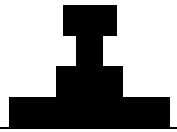
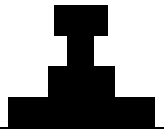
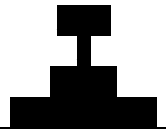
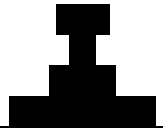
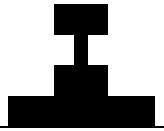
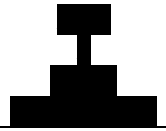
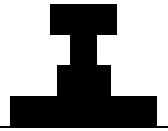
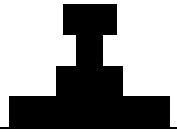
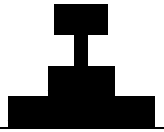
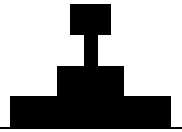
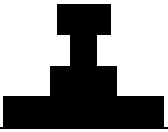
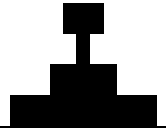
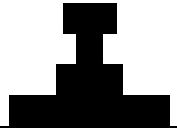
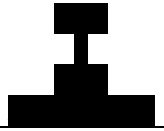
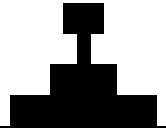
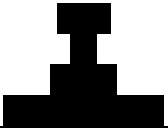
The most frequent SAEs by SOC (≥5% patients) were [redacted]

The proportion of patients who required dose interruptions due to a SAE was [redacted]

[redacted]

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Table 97: Serious adverse event rate adjusted for patient-years at risk by six month period and overall serious adverse events (JEWELFISH: safety-evaluable patients)

	RO6885247 (n=13)	Nusinersen (n=76)	Olesoxime (n=70)	AVXS-101 (n=14)	All patients (n=173)
Total treatment period Total patient-years at risk Number of adverse events Number of adverse events per 100 patient-years 95% CI					
0 - ≤12 months Total patient-years at risk Number of adverse events Number of adverse events per 100 patient-years 95% CI					
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>0 - ≤6 months Total patient-years at risk Number of adverse events Number of adverse events per 100 patient-years 95% CI					
>6 - ≤12 months Total patient-years at risk Number of adverse events Number of adverse events per 100 patient-years 95% CI					

Total patient-years at risk is the sum over all patients of the time intervals (in years) from the start of study treatment to the earliest date of study withdrawal, last treatment date or the clinical cut-off date. Only treatment emergent AEs are counted.

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Adverse events that led to withdrawal of treatment

The proportion of patients who experienced AEs leading to discontinuation of treatment in the all patients population was [redacted]

Adverse events that led to dose modification / interruption

The proportion of patients who experienced AEs leading to dose interruptions in the all patients population was [redacted] There were [redacted] leading to dose interruption. The most frequent AEs by PT (≥2 patients) that led to dose interruptions were; [redacted].

B.2.11 Ongoing studies

Several studies in the risdiplam clinical programme are ongoing, with anticipated timelines for final analyses summarised below:

Table 98: Risdiplam clinical development programme – planned analysis

Study	Analysis
FIREFISH	FIREFISH has recently closed, as the last patients reached 60 months of treatment. The final 5-year analysis will be provided as part of this submission in Q3 2024.
RAINBOWFISH	The primary analysis following 12 months of treatment has been completed. A final analysis will be conducted upon completion of the OLE, when all patients have 5 years of data (expected Q3 2027).
JEWELFISH	The primary analysis following 24 months of treatment has been completed. The final analysis will be conducted at the end of the OLE, when all patients have 5 years of data (expected Q3 2025).
REACH registries	A further report is expected Q2/3 2025.

B.2.12 Interpretation of clinical effectiveness and safety evidence

Risdiplam provides a substantial treatment benefit in patients across the SMA disease continuum and represents an important advancement in the treatment of SMA. The robust efficacy results observed in the clinical studies yield substantial divergence from the natural history of disease in patients with Type 1, 2 and 3 SMA when assessing patients' survival, achievement of critical motor development milestones and improvement in motor function. The clinical development programme demonstrates consistent efficacy across the spectrum of SMA and provides substantial evidence of effectiveness for risdiplam to a broad and heterogeneous population of people with SMA that is generally reflective of the prevalent SMA population seen in UK clinical practice.

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In the rare disease setting of SMA, the safety profile of risdiplam, as characterized in the studies described in this dossier, demonstrates that risdiplam was well tolerated. The safety profile of risdiplam supports the positive benefit versus risk profile across all types of SMA.

FIREFISH (infantile-onset, type 1 SMA)

Risdiplam treatment was associated with a clear gain of clinically important motor milestones including the primary endpoint of sitting without support. Furthermore, these milestones, which would never be achieved in patients with Type 1 SMA without treatment, were maintained throughout the treatment period. Patients who received risdiplam also had improvements in muscle electrophysiology, and maintenance of the bulbar function (particularly swallowing), while showing continuous growth and development. Additionally, the high proportion of risdiplam-treated patients who achieved ventilation-free survival represents a significant deviation from the expected natural history trajectory of survival consistently described across studies in infantile-onset type 1 SMA.

- **With [redacted], the difference from natural history is stark.** These patients would otherwise often die before the age of 2 due to respiratory complications (24, 30).
- **With regards to motor milestone development, children treated with risdiplam maintained or continued to improve in their abilities.** The primary endpoint of sitting without support for 5 seconds (assessed by BSID-III) would never be achieved by untreated children with type 1 SMA (24, 30, 112, 143, 144). Furthermore, [redacted], had developed the ability to stand or walk independently, respectively, which is a huge breakthrough for these patients that will positively impact their, and their families, lives. Focusing on HINE-2 and CHOP-INTEND, treated infants were gaining the ability to perform basic motor skills needed for children's development, with CHOP-INTEND scores that would never be attained by untreated infants with type 1 SMA (23) and HINE-2 response rates (defined as having more milestones that showed improvement than worsening) of 78% at month 48.
- **Swallowing and feeding ability was maintained by the majority of infants alive at Month 48**. In a natural history cohort, all infants with type 1 SMA older than 12 months required feeding support (24).
- **Risdiplam treatment dramatically reduced healthcare utilisation and overnight hospitalisation, the rate of which continued to decrease over time.** During the first 12 months of treatment, 49% of patients (90% CI: 35.1%, 62.6%) did not require any overnight hospitalisation. By month 48, the rate of hospitalisations was [redacted] hospitalisations per patient-year. In comparison, a natural history study of infantile-onset SMA, 91% of infants experienced ≥1 in-patient hospitalisation over a mean of 11 months after symptom onset (145).

Risdiplam was well tolerated in patients with Type 1 SMA. Furthermore, the rate of AEs and SAEs declined over 48 months in infants treated with risdiplam. No risks were identified following the review of the type and frequency of AEs as well as vital signs, physical examinations, ECG, ophthalmological assessments, and safety laboratory data. None of the

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nonclinical safety findings (effects on epithelial tissues, hematological effects, and retinal toxicity) were observed in these patients with infantile onset SMA.

An unanchored MAIC analyses was performed. using data from FIREFISH and ENDEAR to compare risdiplam with nusinersen for the treatment of infants with infantile-onset (Type 1) SMA. Improvements observed in survival and motor milestones were observed for risdiplam versus nusinersen, however the results could be confounded by unadjusted characteristics or unreported study differences. The comparison of risdiplam to OA was limited by the short follow-up data publicly available for STR1VE studies. It was not feasible to conduct an updated comparison to BSC (versus what was presented in TA755) as patients in the sham arm of ENDEAR switched to nusinersen after 12 months.

SUNFISH (later-onset, type 2 and 3 SMA)

Risdiplam treatment for up to 5 years resulted in an improvement or stabilisation in motor function in a broad and heterogeneous population of patients with later-onset, type 2 and type 3 SMA. SUNFISH included the broadest patient population in a placebo-controlled double-blind study that has been studied to date. There were no exclusion criteria for SMA complications such as severe scoliosis and joint contractures as in other clinical studies of active treatments for SMA, and the upper age limit was 25, thus the recruited population resembled the global spectrum of the disease, supporting the external validity of the trial results. Clinical opinion confirmed that the initial improvement in motor function, followed by long-term stabilisation is the trajectory they would expect to see for patients receiving a DMT. Furthermore, they believe this represents a halting of disease, which over 5 years is clinically meaningful, versus the continued decline in ability they would expect to see in these patients before treatments became available (146).

- **The improvement in motor function seen in patients treated with risdiplam at Month 12 was clinically meaningful and statistically significantly better than the placebo control data**. This coupled with the greater proportion of patients in the risdiplam arm (38.3%) than in the placebo arm (23.7%), having a clinically meaningful and statistically significant improvement in MFM32 total score ≥3 points confirms risdiplam's beneficial effect on motor function. Natural history suggests type 2/3 SMA patients would expect a yearly decline in the MFM32 scale without treatment (25), while the change from baseline MFM32 total score at 5 years shows that risdiplam treatment resulted in stabilisation in motor function, which is considered clinically meaningful for these patients, particularly over this long timeframe (146).
- Change from baseline in the MFM32 total score at 5 years shows that risdiplam treatment resulted in stabilisation of motor function, whereas natural history suggests type 2/3 SMA patients would expect a yearly decline without treatment.
- When considering upper limb function the **RULM showed a clinically meaningful and statistically significant difference between risdiplam and placebo in favour of risdiplam at 12 months.** The increase in RULM total score from baseline was sustained long-term up to month 60 with risdiplam treatment. For non-ambulant patients, preservation of upper limb function is essential for independent living and therefore stabilisation is of vital importance for these patients (146). Indeed, natural history data shows that adult SMA patients would expect to see a deterioration in the

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RULM over 24 months, so stabilisation for 5 years is a very positive outcome for patients.

- **There was a numerical improvement in favour of risdiplam in the HFMSE**, but the difference at Month 12 was not statistically significant. The small change was expected in the enrolled population with significant fixed disability and very low motor function scores at baseline, given that the HFMSE is not sensitive to capture change in people with a baseline HFMSE score <10 (41% had HFMSE baseline scores below 10) (28, 31, 32). This is an important consideration since severe complications such as contractures are associated with diminished motor ability and can impact performance on the HFMSE scale, thereby limiting a person's ability to attain a functional skill and realise a benefit from treatment (34).Given the variation in age and functional range together with differences in study enrolment criteria, the SUNFISH patient population is not directly comparable with those of other studies, which included patients that were generally younger and with less SMA complications or disability (76, 147). This is the first time the HFMSE and MFM32 have been used in the same clinical trial assessing a broad range of people with type 2 and 3 SMA. Both scales have different ability to capture clinical change; the MFM32 scale includes 3 domains that capture a broad range of motor function, including items relating to distal motor function that are primarily not assessed by the HFMSE, making the MFM32 a more relevant measure in those patients severely impacted by a more advanced disease (25, 31, 33).
- **Increases in motor function scores observed in the first year of risdiplam treatment were sustained for 5 years of treatment,** as demonstrated by the proportion of patients with a change from baseline of any threshold ≥0 across motor function scales, representing stabilisation or improvement in these measures**.** This is important, given avoiding deterioration (i.e. achieving disease stabilisation or improvement) was ranked as the most important treatment attribute by UK SMA patients in a discrete choice experiment (36).
- **Patients and caregivers reported continuous improvement or stabilisation in the level of help needed for activities of daily living.** Independence and the ability to perform basic personal tasks has been described by patients as a priority for type 2 and 3 SMA patients (73). SMAIS-ULM items focus on upper limb related activities of daily living with higher scores indicating greater independence in completing activities such as writing, using a touchscreen, dressing and washing the upper body, particularly relevant for the recruited population who are non-ambulant and wheelchair bound. These results indicate important improvements in patients' everyday lives with regards to increased independence.

Based on review of all available safety data, risdiplam was well tolerated without any adverse findings associated with risdiplam treatment, and AEs and SAEs reported reflective of underlying disease. None of the nonclinical safety findings were observed in these patients with later-onset SMA. The overall rate of AEs decreased over the first 48 months of treatment, and then stabilised from the third year of treatment onwards. Overall, the benefit–risk profile of risdiplam is favorable, in the absence of any identified risks and with evidence of clinically meaningful benefits.

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ITC analyses were conducted using data from SUNFISH and CHERISH to compare risdiplam with nusinersen for the treatment of Type 2 and 3 SMA. The comparisons were limited by the small overlap between the SUNFISH and CHERISH populations: SUNFISH had a significantly worse patient population at baseline and therefore the likelihood of capturing improvements in motor milestones is going to be more challenging compared to the CHERISH population, due to the breadth of difference in enrolment criteria. The MAIC methodology was used to further adjust for remaining differences in mean patient characteristics (e.g, age, HFMSE baseline score) between the SUNFISH subset and the CHERISH population. However, the ESS was greatly reduced after the matching-adjustment, particularly in the placebo arm. This resulted in wide confidence intervals around the relative effect estimates. Furthermore, due to differences observed in HFMSE and safety outcomes between the FIREFISH placebo and CHERISH sham arms, only the RULM endpoint was explored for the longer-term comparisons. Although a comparative estimate was produced, the MAIC did not provide sufficient evidence to draw definite conclusions on the comparison at year 1, 2 or 3. A key limitation to this comparison is that the population differences between SUNFISH and CHERISH/SHINE led to a large reduction in the effective sample size, which resulted in substantial uncertainty of the relative effects. Moreover, there are also differences and imbalances between the study populations that the analyses could not account for. A final limitation in the interpretation of the estimates produced, the MAIC approach assumes that the target population and comparator trials are similar, however the majority of patients in SUNFISH would not have been enrolled in CHERISH. The implication is that no inference of relative efficacy of risdiplam versus nusinersen can be made in patients that were excluded from CHERISH, such as adolescents and adults, patients with scoliosis and patients with weaker motor functions.

RAINBOWFISH (Paediatric, pre-symptomatic, genetically-diagnosed SMA)

In RAINBOWFISH, up to the CCOD (1 July 2021), the efficacy data demonstrated that presymptomatic patients who started risdiplam therapy before the age of 2 months and completed at least 12 months of therapy achieved important motor milestones, including sitting, standing, and walking, and developed high levels of motor function, irrespective of the number of *SMN2* copies. All but one of the patients were sitting without support at month 12, as assessed by BSID-III. Most of the patients achieved motor milestones within the WHO windows for healthy children. In addition, all patients were able to feed orally and none required hospitalization during the first year of treatment. Importantly, the milestones and motor function achieved deviated from the natural history of Type 1 and Type 2 SMA.

Risdiplam was well tolerated in presymptomatic patients with SMA, aged 16–40 days at first dose, who were exposed to risdiplam treatment for a median of 8.7 months (range: 0.5–22.8 months). Overall, the nature and incidence of AEs observed in this patient population were consistent with the known safety profile of risdiplam and as could be expected for infants of this age. No deaths or SAEs occurred up to the CCOD for this analysis. No new risks were identified following the review of the type and frequency of AEs as well as vital signs, physical examinations, ECG, ophthalmological assessments, and safety laboratory data. None of the nonclinical safety findings (effects on epithelial tissues, hematological effects, and retinal toxicity) were observed. The data supports a positive benefit/risk evaluation for the use of risdiplam for the treatment of SMA patients below the age of 2 months.

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ITCs were explored to compare the efficacy of risdiplam with nusinersen and onasemnogene abeparvovec for the treatment of patients with presymptomatic SMA. Three trials looking at these therapies were identified by a SLR: RAINBOWFISH, NURTURE and SPR1NT. However, owing to the small number of patients across studies, only naïve, unadjusted comparisons could be performed. These comparisons did not find any differences between risdiplam and other treatments.

JEWELFISH (previously-treated SMA patients)

The safety profile of risdiplam is consistent with the known safety profile thus far and no new findings were observed. Risdiplam was well tolerated in adult and adolescent patients who had received previous treatment with nusinersen, olesoxime, onasemnogene abeparvovec or RO6885247. No risks were identified following the review of the type and frequency of AEs as well as vital signs, physical examinations, ECG and safety laboratory data.

Registries (SMA in clinical practice)

The adult and paediatric SMA registry datasets, Adult SMA REACH and SMA REACH UK, were included in the DCA to observe how risdiplam is used within the real world, and aimed to capture data on key motor milestones to improve understanding of patient outcomes. However, at the time of the data cut for the analysis used in this submission very few patients had long-term follow up; most patients have a maximum of 12-month data, making it challenging to fully appreciate if there is any meaningful long-term benefits. Moreover, the severity of the population at baseline must be taken into account. A substantial proportion of patients included in this cohort (and likely the majority of those with long-term data) were patients who started receiving risdiplam initially through the EAMS. Patients received risdiplam through the EAMS as they were ineligible for nusinersen; this was likely due to spinal complications that made delivering a lumbar puncture too challenging, a clear marker of severity. In this cohort, clinicians confirmed they would expect improvements with treatment to be low (148). Overall, the incompleteness of the long-term registry outcomes coupled with the potential skew of the results due to baseline severity means the data should be interpreted with extreme caution and not given the same weighting as that obtained from the controlled clinical trials presented in this submission.

Despite the limitations of the data and the small patient numbers, a crude evaluation could be taken from the descriptive analyses provided. The paediatric cohort showed signs of motor function improvement in type 1 and an initial improvement followed by stabilisation in the type 2/3 patients. Furthermore, the adult cohort showed signs of improvement or stabilisation in upper limb function, particularly across measures designed to capture more subtle motor skills that might indicate preservation of independence. This is reflective of that observed in SMA clinical trials, whereby an initial improvement is observed followed by longer-term stabilisation when patients receive a DMT. As reported by both adult SMA patients and clinicians, stabilisation is of crucial importance and a desired treatment attribute (36, 146).

Conclusion

As discussed in Section B.1.3, there remains a clear unmet medical need in the field of SMA, particularly for those patients who prefer not to receive, or are ineligible for nusinersen or onasemnogene abeparvovec. In the case of nusinersen, patients may respond poorly, or cannot tolerate this intrathecally administered treatment due to fear surrounding or their

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inability to receive this invasive procedure. With regards to zolgensma, patients may be ineligible due to elevated anti-AAV serotype 9 antibodies, or families may be reluctant to choose this treatment option for their infant given the uncertainties surrounding the unknown long-term benefits. This clearly demonstrates the need for risdiplam as a disease-modifying therapy option for SMA patients.

By binding to two sites on the *SMN2* pre-mRNA, risdiplam increases levels of full length SMN mRNA and protein while reducing the possibility of off-target effects (149). Furthermore, by crossing the blood-brain barrier, risdiplam promotes a rapid and sustained increase in SMN protein in both the CNS and systemically throughout the body (99, 100) and is therefore hypothesised to bring greater efficacy in people with SMA than treatments targeting increases of functional SMN protein in the CNS alone.

The totality of data from studies in a heterogeneous patient population that is reflective of UK clinical practice demonstrates that risdiplam is highly effective in people with pre-symptomatic, infantile and late-onset disease, supporting the proposed broad indication for risdiplam as a treatment option for all people with SMA. Taken together with a favourable safety profile in paediatric and adult treatment-naïve and pre-treated patients with up to 5 years exposure, the evidence demonstrates a clearly positive benefit/risk profile for risdiplam and it is therefore anticipated to provide an additional innovative disease modifying therapy for all patients across the continuum of SMA (i.e., irrespective of the patient's age, type of SMA, or physical status).

As an oral therapy, risdiplam provides an easy and sustainable route of administration at home to best support a life-long chronic disease. Not only will this provide benefits to people with SMA and their caregivers, home care therapy will alleviate the burden on health care systems, resources and budgets, while expanding the population able to receive treatment with a disease modifying therapy.

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B.3 Cost effectiveness

B.3.1 Published cost-effectiveness studies

The *de novo* SLR and SLR updates were conducted on the 29th August 2019 and 22nd January 2024, respectively, to identify economic evaluations for treatment options in SMA. Eligibility criteria were not limited by type of SMA, severity or age of onset.

A total of 2,039 articles were identified from the searches. Finally, 15 full paper publications, reporting on 14 unique studies met the eligibility criteria and were included in the review.

The methodological details and results of the cost-effectiveness SLR for studies relevant to the UK setting are presented in Table 99; full details of the search strategy and the complete results are presented in Appendix G. The original risdiplam NICE submission [TA755] has not been extracted within the SLR, but will be presented and discussed in the main body of the submission.

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Table 99: Summary list of published economic evaluations included in the SLR

Study	Summary of model	Intervention/ comparator	Participant population	Base case costs (currency, year)	Base case health outcomes	Base case ICER	Relevance to decision problem (including NICE reference case)
Economic evaluations identified in SLR update							
SMC2401, 2022(150)	Model structure: Cost-utility analysis Separate Markov models provided for Type 1 and Type 2/3 SMA Both models included 6 states including death, 'Not sitting', 'sitting' 'standing' and 'walking' Type 1 model: 'Permanent ventilation' also included as a health state Type 2/3 model: 'Sitting' state split into 'sitting without support' and 'sitting with support' Model inputs: Clinical inputs sourced from FIREFISH/SUNFISH trials (risdiplam) and ENDEAR/CHERISH (nusinersen) trials ITCs (unanchored MAIC for Type 1 SMA; anchored MAIC for Type 2/3 SMA) were used for comparisons between risdiplam and nusinersen Utility data were derived from the literature or NICE TA588	Risdiplam with BSC (up to 5 mg orally, daily) Nusinersen with BSC (NR)	Type 1 model: Infants with symptomatic Type 1 SMA, aged 2−7 months Type 2/3 model: Ambulant and non-ambulant individuals with Type 2/3 SMA, aged 2−25 years	Total costs (GBP, 2021): Risdiplam: £239,633 per year (list price) Nusinersen: NR	NR	Type 1 model: Risdiplam dominated nusinersen at list prices Type 2/3 model: Risdiplam dominated nusinersen at list prices	Consistency with NICE reference case The study was conducted from a UK payer perspective; the results are therefore applicable to the UK setting Relevance to decision problem The study population (people with SMA Types 1−3) and interventions are relevant to the decision problem

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Study	Summary of model	Intervention/ comparator	Participant population	Base case costs (currency, year)	Base case health outcomes	Base case ICER	Relevance to decision problem (including NICE reference case)
	Drug acquisition, administration and resource use costs for intervention and comparator were estimated from real-world studies Time Horizon: Lifetime Perspective: Payer Cycle Length: One month (both models) Discount Rate: NR Health Benefits: NR; ICER only						
SMC1318 /18, 2018(151)	Model structure: Cost-utility analysis Two Markov models (one for infantile-onset SMA [Type 1] and one for later-onset SMA [Type 2 or 3]) Both models included ten states from baseline to alternative health states: worsen, stabilise, improve and death. Model inputs: Clinical evidence for the infantile and later-onset models based on the Phase 3 ENDEAR and CHERISH studies, respectively. Long-term extrapolation was applied to mortality, using	Intervention: nusinersen + RWC Comparator: RWC	Infantile-onset (Type 1 SMA): mean age: 5.6 months, 55% female Later-onset (those who have or who are most likely to develop Type 2 or 3 SMA): mean age: 43.7 months, 53% female NB Both models excluded individuals with pre-symptomatic SMA	Total costs (GBP, 2017): Nusinersen (Year 1): £450,000 Nusinersen (subsequent years): £225,000 Incremental costs (GBP, 2018): Infantile-onset model, nusinersen + RWC vs	Incremental LYG: Infantile-onset model, nusinersen + RWC vs RWC: 5.55 Later-onset model, nusinersen + RWC vs RWC: 1.38 Incremental QALYs: Infantile-onset model, nusinersen + RWC vs RWC: 5.02	ICER (£/QALY): Infantile-onset model, nusinersen + RWC vs RWC: £428,964 Later-onset model, nusinersen + RWC vs RWC: £1,624,951	Consistency with NICE reference case The study was conducted from a UK perspective; the results are therefore applicable to the UK setting Relevance to decision problem The study population and interventions considered align with the decision problem (people with SMA Types 1–3)

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Study	Summary of model	Intervention/ comparator	Participant population	Base case costs (currency, year)	Base case health outcomes	Base case ICER	Relevance to decision problem (including NICE reference case)
	data from other published studies Health state utilities in the later-onset model were derived from mapping PedsQL to the EQ-5D using a published algorithm. These were adapted to generate health state utilities for the infantile model Analysis included medicine acquisition and administration costs for nusinersen (administered via lumbar puncture) as well as SMA management and end of life costs Time Horizon: Infantile model: 40 years Later-onset model: 80 years Perspective: NHS Scotland and social work Cycle Length: NR Discount Rate: NR Health Benefits: LYG, QALYs, ICER			RWC: £2,151,509 Later-onset model, nusinersen + RWC vs RWC: £3,728,246	Later-onset model, nusinersen + RWC vs RWC: 2.29		
HST15, 2021(152)	Model structure: Cohort Markov state-transition model, consisting of two parts: Short-term model concordant with observed clinical trial data	Intervention: OA (one-time dose by IV infusion over ~60 mins, dose: 1.1x1014 vg/kg) + BSC	Infants with a diagnosis of 5q13 SMA Type 1, including those: with 2 copies of SMN2 gene, who had	Total costs (GBP, 2021): BSC: £707,836	Total LYG: BSC: 3.44 Nusinersen: 6.97 OA: 18.27	ICER (£/QALY vs BSC): Nusinersen: £1,354,762	Consistency with NICE reference case The study was conducted from a UK payer perspective; the results are therefore applicable to the UK setting

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Study	Summary of model	Intervention/ comparator	Participant population	Base case costs (currency, year)	Base case health outcomes	Base case ICER	Relevance to decision problem (including NICE reference case)
	Long-term (beyond three years) extrapolation model Clinical outcomes captured by moving treated individuals into higher functioning health states, which were associated with longer survival, higher QoL, and lower HCRU costs No individuals in the BSC arm were assumed to achieve any motor function milestones at any time point in accordance with observed data from several natural history studies; people receiving best supportive care could therefore only transition to worse health states Model health states differed based on the motor function milestones achieved by the person with SMA, the need for permanent assisted ventilation and time to death. The model included 2 health states that reflect the natural history of SMA Type 1 (not sitting and permanent assisted ventilation). Three higher functioning health states were possible for	Comparators: Nusinersen (12 mg per administration, in 4 loading doses) + BSC BSC	onset of symptoms at age ≤6 months, who were symptomatic at baseline of the clinical trials An equivalent genetic profile was also used for modelling the BSC arm in the base case	Nusinersen: £2,270,315 OA: £2,614,400 Incremental costs (GBP, vs BSC): Nusinersen: £1,562,479 OA: £1,906,564	Incremental LYG (vs BSC): Nusinersen: 3.53 OA: 14.83 Total QALYs: BSC: 0.65 Nusinersen: 1.81 OA: 11.42 Incremental QALYs (vs BSC): Nusinersen: 1.16 OA: 10.77	OA: £177,061	Relevance to decision problem The study population (people with SMA Types 1−3) and interventions are relevant to the decision problem

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Study	Summary of model	Intervention/ comparator	Participant population	Base case costs (currency, year)	Base case health outcomes	Base case ICER	Relevance to decision problem (including NICE reference case)
	people in the pharmacotherapy-treated arms (sits unassisted, walks unassisted and within a broad range of normal development) At model baseline, all individuals were in the not sitting state In the base case analysis, it was assumed that the motor function milestones achieved at the end of follow-up in the clinical trials were sustained until death Model inputs: Clinical input data for OA was taken from observed data in START (with the final evaluation document noting data was also pooled with the STR1VE-US study). Clinical input data for nusinersen was taken from observed data from SHINE. An external natural history control data set was required to model the BSC arm HCRU data was obtained from a de novo study with UK clinical experts and literature searches						

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Study	Summary of model	Intervention/ comparator	Participant population	Base case costs (currency, year)	Base case health outcomes	Base case ICER	Relevance to decision problem (including NICE reference case)
	Base case utility sources were based on the USA ICER's model, input from the EAG's clinical advisers and the published literature. An assumption was made that the independent walking health state would be equal to that of the age matched general population, aligned with the USA ICER report. No caregiver utilities were included in the model UK HCRU costs and utilities for untreated individuals with SMA who sit unassisted (SMA Type 2 used as proxy) and walk unassisted (SMA Type 3 used as proxy) were used to predict the costs and utilities of pharmacotherapy-treated SMA Type 1 individuals who achieve motor milestones Time Horizon: Lifetime horizon Perspective: NHS and PSS in England Cycle Length: 6 months for first 3 years, then annually Discount Rate: 3.5%; 1.5% A discount rate used for decision making as OA was						

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Study	Summary of model	Intervention/ comparator	Participant population	Base case costs (currency, year)	Base case health outcomes	Base case ICER	Relevance to decision problem (including NICE reference case)
	considered likely to have long-term benefits and may restore a proportion of people to near-full health Health Benefits: LYG, QALYs, ICER						
SMC2311, 2021(153)	Model structure: Cost-utility analysis framework Markov 6-state transition model defined by milestones for people with SMA for selected motor development outcomes from birth: 'normal development', 'walking unassisted', 'sitting unassisted', 'not sitting', permanent assisted ventilation' and 'death' Regression from states (i.e. deterioration) was only possible upon cessation of treatment (only possible for the comparator treatment nusinersen). Remaining on treatment, individuals would stay in the state for which they had achieved the highest motor milestone Model inputs: Clinical data in the model base case used the MAIC	Intervention: OA Comparator: nusinersen	Individuals with 5q SMA with a bi-allelic mutation in SMN1 and a clinical diagnosis of SMA Type 1	Total costs (GBP, 2021): OA: £2,704,737 Nusinersen: £2,800,590 Incremental costs: OA vs nusinersen: −£95,853	Total LYG: OA: 12.87 Nusinersen: 8.46 Incremental LYG: OA vs nusinersen: 4.41 Total QALYs: OA: 7.50 Nusinersen: 3.77 Incremental QALYs: OA vs nusinersen: 3.72	ICER (£/QALY): OA vs nusinersen: −£25,740	Consistency with NICE reference case The study was conducted from a UK payer perspective; the results are therefore applicable to the UK setting Relevance to decision problem The study population (people with SMA Type 1) was narrower than the decision problem population (people with SMA Types 1–3). The interventions considered are relevant to the decision problem

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Study	Summary of model	Intervention/ comparator	Participant population	Base case costs (currency, year)	Base case health outcomes	Base case ICER	Relevance to decision problem (including NICE reference case)
	values from the ITC; base case values had to be adjusted to account for the fact that the states individuals transition to relate to meeting motor development milestones, and so are based on age rather than time since treatment commenced Clinical data was supplemented by natural history datasets. Additional data sources include expert advice from clinicians and proxy use of BSC survival outcomes for individuals with SMA Type 2 and 3 Utility values were sourced from the literature using proxy parental or carer values and/or clinical advice Resource use was estimated via telephone survey of clinicians in the UK Time Horizon: Lifetime Perspective: Health and social care Cycle Length: 6 months for the first 3 years and annually thereafter Discount Rate: NR						

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Study	Summary of model	Intervention/ comparator	Participant population	Base case costs (currency, year)	Base case health outcomes	Base case ICER	Relevance to decision problem (including NICE reference case)
	Health Benefits: LYG, QALYs, ICER						
HST24, 2023(154)	Model structure: Cohort Markov state-transition model For the OA arm, the model consists of two parts: Short-term model concordant with observed clinical trial data Long-term extrapolation model For the BSC arm, a long-term extrapolation model is used to model the entire lifetime time horizon, as SPR1NT was a single-arm trial and clinical trial data were not available from SPR1NT for the BSC arm Model health states differed based on the highest motor function milestones achieved by the person with SMA, the need for permanent assisted ventilation and time to death. The model included not sitting and permanent assisted ventilation, not sitting and no permanent assisted ventilation, sitters, delayed walker, late-onset SMA health state and within	Intervention: OA (one-time, single-dose by IV infusion over ~60 mins, dose: 1.1x1014 vg/kg) Comparator: BSC	Newborn infants with genetically confirmed, pre-symptomatic SMA with 2 or 3 copies of the SMN2 gene, who were age ≤6 weeks (≤42 days) at time of treatment	Total costs (GBP, 2021): BSC: £882,564 OA: £2,096,927 Incremental costs (GBP, vs BSC): OA: £1,214,363	LYG/QALYs were redacted	ICER (£/QALY vs BSC): OA: £70,610	Consistency with NICE reference case The study was conducted from a UK payer perspective; the results are therefore applicable to the UK setting Relevance to decision problem The study population (people with SMA Type 1−3) and interventions are relevant to the decision problem

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Study	Summary of model	Intervention/ comparator	Participant population	Base case costs (currency, year)	Base case health outcomes	Base case ICER	Relevance to decision problem (including NICE reference case)
	a broad range of normal development Observed clinical outcomes are captured in the model by moving individuals into lower functioning health states if they do not meet developmental milestones; lower functioning health states are associated with poorer survival, lower QoL, and higher HCRU costs. Individuals can only be in one state at a time and all participants must be captured in a state; individuals can progress to death from any health state Model inputs: Sources of clinical input data were the Phase 3 SPR1NT trial and the long term follow up trial LT-002 for the OA arm, and well-characterised natural history data sets for the BSC arm, identified through an SLR Utility value inputs were sourced from published literature Cost data were sourced from a UK HCRU study and the						

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Study	Summary of model	Intervention/ comparator	Participant population	Base case costs (currency, year)	Base case health outcomes	Base case ICER	Relevance to decision problem (including NICE reference case)
	NHS Schedule of Reference Costs 2017–18 Time Horizon: Lifetime horizon (100 years) Perspective: NHS and PSS in England Cycle Length: 1 month (with half cycle correction applied) Discount Rate: 3.5% Health Benefits: ICER (LYG and QALYs redacted)						
Economic evaluations identified in original SLR							
CADTH, 2018(155) Country: Canada	Model structure: Three Markov models for SMA Type 1, 2 and 3 Time horizon: SMA Type 1: 25 years SMA Type 2: 50 years SMA Type 3: 80 years Perspective: Canadian public health care system Cycle length: SMA Type 1: Individuals could transition between health states at 2-, 6-, 10-, 13- and 14-months SMA Type 2: 3 months conforming to CHERISH, subsequent cycles every 4 months	Nusinersen RWC	People with SMA – stratified by SMA type (Type 1, 2 and 3)	Total costs (CAD, 2017): SMA Type 1: Nusinersen: $3,534,854 RWC: $339,683 SMA Type 2: Nusinersen: $8,336.271 RWC: $708,620 SMA Type 3:	Total LYs: SMA Type 1: Nusinersen: 8.373 RWC: 3.583 SMA Type 2: Nusinersen: 28.527 RWC: 26.348 SMA Type 3: Nusinersen: 44.155 RWC: 44.155 Total QALYs: SMA Type 1: Nusinersen: 3.919 RWC: -0.881 SMA Type 2: Nusinersen: 23.278	ICER/QALY: SMA Type 1: Nusinersen vs RWC: $665,570 SMA Type 2: Nusinersen vs RWC: $2,075,435 SMA Type 3: Nusinersen vs RWC:	The study population is relevant (people with SMA Type 1, 2 and 3) The manufacturer reported that the probability that nusinersen was cost-effective assuming a willingness to pay of $300,000 per QALY was 0% for all SMA types The study was conducted from a USA payer perspective; it is therefore unclear if results are applicable to UK setting

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Study	Summary of model	Intervention/ comparator	Participant population	Base case costs (currency, year)	Base case health outcomes	Base case ICER	Relevance to decision problem (including NICE reference case)
	SMA Type 3: 3 months (for the first 27 months, subsequent cycles every 4 months) Discount rate: 1.5% costs and benefits Health benefits: LYs, QALYs			Nusinersen: $5,554,707 RWC: $1,091,307	RWC: 19.602 SMA Type 3: Nusinersen: 12.053 RWC: 10.490	$2,855,818	
ICER, 2019(156) Country: USA	Model: Three de novo Markov models: Symptomatic infantile-onset model Symptomatic later-onset model Pre-symptomatic model Time horizon: Lifetime (all models) Perspective: USA health care sector perspective Cycle length: 1 month Discount rate: 3.0% costs and benefits Health benefits: LYs, QALYs	Nusinersen vs BSC OA vs BSC	People with SMA of all ages and types	Total costs (USD, 2002): Infantile-onset: Nusinersen: $3,884,000 BSC: $789,000 Infantile-onset: OA: $3,657,000 BSC: $789,000 Later-onset: Nusinersen: $9,148,000 BSC: $1,442,000	Total LYs: Infantile-onset: Nusinersen: 7.64 BSC: 2.40 Infantile-onset: OA: 18.17 BSC: 2.40 Later onset: Nusinersen: 18.90 BSC: 18.90 Pre-symptomatic: Nusinersen: 26.58 BSC: 9.51 Total QALYs: Infantile-onset: Nusinersen: 3.24 BSC: 0.46 Infantile-onset: OA: 12.23 BSC: 0.46 Later-onset:	ICER/LYG: Infantile-onset: Nusinersen vs BSC: $590,000 OA vs BSC: $182,000 Later-onset: Nusinersen vs BSC: Dominated Pre-symptomatic: Nusinersen vs BSC: $652,000 ICER/QALY:	The study population is relevant (people with SMA) Nusinersen did not meet the cost-effectiveness thresholds in any of the populations OA did not meet traditional cost-effectiveness benchmarks for use in individuals with SMA Type 1 and would have to reduce its price to meet a $150,000 per QALY threshold The study was conducted from a USA payer perspective; it is therefore unclear if results are applicable to UK setting

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Study	Summary of model	Intervention/ comparator	Participant population	Base case costs (currency, year)	Base case health outcomes	Base case ICER	Relevance to decision problem (including NICE reference case)
				Pre-symptomatic: Nusinersen: $11,929,000 BSC: $801,000	Nusinersen: 12.28 BSC: 11.34 Pre-symptomatic: Nusinersen: 21.94 BSC: 6.25	Infantile-onset: Nusinersen vs BSC: $1,112,000 Infantile-onset: OA vs BSC: $243,000 Later-onset: Nusinersen vs BSC: $8,156,000 Pre-symptomatic: Nusinersen vs BSC: $709,000	
NICE TA588, 2019(157) Country: UK	Model: Two Markov models: Early-onset: Later-onset Time horizon: Infantile-onset: 40 years (lifetime) Later-onset: 80 years Perspective: Payer (UK NHS and PSS; including caregiver	Nusinersen RWC	People with infantile (Type 1) and later-onset (Type 2/3) SMA	Total costs (GBP, 2016): Early-onset SMA: RWC: £71,540	Total LYG: Early-onset SMA (individual with SMA): RWC: 3.39 Nusinersen: 9.34 Later-onset SMA (individual	ICER/QALY: Early-onset SMA (individual with SMA): Nusinersen vs	The study population is relevant (people with SMA Type 1, 2 and 3) The cost per QALY ratio is in excess of NICE's conventional benchmarks of £20-30,000 per QALY; it should therefore be evaluated alongside the

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Study	Summary of model	Intervention/ comparator	Participant population	Base case costs (currency, year)	Base case health outcomes	Base case ICER	Relevance to decision problem (including NICE reference case)
	burden; societal perspective considered in scenario analysis) Cycle length: Early-onset: 2, 6, 10, 13 and 14, 18 and every 4 months after Later-onset: 3, 6, 9, 12, 15, 19, 23 and every 4 months thereafter Discount rate: 3.5% costs and benefits Health benefits: LYs, QALYs			Nusinersen: £2,258,852 Later-onset SMA: RWC: £184,312 Nusinersen: £3,148,754 Early-onset SMA: RWC: £71,540 Nusinersen: £2,258,852 Later-onset SMA RWC: £184,312 Nusinersen: £3,148,754	with SMA; list price): Nusinersen: 19.61 RWC: 20.99 Early-onset SMA Individual with SMA and carer): RWC: 3.39 Nusinersen: 9.33 Later-onset SMA (individual with SMA and carer): RWC: 19.61 Nusinersen: 20.99 Total QALYs: Early-onset SMA (individual with SMA): RWC: 2.49 Nusinersen: 7.86 Later-onset SMA (individual with SMA): Nusinersen: 14.52 RWC: 16.88	RWC: £407,605 Later-onset SMA (list price; individual with SMA): Nusinersen vs RWC: £1,252,991 Early-onset SMA (individual with SMA and caregiver): Nusinersen vs RWC: £402,361 Later-onset SMA (list price; individual with SMA and	range of outcomes generated by nusinersen The ERG noted that given the acquisition cost of nusinersen, the level of decision uncertainty with respect to NICE's usual thresholds for cost-effectiveness is low The study was conducted from a UK payer perspective; therefore, results are applicable to UK setting

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Study	Summary of model	Intervention/ comparator	Participant population	Base case costs (currency, year)	Base case health outcomes	Base case ICER	Relevance to decision problem (including NICE reference case)
					Early-onset SMA (individual with SMA and caregiver): RWC: 2.17 Nusinersen: 7.61 Later-onset SMA (individual with SMA and caregiver): Nusinersen: 12.36 RWC: 15.66	caregiver) : Nusinersen vs RWC: £898,164	
Malone, 2019a(158) Country: USA (Linked to Malone, 2019b(159))	Model: Markov model Time horizon: Lifetime Perspective: USA commercial payer Cycle length: six months for the first three years, and then 12 months for all cycles thereafter Discount rate: 3.0% costs and benefits Health benefits: LYs, QALYs	OA Nusinersen	Paediatric individuals with SMA Type 1 and two copies of SMN2, diagnosed before the age of six months, and treated with either therapeutic dose of OA or nusinersen	Total average cost per year per person (USD, reference year NR): OA (reported by hypothetical cost): $2.5M: $4,214,379, $3M: $4,699,816, $4M: $5,670,690	Total LYs: Undiscounted: OA: 37.20 Nusinersen: 9.68 Discounted: OA: 19.81 Nusinersen: 7.11 Total QALYs: Discounted: OA: 15.65 Nusinersen: 5.29 Undiscounted: OA: 29.86 Nusinersen: 7.21	ICER/QALY, OA vs nusinersen (reported by hypothetical costs): $2.5M: OA dominates $3M: OA dominates $4M: OA dominates	The study population is relevant (people with SMA Type 1) Single-dose OA was cost-effective compared with chronic nusinersen for people with SMA Type 1 The study was conducted from a USA payer perspective; it is therefore unclear if results are applicable to UK setting

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Study	Summary of model	Intervention/ comparator	Participant population	Base case costs (currency, year)	Base case health outcomes	Base case ICER	Relevance to decision problem (including NICE reference case)
				, $5M: $6,641,564 Nusinersen: $6,316,711		$5M: $31,379	
Malone, 2019b(159) Country: USA (Linked to Malone, 2019a)(158)	Model: Markov model Time horizon: Lifetime Perspective: NR Cycle length: NR Discount rate: 3.0% costs and benefits Health benefits: QALYs	OA Nusinersen	People with SMA Type 1	NR	Total QALYs: Undiscounted: OA: 30.3 Nusinersen: 7.2 Discounted: OA: 15.9 Nusinersen: 5.3	ICER/QALY: OA vs nusinersen: OA dominates	The study population is relevant (people with SMA) OA is cost-effective compared to nusinersen Discounting QALYs at the USA standard rate of 3% results in a substantial underestimate of health benefits; undiscounted QALYs should be considered when assessing the value of innovative therapies The study was conducted from a USA payer perspective; it is therefore unclear if results are applicable to UK setting
Thokala, 2019(160) Country: USA	Model: de novo economic model Time horizon: NR Perspective: USA health care sector perspective Cycle length: NR Discount rate: 3.0% cost and benefits Health benefits: QALYs	Nusinersen OA BSC	People diagnosed with infantile-onset SMA in the USA	NR	NR	ICER/QALY: Nusinersen vs BSC: did not fall below $1 million (scenario/ one-way	The study population is relevant (people with SMA) The estimated Incremental cost-effectiveness of nusinersen and OA from a USA health care sector perspective exceeded commonly cited cost-

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Study	Summary of model	Intervention/ comparator	Participant population	Base case costs (currency, year)	Base case health outcomes	Base case ICER	Relevance to decision problem (including NICE reference case)
						sensitivity analyses) OA vs BSC: $205,000-$412,000	effectiveness thresholds of $50,000 to $150,000 per QALY Due to the relatively short-term effectiveness data available for SMA therapies, a registry to collect long-term data of people with SMA is recommended The study was conducted from a USA payer perspective; it is therefore unclear if results are applicable to UK setting
Zuluaga-Sanchez, 2019a(161) Country: Sweden	Model: Markov model: Infantile-onset Later-onset Time horizon: Infantile onset: 40 years Later-onset: 80 years Perspective: Societal perspective in Sweden Cycle length: 4 months Discount rate: 3% discount for both costs and benefits Health benefits: LYs and QALYs	Nusinersen + SOC SOC	Individuals with infantile-onset and later-onset SMA	Total infantile-onset costs (SEK, 2018): Nusinersen + SOC: 23,920,567 SOC: 2,066,516 Incremental: 21,854,051 Total later-onset costs	Total LYs (discounted): Infantile-onset: Nusinersen + SOC: 7.23 SOC: 1.01 Later-onset: Nusinersen + SOC: 23.13 SOC: 21.28 Total individual with SMA QALYs (discounted): Infantile-onset: Nusinersen + SOC: 3.65 SOC: −0.20	ICER/QALY, nusinersen + SOC vs SOC: Infantile-onset: 5,635,978 SEK Later-onset: 3,187,222 SEK	The study population is relevant (people with SMA) Nusinersen was associated with improved survival, and QALY, however it was not considered cost-effective when using a willingness-to-pay threshold of 2 million SEK (€195,600) The study was conducted from a Swedish societal perspective; it is therefore unclear if results are applicable to UK setting

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Study	Summary of model	Intervention/ comparator	Participant population	Base case costs (currency, year)	Base case health outcomes	Base case ICER	Relevance to decision problem (including NICE reference case)
				(SEK, 2018): Nusinersen + SOC: 66,053,350 SOC: 28,029,941 Incremental: 38,023,409	Later-onset: Nusinersen + SOC: 9.25 SOC: −0.29 Total caregiver QALYs (discounted): Infantile-onset: Nusinersen + SOC: −0.10 SOC: −0.12 Later-onset: Nusinersen + SOC: −1.37 SOC: −3.76		
Zuluaga-Sanchez, 2019b(162) Country: USA	Model: Markov model Time horizon: 80 years Perspective: Third-party payer perspective Cycle length: NR Discount rate: NR Health benefits: LYs and QALYs	Nusinersen SOC	Later-onset SMA	NR	Total LYs (discounted): Nusinersen: 21.39 SOC: 21.04 Total QALYs (discounted): Nusinersen: 13.89 SOC: 12.71	ICER/QALY: Nusinersen vs SOC: Exceeded $500,000/QALY	The study population is relevant (people with SMA) Despite the ICER for nusinersen vs SOC exceeding the orphan drug threshold; an estimated incremental cost offset of direct disease management of $133,996 and incremental QALY benefit for caregivers of 4.08 for nusinersen-treated individuals compared with SOC was reported by the model

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Study	Summary of model	Intervention/ comparator	Participant population	Base case costs (currency, year)	Base case health outcomes	Base case ICER	Relevance to decision problem (including NICE reference case)
							The study was conducted from a USA payer perspective; it is therefore unclear if results are applicable to UK setting
Zuluaga-Sanchez, 2019c(163) Country: USA	Model: Markov model Time horizon: 60 years Perspective: Third-party payer Cycle length: NR Discount rate: NR Health benefits: LYs, QALYs	Nusinersen SOC	Individuals with infantile-onset SMA (most likely to develop SMA Type 1 or 2)	NR	Total LYs (discounted): Nusinersen: 4.37 SOC: 2.15 Total QALYs (discounted): Nusinersen: 2.05 SOC: 0.41	ICER/QALY: Nusinersen vs SOC: Exceeded $500,000/QALY	The study population is relevant (people with SMA) Despite nusinersen vs SOC exceeding the orphan drug threshold, the incremental cost offset of direct disease management was $175,772 for individuals treated with nusinersen vs SOC who had not achieved any milestones The study was conducted from a USA payer perspective; it is therefore unclear if results are applicable to UK setting

Abbreviations: BSC: best supportive care; CAD: Canadian Dollar; GBP: Great British Pound; EAG: Expert Advisory Group; ERG: Evidence Review Group; HCRU: healthcare resource use; HST: highly specialised technology; ICER: incremental cost-effectiveness ratio/ Institute for Clinical and Economic Review; ITC: indirect treatment comparison; IV: intravenous; LY: life-year; LYG: life-years gained; MAIC: matching adjusted indirect comparison; NHS: National Health Service; NICE: National Institute for Health and Care Excellence; NR: not reported; OA: onasemnogene abeparvovec; PedsQL: Paediatric Quality of Life Inventory; PSS: Personal Social Services; QALY: quality-adjusted life year; QoL: quality of life; RWC: real-world care; SEK: Swedish Krona; SLR: systematic literature review; SMA: spinal muscular atrophy; SMC: Scottish Medicines Consortium; SMN: survival of motor neuron; SOC: standard of care; TA: technology appraisal; UK: United Kingdom; USA: United States of America; vg/kg: vector genomes per kilogram; USD: United States Dollar.

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B.3.2 Economic analysis

The three economic models have been developed based on the TA755 economic evaluation to determine the cost-effectiveness of risdiplam in presymptomatic SMA, SMA type 1 and SMA type 2/3. It is necessary to model patients with presymptomatic SMA, type 1 and type 2/3 separately due to the differences in natural history, severity and prognosis between the individual types of SMA. The structure of the models was informed by previous SMA models, clinical guidelines and clinical expert opinion, as described below.

Within each subsection of Section B3, unless the same methodology applies for all three models, the specific patient model will be denoted.

B.3.2.1. Patient population

Presymptomatic model: The patient population of this model mirrors that of the RAINBOWFISH clinical trial for risidiplam; presymptomatic infants aged 1 to 42 days (6 weeks), without any treatment, who would develop a phenotype of Type 1 SMA. The patient population is in line with the marketing authorisation for risdiplam and the final scope for this submission.

Type 1 model: The patient population of this model mirrors that of the FIREFISH phase 2/3 clinical trial for risdiplam, which included infants with symptomatic type 1 SMA aged 1–7 months at the time of enrolment. The patient population is in line with the marketing authorisation for risdiplam and the final scope for this submission.

Type 2/3 model: The patient population of this model mirrors that of the SUNFISH phase 2/3 randomised clinical trial for risdiplam, which included both ambulant and non-ambulant patients aged 2–25 years at the time of enrolment with type 2 and 3 SMA. The patient population is in line with the marketing authorisation for risdiplam and the final scope for this submission.

The detailed eligibility criteria for the FIREFISH and SUNFISH trials are described in B.2.3.

B.3.2.2 Model structure

The design of the structure for the three economic models were informed by a number of sources including literature reviews, clinical guidelines, prior HTA reports and consultations with expert clinicians and physiotherapists working with SMA patients on a regular basis. TA755 had initially ran two UK advisory boards with clinical experts to further validate the model structures. At the UK advisory boards, 10 neurology/neuromuscular disorder experts (8 clinicians and 2 physiotherapists) with experience of treating a broad population of SMA patients in the UK were consulted (Appendix Q). Focus was placed on understanding the natural history and survival of SMA patients in order to model this as accurately as possible (67). The key finding from consultation of these sources was that SMA is highly driven by patients' achievement of developmental motor abilities, and additionally for type 1 permanent ventilation was included to reflect the greater severity and inferior prognosis when compared to type 2/3.

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For the presymptomatic model, a similar exercise was carried out with expert review of the model by clinical experts, external review of the model for error and sense checking and the comparison of the model to other economic models such as for SMA type 1.

Following TA755 and as part of the data collection arrangement (DCA) portion of the MAA, a UK advisory board was held with academic health economics experts to discuss potential modelling approaches for the updated cost-effectiveness model of risdiplam in SMA (164). During the advisory board, 3 academic experts were consulted to understand how the economic models could better capture the challenges of living with SMA. As with TA755, it was noted that the models have inherent limitations and cannot capture all aspects of SMA experienced by patients and their carers. This is a well-documented limitation of most economic models, which are a simplification of reality and cannot fully capture all elements of a disease. For example, the clinical experts noted that factors such as ability to feed and frequency of hospital visits may also affect patient and carer HRQoL. There may also be within-milestone improvements that positively affect patient and carer HRQoL, such as improvements in upper limb function for patients in wheelchairs. As a result, the full value of SMA treatments such as risdiplam cannot be captured in their entirety in cost-effectiveness models. This was further acknowledged by NICE in the appraisal of nusinersen (TA588 (18)) and during the initial appraisal of risdiplam (TA755 (67)), where it was noted that the broad and severe impact of SMA on patients and carers cannot fully be captured by the economic models or the NICE reference case. Therefore, in order to ensure consistency in NICE decision-making, similar flexibility should be acknowledged in the re-appraisal of risdiplam to recognise that some benefits of risdiplam in SMA cannot be fully captured by health economic modelling.

The outputs of the 13th April 2022 advisory board had made recommendations such as the addition of treatment responders and non-responders and modelling additional benefits such as upper limb function for patients, however the incorporation of these additions is limited by the availability of data (164).

The structures of each economic model are described further below.

Presymptomatic SMA (RAINBOWFISH) model and type 1 SMA (FIREFISH) model

A Markov model was developed in Microsoft Excel with four health states representing key motor milestones, in addition to a ‘permanent ventilation’ health state and an absorbing ‘death’ health state. The motor milestone health states comprised ‘not sitting’, ‘sitting’, ‘standing’ and ‘walking’. This set of motor milestones was validated by clinical experts as being feasible for presymptomatic and type 1 SMA patients to achieve in their lifetime when receiving disease-modifying therapy, as well as clinically meaningful to patients and their caregivers. Additionally, this model structure was similar to that considered for the economic models in TA588 and developed by ICER (18, 165). A diagram of the presymptomatic and type 1 SMA (FIREFISH) model is presented in Figure 28.

The definition of the ‘not sitting,’ ‘sitting’ (with or without support), ‘standing’ (with or without support) and ‘walking’ (with or without support) health states is informed by items of the HINE-2 scale, a measure of motor ability included as a key secondary outcome of both the RAINBOWFISH and FIREFISH trials.

The RAINBOWFISH and FIREFISH studies captured several motor-milestone outcome measures including HINE-2, BSID-III and CHOP-INTEND. In addition, HINE-2 is also

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commonly used in the regular development of infants (166). Previous evidence has shown that without intervention, SMN2 copy and type 1 infants were not able to achieve many indicators within HINE-2 during natural history (30). Hence, any achievements for type I patients within this scale would indicate an improvement from natural history or the disease and provide a comparison for the potential of normal development for infants (114).

The HINE-2 scores representing these health states are presented in Table 100. The items of the HINE-2 selected to represent the motor milestones was validated within clinicians during model design.

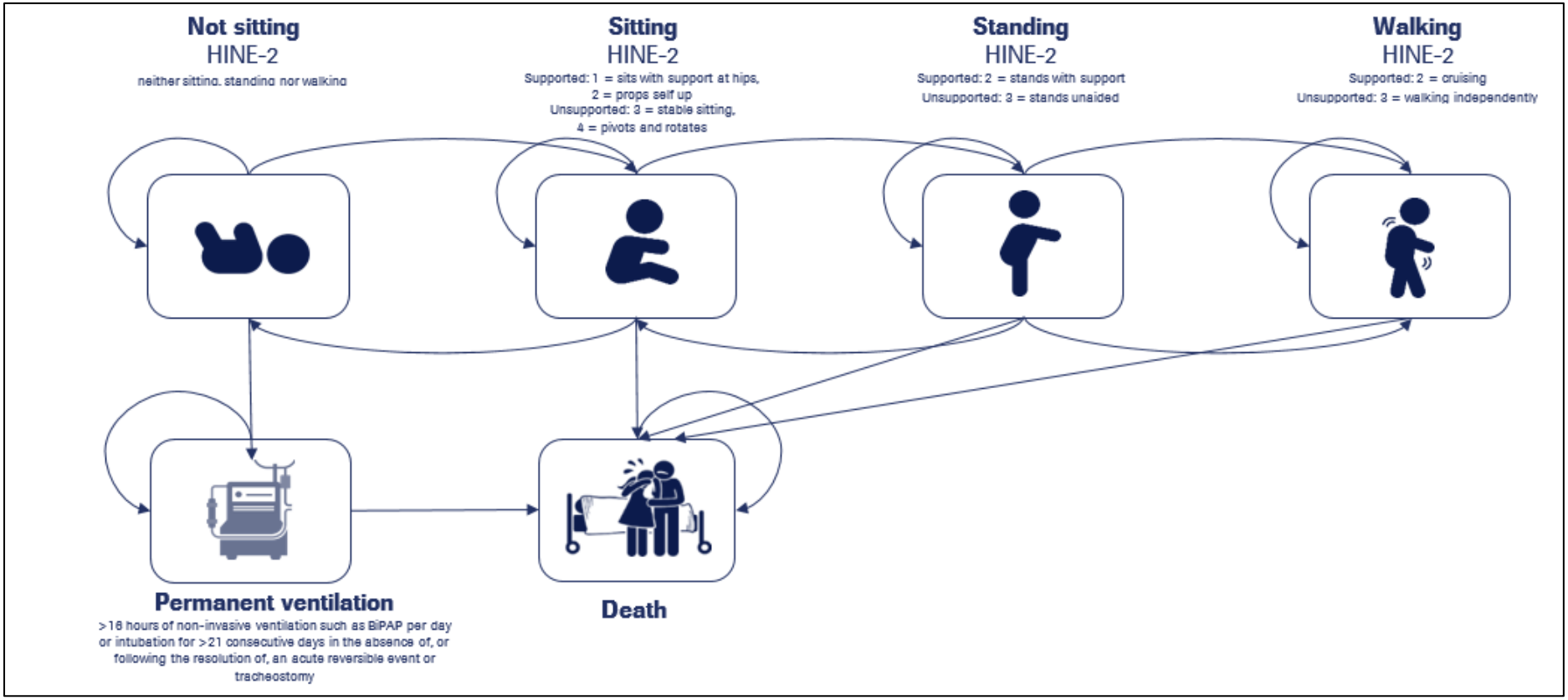
Table 100. HINE-2 scores representing motor milestone health state in presymptomatic (RAINBOWFISH) and type 1 SMA (FIREFISH) model

Health state	HINE-2 motor function group	Milestone progression score
Not sitting	NA	NA
Sitting (with or without support)	Sitting	1, 2, 3, 4
Standing (with or without support)	Standing	2, 3
Walking (with or without support)	Walking	2, 3

HINE-2: Hammersmith Infant Neurological Examination; NA: not applicable

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Figure 28. Diagram of the presymptomatic and type 1 SMA (FIREFISH) model



HINE-2, Hammersmith Infant Neurological Examination.

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The HINE-2 measure is also the common endpoint to facilitate the ITC to BSC and nusinersen for type 1 (Section B.2.9). Clinical experts consulted during model development and during the UK advisory boards concurred that the HINE-2 is an appropriate measure to demonstrate achievement of motor function milestones for presymptomatic and type 1 patients (Section B.3.14).

Due to the inferior prognosis of presymptomatic and type 1 SMA patients compared to type 2/3 patients, and the corresponding greater likelihood of a need for permanent ventilation (167), an additional 'permanent ventilation' health state was included in the type 1 model. Feedback from expert clinicians practicing in the UK was that due to advances in therapies for SMA in recent years, parents and physicians have become more willing to prolong patients' lives utilising permanent ventilation in the UK, despite the poor levels of quality of life associated with such treatment (67). Accordingly, it was deemed appropriate to include this health state within the model to reflect current clinical practice. Within the model, permanent ventilation is consistent with the definition in the FIREFISH trial: >16 hours of non-invasive ventilation such as Bilevel Positive Airway Pressure (BiPAP) per day or intubation for >21 consecutive days in the absence of, or following the resolution of, an acute reversible event or tracheostomy (108).

In line with the baseline characteristics observed in the FIREFISH trial, patients start in the 'not sitting' health state (see Section B.3.3.2) and are assigned to treatment with risdiplam or BSC. From this health state, patients' motor abilities may improve or the stay the same, or a patient may deteriorate to the 'permanent ventilation' health state. Once patients have transitioned to the 'permanent ventilation' health state, they may not progress to any motor milestone gains; patients remain within this state until death. Within the cycle length of one month, patients may improve or deteriorate by no more than one health state, as informed by clinician input.

In line with the NICE reference case (77), the cost-effectiveness analysis for the presymptomatic and the type 1 model is conducted from the perspective of the NHS and Personal Social Services in the base case, taking account of costs directly related to the medical treatment of SMA patients, and the quality of life of SMA patients and their carers. The approach to including cost and resource use in the model is described further in Section B.3.5.2. The approach to modelling HSUVs for patients and carers is outlined in Section B.3.4.5. As noted above, the model cycle length is one month and a half cycle correction is applied to account for mid-cycle transitions. Costs and benefits are discounted at 3.5% per year, as per the NICE reference case (168).

Features of the economic analysis for the presymptomatic and type 1 SMA model can be seen at Table 101.

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Table 101. Features of the economic analysis (presymptomatic and type 1) model

Factor	Previous appraisals		Current appraisal presymptomatic and type 1	
	TA588	HST15	Chosen values	Justification
Time horizon	Lifetime (60 years)	Lifetime (years not provided)	Lifetime ([redacted])	The mean baseline age in the model is 0.48 years (5.8 months). In line with the NICE reference case (168) a lifetime time horizon has been selected that is reflective of what type 1 patients would achieve. 30 years was selected to capture all costs and benefits associated with risdiplam or treatment with BSC. A time horizon of [redacted] was selected so that effectively all patients in both treatment arms of the model would be dead by the end of the time horizon, therefore allowing for all cost benefits to be captured (see Section B.3.14).
Long-term clinical outcomes	In the manufacturer's original base case early-onset SMA model, on-treatment transition probabilities during trial follow-up reflect motor milestone achievements from the ENDEAR trial. After trial follow-up, patients on nusinersen could only improve in health state, whilst patients on BSC could only decline or remain constant. As the ENDEAR trial included a placebo arm,	Clinical input data for OA was taken from observed data in START (with the final evaluation document noting data was also pooled with the STR1VE-US study). Limited longer-term data was provided from LT-001 (n=10). Clinical input data for nusinersen was taken from observed data from SHINE. An external natural	In the base case, patients on risdiplam treatment are assumed to either improve (in terms of health states achieved) or remain stable in the long-term. It was observed that 12% of patients advanced to walking during the	This approach was validated by UK clinical expert, which stated that the majority of patients receiving active treatment would remain stable or improve in the long-term. Clinicians also noted that it was clinically plausible for

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	the placebo data could be used to inform transition probabilities to worse health states for BSC in TA588. The Committee deemed that this approach substantially overestimated the proportion of patients receiving nusinersen who reached the best health states, as those who remained on treatment would continue to improve indefinitely. The company's final iteration of the model included an option for patients to plateau whilst remaining on treatment, resulting in a more plausible proportion of patients who could reach the best health states.	history control data set was required to model the BSC arm. The Committee pointed out that there are substantial clinical benefits with OA for type 1 SMA, but the short follow up mean that long-term outcomes and effectiveness were uncertain.	FIREFISH trial (up to the latest cut-off), in the base case, a transition to the 'walking' health state for risdiplam has been applied, on the basis that some patients in the study acquired further developmental milestones in walking as per the HINE-2 motor milestones, within the 48 month data. Patients receiving BSC are assumed to remain stable or deteriorate in the long-term.	type 1 patients treated with BSC to only deteriorate in the long term, and to not remain stable when considering motor milestones in the long term (Appendix Q). Evidence from the literature further illustrates that type 1 patients treated with BSC deteriorate over time (30).
Source of utilities	The manufacturer included both patients and carer utilities in their early-onset SMA model. No HRQoL measures were included in the ENDEAR trial due to difficulties of these measurements in children. Therefore, in the original manufacturer's early-onset model, PedsQL collected from patients in the CHERISH trial were mapped to the EQ-5D, however, the revised base case (and ERG-preferred approach) was based on the Lloyd et al. 2019 EQ-5D vignette study (169). Estimates provided by clinical advisors were explored in scenario analyses and expected to show greater face validity but were not preference based. For caregiver utilities, the 'best' health state was assumed to be equal to general population utilities, and 'worst' health was assumed to be equal to mean caregiver	Base case utility sources were based on the USA ICER's model, input from the EAG's clinical advisers and the published literature, as no HRQoL measures were included in the trials. An assumption was made that the independent walking health state would be equal to that of the age matched general population, aligned with the USA ICER report. The committee understood that obtaining robust health-utility values was challenging. It considered that there was uncertainty around the health-state utilities used in the model and that they had major effect on estimates of cost effectiveness. However, it concluded that they appeared to be the most appropriate to use in decision making.	**Patient HSUVs** HSUVs provided by Biogen's clinical advisors in the TA588 ERG report were selected for the base case due to their greater face validity and clinical plausibility. The Lloyd et al. 2019 EQ-5D vignette study (also used in TA588) will be explored in a scenario analysis (67, 169). **Carer HSUVs** In line with the approach taken in TA588, carer HSUVs in the model were informed by Bastida et al. 2017 and general	**Patient HSUVs** Assessment of available sources of patient HSUVs for type 1 patients was conducted by UK clinical experts, who deemed the values provided by the ERG clinical advisors in TA588 to possess the greatest face validity in type 1 patients (see Section B.3.14). **Carer HSUVs** Assessment of possible carer HSUVs was conducted by UK clinical experts, who deemed that the utility values informed by Bastida et al. and Ara et al. in TA588 demonstrated

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	utility scores from Bastida et al. 2017 (170). An equal difference in utility was assumed between adjacent health states.	No caregiver utilities were included in the model due to a lack of robust estimates available and the inclusion of caregiver utilities increases the ICER due caregiver needs over a lifetime horizon. The committee concluded that accounting for carer quality of life was important in appraising treatments for SMA, but that their inclusion in the health economic analysis is complex	population utility (171, 172). For scenario analyses, EQ-5D-5L utility values were additionally collected from caregivers of SMA patients in both the initial Roche UK burden of illness study, and a recently run Roche UK utility study. For both studies, the values have been cross-walked to the EQ-5D-3L and valued using UK tariffs.	greater face validity than those collected as part of the Roche UK burden of illness study and the Roche UK utility study (see Section B.4.3.3).
Source of costs	Health state resource use was initially sourced from Bastida et al. 2017 (170). Following critique from the ERG that the Bastida et al. study greatly underestimated costs associated with SMA treatment, cost inputs were subsequently based on a UK real-world study using HES data linked to motor milestones. The costs relating to 'Type 1 milestones' had to be adjusted upwards, as clinical experts felt that the UK real-world study was still underestimating resource use for these patients.	UK HCRU costs and utilities for untreated individuals with SMA who sit unassisted (SMA Type 2 used as proxy) and walk unassisted (SMA Type 3 used as proxy) were used to predict the costs and utilities of pharmacotherapy-treated SMA Type 1 individuals who achieve motor milestones. Various other sources were also used to inform resources in the treatment and management of SMA. The committee concluded that the company had carried out an extensive costing analysis, but that there was still uncertainty surrounding the health-state cost estimates used in the model. This was because they were based on proxy assumptions and assumed to be constant over time.	Cost and resource use are informed by a *de novo* Delphi study which was conducted to elicit healthcare resource use values, The UK-based real-world study applied during TA588 has been used to inform a scenario analysis.	In an attempt to resolve the uncertainty on the underestimation of costs from TA588 and TA755, a *de novo* cost and resource use clinician Delphi panel was conducted. For consistency, the costs used in TA588 have been presented in a scenario analysis. For this source, the permanent ventilation state was assumed to be associated with increased cost compared to the not sitting health state, as confirmed by UK clinical experts.

Presymptomatic differences have been highlighted in *italics*.

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3L: 3-level; 5L: 5-level; BSC: best supportive care; EQ-5D: Euro-QoL 5 Dimensions; ERG: Evidence Review Group; HCRU: healthcare resource use; HES: hospital episode statistics; HRQoL: health-related quality of life; HSUV: health state utility value; ICER: Institute for clinical and economic review; ITC: indirect treatment comparison; OA: onasemnogene abeparvovec; PedsQL: Paediatric Quality of Life Inventory; RCT: randomised controlled trial; SMA: spinal muscular atrophy.

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Type 2/3 SMA (SUNFISH) model

A Markov model was developed in Microsoft Excel with five health states representing key motor milestones that type 2/3 SMA patients may achieve during their lifetime, in addition to an absorbing 'death' health state. The motor milestone health states comprised 'not sitting', 'sitting with support', 'sitting unsupported', 'standing' (with or without support) and 'walking' (with or without support). This set of motor milestones was validated by UK and international clinical experts as being feasible for type 2/3 patients to achieve in their lifetime as well as clinically meaningful to patients and their caregivers (166). The 'sitting' health state was split into sitting 'with' and 'without support', as it was deemed important to represent the clinical significance for patients with type 2/3 SMA of being able to progress from being dependent on a form of support to sitting independently. Furthermore, whilst type 2/3 patients are expected to reach relatively more advanced motor milestones compared to type 1 patients, it was deemed appropriate to include the 'not sitting' health state, as without disease-modifying therapy, patients are likely to lose the functional gains they have made over time (25).

A diagram of the type 2/3 SMA (SUNFISH) model is presented in Figure 29.

The definition of the 'not sitting', 'sitting with support', 'sitting unsupported' and 'standing' health states is informed by items of the MFM-32 scale, a measure of motor ability described in Table 102. The health states of the model thus align with the primary endpoint from the SUNFISH trial. Clinical experts consulted during the initial model development concurred that the MFM-32 is an appropriate measure to demonstrate achievement of motor function milestones for the broad population of type 2/3 SMA patients recruited in SUNFISH, and validated the questionnaire items used to represent the selected health states. Furthermore, feedback from UK clinical experts sought at the advisory boards was that the MFM-32 scale is able to capture a wider spectrum from the weakest to strongest patients than the Hammersmith Functional Motor Scale Expanded (HFMSE) scale, and is therefore appropriate for use in the broad SUNFISH patient population.

The MFM-32 items and scores underpinning these model health states are presented below.

Table 102. MFM-32 scores representing health states in the type 2/3 SMA (SUNFISH) model

Health state	MFM-32 item	Score
Not sitting	Item 9 (maintain seated position)	0
Sitting with support	Item 9 (maintain seated position)	1
Sitting without support	Item 9 (maintain seated position)	2, 3
Standing (with or without support)	Item 25 (maintain standing position)	1, 2, 3

MFM32, 32 item Motor Function Measure.

With regards to the definition of the walking health state, given that neither the MFM-32 nor the HFMSE scale contain items that can appropriately capture the 'Walking' health state, data regarding the motor milestone achieved by patients was informed by the HFMSE 'level of independent mobility: highest current level of independent mobility', as recorded on patients' electronic Case Report Forms (eCRFs) in SUNFISH. Responses of 'Walks with

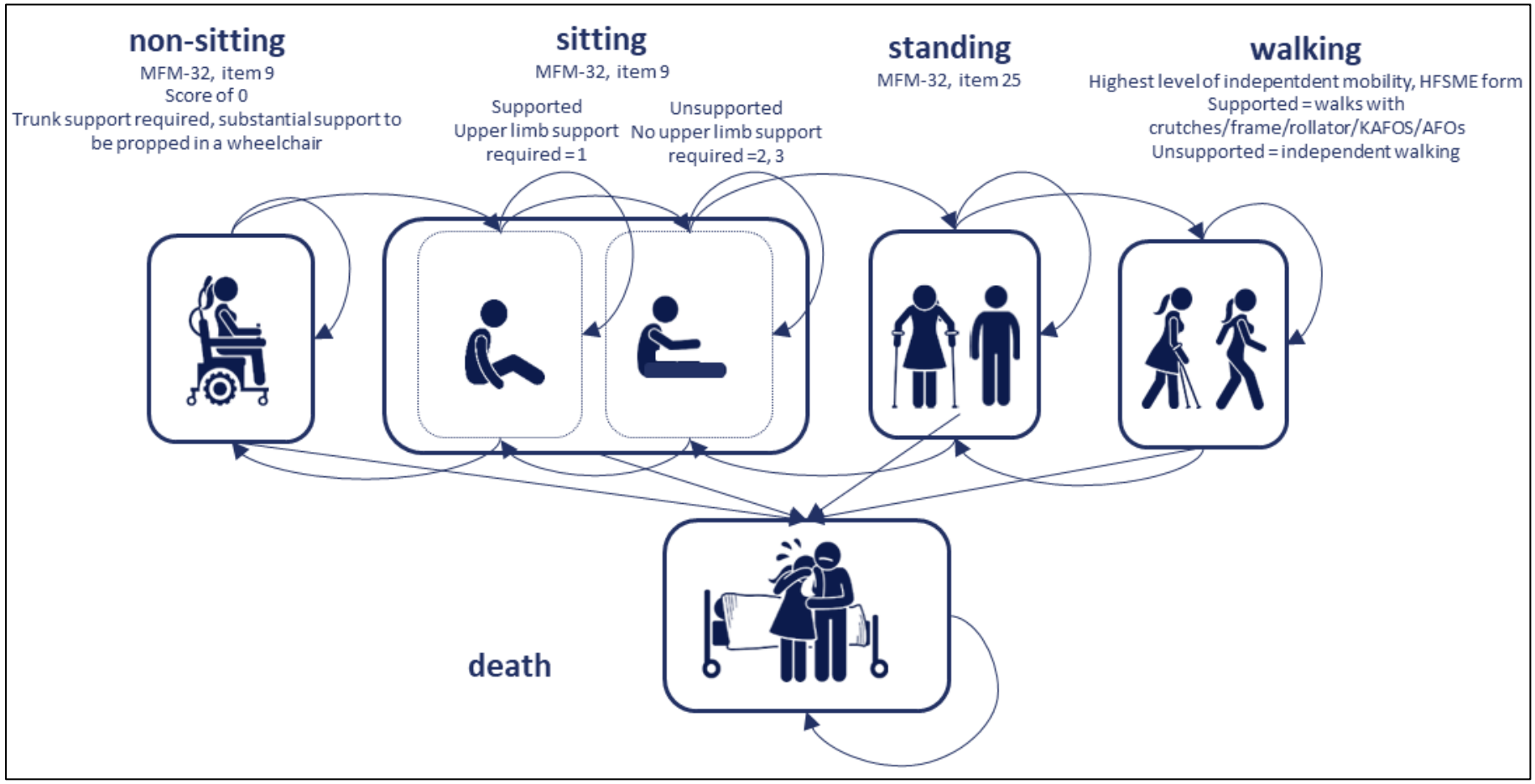
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crutches/frame/rollator', 'Walks with knee-ankle-foot-orthosis/ankle-foot orthosis' or 'independent walking' were deemed to meet the definition of the 'walking' health state.

In line with the baseline characteristics observed in the SUNFISH trial, patients start in one of the five motor milestone health states and are assigned to treatment with either risdiplam, nusinersen or BSC. From these health states, patients' motor abilities may improve, decline, or stay the same in each model cycle. A cycle length of one month was considered sufficiently granular to capture changes in patient outcomes and costs. Within the cycle length of one month, patients may improve or deteriorate by no more than one health state, as informed by clinical opinion.

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Figure 29. Diagram of the type 2/3 SMA (SUNFISH) model



AFO: ankle-foot orthosis; HFMSE: Hammersmith Functional Motor Scale Expanded; KAFOS: knee-ankle-foot-orthosis; MFM32: 32 Item Motor Function Measure.

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In accordance with the NICE reference case, the cost-effectiveness analysis is conducted from the perspective of the NHS and Personal Social Services in the base case, taking account of the costs directly related to the medical treatment of SMA patients and the quality of life of SMA patients and their carers. The approach to including cost and resource use in the model is described further in Section B.3.5.2. The approach to modelling health state utility values (HSUVs) for patients and carers is outlined in Section B.3.4.5. As noted above, the model cycle length is one month, and a half cycle correction is applied to account for mid-cycle transitions. Costs and benefits are discounted at 3.5% per year, as per the NICE reference case (168). Table 103 details the economic features of the type 2/3 SMA model.

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Table 103. Features of the economic analysis (type 2/3 model)

Factor	Previous appraisals	Current appraisal	
	TA588	Chosen values	Justification
Time horizon	Lifetime (80 years)	Lifetime ([redacted] years)	In line with the NICE reference case, and considering the life expectancy of type 2/3 SMA patients, a lifetime horizon of 90 yeas is assumed. The mean baseline age in the model is [redacted]. In line with the NICE reference case (168), a lifetime time horizon of 80 years was selected to capture all costs and benefits associated with risdiplam or treatment with BSC.
Long-term clinical outcomes	In the manufacturer's original base case later-onset SMA model, on-treatment transition probabilities during trial follow-up reflect motor milestone achievements from the CHERISH trial. After trial follow-up, patients on nusinersen could only improve in health state, whilst patients on BSC could only decline or remain constant. The Committee deemed that this approach substantially overestimated the proportion of patients receiving nusinersen who reached the best health states, as those who remained on treatment would continue to improve indefinitely. The company's final iteration of the model included an option for patients to plateau whilst remaining on treatment, resulting in a more plausible proportion of patients who could reach the best health states.	In the base case, after a period of 24 months, the majority of patients on risdiplam treatment either improve (in terms of health states achieved) or remain stable. Patients receiving BSC are assumed to remain stable or deteriorate.	This approach was informed by clinical expert opinion sought at UK advisory boards, which stated that the majority of patients receiving active treatment would remain stable or improve in the long-term (TA755 (67)). This is in line with data from Part 1 and Part 2 of the SUNFISH trial, where the majority of patients in the risdiplam arm demonstrated improvement or stabilisation of the disease. Furthermore, the proportion of patients improving and stabilising was greater with risdiplam than in the placebo arm. This was further confirmed by the 24-months follow-up data from Part 1 of the SUNFISH trial. Clinicians at the advisory boards also noted that it was clinically appropriate to assume that patients treated with BSC remain stable or deteriorate in the long term (TA755

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			(67)). Evidence from the literature further illustrates that type 2/3 patients treated with BSC deteriorate over time (25).
Source of utilities	The manufacturer included both patient and carer utilities in their later-onset SMA model. In the original manufacturer's later-onset model, PedsQL collected from patients in the CHERISH trial were mapped to the EQ-5D, however, the revised base case (and ERG-preferred approach) was based on the Lloyd et al. 2019 EQ-5D vignette study (169). Estimates provided by the clinical advisors were additionally explored in scenario analyses, and whilst not preference-based, were deemed to show face validity. For caregiver utilities, the 'best' health state was assumed to be equal to general population utilities, and 'worst' health was assumed to be equal to mean caregiver utility scores from Bastida et al. 2017 (171). An equal difference in utility was assumed between adjacent health states.	**Patient HSUVs** Utility values from the Lloyd et al. 2019 EQ-5D vignette study were selected to inform the base case in accordance with the ERG and Committee's preference for final decision-making in TA588 (169). The utility values provided by the ERG's clinical advisors were explored in a scenario analyses. EQ-5D data collected from the SUNFISH study are additionally explored as a scenario analysis. **Carer HSUVs** In line with the approach taken in TA588, carer HSUVs in the model were informed by Bastida et al. 2017 (171). For scenario analyses, EQ-5D-5L utility values were additionally collected from caregivers of SMA patients in both the initial Roche UK burden of illness study, and a recently run Roche UK utility study (173). For both studies, the values have been cross-walked to the EQ-5D-3L and valued using UK tariffs.	**Patient HSUVs** In the base case analysis, HSUVs from the Lloyd et al. 2019 vignette study (169) were selected on the basis that they were previously deemed acceptable by the ERG in the TA588 appraisal in SMA (18) and were also selected as more clinically plausible by UK clinical experts consulted by Roche (see Section B.3.14. EQ-5D-5L utility values (cross-walked to the EQ-5D-3L and valued using UK tariffs) elicited from type 2/3 SMA patients in the SUNFISH RCT underwent assessment by UK clinical experts, who concluded that the utilities lacked clinical validity, as they were too low and did not reflect the broad range of HRQoL levels observed between motor milestones, see Section B.3.14. Accordingly, the EQ-5D values collected in SUNFISH were not applied in the base case, but explored in a scenario analysis for completeness. This also applies to the utility estimates provided by the clinical advisors during TA588. **Carer HSUVs** Assessment of possible carer HSUVs was conducted by UK clinical experts. HSUVs used in TA588 (based on Bastida et al (171) and general

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			population utility (172) were explored. Additionally, a UK burden of illness study and UK utility study was conducted by Roche, further details of which are presented in Section B.3.5.2, and resulting carer HSUVs were assessed by the UK clinical experts. The clinical experts deemed that the utility values informed by Bastida et al. and general population utility in TA588 demonstrated greater face validity than those collected as part of the Roche UK burden of illness study and UK utility study (see Section B.3.14). As such, the former set of values were applied in the base case, and the latter options applied in a scenario analysis.
Source of costs	Health state resource use was initially sourced from Bastida et al. 2017 (174). Following critique from the ERG that the Bastida et al. study greatly underestimated costs associated with SMA treatment, cost inputs were subsequently based on a UK real-world study using HES data linked to motor milestones. The costs relating to 'Type 1 milestones' had to be adjusted upwards, as clinical experts felt that the UK real-world study was still underestimating resource use in these patients.	Cost and resource use are informed by a *de novo* Delphi study, conducted to elicit healthcare resource use values, The UK-based real-world study applied during TA588 has been used to inform a scenario analysis.	In an attempt to resolve the uncertainity on the underestimation of costs from TA588 and TA755, a *de novo* cost and resource use clinician Delphi panel was conducted. For consistency, the costs used in TA588 have been presented in a scenario analysis.

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B.3.2.3 Intervention technology and comparators

In the presymptomatic cost-effectiveness model, risdiplam is compared to nusinersen and OA. BSC is not considered a relevant comparator for this patient population, as patients are likely to be treated with a disease modifying treatment upon confirmed diagnosis. In the type 1 cost-effectiveness model, risdiplam is compared to BSC, nusinersen and OA. Finally in the type 2/3 cost effectiveness model, risdiplam is compared to BSC and nusinersen as per the final NICE scope for this appraisal.

In line with the SmPC wording, risdiplam has been implemented in the models to be taken orally once a day (175). The recommended once daily dose of risdiplam is determined by patients' age and body weight, as presented in Table 104.

Table 104. Risdiplam dosing regimen by age and weight

Age	Recommended daily dose
16 days to 2 months of age	0.15 mg/kg
2 months to <2 years of age	0.20 mg/kg
≥2 years of age (< 20 kg)	0.25 mg/kg
≥2 years of age (≥ 20 kg)	5 mg

Source: Risdiplam SmPC (175)

In the presymptomatic model, as mentioned in Section B.2.6.3 time-to-event endpoints were not analysed for risdiplam due to a lack of observed events in the RAINBOWFISH study. For risdiplam, overall survival in the model is informed by national life tables for England and Wales for all states other than permanent ventilation. Nusinersen is informed by the NURTURE study and OA informed by the SPR1NT data. For the permanent ventilaiation health state, the same general population mortality is applied across risdiplam, nusinersen and OA. The model does allow for BSC-specific mortality as an option. As outlined in Section B.2.9.4 Results, no comparison between event-free survival and overall survival was able to be conducted, due to low sample sizes and a lack of events between risdiplam, nusinersen and OA. Based on the naïve unadjusted comparison, there were no considerable differences observed for mean HINE-2, CHOP-INTEND and BSID-III scores. As a result, efficacy between these treatments is assumed to be the same in the model (hazard ratio of 1); with the Markov trace in the engines being identical across the respective treatment durations. The sample sizes of all studies included in the analysis are very small, resulting in high uncertainty inherent in any comparisons between these treatments. Therefore, an assumption of equal efficacy was considered appropriate.

In the type 1 model, efficacy and safety for risdiplam is informed by the single arm FIREFISH trial. Nusinersen efficacy and safety inputs have been informed by the ITC presented in Section B.2.9.4 Results (FIREFISH v ENDEAR/ENDEAR-SHINE). Efficacy and safety inputs for OA is informed by two different data source options, STR1VE-EU and STR1VE-US.As described in Section B.2.9.4 Results, both studies are notably different to the FIREFISH population (FIREFISH patients are older and more severe disease progression at baseline as measured by CHOP-INTEND when compared to both STR1VE studies). Due to these large differences, matching was unable to be conducted and it was not feasible to generate accurate statistical evidence to provide a comparative assessment in efficacy, leading to high uncertainty around the point estimates used. However, in order to provide a comparison for the purposes of the submission, the hazard ratio at 1 year for both studies has been

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applied over the long-term time horizon – these should be interpreted with caution given the large uncertainty. As there is head-to-head data available for BSC and no longer-term data available for BSC past the 12 month mark (as described in Section B.2.9.4 Results), the cost-effectiveness model extrapolates the initial transitions over the entire time horizon.

In the type 2/3 model, efficacy and safety for risdiplam is informed by the SUNFISH clinical trial. Nusinersen efficacy and safety data is informed by the RULM MAIC as detailed in Section B.2.9.4 Results. As there is no longer term sources to inform efficacy and safety inputs for BSC, the 1-year data from the SUNFISH part 2 intent-to-treat population has been used, with the assumption as per TA588 that there is no continued improvement in BSC efficacy over time (18).

Whilst BSC comparisons have been provided to fulfil the final NICE scope, it is believed that BSC is no longer a relevant comparator given the availability of DMTs for SMA patients (see Section B.3.7 Uncertainty. Clinical expert opinion states that if DMTs are available, and SMA patients are both eligible and choose to have the treatment, this is what will be prescribed (see Section B.3.14). BSC is only relevant for those patients who opt for no DMT treatment or are ineligible for any active treatment, which is no longer a comparable population to those who would have DMTs.

B.3.3 Clinical parameters and variables

B.3.3.1 Presymptomatic SMA (RAINBOWFISH) Model

Baseline characteristics

The baseline characteristics for patients included in the presymptomatic (RAINBOWFISH) model are presented in Table 105.

Table 105. Patient baseline characteristics from RAINBOWFISH

	ITT Overall (N=18)	ITT SMN2 copy number 2 copies (N=7)	ITT SMN2 copy number >2 copies (N=11)	Primary Efficacy (N=4)
Age at first dose, days, median (range)	27.33 (7.28)	22.86 (5.37)	30.18 (7.07)	25.25 (5.32)
Gender, Female n (%)	10 (55.56%)	3 (42.86%)	7 (63.64%)	2 (50%)
CMAP mV mean (SD; range)	3.53 (1.85; 0.46-6.7)	2.02 (1.26; 0.46-3.79)	4.49 (1.5; 2.1-6.7)	2.94 (0.61; 2.4-3.79)
Baseline weight in kg, (SD) Baseline height/length in cm (SD)	3.98 (0.725) 53.28 (2.32; 49-59)	3.76 (0.427) 52.71 (1.89; 49-55)	4.12 (0.853) 53.64 (2.58; 50-59)	3.99 (0.102) 53.75 (0.96; 53-55)
SMN2 copy 2 copies 3 copies >= 4 copies	 7 (38.89%) 7 (38.89%) 4 (22.22%)	 7 (100%) 0 (0%) 0 (0%)	 0 (0%) 7 (63.64%) 4 (36.36%)	 4 (100%) 0 (0%) 0 (0%)

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Abbreviations: CMAP, Compound muscle action potential; ITT, Intention to treat; SD, Standard deviation

Motor milestone transition probabilities

Data from the RAINBOWFISH study at one-year (CCOD 20 Feb 2023) were used to calculate transition probabilities between the not sitting, sitting, standing and walking health states for risdiplam. Since RAINBOWFISH was a single-arm study, transition probabilities for BSC could not be directly estimated from the study. In order to estimate comparator efficacy data, an ITC was attempted, but neither a MAIC or STC was feasible due to small sample sizes and substantial differences at baseline (see Section B.2.9.4 Results). The naïve comparison conducted demonstrates similar outcome progression trajectories and non-statistically significant results of risdiplam in comparison to nusinersen and OA when evaluating mean changes in motor-milestones Therefore within the cost-effectiveness model we have assumed equal efficacy (hazard ratio of 1) between risdiplam, nusinersen and OA for this patient population.

As described in Section B.3.2.2, the motor milestone health states of 'not sitting', 'sitting' and 'standing' were defined by HINE-2 scores. In order to estimate the probability of transitions between motor milestone health states, a continuous time Markov multi-state model was fitted to the data from the trial using the R version 4.0.3 with package msm 1.7.1 (176). A patient's improvement in motor milestone achievement was assumed to be sequential. Therefore, the multi-state model was specified so that movements between non-adjacent health states were not allowed. i.e., if a patient was observed at a worse motor function (e.g. not sitting) during one visit and at a better motor function (e.g. standing) during the next visit, it was assumed that the patient was capable of the intermediate motor function (e.g. sitting), even if it was not explicitly observed. This was applied to both improvement and deterioration of motor function.

The transition probabilities are outlined in Table 106. As equal efficacy is assumed, the transition probabilities are the same for risdiplam, nusinersen and OA.

Table 106. Risdiplam, nusinersen and OA motor milestone transition probabilities (presymptomatic model base case)

	Non-sitting	Sitting	Standing	Walking
Non-sitting	[redacted]	[redacted]		
Sitting	[redacted]	[redacted]	[redacted]	
Standing		[redacted]	[redacted]	[redacted]
Walking			[redacted]	[redacted]

Time to event outcomes

Given a lack of observed events in the one-year data (CCOD 20 Feb 2023) of the RAINBOWFISH study, no analysis of time-to-event endpoints was conducted. No events were observed for death, permanent ventilation, or the loss in the ability to feed (swallow). Only one event was observed related to respiratory support. Time-to-event could not be analysed for endpoints related to bulbar impairment, severe scoliosis or respiratory support. In the CEM, overall survival data for risidiplam, is informed by the national life tables for England and Wales for all states other than permanent ventilation, where transition to the

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death state is assumed to be equal to BSC. The overall survival is assumed equal between risdiplam, nusinersen and OA.

As a result of a lack of events, data from a PNCR analysis has been used to inform the time to scoliosis, time to respiratory support and time to bulbar dysfunction (177). Scenario analyses have been performed utilising published literature also used in the type 1 SMA cost-effectiveness model.

Discontinuation

Within the follow-up period observed (12 months to the clinical cut-off date), no treatment discontinuations were observed. Combined with clinical expert feedback, it was concluded that discontinuation of risdiplam was unlikely to take place in clinical practice, and therefore no discontinuation was assumed. This also applies to nusinersen.

B.3.3.2 Type 1 SMA (FIREFISH) Model

Baseline characteristics

The baseline characteristics for patients included in the type 1 (FIREFISH) model are presented in Table 107.

Table 107. Baseline characteristics (type 1 model base case)

Baseline characteristic	Value
Age, years; mean (SE)	0.48 (0.048)
Female (SE)	57% (0.057)
Body weight, kg; mean (SE)	5
Permanent ventilation, %	0%
Not sitting, %	100%
Sitting, %	0%
Standing, %	0%
Walking, %	0%
Non-permanent respiratory support, %	28%
Severe scoliosis (>40 degrees curvature), %	0%

SE, standard error

Motor milestone transition probabilities

Clinical data from the population who received the final dose of risdiplam in the FIREFISH trial in the 48 months follow-up were utilised to develop transition probabilities between motor milestone health states for the risdiplam arm in the type 1 cost-effectiveness model. The decision was made to incorporate Part 1 patients (who achieved the final risdiplam dose) so that the transition probabilities would be informed by a greater number of patients, and results would have greater robustness and statistical power. A subgroup analysis excluding patients in some regions (similarly to the SUNFISH model) was not performed, as the lower number of patients in the FIREFISH study was not deemed sufficient to generate robust transition probabilities.

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As described in Section B.3.2.2 Model structure, the motor milestone health states of 'not sitting', 'sitting' and 'standing' were defined by HINE-2 scores. In order to estimate the probability of transitions between motor milestone health states, a continuous time Markov multi-state model was fitted to the data from the trial using the R version 4.0.3 with package msm 1.7.1 (176). Baseline HINE-2 total score centred around the mean was included as a covariate for the "not sitting" to "sitting" transition only, as this transition occurred more frequently in the clinical data compared to transitions between other motor health states. The transition from "standing" to "walking" is informed by the chosen trial data source within the model and applied uniformly from Cycle 1.

Furthermore, after 48 months patients treated with risdiplam remain stable or improve in the long-term, whilst patients in the BSC arm have no continued improvement post follow-up period, aligned with TA588. These long-term assumptions are informed by UK clinical expert opinion, and are further explored in scenario analyses (Section B.3.11.3).

Finally, the assumption was made that a patient's improvement or deterioration in motor milestone achievement was sequential. Accordingly, if the raw data indicated that a patient was observed to be at a milestone such as 'sitting' during one visit and a better, non-sequential motor milestone at the next visit (e.g. walking), it was assumed the patient was capable of the intermediate motor function (e.g. standing). Therefore, whilst the multi-state model automatically calculates non-sequential health state transitions, these were not incorporated into the cost-effectiveness model. It was clinically validated that improvement or deterioration by greater than one milestone within the period of one month would not be expected in type 1 patients (see Section B.3.14).

Since FIREFISH was a single-arm study, transition probabilities for the BSC arm could not be directly estimated from the study. However, as noted in Section B.2.9.4 Results, it was not feasible to conduct an updated comparison to BSC (versus what was presented in TA755). The ITC used in the base case of the economic model, as described in TA755 (Section B.3.3.2) (67), has been applied over time. For nusinersen, transition probabilities have been based on the MAIC conducted on the HINE-2 endpoint. For OA, although there is high uncertainty around the point estimates for the purposes of providing a comparison within the model, the transition probabilities have based on the unanchored MAIC conducted on the BSID-III endpoint from the STR1VE-EU dataset, scenarios STC with the STR1VE-US dataset.

The transition probabilities are outlined in Table 108, Table 109, Table 110 and Table 111 and provide the base case for risdiplam, nusinersen, OA and BSC, respectively.

Table 108. Risdiplam motor milestone transition probabilities (type 1 model base case)

	Non-sitting	Sitting	Standing	Walking
Non-sitting	[redacted]	[redacted]		
Sitting	[redacted]	[redacted]	[redacted]	
Standing		[redacted]	[redacted]	[redacted]
Walking			[redacted]	[redacted]

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Table 109. Nusinersen motor milestone transition probabilities (type 1 model base case)

	Non-sitting	Sitting	Standing	Walking
Non-sitting	[redacted]	[redacted]		
Sitting	[redacted]	[redacted]	[redacted]	
Standing		[redacted]	[redacted]	[redacted]
Walking			[redacted]	[redacted]

Table 110. OA motor milestone transition probabilities (type 1 model base case)

	Non-sitting	Sitting	Standing	Walking
Non-sitting	[redacted]	[redacted]		
Sitting	[redacted]	[redacted]	[redacted]	
Standing		[redacted]	[redacted]	[redacted]
Walking			[redacted]	[redacted]

Table 111. BSC motor milestone transition probabilities (Type 1 model base case)

	Non-sitting	Sitting	Standing	Walking
Non-sitting	[redacted]	[redacted]		
Sitting	[redacted]	[redacted]	[redacted]	
Standing		[redacted]	[redacted]	[redacted]
Walking			[redacted]	[redacted]

Footnotes: Top row represents resulting health state; left column represents originating health state. A patient's improvement or deterioration in motor milestone achievement was sequential; grey boxes represent transitions that are not possible.

Transitions to permanent ventilation

Transitions to the 'permanent ventilation' can only be made from the 'not sitting' health state, and this transition was informed through parametric survival analysis of ventilation-free survival data for risdiplam from Part 1 and 2 patients from FIREFISH who had received the final risdiplam dose at the 48-month cut-off date. The definition of permanent ventilation in the trial is >16 hours of non-invasive ventilation, such as BiPAP, per day or intubation for >21 consecutive days in the absence of, or following the resolution of, an acute reversible event or tracheostomy. Ventilation-free survival is a composite endpoint of time to permanent ventilation or death, and is measured as time in months from the date of enrolment. Accordingly, in order to isolate transitions to the 'permanent ventilation' health state only, it was necessary to subtract the ventilation-free survival curves from the overall survival curves (please see below for overall survival).

As described in Section B.2.6.1.2, time to permanent ventilation data from the FIREFISH trial were immature, with median time to permanent ventilation not having been reached at the time of data cut-off (48 months). Given the few data available at this cut-off and finite length of the FIREFISH trial, it was necessary to use techniques to extrapolate the trial data for the length of the model time horizon. Given that data are extrapolated into the long term, this process is associated with uncertainty, which has been mitigated as far as possible through

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informing parametric survival curve selection with clinical opinion, and varying curve selection in scenario analyses, as recommended by NICE TSD (178). Survival analysis was conducted to fit the most appropriate parametric survival functions to the Kaplan-Meier data for risdiplam from FIREFISH. Goodness-of-fit statistics were obtained to understand which parametric form had the best fit to the Kaplan-Meier data from the FIREFISH trial, UK clinical expert opinion was sought regarding the plausibility of the long-term extrapolations of each function. Due to the lack of events observed in the FIREFISH trial, performing an assessment of visual fit of the curves to the short-term Kaplan-Meier data was not feasible.

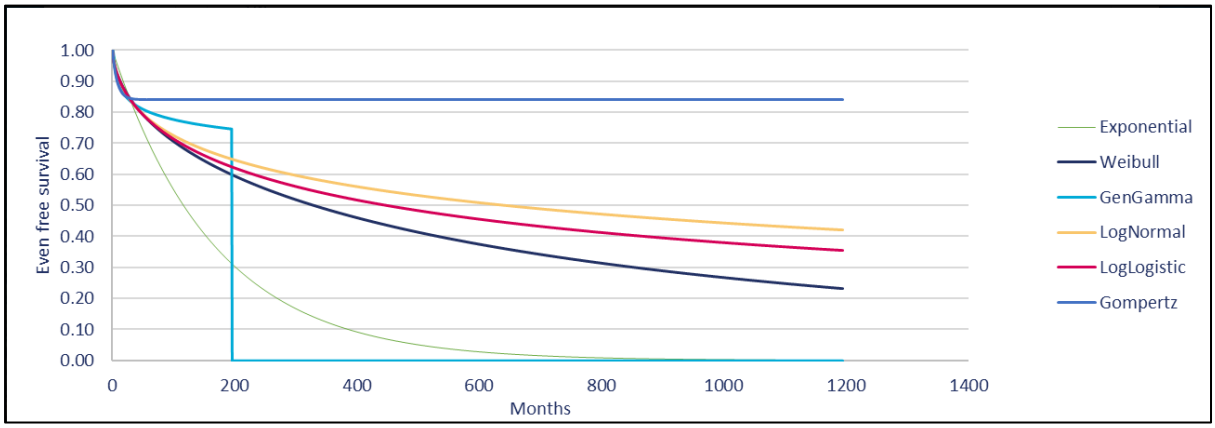
The parametric survival functions for ventilation-free survival are presented in Figure 30. The goodness-of-fit statistics are presented in Table 112 which suggest that all curves offer a similar fit to ventilation-free survival data from FIREFISH, but that Generalised gamma offers the best fit to the data. However, due the short follow-up duration of the FIREFISH trial in the context of a life time horizon, emphasis was placed on the long-term clinical plausibility of the survival curves. UK clinical experts were consulted to assess the curves, and it was deemed that the exponential curve offered the greatest clinical plausibility in terms of long-term predictions for ventilation-free survival in type 1 patients, the same as in TA755. As such, the exponential parametric form was selected for the model base case. Other parametric models were not explored in scenario analyses, as the clinicians did not deem them to have clinical validity.

Table 112: Goodness-of-fit statistics for type 1 ventilation-free survival

Parametric distribution	AIC (rank)	BIC (rank)
Exponential	144.3 (6)	146.4 (6)
Weibull	140.2 (5)	144.3 (5)
Log-normal	138.7 (3)	142.9 (3)
Generalised gamma	132.8 (1)	139.0 (1)
Log-logistic	139.9 (4)	144.0 (4)
Gompertz	137.9 (2)	142.0 (2)

AIC: Akaike information criterion; BIC: Bayesian information criterion

Figure 30: Type 1 ventilation-free survival parametric functions



Footnotes: Kaplan-Meier data are not shown due to the short follow-up for which survival data are available. The generalised gamma curve is not presented as it did not converge.

Overall survival

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In order to estimate mortality for patients in the type 1 model, parametric survival analysis of OS data for risdiplam from Part 1 and 2 patients from FIREFISH who had received the final risdiplam dose at the 4-year cut-off date was conducted. Time to death was a secondary efficacy endpoint in the FIREFISH study and is defined as time in months from date of enrolment until the date of death from any cause. As described above for EFS, OS data from the FIREFISH trial were immature, with median time to death not having been reached at the time of data cut-off (Section B.2.6.1.2). As per permanent ventilation, survival analysis was conducted in line with NICE TSD 14, with goodness-of-fit statistics obtained to understand which parametric form had the best fit to the Kaplan-Meier data from the FIREFISH trial and UK clinical expert opinion sought regarding the plausibility of the long-term extrapolations of each function.

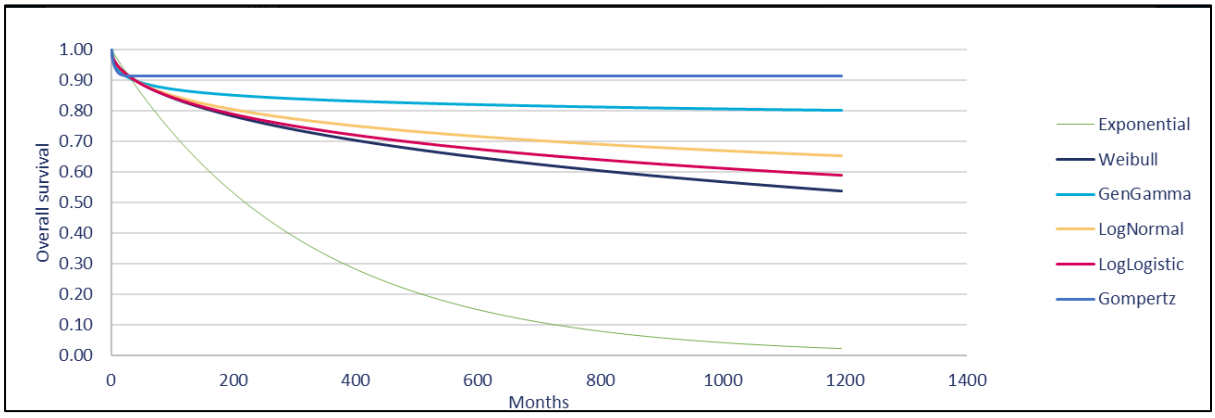
The parametric survival functions for overall survival are presented in Figure 31. The goodness-of-fit statistics are presented in Table 113, which suggest that the Gompertz curve offer the best fit to the data. However, in line with ventilation-free survival, the timeframe over which overall survival data are available is currently short, and emphasis was placed on the long-term clinical plausibility of the curves over fit to trial data. UK clinical experts consulted deemed the exponential to be the most plausible extrapolation, the same as TA755. The exponential parametric model was therefore selected for the base case analysis. Other parametric models were not explored in scenario analyses, as clinicians did not deem them clinically viable.

Table 113: Goodness-of-fit statistics for type 1 overall survival

Parametric distribution	AIC (rank)	BIC (rank)
Exponential	75.3 (6)	77.3 (6)
Weibull	71.2 (5)	75.3 (5)
Log-normal	70.4 (3)	74.5 (3)
Generalised gamma	66.3 (2)	72.4 (2)
Log-logistic	71.1 (4)	75.2 (4)
Gompertz	65.0 (1)	69.1 (1)

AIC: Akaike information criterion; BIC: Bayesian information criterion

Figure 31: Type 1 overall survival parametric functions



Discontinuation

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Within the FIREFISH trial at the 4-year cut off, of the 11 children who were not deemed 'event free', six (10.3%) children met the definition of permanent ventilation and five had died. One additional infant died approximately 3.5 months after discontinuing treatment and was censored at age 22.9 months. Two participants withdrew from the study, one censored at age 34.1 months and one at 48.2 months. Another five children were censored as they had not reached 54 months of age as of the data cut-off. Feedback from UK clinicians regarding conditions in which they would discontinue risdiplam treatment was sought in TA755 (see Appendix Q). This is further reinforced by only n=1 type 1 SMA patient stopping risdiplam within the REACH dataset (see Section B.2.6.4) (patient switched to OA after 6 months of risdiplam treatment). Based on the trial data, REACH data and clinical expert feedback, it was concluded that discontinuation of risdiplam was unlikely to take place in clinical practice, and therefore no discontinuation was assumed.

Disease related events

For disease-related events, the base case assumptions for the time to scoliosis (179), time to respiratory support (180) and time to bulbar dysfunction (181) are informed by the literature as they are sources of natural history with higher sample sizes. The data for these events can also be modelled by using the fixed proportions over time collected from FIREFISH – these are used in scenario analyses. This also applies to nusinersen.

B.3.3.3 Type 2 SMA (SUNFISH) Model

Baseline characteristics

The baseline characteristics for patients included in the type 2/3 (SUNFISH) model are presented in Table 114.

Table 114. Baseline characteristics (type 2/3 model base case)

Baseline characteristic	Value
Age, years; mean (SE)	10.0 (1.0)
Female (SE)	50.6% (0.05)
Type 2	71.1%
Type 3	28.9%
Not sitting	0%
Sitting (supported)	13%
Sitting (unsupported)	74%
Standing	6%
Walking	7%
Respiratory support	31.7%
Severe scoliosis (>40 degrees curvature)	31.7%

SE, standard error

It may be noted the baseline characteristics presented for the cost-effectiveness analysis differ from those presented in Section B.2.3. This is due to the following reasons: 1. in the model, the health states are mutually exclusive. Although patients that are able to walk are also able to stand, these will not appear in the model baseline proportions in the 'standing' state, but will be assigned to the 'walking' state due to their ability to walk. This is different from Section B.2.3, where all patients with the ability to stand are counted (irrespective if they are

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also able to walk or not). 2. Walking was defined differently in Section B.2.3 as compared to the model. In Section B.2.3, 'walking' is defined as HFMSE item 20 score ≥2 at baseline. However, in the model, 'walking' is defined as the highest current level of independent mobility.

Motor milestone transition probabilities

Clinical data from Part 2 of the SUNFISH trial up to the 5-year data cut off were utilised to develop transition probabilities for the risdiplam arm in the type 2/3 cost-effectiveness model. For the base case, the transition probabilities were informed by a subgroup of patients from the SUNFISH trial that excluded patients from Asia: Risdiplam arm numbers ITT at baseline n=120, at 5 years n=99 and the ITT excluding Asia at baseline n=99, at 5 years n=81. This exclusion was performed to take into account UK clinical expert opinion at the advisory boards that potential differences in standard of care, such as physiotherapy practices, could mean that baseline characteristics may vary between regions (67). Transition probabilities from the natural history data are used in a scenario analysis (182). As there is no longer term data for the BSC arm, the SUNFISH Part 2 placebo data from the 52 week cut-off has been utilised. Although there was high uncertainty around the point estimate of the odds ratio for the RULM MAIC between risdiplam and nusinersen (presented in Section B.2.9.4 Results), this has been used to inform the comparison within the type 2/3 model base case. The selection of the RULM endpoint to inform the comparison between risdiplam and nusinersen is further justified by clinical experts, who stated that the RULM better reflects what is achieved by patients versus what HFMSE is able to show.

As described in Section B.3.2.2, the motor milestone health states of 'not sitting', 'sitting supported', 'sitting unsupported' and 'standing' were defined by MFM-32 score, whilst the 'walking' health state was defined by HFMSE highest current level of independent mobility. In order to estimate the probability of transitions between motor milestone health states, continuous time Markov multi-state models were fitted to the data from the trial using the R version 4.0.3 with package msm 1.7.1 (176). A single covariate for treatment effect was applied in the generation of transition probabilities. No further covariates were applied to avoid risking 'over-fitting' to the data.

A set of assumptions were made during the calculation of transition probabilities. Firstly, imputation was conducted to account for missing inputs in the calculation of transition probabilities. Specifically, if the motor milestone achieved in the next assessment to take place was equal to or better than the previously conducted assessment, the imputation was based on the last observation carried forward (LOCF). If the motor milestone achieved in the next assessment to take place was worse than the previous assessment, the imputation was based on the next observation carried backwards (NOCB). No values were imputed after patients discontinued the study (n=17 in Part 2 of SUNFISH) (110). Imputed transition probabilities are utilised in the base case, whilst non-imputed transition probabilities are explored in a scenario analysis (Section B.3.8.3).

Finally, the assumption was made that a patient's improvement or deterioration in motor milestone achievement was sequential. Accordingly, if the raw data indicated that a patient was observed to be at a milestone such as 'not sitting' during one visit and a better, non-sequential motor milestone at the next visit (e.g. 'standing' [item 25]), it was assumed the patient was capable of the intermediate motor function (e.g. 'sitting' [item 9]). Accordingly, whilst the multi-state model automatically calculates non-sequential health state transitions, these were not incorporated into the cost-effectiveness model. This assumption was

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consistent with clinical opinion that improvement or deterioration by greater than one milestone within the period of one month would not be expected in type 2/3 patients (see Section B.3.14).

UK clinical experts agreed the majority of SMA type 2 or 3 patients receiving active treatment will have a favourable trajectory versus BSC, even if a slight decline is observed. Patients on active treatment are likely to maintain or improve their health states in the long-term (see Section B.3.14). Therefore, the risdiplam transition probabilities were adjusted so that post trial follow-up patients can only either improve or remain stable. Similarly, feedback from the clinicians, and as per TA588, was that in the long term, patients receiving BSC have no continued improvement (see Section B.3.14). Accordingly, after 24 months, transition probabilities were adjusted such that transitions to improved motor milestones were set to 0%.

The transition probabilities utilised in the base case for risdiplam, nusinersen and BSC are presented in Table 115, Table 116 and Table 117, respectively.

Table 115. Risdiplam motor milestone monthly transition probabilities (Type 2/3 model base case)

	Non-sitting	Sitting (supported)	Sitting (unsupported)	Standing	Walking
Non-sitting	[redacted]	[redacted]			
Sitting (supported)	[redacted]	[redacted]	[redacted]		
Sitting (unsupported)		[redacted]	[redacted]	[redacted]	
Standing			[redacted]	[redacted]	[redacted]
Walking				[redacted]	[redacted]

Footnotes: Top row represents resulting health state; left column represents originating health state. A patient's improvement or deterioration in motor milestone achievement was sequential; grey boxes represent transitions that are not possible.

Table 116: Nusinersen motor milestone monthly transition probabilities (Type 2/3 model base case)

	Non-sitting	Sitting (supported)	Sitting (unsupported)	Standing	Walking
Non-sitting	[redacted]	[redacted]			
Sitting (supported)	[redacted]	[redacted]	[redacted]		
Sitting (unsupported)		[redacted]	[redacted]	[redacted]	
Standing			[redacted]	[redacted]	[redacted]
Walking				[redacted]	[redacted]

Footnotes: Top row represents resulting health state; left column represents originating health state. A patient's improvement or deterioration in motor milestone achievement was sequential; grey boxes represent transitions that are not possible.

Table 117. BSC motor milestone monthly transition probabilities (Type 2/3 model base case)

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	Non-sitting	Sitting (supported)	Sitting (unsupported)	Standing	Walking
Non-sitting	[redacted]	[redacted]			
Sitting (supported)	[redacted]	[redacted]	[redacted]		
Sitting (unsupported)		[redacted]	[redacted]	[redacted]	
Standing			[redacted]	[redacted]	[redacted]
Walking				[redacted]	[redacted]

Footnotes: Top row represents resulting health state; left column represents originating health state. A patient's improvement or deterioration in motor milestone achievement was sequential; grey boxes represent transitions that are not possible.

Assumptions around the long-term efficacy post follow-up for risdiplam and BSC were varied in scenario analyses (see Section B.3.11.3, Table 154)

Overall survival

Mortality is treated separately in the model for type 2 and type 3 SMA patients. In order to inform mortality for type 2 patients in a systematic and explicit manner, the SLR conducted to identify HSUV data in TA755 was expanded to explore the natural history and survival of type 2 SMA patients. Briefly, search terms for mortality and survival were included in the electronic database searches of this SLR. Following title/abstract screening a total of 79 publications were tagged as potentially relevant. At full publication review, seven studies were identified reporting type 2 SMA survival curves: Belter et al. 2018 (183), Chung et al. 2004 (184), Farrar et al. 2013 (185), Ge et al. 2012 (186), Mannaa et al. 2009 (187), Petit et al. 2011 (188) and Zerres et al. 1997 (189). Given the likely heterogeneity between the studies captured, further consideration was given to the most appropriate studies to utilise to inform final survival estimates. Upon inspection of the individual and pooled Kaplan-Meier curves, it was observed that the study by Belter et al. reported higher survival compared to the other studies. The Belter et al. study used data from the Cure SMA database, a patient-reported data repository on SMA patients (183). As noted by the authors, limitations of the study include enrolment bias (Cure SMA membership may represent a more engaged population) and that data was patient reported, which is prone to reporting inaccuracies, incomplete information and errors in memory. As such, the Belter et al. study was conservatively excluded from the data set.

Data from the selected six studies were reported in the form of Kaplan-Meier curves, which were digitised and subsequently used to apply an algorithm devised by Guyot 2012 (190) using statistical software in R, in order to recreate pseudo-individual patient data (IPD). Following recreation of the pseudo-IPD, the data for each study were pooled to create one data set for survival in type 2 patients, which is presented in Figure 32. The survival predictions based on the pooled dataset alongside predictions made by clinicians are presented in Table 118, from TA755 (67).

Table 118: Long-term survival in type 2 patients: clinical opinion and pooled analysis excluding Belter et al. 2018

Year	Clinical opinion	Pooling scenario excluding Belter 2018

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15	[redacted]	84%
30	[redacted]	71%
50	[redacted]	31%

Figure 32. Pseudo-IPD generated from studies identified in type 2 overall survival SLR (excluding Belter et al. 2018)

[redacted]

Footnotes: Units of time are months

Survival analysis based on the NICE decision support unit (DSU) guidance provided in NICE TSD 14 (178) was subsequently conducted in order to fit the most appropriate parametric survival function to the pseudo-IPD data. Specifically, goodness-of-fit statistics were obtained to understand which parametric form had the best fit to the SLR data, assessment of visual fit was conducted, and clinical expert opinion was sought regarding the plausibility of the long-term extrapolations of each function.

The parametric survival functions are presented in Figure 33. The goodness-of-fit statistics are presented in Table 119, which suggest that the Generalised gamma offers the best fit to the data, followed by the Gompertz and the Weibull curves.

Feedback from the UK clinical experts was that the Gompertz and Weibull offer the most plausible long-term extrapolations for type 2 survival. The Gompertz is therefore used in the base case, with the Weibull explored in a scenario analysis (see Section B.3.11.3, Table 154).

Figure 33: Type 2 SMA overall survival parametric functions versus SLR Kaplan-Meier data (excluding Belter et al. 2018 (183))

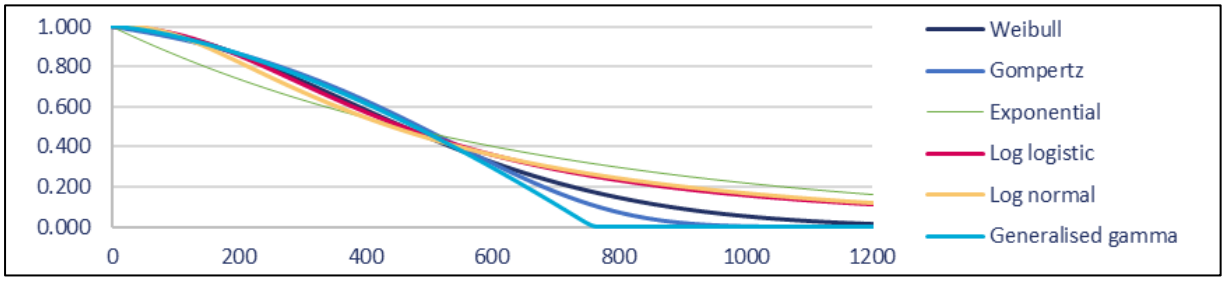


Table 119: Goodness-of-fit statistics for type 2 overall survival

Parametric distribution	AIC (rank)	BIC (rank)
Exponential	3434.1 (6)	3438.2 (6)
Weibull	3338.0 (3)	3346.1 (3)
Log-normal	3376.9 (5)	3385.1 (5)
Generalised gamma	3314.2 (1)	3326.5 (1)
Log-logistic	3363.9 (4)	3372.1 (4)
Gompertz	3328.0 (2)	3336.1 (2)

AIC: Akaike information criterion; BIC: Bayesian information criterion

There is evidence from the literature that the overall survival of type 3 patients is similar to that of the general population (191). Accordingly, type 3 patients in the model followed

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mortality estimates generated by the Office for National Statistics (ONS) for England (2024) (192).

In addition, as informed by the approach taken by the manufacturer in TA588, TA755 and UK clinical expert opinion, who noted that patients who reach advanced motor milestones are likely to follow an improved survival trajectory, type 2 patients who reach the advanced motor milestone of standing or walking, switch to the overall survival estimates generated by the ONS 2024 data (192).

Finally, in line with the approach taken for nusinersen in TA588, a 0.75 hazard ratio (HR) is applied to the risdiplam arm for type 2 patients, to reflect the anticipated reduced likelihood of mortality associated with treatment with risdiplam compared to BSC.

Discontinuation

Within Part 2 of the SUNFISH trial, 17 patients discontinued treatment at the 60 month cut-off. During the placebo-controlled period 4 patients discontinued treatment; 3 patients in the risdiplam and 1 patient in the placebo arm. All 4 patients discontinued in order to switch to another treatment, specified as nusinersen in 3 patients and not specified in 1 patient. Between 12 and 24 months, 1 patient was withdrawn from the risdiplam arm due to COVID-19 measures. Between 24 to 60 months, 13 patients discontinued from the risdiplam arm and 6 patients from the placebo/risdiplam arm due to withdrawal from patient/caregiver choice. As such, there were very few data to inform likely discontinuation from risdiplam in clinical practice. This is further reinforced by only n=1 type 2/3 SMA patient in the REACH dataset stopping risdiplam treatment after 6 months (due to side effects) (See section B.2.6.4). Accordingly, it was necessary to seek UK clinical expert opinion on the likely discontinuation rate of risdiplam in clinical practice. Clinical experts indicated that they would not discontinue treatment in response to a patient plateauing. Furthermore, even if a patient worsened on risdiplam treatment, clinical experts would base their decision on discontinuation on whether the patient is declining at a slower rate than expected without treatment (i.e BSC) and whether alternative treatments are available (see Section B.3.14).

Based on the trial data, REACH data and clinical expert feedback, it was concluded that discontinuation of risdiplam was likely to take place rarely in clinical practice, and therefore no discontinuation was assumed. This also applies to nusinersen.

Disease related events

For disease-related events, the base case assumptions for the time to scoliosis, time to respiratory support and time to bulbar dysfunction are informed by a published SLR of the natural history of SMA, as they are sources of natural history with higher sample sizes (182). The data for these events can also be modelled by using the published literature (in the FIREFISH base case) as a scenario analysis.

B.3.4 Measurement and valuation of health effects

B.3.3.1 Health-related quality-of-life data from clinical trials

Presymptomatic (RAINBOWFISH) and Type 1 (FIREFISH) model

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Within the FIREFISH study, the Infant Toddler Quality of Life (ITQOL) Questionnaire was used. However, utility data were not collected in either study, as the EQ-5D is not validated in children and there are well-known limitations in conceptualising, collecting and measuring utility data in infants and young children (193). Proxy assessments of patient HRQoL may be possible by parents or carers, but may nevertheless fail to produce a balanced assessment of HRQoL in SMA.

Type 2/3 (SUNFISH) model

EQ-5D-5L data were collected from patients within the SUNFISH trial (110). As described in Section B.3.4.5, these data were cross-walked to the EQ-5D-3L and valued using the UK value set (194), and utilised in a scenario analysis for type 2/3 cost-effectiveness analysis. However, the health-related quality-of-life data from the SUNFISH trial lacked differentiation between health states and face validity compared to the values from TA588 according to UK clinical expert opinion (Section B.3.14).

B.3.3.2 Mapping

Due to the availability of the EQ-5D data to inform both the type 2/3 and type 1 models, sourced from the literature and previous NICE appraisals (18, 67, 169), it was not deemed necessary to undertake any mapping from HRQoL scales to HSUVs for either cost-effectiveness model.

B.3.3.3 Health-related quality-of-life studies

The *de novo* SLR and SLR updates were conducted on the 29th August 2019 and 22nd January 2024, respectively, to identify HSUV data for treatment options in SMA. Eligibility criteria were not limited by type of SMA, severity or age of onset.

A total of 6,445 articles were identified from the searches. Finally, 13 full paper publications, reporting on 11 unique studies met the eligibility criteria and were included in the review.

The methodological details and results of the cost-effectiveness SLR for studies relevant to the UK setting are presented in Table 120; full details of the search strategy and the complete results are presented in Appendix G. The original risdiplam NICE submission [TA755] has not been extracted within the SLR, but will be presented and discussed in the main body of the submission.

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Table 120. Summary of list of publoshed HRQoL/utility studies, n=11

Source, country	Population (sample size)	Interventions/ comparators	Methods of elicitation, valuation and mapping	Health states	Utility values and uncertainty around values	Appropriateness of study for cost-effectiveness evaluation
HRQoL/utility studies identified in SLR update						
Bromilow, 2021(195) Country UK (Linked to Smith, 2022)(196)	Population Representative sample of the UK adult population (N=321). Participants were asked to imagine themselves as parents to a child with SMA SMA Type Vignettes describing SMA Type 1 health states Age Range: 18–67 Gender Female (n=160), male (n=161), one participant preferred not to provide their gender (n=1) Female, 49.7% Recruitment Participants recruited by a third party (Qualtrics LLC) which maintains a series of	NA	Instrument Health utilities were derived via vignettes. Participants were presented with 4 vignettes describing SMA Type 1 health states. For each vignette, participants determined whether the state was WTD using a VAS (range: −100 to 100) Valuation method UK setting. Health state utilities were captured using TTO, SG and VAS. Utilities for the VAS were derived by dividing each response by 100	PAV Non-sitting Sitting Walking	TTO valuation, mean (SD, SE) [95% CI]: PAV: −0.0243 (0.6143, 0.0342) [−0.0914, 0.0428] Non-sitting: −0.0264 (0.6429, 0.0358) ` [−0.0966, 0.0438] Sitting: 0.0977 (0.6282, 0.0350) [0.0291, 0.1664] Walking: 0.3844 (0.5670, 0.0316) [0.3225, 0.4463] SG valuation, mean (SD, SE) [95% CI]: PAV: 0.0028 (0.5850,	Consistency with NICE reference case This is a UK study which would likely be relevant for a UK setting EQ-5D values were not reported in this study. However, vignettes were valued by a sample of the general UK population using appropriate elicitation techniques (TTO and SG) Relevance to decision problem Health states describe individuals with SMA Type 1 only (not all individuals with 5q SMA)

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Source, country	Population (sample size)	Interventions/ comparators	Methods of elicitation, valuation and mapping	Health states	Utility values and uncertainty around values	Appropriateness of study for cost-effectiveness evaluation
	online panel respondents				0.0326) [−0.0611, 0.0667] Non-sitting: 0.0139 (0.5899, 0.0329) [−0.0505, 0.0783] Sitting: 0.0946 (0.5901, 0.0329) [0.0302, 0.1591] Walking: 0.3782 (0.5548, 0.0309) [0.3176, 0.4388] VAS valuation, mean (SD, SE) [95% CI]: PAV: −0.1193 (0.5271, 0.0294) [−0.1769, −0.0618] Non-sitting: −0.1011 (0.5312, 0.0296) [−0.1591, −0.0431]	

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Source, country	Population (sample size)	Interventions/ comparators	Methods of elicitation, valuation and mapping	Health states	Utility values and uncertainty around values	Appropriateness of study for cost-effectiveness evaluation
					Sitting: 0.0524 (0.4585, 0.0256) [0.0023, 0.1025] Walking: 0.3554 (0.4092, 0.0228) [0.3107, 0.4001]	
NURTURE (Kirschner 2022a(197), Kirschner 2022b(198)) Country NR (Multinational)	Population Caregivers of participants who initiated nusinersen treatment in the presymptomatic stage of SMA as part of the NURTURE study (ongoing, Phase 2, open-label, multinational, single-arm study) HRQoL data were reported for N=25 caregivers (interim data cut: February 2021). SMA type Presymptomatic SMA (type NR)	Intervention Nusinersen (dose NR) Comparators NA	Caregiver-reported HRQoL data from first assessment to Day 1440 Timing of HRQoL evaluation, median (range), years after nusinersen initiation: PedsQL Parent Proxy (GCS and NM modules): 3.1 (1.9–4.4) Instrument PedsQL Parent Proxy (GCS and NM module; 0–100), higher scores indicate improved HRQoL	Utilities NR for particular SMA health states	Mean (SD) scores of PedsQL-GCS reported among caregivers of participants with 3 SMN2 copies: First assessment: 93.7 (5.9) Day 1440: 88.3 (10.8)	Consistency with NICE reference case Although the NURTURE study included a UK site, the proportion of caregivers from the UK included in this study was NR. As such, it is unclear to what extent these results are directly relevant to clinical practice in the UK HRQoL values are reported rather than utility values, which deviate from the NICE reference case Relevance to decision problem The population includes individuals with

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Source, country	Population (sample size)	Interventions/ comparators	Methods of elicitation, valuation and mapping	Health states	Utility values and uncertainty around values	Appropriateness of study for cost-effectiveness evaluation
	SMN2 copy number: 2 (n=15), 3 (n=10) Age NR Gender NR Recruitment Caregivers of participants in the NURTURE clinical trial		for people with SMA (proxy-reported by caregivers) Valuation method NA (no valuation of HRQoL data)			presymptomatic SMA (type NR) with 2 to 3 SMN2 copies, which is aligned to one of the subgroups considered as part of the decision problem However, health state utility values are not reported for particular SMA health states, which limits their applicability for cost-effectiveness evaluation
Lo, 2022(199) Country UK	Population Representative sample of the UK general public (N=500) SMA type SMA Type 2 or non-ambulatory SMA Type 3 Age Participants were ≥18 years; Mean age: 48.7 years Gender Male: 49% Female: 51%	NA	Instrument DCE (life expectancy attribute added as a corollary of the TTO method) Valuation method DCE, originally developed to describe treatment attributes for people with SMA Type 2 and non-ambulatory SMA Type 3, adapted for use in the general public	Health state/ treatment attribute for people with Type 2 or non-ambulatory Type 3 SMA	Disutility (95% CI)	Consistency with NICE reference case (Dis)utility values are reported, in line with the reference case. However, these values were not measured using EQ-5D, the preferred measure of HRQoL; the utilities were derived from a UK general public sample using an experimental method which deviates from the NICE reference case Relevance to decision problem
				Reference: can sit, stand and walk independently		
				Can sit, stand and walk with assistance	−0.068 (−0.083, 0.053)	
				Can sit but cannot stand	−0.222 (−0.242, −0.201)	
				Cannot sit	−0.408 (−0.440, −0.377)	
				Reference: can breathe without mechanical support		

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Source, country	Population (sample size)	Interventions/ comparators	Methods of elicitation, valuation and mapping	Health states	Utility values and uncertainty around values	Appropriateness of study for cost-effectiveness evaluation
	Recruitment Recruited through specialist recruitment panels; contacted via email and screened for eligibility. Quote sampling used to ensure geographical, gender and age representativeness based on UK census data		An overall life expectancy attribute was added The motor function attribute was adapted to describe four absolute levels of motor function (unable to sit, sitting, standing, walking independently for over 10 m) The breathing function attribute was adapted to describe three levels (mechanical breathing support >16 hours per day, <16 hours a day or none at all) Analysis Mixed-effect logit regression model Attributes initially specified as random coefficients;	Mechanical support for some of the day (<16 hours)	−0.159 (−0.174, −0.143)	Health state/treatment attributes are driven by the differences between nusinersen and risdiplam, which is relevant to the decision problem. However, while the health states describe people with 5q SMA, they specifically describe SMA Type 2 or non-ambulatory SMA Type 3, which is narrower than the population specified by the decision problem
				Mechanical support for >16 hours a day	−0.304 (−0.328, −0.281)	
				Reference: oral liquid taken once a day at home		
				Injection into spine in hospital every four months	−0.071 (−0.085, −0.057)	
				Reference: No treatment reactions		
				Reaction for 12 hours every four months	−0.057 (−0.071, −0.042)	
				Reaction for 1–2 days every four months	−0.060 (−0.078, −0.042)	
				Reaction for 3–4 days every four months	−0.087 (−0.103, −0.071)	
				Reference: No eye monitoring required		
				Monitoring if symptoms present	−0.024 (−0.0 36, −0.012)	
				Monitoring twice a year for the first two years	−0.023 (−0.037, −0.009)	
				Reference: No requirement to use contraception		

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Source, country	Population (sample size)	Interventions/ comparators	Methods of elicitation, valuation and mapping	Health states	Utility values and uncertainty around values	Appropriateness of study for cost-effectiveness evaluation
			choice scenarios identified using a grouping variable. MRS were obtained by taking a ratio of the life expectancy coefficient for 1 year and another treatment attribute Disutilities calculated by estimating remaining life expectancy; MRS estimates were then used to estimate utilities for changes in treatment profiles	Must agree to use effective contraception	−0.012 (−0.021, −0.002)	
McCluskey, 2023(200) Country Northern Ireland	Population Adult individuals with SMA Type 2, who had age at onset of <18 months, never walked independently without aids and had a confirmed SMN1 5q deletion (N=6) SMA type SMA Type 2	Intervention Risdiplam Comparator NA	Participants were emailed the QOLM questionnaire at 3 monthly intervals. Mean scores reported for baseline and 9 months of risdiplam treatment Instrument QOLM	Utilities NR for particular SMA health states	QOLM mean scores At baseline 41.8 At 9 months: 52.5 Mean change (SD) [95% CI]: +10.7 (8.4) [1.84, 19.5] p=0.027	Consistency with NICE reference case HRQoL values are reported rather than HSUVs, which deviates from the NICE reference case Relevance to decision problem Individuals with 5q SMA receiving risdiplam were included, which is

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Source, country	Population (sample size)	Interventions/ comparators	Methods of elicitation, valuation and mapping	Health states	Utility values and uncertainty around values	Appropriateness of study for cost-effectiveness evaluation
	Age Mean (range) age: 33.7 (26–44) years Gender Female (n=5), male (n=1) Recruitment All adults with SMA Type 2 attending the Northern Ireland neuromuscular clinic in January 2021 who met the eligibility criteria, were offered treatment via the UK EAMS		Valuation method NA; no valuation of HRQoL data			relevant to the decision problem. Only adults with SMA Type 2 were included, which is narrower than the population outlined in the decision problem
Montes, 2021(201) (SHINE; NCT02594124) Multinational (including UK data)	Population Caregivers of participants with later-onset SMA treated with nusinersen in the Phase 1b/2a CS2 (NCT01703988) and CS12 study (NCT02052791) were eligible to enrol HRQoL reported for N=24 caregivers of people with SMA (no utility data) SMA Type	Nusinersen	Parent-proxy report of HRQoL change from baseline (of CS2 study) to Day 1290 of SHINE Instrument PedsQL Parent Proxy (GCS and NM Modules; 0−100), higher scores indicate improved HRQoL for people with SMA (proxy-	Utilities NR for particular SMA health states	PedsQL Parent Proxy mean (95% CI) change scores for CS2 baseline to Day 1290 in SHINE: SMA Type 2 (n=10) GCS: 0.3 (−6.50, 7.13) NM Module: 2.5 (−4.89, 9.79) SMA Type 3 (n=14)	Consistency with NICE reference case HRQoL values are reported rather than utility values, which deviates from the NICE reference case This was an international study, with participants from the UK. However, specific data are not presented for UK participants, and it is unclear how many were from the UK. As such, the results may not be

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Source, country	Population (sample size)	Interventions/ comparators	Methods of elicitation, valuation and mapping	Health states	Utility values and uncertainty around values	Appropriateness of study for cost-effectiveness evaluation
	SMA Type 2: n=10 SMA Type 3: n=14 Age at screening in CS2 SMA Type 2, mean (SD): 4.4 (4.0) SMA Type 3, mean (SD): 8.9 (4.4) Gender NR Recruitment Participants recruited from Phase 1b/2a CS2 (NCT01703988) and CS12 studies (NCT02052791)		reported by caregivers) Valuation method NA; no valuation of HRQoL data		GCS: 7.8 (−0.36, 15.86) NM Module: 5.6 (−0.63, 11.78) NB Positive changes indicate improvements in HRQoL on the PedsQL Parent Proxy	directly relevant to clinical practice in the UK Relevance to decision problem Individuals with 5q SMA receiving nusinersen are included which is aligned to the decision problem. However, HSUVs are not reported for particular SMA health states, limiting their applicability for cost-effectiveness evaluation
Pena-Longobardo, 2020(202) Country UK, France and Germany Please note N is data for all countries and n is specific to the UK (Linked to Aranda-Reneo, 2020(203))	Population Children and adolescents with SMA (N= 86; n=34)) and their caregivers (N= 41; n=11) SMA type SMA Type 1, n = 7 SMA Type 2, n = 20 SMA Type 3, n = 7 Age	NR	Instrument People with SMA: proxy version of EQ-5D-3L; VAS Caregivers: EQ-5D-5L; VAS Valuation method Participants with SMA and caregiver EQ-5D-5L/EQ-5D-3L responses were valued using a	NA	HRQoL of UK people with SMA, Mean (SD): TTO social tariff score: 0.167 (0.277) VAS: 75.44 (19.36) HRQoL of UK caregivers, Mean (SD):	Consistency with NICE reference case TTO values are reported as utility values, which aligns with the NICE reference case This was an international study, with participants from the UK. Additionally, specific data are presented for UK participants. As such, the results are relevant to clinical practice in the UK

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Source, country	Population (sample size)	Interventions/ comparators	Methods of elicitation, valuation and mapping	Health states	Utility values and uncertainty around values	Appropriateness of study for cost-effectiveness evaluation
	People with SMA: mean age, n=5.5 (SD: 4.79) Caregivers: mean age, n=41.09 (SD: 11.56) Gender People with SMA: Female (n=17), male NR Caregivers: Female (n=7), male NR Recruitment Participants included those diagnosed with SMA who received outpatient care at the time of the study (July 2015 – November 2015) in the UK, France and Germany		TTO social tariff score		TTO social tariff score: 0.852 (0.155) VAS: 80.36 (17.01)	Relevance to decision problem Individuals with 5q SMA are included which is aligned to the decision problem. However, HSUVs are not reported for particular SMA health states, limiting their applicability for cost-effectiveness evaluation
HRQoL/utility studies identified in original SLR						
Lloyd, 2019(204) Country UK (full publication; supplemented by health-state	UK clinical experts on behalf of people with SMA Type 1 and 2 (N=5)	Nusinersen SOC	Instrument: EQ-5D-Y Valuation method: UK tariff	Individuals with SMA Type 1, baseline	−0.120 [0.19]	This study does not meet the requirements of the NICE reference case; clinical experts were used to provide a proxy assessment for people with SMA
				Individuals with SMA Type 1, worsened	−0.240 [0.14]	
				Individuals with SMA Type 1, improvement	−0.170 [0.17]	

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Source, country	Population (sample size)	Interventions/ comparators	Methods of elicitation, valuation and mapping	Health states	Utility values and uncertainty around values	Appropriateness of study for cost-effectiveness evaluation
caregiver disutility values taken from Zuluaga-Sanchez, 2019(161); likely used as a source of utilities in the CADTH HTA submission(205))				Individuals with SMA Type 1, sits without support [reclassified as Type 2]	−0.040 [0.12]	This is a UK study which would likely be relevant for a UK setting Absence of measures of uncertainty for caregiver utilities may restrict their usefulness for informing economic evaluation However, the standard deviations around the mean scores reported for participants are quite low, despite the fact that the study included only a small number of experts (n=5) Small sample size and absence of details regarding response rates and missing data
				Individuals with SMA Type 1, stands with assistance	0.040 [0.09]	
				Individuals with SMA Type 1, walks with assistance‡	0.520 [0.22]	
				Individuals with SMA Type 1, stand/walks unaided [reclassified as SMA Type 3]	0.710 [0.14]	
				Individuals with SMA Type 1, after scoliosis surgery	−0.22 [0.22]	
				Individuals with SMA Type 1, gastric/nasogastric tube	−0.17 [0.17]	
				Individuals with SMA Type 1, requires ventilation	−0.33 [0.27]	
				Individuals with SMA Type 2, baseline	0.04 [0.10]	
				Individuals with SMA Type 2, worsened	−0.130 [0.06]	

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Source, country	Population (sample size)	Interventions/ comparators	Methods of elicitation, valuation and mapping	Health states	Utility values and uncertainty around values	Appropriateness of study for cost-effectiveness evaluation
				Individuals with SMA Type 2, mild improvement	0.040 [0.11]	
				Individuals with SMA Type 2, moderate improvement	0.100 [0.09]	
				Individuals with SMA Type 2, stands/walks with assistance‡	0.390 [0.29]	
				Individuals with SMA Type 2, stands/walks unaided‡	0.720 [0.12]	
				Individuals with SMA Type 2, loss of ambulation with/without assistance‡	−0.120 [0.16]	
				Caregiver SMA Type 1/2, worsened	−0.160 (NR)	
				Caregiver SMA Type 1/2, stabilisation of baseline function	−0.040 (NR)	
				Caregiver SMA Type 1/2, improvement	−0.090 (NR)	
				Caregiver SMA Type 1/2, sits without support	0.000 (NR)	

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Source, country	Population (sample size)	Interventions/ comparators	Methods of elicitation, valuation and mapping	Health states	Utility values and uncertainty around values	Appropriateness of study for cost-effectiveness evaluation
				Caregiver SMA Type 1/2, stands with assistance	0.000 (NR)	
				Caregiver SMA Type 1/2, walks with assistance	0.000 (NR)	
				Caregiver SMA Type 1/2, stands/walks unaided	0.000 (NR)	
				Caregiver SMA Type 1/2, loss of later-onset SMA advanced motor function	−0.160 (NR)	
Lopez-Bastida, 2017(171) Country Spain (full publication)	Caregivers on behalf of individuals with SMA Type 1 (N=8), SMA Type 2 (N=60), and SMA Type 3 (N=13)	NA	Instrument: EQ-5D-3L (caregivers as proxies for individuals with SMA) EQ-5D-5L (for caregivers) Valuation method: NR	Caregivers on behalf of people with SMA, all participants N=81)	0.158 [0.44]	This study does not meet the requirements of the NICE reference case; caregivers were used as proxy respondents on behalf of people with SMA This study was based in Spain and utilised Spanish data; it is unclear if the results are generalisable to the UK setting Small sample size and absence of details regarding response rates and missing data
				Caregivers on behalf of people with SMA Type 2 (N=60)	−0.012 [0.347]	
				Caregivers of people with SMA (N=81)	0.484 [0.448]	
				Caregivers of people with SMA Type 2 (N=60)	0.472 [0.475)]	

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Source, country	Population (sample size)	Interventions/ comparators	Methods of elicitation, valuation and mapping	Health states	Utility values and uncertainty around values	Appropriateness of study for cost-effectiveness evaluation
Malone, 2019(158) Country USA (full publication)	People with SMA Type 1 (sample size, NR)	OA Nusinersen	Instrument: PedsQL data (from CHERISH trial) mapped to EQ-5D-Y(206) Valuation method: NA	People with SMA Type 1, permanent ventilation	0.730	This study does not meet the requirements of the NICE reference case; PedsQL data from the CHERISH trial was mapped to EQ-5D-Y utilities using a published algorithm(206) This study was based in the USA and utilised American data; it is unclear if the results are generalisable to the UK setting Absence of measures of uncertainty for reported utilities may restrict their usefulness for informing economic evaluation Absence of details regarding response rates, loss to follow up, and missing data
				People with SMA Type 1, aligns with SMA 1	0.756	
				People with SMA Type 1, aligns with SMA 1	0.764	
				People with SMA Type 1, aligns with SMA 3	0.878	
				People with SMA Type 1, aligns with a broad spectrum of normal development	0.878	
Sampson, 2018(207) Country: Europe (France, Germany, Spain, and the UK) (full publication; linked to BURQOL-RD study (208)†;	Caregivers of people with SMA (no further details provided) (sample size, NR)	NA	Instrument : EQ-5D-3L (parent-proxy) Valuation method: NR	Caregivers on behalf of people with SMA	0.22	This study does not meet the requirements of the NICE reference case; caregivers were used as proxy respondents on behalf of people with SMA The study enrolled caregivers across France, Germany, Spain,

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Source, country	Population (sample size)	Interventions/ comparators	Methods of elicitation, valuation and mapping	Health states	Utility values and uncertainty around values	Appropriateness of study for cost-effectiveness evaluation
used as a source of caregiver utilities in NICE TA588(209))						and the UK; the results are therefore likely to be generalisable to the UK setting Absence of details regarding response rates and missing data
Thompson, 2017(210) Country: Europe (France, Germany, Spain, and the UK) (abstract/ poster only; also reports duplicate data from Lloyd, 2017(211); used as a source of utilities in the ICER report(212))	Parents of paediatric participants with SMA (N=167) and people with SMA type 2 (sample size, NR)	NA	Instrument: EQ-5D-3L (parent-proxy) PedsQL mapped to EQ-5D-Y(206) Valuation method: NR	Parents on behalf of participants with SMA, Spain (N=81)	0.158	
				Parents on behalf of participants with SMA, UK (N=34)	0.167	
				Parents on behalf of participants with SMA, France (N=26)	0.116	
				Parents on behalf of participants with SMA, Germany (N=26)	0.532	
				People with SMA type 2, worsened (N=131)	0.730 [SE 0.0132]	
				People with SMA type 2, stabilisation of baseline function (N=146)	0.756 [SE 0.0188]	

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Source, country	Population (sample size)	Interventions/ comparators	Methods of elicitation, valuation and mapping	Health states	Utility values and uncertainty around values	Appropriateness of study for cost-effectiveness evaluation
				People with SMA type 2, mild improvement (N=79)	0.716 [SE 0.0174]	
				People with SMA type 2, moderate improvement (N=154)	0.764 [SE 0.0142]	
				People with SMA type 2, stands/walks with assistance (N=53)	0.807 [SE 0.0182]	
				People with SMA type 2, stands unaided (N=28)	0.805 [SE 0.0256]	
				People with SMA type 2, walks unaided (N=10)	0.878 [SE 0.0297]	
				People with SMA type 2, loss of motor function (N=11)	0.774 [SE 0.0303]	

Footnotes: †Data referenced from López-Bastida et al (2016) (50); however, utility data for SMA are not reported in this publication. ‡Denotes health states where two index scores were calculated by one of the participants. This clinician had some difficulties providing a rating for some domains of the EQ-5D-Y for some case studies. In order to reflect this uncertainty, for these health states two index scores were calculated for this clinician, one using the less severe response and one using the more severe response; both index scores were included in the calculation of the mean score and standard deviation for those health states.

Abbreviations: BURQOL-RD: Burden and Health-Related Quality of Life in Patients with Rare Diseases in Europe; CI: confidence interval; CIH: confidence interval higher; CIL: confidence interval lower; DCE: discrete choice experiment; EAMS: Early Access to Medicines Scheme; GCS: generic core scale; HRQoL: health related quality of life; HSUV: health-state utility values; HTA: health technology assessment; MRS: Marginal rates of substitution; NA: not applicable; NICE: National Institute for Health and Care

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Source, country	Population (sample size)	Interventions/ comparators	Methods of elicitation, valuation and mapping	Health states	Utility values and uncertainty around values	Appropriateness of study for cost-effectiveness evaluation
Excellence; NM: neuromuscular; NR: not reported; PAV: permanent assisted ventilation; PedsQL: Pediatric Quality of Life Inventory; QOLM: Quality of Life Measure for People with Slowly Progressive and Genetic Neuromuscular Disease; SD: standard deviation; SE: standard error; SG: standard gamble; SMA: spinal muscular atrophy; SMN: survival of motor neuron; SMN2: Survival of Motor Neuron 2; SOC: standard of care; TTO: time trade off; UK: United Kingdom; USA: United States of America; VAS: visual analogue scale; WTD: worse than death.						

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B.3.3.4 Adverse reactions

Treatment related adverse events of Grade 3+ were planned to be included in the models if they occurred in >5% of patients in the risdiplam trials. However, as the incidence of adverse events experienced by patients that were considered to be related to treatment in the RAINBOWFISH, FIREFISH and SUNFISH trials was very low (<5% overall), adverse events have not been included in either the presymptomatic, type 1 or type 2/3 models. This is in line with the nusinersen NICE submission (TA588 (18)) and TA755 (67) where adverse events were also excluded.

B.3.3.5 Health-related quality-of-life data used in the cost-effectiveness analysis

Within the model base case, given the substantial amount of care that SMA patients require from family members or professional carers, and in line with the approach taken in TA588 (18) and the NICE reference case (67), HSUVs are included in the model for both patients and carers.

As part of the DCA, Roche committed to conducting a new utility study to collectnew utility data for both SMA patients and their respective carers. As such, health economic and academic experts specialising in utility methodology, alongside SMA patient groups were consulted to determine the most appropriate methodology to collect the data. After evaluating several HRQoL tools to determine the most relevant domains to be measured (213), the following HRQoL tools were selected for use based on maximising the coverage of SMA-relevant domains whilst also balancing the level of survey fatigue to participants:

- For people living with SMA:
    - PedsQL self-report (acute version)
    - DMD-QoL-8D self-report
- For the caregivers of people with SMA:
    - PedsQL proxy report (acute version)
    - DMD-QoL-8D proxy report
    - EQ-5D 5L
    - Supplementary questions on QoL and burden

Despite n=40 patients (or carers of patients) completing the study, unfortunately the patient utility values collected across all SMA types had considerable heterogeneity and lacked clinical validity, therefore have not been presented. Whilst the tool selection, rationale and methodology had been validated at multiple stages, ultimately the data was limited by small sample sizes.

For caregivers, n=27 responses were collected and the results fitted a linear pattern with the SMA health states. A linear pattern was seen between the utility values reported and the SMA health states. However it should be noted that the study sample sizes were limited and as the survey was online and self-reported, responses were not validated or verified by a secondary source, which may result in bias and could introduce the possibility of caregivers erroneously responding on behalf of the person they care for, for the caregiver-related questions (173).

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Methodological challenges and uncertainty associated with the modelling of caregiver utility values were also investigated during the MAA period, in order to overcome the "QALY trap" around life extension for patients and carers. Various methods were explored, including accounting for the health effects associated with bereavement (e.g. depression, anxiety, and inability to participate in usual activities due to grief), consideration of wellbeing as an alternative to HRQoL and carer modifier/multiplier for family health spillovers.

During a roundtable discussion with academic experts, whilst it was thought that a patient's death would not have a positive impact on carers, it would remove the caring burden and potentially lead to positive effects in the longer term. It was agreed that bereavement effect is conceptually different to issues that arise from comparing QALYs between a patient with a carer to a patient with no carer. Finally in practice, the impact of accounting for "delayed bereavement" would be very small is most cases and it is likely the QALY trap would still exist even if bereavement effect is considered. For the consideration of wellbeing, whilst as a concept it may capture more effects, including bereavement, the trap could become even worse as wellbeing may be a more sensitive measure to the burdens of caring (214). Overall, the roundtable participants did not feel that a technical fix was practical or necessary and so the approach to modelling caregiver utility values aligns with the ERG preference in TA588 and TA755.

Presymptomatic SMA (RAINBOWFISH) and Type 1 SMA (FIREFISH) models

As noted in Section B.3.4.1, utility data were not collected in the RAINBOWFISH or FIREFISH trial. As such, sources of patient HSUVs from TA755 were applied. These were initially sourced from the nusinersen appraisal (TA588) sourced from the Lloyd et al. case vignette study (169), the ERG clinical advisor values from TA588 and ERG TA588 early onset model values (18). During the development of TA755, the above options were explored with clinical advisors. From a clinical observation, it was felt that patients would not experience a state worse than death, the most plausible set of utility values were those reported in the TA588 ERG report early onset model (Biogen clinical advisors). In the most recent clinical expert elicitation for this appraisal, another preference was given towards Lloyd et al. 2019 for the fact the walking utility values seemed too high in the Biogen clinical advisor value set. Lloyd et al 2019 will be explored in a scenario analysis.

The HSUVs utilised in the base case of the type 1 SMA model are presented in Table 121. Values from Lloyd et al. 2019 are presented in Table 122 and the TA588 ERG values from the early onset model are presented in Table 123 and were explored in scenario analyses. The same values have also been utilised for the presymptomatic SMA model.

Table 121: Summary of patient utility values for cost-effectiveness analysis (presymptomatic and type 1 base case model) (TA588 ERG report early onset model, Biogen clinical Advisors)

State	Utility value: mean	95% confidence interval	Reference in submission (section and page number)	Justification
Permanent ventilation	-0.020	NA	Section B.3.4.5	Based on TA755 and UK clinical experts
Not sitting	0.100	NA		
Sitting	0.200	NA		
Standing	0.700	NA		

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Walking	0.850	NA		

NA, not applicable

Table 122: Summary of patient utility values for cost-effectiveness analysis (presymptomatic and type 1 scenario model) (Lloyd et al. 2019)

State	Utility value: mean	Standard error	Reference in submission (section and page number)	Justification
Permanent ventilation	−0.330	0.02	Section B.3.4.5	Alternative patient utility values available from TA588 (18)
Not sitting	−0.120	0.01		
Sitting	−0.040	0.01		
Standing	0.375	0.04		
Walking	0.615	0.06		

Table 123. Summary of patient utility values for cost-effectiveness analysis (presymptomatic and type 1 scenario model) (TA588 ERG values from early onset model, aligned with the case vignettes – using an average for sitting (based on -0.17 and -0.04), standing (0.04; 0.71) and walking (0.52; 0.71)).

State	Utility value: mean	Standard error	Reference in submission (section and page number)	Justification
Permanent ventilation	−0.240	0.02	Section B.3.4.5	Alternative patient utility values available from TA588 (18)
Not sitting	−0.120	0.01		
Sitting	−0.105	0.01		
Standing	0.375	0.04		
Walking	0.615	0.06		

In line with the approach taken for patient utilities, alternative sources were considered for carer HSUVs. Firstly, values were available from the Roche UK burden of illness study conducted by Roche in caregivers of SMA patients in the UK (Appendix R). Within this study, carers were administered the EQ-5D-5L questionnaire and scores were subsequently cross-walked to the EQ-5D-3L and valued using UK tariffs (194). The motor milestone level of the patient for whom the carer was associated with was recorded; carer utilities associated with the motor milestone health states for patients in the cost-effectiveness model were thereby obtained. Further details of the study methodology can be found in Appendix R. The results of this study demonstrated that the overall mean EQ-5D-5L cross-walked value for carers was 0.739, with similar values recorded for carers of patients in all mobility groups.

Another methodology was also employed by Roche to generate caregiver utility values in SMA, in which informal caregivers completed the caregiver survey from their own perspective about their own quality of life, comprising the EQ-5D-5L tool and supplementary caregiver questions. The EQ-5D 5L values were cross-walked to the EQ-5D 3L and valued using UK tariffs (194). Similar to the burden of illness study, the motor milestone level of the patient for whom the carer was associated with was recorded, and thus carer utilities were

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then associated with the patients' motor milestones healthstate for use in the cost-effectiveness model (see report on file Roche report on file, 2024 #241}).

Carer HSUVs were available from a study by Bastida et al. (171), which were also used to inform carer utilities in TA588 (18). As per the approach taken in TA588, the utility derived from Bastida et al. was assigned to the lowest health state ('not sitting'), whilst general population utility derived from a study by Ara et al. was assigned to the highest health state (172). HSUVs for intermediate health states were then calculated with an even distribution. Similarly to the patient HSUVs, the carer utility value sets were presented to UK clinical experts to understand which would be most appropriate to include in the model base case. The consensus was that the value set based on Bastida et al. and general population utility was more plausible than the set sourced from the Roche UK burden of illness study and the Roche UK utility survey, due to the distribution of values more accurately reflecting the levels of dependence of patients on their carers at the different health states (67) (see Section B.3.14). Furthermore, UK clinical experts thought that the carer utility values from the Roche UK burden of illness study were too high with little differentiation between health states, particularly for the lower health states (67) (see Section B.3.14). There was also uncertainty in the caregiver utility values being reported as the same for "permanent ventilation" and "not sitting" as well as "standing and walking", although both Table 124 and Table 126 were considered to be plausible utility value sets. As such, the HSUVs based on the Bastida et al. study, presented in Table 124, were included in the base case, to ensure consistency in NICE decision-making with TA588, whilst the carer utilities from the Roche UK burden of illness study (Table 125) and Roche UK utility survey (Table 126) were explored in a scenario analysis.

Table 124: Summary of carer utility values for cost-effectiveness analysis (presymptomatic and type 1 base case model) (Bastida et al. 2017 and Ara et al. 2010)

State	Utility value: mean	95% confidence interval	Reference in submission (section and page number)	Justification
Permanent ventilation	0.484	NA	Section B.3.4.5	Feedback from UK clinical experts was that HSUVs sourced from the Bastida et al. study and general population utility (Ara et al.) possessed the greatest clinical validity for carers of SMA patients (67, 171) (172)
Not sitting	0.484	NA		
Sitting	0.628	NA		
Standing	0.771	NA		
Walking	0.915	NA		

HSUV, health state utility value; NA, not applicable; SMA, spinal muscular atrophy

Table 125: Summary of carer utility values for cost-effectiveness analysis (type 1 scenario model) (Roche UK burden of illness study)

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State	Utility value: mean	95% confidence interval	Reference in submission (section and page number)	Justification
Permanent ventilation	0.633	NA	Section B.3.4.5	Feedback from UK clinical experts was that HSUVs sourced from the Bastida et al. and Ara et al. 2010 studies possessed the greatest clinical validity for carers of SMA patients (67, 171) (172) and see Section B.3.14 .
Not sitting	0.751	NA		
Sitting	0.737	NA		
Standing	0.720	NA		
Walking	0.754	NA		

NA, not applicable; SMA, spinal muscular atrophy

Table 126: Summary of carer utility values for cost-effectiveness analysis (type 1 scenario model) (Roche UK utility survey)

State	Utility value: mean	95% confidence interval	Reference in submission (section and page number)	Justification
Permanent ventilation	0.396	NA	Section B.3.4.5	Feedback from UK clinical experts was that HSUVs sourced from the Bastida et al. and Ara et al. 2010 studies possessed the greatest clinical validity for carers of SMA patients (67, 171) (172).
Not sitting	0.396	NA		
Sitting	0.660	NA		
Standing	0.866	NA		
Walking	0.866	NA		

The average number of caregivers per SMA patient applied in the type 1 model was 2.2, based on data obtained in the Roche UK burden of illness study.

Type 2/3 SMA (SUNFISH) model

With regards to HSUVs for patients, as described in Section B.3.4.1, HSUVs were available from the RCT for risdiplam in type 2/3 patients (SUNFISH). In order to understand the effects of motor milestone achievement on utility values, a repeated measures model with fixed and random effects was applied to the EQ-5D-5L data from the ITT population of Part 2 of the SUNFISH study. Analyses by presence of scoliosis and respiratory support at baseline were also conducted, the results of which identified scoliosis and respiratory support to be drivers of additional disutility. Disutilities for these two morbidities were calculated accordingly. In addition to scoliosis and respiratory support, the model also showed improvements to utility

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when patients were old enough to self-report (12 years old and older), and an additional utility was applied upon patients reaching this age. This highlights again the difficulties of capturing utilities in young children. Data were subsequently cross-walked to the EQ-5D-3L and valued using the UK tariffs using the algorithm by van Hout et al. 2012 (194).

In addition, a number of utility sources for type 2/3 patients explored in TA588 were available (18). Within the appraisal for nusinersen, the two sets of utilities considered to have the greatest face validity by the ERG were those estimated in an EQ-5D vignette study of SMA patients by Lloyd et al (169) and values estimated by clinical advisors to the ERG (18). These two sets, in addition to those sourced from the SUNFISH trial, were presented to UK clinical experts (both in TA755 and in this most re-appraisal) to receive clinical opinion on the validity of the values. Within TA755, feedback was that the utility values from TA588 were more realistic than the SUNFISH values, as they better reflect the broad range of HRQoL between milestones. Whilst the HSUVs elicited from the SUNFISH trial align with the requirements of the NICE reference case, the clinicians deemed the minimal difference between HSUVs of different health states, and overall low scores, to be unreflective of the independence and gains in quality of life with each motor milestone advance made by a patient. UK clinical experts advised that utilities would be expected to increase with higher motor milestones (see Section B.3.14). Moreover, it is thought that type 2 and type 3 SMA patients experience higher levels of anxiety and depression versus type 1 SMA patients (215). The utility values sourced from the Lloyd et al (2019) vignette study were chosen as the base case to align with what was considered for final decision-making in the TA755 and TA588 (18, 67, 169), while the utility values derived from the TA588 ERG clinical advisers and SUNFISH were included as scenario analyses.

As the modelled health states used in TA588 differ slightly from the risdiplam model, as in TA755 (18, 67). HSUVs from the TA588 model were applied to the closest corresponding motor milestone health states in the risdiplam model. Where a health state in the risdiplam model was deemed to fall between two health states, the mid-point HSUV was calculated. The same principle applies for the carer utilities and type 1 utilities (patients and carers) described below.

The HSUVs utilised in the base case are presented in Table 127. The HSUVs elicited from the TA588 ERG report, Biogen clinical experts and those from SUNFISH were explored in scenario analyses and are presented in Table 128 and Table 129, respectively.

Table 127: Summary of patient utility values for cost-effectiveness analysis (type 2/3 base case model) (Lloyd et al. 2019)

State	Utility value: mean	95% confidence interval	Reference in submission	Justification
Not sitting	−0.170	NA	Section B.3.4.5	Feedback from UK clinical experts was that HSUVs sourced from the Lloyd et al. study possessed the greatest clinical validity for type
Sitting (supported)	0.040	NA		
Sitting (unsupported)	0.040	NA		
Standing	0.555	NA		
Walking	0.555	NA		

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				2/3 patients (Section B.3.14).
Disutilities				
Bulbar function	-0.170	NA		

HSUV, health state utility value; NA, not applicable

Table 128: Summary of patient utility values for cost-effectiveness analysis (type 2/3 scenario analysis) (utilities from TA588 ERG report, Biogen clinical experts)

State	Utility value: mean	95% confidence interval	Reference in submission	Justification
Not sitting	0.200	NA	Section B.3.4.5	Feedback from UK clinical experts was that HSUVs sourced from the Lloyd et al. study possessed the greatest clinical validity for type 2/3 patients (Section B.3.14) (67, 169).
Sitting (supported)	0.400	NA		
Sitting (unsupported)	0.500	NA		
Standing	0.700	NA		
Walking	0.850	NA		

HSUV, health state utility value; NA, not applicable

Table 129: Summary of patient utility values for cost-effectiveness analysis (type 2/3 scenario analysis) (SUNFISH EQ-5D-3L utilities)

State	Utility value: mean	95% confidence interval	Reference in submission	Justification
Not sitting	[redacted]	[redacted]	Section B.3.4.5	HSUVs (EQ-5D-5L) were directly elicited from patients in the SUNFISH trial. However, feedback from UK clinical experts was that HSUVs sourced from the Lloyd et al. study possessed the greatest clinical validity for type 2/3 patients (Section B.3.14) (67, 169)..
Sitting (supported)	[redacted]	[redacted]		
Sitting (unsupported)	[redacted]	[redacted]		
Standing	[redacted]	[redacted]		
Walking	[redacted]	[redacted]		
Disutilities				
Severe scoliosis	[redacted]	[redacted]	Section B.3.4.5	As above, in addition, scoliosis and respiratory support were deemed to have a significant impact
Respiratory support	[redacted]	[redacted]		

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				on utility. Disutilities were used as part of a scenario analysis exploring the impact of severe scoliosis and the need for respiratory support.
Additional utility				
Patient-reported utilities (over 12 years old)	[redacted]	[redacted]	Section B.3.4.5	Age over 12 was deemed to have a significant impact on utility

EQ-5D-3L, European Quality of Life-5 Dimensions-3 levels; HSUV, health state utility value

Similar to the presymptomatic and type 1 approach, carer utility values from Bastida et al. and the general population utility were deemed more appropriate than the values from the Roche UK burden of illness study by the clinical experts during the advisory board (as assessed in TA755) (see Appendix Q) and from the *de novo* Roche UK utility survey (18, 171-173). As such, the carer utility values based on the Bastida et al. study and general population utility (Table 130) were applied in the type 2/3 model base case, with the Roche UK burden of illness study (Table 131) and Roche UK utility survey (Table 132) values explored in scenario analyses, for consistency across the models. In the most recent clinical expert elicitation for this appraisal, another preference was given towards the Roche UK utility study, in which the values reported for walking and standing are not too dissimilar However, it is thought that the burden of caring for type 2/3 patients is lower than what it would be for poorer prognosis patients, and so the utility values based on the Bastida et al. study and general population are still considered to be the most relevant base case.

Table 130: Summary of carer utility values for cost-effectiveness analysis (type 2/3 base case model) (TA588/TA755 ERG report)

State	Utility value: mean	95% confidence interval	Reference in submission	Justification
Not sitting	0.700	NA	Section B.3.4.5	Feedback from UK clinical experts was that HSUVs sourced from the TA588/TA755 ERG report possessed the greatest clinical validity for carers of SMA patients (see Section B.3.14.1) (171, 172)
Sitting (supported)	0.772	NA		
Sitting (unsupported)	0.843	NA		
Standing	0.915	NA		
Walking	0.915	NA		

HSUV, health state utility value; NA, not applicable

Table 131: Summary of carer utility values for cost-effectiveness analysis (type 2/3 scenario model) (Roche UK burden of illness study)

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State	Utility value: mean	95% confidence interval	Reference in submission	Justification
Not sitting	0.751	NA	Section B.3.4.5	Feedback from UK clinical experts was that HSUVs sourced from the Bastida et al. and Ara et al. studies possessed the greatest clinical validity for carers of SMA patients (Appendix Q, Section B.3.14.1) (171, 172)
Sitting (supported)	0.737	NA		
Sitting (unsupported)	0.737	NA		
Standing	0.720	NA		
Walking	0.754	NA		

HSUV, health state utility value; NA, not applicable

Table 132: Summary of carer utility values for cost-effectiveness analysis (type 2/3 scenario model) (Roche UK utility survey)

State	Utility value: mean (standard error)	95% confidence interval	Reference in submission (section and page number)	Justification
Not sitting	0.396	NA	Section B.3.4.5	Feedback from UK clinical experts was that HSUVs sourced from the Bastida et al. and Ara et al. 2010 studies possessed the greatest clinical validity for carers of SMA patients (67, 171, 172).
Sitting (supported)	0.396	NA		
Sitting (unsupported)	0.660	NA		
Standing	0.866	NA		
Walking	0.866	NA		

Similar to presymptomatic and type 1 SMA, the average number of caregivers per SMA patient applied in the type 1 model was 2.2, based on data obtained in the Roche UK burden of illness study.

B.3.5 Cost and healthcare resource use identification, measurement and valuation

The de novo SLR and SLR updates were conducted on the 29th August 2019 and 22nd January 2024, respectively, to identify HSUV data for treatment options in SMA. Eligibility criteria were not limited by type of SMA, severity or age of onset.

A total of 1,476 articles were identified from the searches. Finally, 51 full paper publications, reporting on 47 unique studies met the eligibility criteria and were included in the review. Due to the size of the table, it has not been presented in the main body of the submission, however full details of the search strategy and the complete results are presented in Company evidence submission template for ID6195: Nusinersen and risdiplam for treating spinal muscular atrophy (MA review of TA588 and TA755)

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Appendix G. Table 133 presents 9 of the studies identified from the SLR search that have direct and clear applicability to UK clinical practice, i.e. UK costs and resource use is clearly reported.

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Table 133. Summary list of published UK-based cost and healthcare resource use studies in SMA, n=9

Study, country, currency (year)	Study design and aim	Population (sample size)	Cost valuations used in the study	Direct costs (medical/ non-medical)	Indirect costs	Total costs and drivers	Resource use	Applicability to clinical practice in England and for cost-effectiveness analysis
Cost and healthcare resource use studies identified in SLR update								
Ali 2019 Country UK Currency GBP Cost year NR	Design Single centre retrospective review of medical records Aim To investigate the respiratory care, hospital utilisation and associated costs in newly treated SMA Type 1	Children with SMA Type 1 treated with nusinersen in a single centre (N=11)	Medical chart review of baseline characteristics and hospital admission data, including: details of ventilatory support, feeding support, number of nusinersen doses, complications and details of hospital admissions, HDU days, PICU days and intubated days	HDU and PICU cost in cohort (N=11): Total over 24 months: £2,200,000.00a aSeparate to the cost of nusinersen	NR	NR	Use of ventilation in cohort (N=11) Any long-term ventilatory support: n=11 Mask ventilation: n=9 Tracheostomy: n=2 Intubation: n=8; n=6 intubated for a total of 38 days Median number of hospital admissions over 24 months per child (median [range]) (N=11) Number of admissions: 11 (1–25) Number of emergency admissions: 3 (0–21) Number of elective admissions: 4 (0–9) Hospital days: 84 (7–235) General paediatric hospital days: 0 (0–63) HDU days: 79 (7–173) PICU days: 13 (0–109) Number of HDU and PICU days in cohort (N=11) HDU: 762 days (2.8 per child per month)	Study located in the UK, with all children receiving care in line with international SMA guidelines. Thus, results can be considered applicable to clinical practice in England, but are limited by a small sample size Study reports relevant CRU in individuals with SMA; however, the cohort was limited to individuals with SMA Type 1 which is narrower than the population considered in the cost-effectiveness evaluation Total costs for HDU and PICU days were calculated using inpatient rather than community costs and will therefore

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Study, country, currency (year)	Study design and aim	Population (sample size)	Cost valuations used in the study	Direct costs (medical/ non-medical)	Indirect costs	Total costs and drivers	Resource use	Applicability to clinical practice in England and for cost-effectiveness analysis
							PICU: 248 days (0.93 per child per month) Number of days in hospital at first admission (N=11) Total for study participants: 426 days Median (range) per participant: 20 days (1–235 days) Physiotherapy adjuncts that study participants required (N=11) Saline nebulisers: n=8 (72%) Suction: n=11 (100%) Percussion: n=9 (82%) Cough assist machine: n=5 (45%) High frequency chest wall oscillation vest: n=1 (9%) Total time cohort spent in hospital (N=11) 1101 days Median (range) proportion of study participants' life spent in hospital 20% (2–72); comprised of ≤10% (n=4), 10%–35% (n=4) and >35% (n=3)	underestimate total costs

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Study, country, currency (year)	Study design and aim	Population (sample size)	Cost valuations used in the study	Direct costs (medical/ non-medical)	Indirect costs	Total costs and drivers	Resource use	Applicability to clinical practice in England and for cost-effectiveness analysis
							Use of general anaesthetic or interventional radiology n=0 Median (range) number of nusinersen doses 6 doses (4–8 doses) Care utilisation in cohort (N=11): Any care package: n=4 (36%) 16 hours of care per week: n=1 (9%) Over 85 hours of care per week: n=3 (27%)	
Aranda-Reneo, 2020 Country UK, France, Germany and Spain Please note all N values are data for all countries, whilst n	Design Cross-sectional analysis Aim To record the time burden of SMA on informal caregivers	Informal caregivers of children diagnosed with SMA (N=68); (n=11 from the UK) SMA Type SMA Type 1, N=11	Questionnaire completed by primary caregivers (utilises questions from BURQOL and altered by SMA expert committee)	NR	NR	NR	Mean daily hours of care: 10.02 (SD: 6.67) Main caregiver provided mean hours per day: 6.89 (SD: 4.62) Other caregivers provided mean hours per day: 3.13 (SD: 3.34) Informal caregiving provided daily to participants with SMA by non-invasive respiratory supply (N=30) Informal caregiving provided daily to participants with SMA not requiring non-invasive respiratory supply (N=35)	This data is applicable to resource use in England as the participants with SMA and caregiver data is based on a UK population Study reports CRU for caregivers of children with SMA, which is the relevant population considered in the cost-effectiveness evaluation

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Study, country, currency (year)	Study design and aim	Population (sample size)	Cost valuations used in the study	Direct costs (medical/ non-medical)	Indirect costs	Total costs and drivers	Resource use	Applicability to clinical practice in England and for cost-effectiveness analysis
values are data specific to the UK only Currency: NR (Linked to Pena-Longobardo, 2020(202))		SMA Type 2: N=42 SMA Type 3: N=15					Mean hours (SD) of informal caregiving daily in the UK Basic hygiene, dressing Main caregiver: 1.07 (0.71) All caregivers: 1.70 (1.13) Feeding the person with SMA Main caregiver: 2.50 (2.73) All caregivers: 3.55 (3.69) Bathing or showering Main caregiver: 0.53 (0.25) All caregivers: 0.96 (0.65) Helping to move Main caregiver: 1.80 (2.31) All caregivers: 2.32 (2.23) Total BADL Main caregiver: 5.89 (4.37) All caregivers: 8.52 (5.56) Cooking and preparing special meals Main caregiver: 0.61 (0.90) All caregivers: 0.82 (1.06) Administering drugs/minor cures Main caregiver: 1.39 (1.46) All caregivers: 1.95 (1.92) Other IADLa Main caregiver: 0.00 (0.01) All caregivers: 0.00 (0.01) Total IADL Main caregiver: 2.00 (1.67) All caregivers: 2.77 (2.22)	

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Study, country, currency (year)	Study design and aim	Population (sample size)	Cost valuations used in the study	Direct costs (medical/ non-medical)	Indirect costs	Total costs and drivers	Resource use	Applicability to clinical practice in England and for cost-effectiveness analysis
							Other activities directly related to the disease Main caregiver: 0.52 (1.02) All caregivers: 1.21 (1.87) All activities Main caregiver: 8.42 (4.67) All caregivers: 12.50 (5.96) Note: time of informal care was capped at a maximum of 16 hours per day per caregiver aOther IADL included the time spent on medical visits, diagnostic tests, traveling, financial, administrative or legal affairs and social and leisure activities	
HST15(216) Country UK Currency GBP Cost year 2017–2018	Design Telephone semi-directive interviews of UK clinical experts Aim To report HCRU associated with SMA	N=16 clinical experts	For consultations, inpatient hospitalisations and A&E visits the main source of unit costs was the NHS National Schedule	Annual SMA-care related costs used in the CE base case: Health state E (SMA Type 1): Drugs: £636	NR	Total costs of OA/person with SMA £1,676,925	Prevalence of use of NIV aids SMA Type 1: 16% non-ventilated; 84% NIV <16 hours/day SMA Type 2: 44% non-ventilated; 66% NIV <16 hours/day SMA Type 3: 80% non-ventilated; 20% NIV <16 hours/day Healthcare settings of individuals with SMA in the UK by ventilatory status	The study is based in the UK, therefore the CRU data are highly applicable to practice in England Both costs and resource use data are reported, making the data applicable for cost-effectiveness analysis

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Study, country, currency (year)	Study design and aim	Population (sample size)	Cost valuations used in the study	Direct costs (medical/ non-medical)	Indirect costs	Total costs and drivers	Resource use	Applicability to clinical practice in England and for cost-effectiveness analysis
	Types 1−3		of Reference Costs, Year 2017–18 and the PSSRU Costs of Health and Social Care 2018 report For resources related to pharmacological therapy, PCA England data, 2018 were used When different formulations were available for a	Medical tests: £225 Medical visits: £2,690 Hospitalisations: £211,235 GP and Emergency: £293 Health material: £2,903 Social services: £46,738 Total: £264,720 Health state D (SMA Type 1) Drugs: £919 Medical tests: £325 Medical visits: £3,890			Ventilation group – paediatric intensive care Participants on NIV <16 hours per day: 5% Participants on NIV >16 hours per day: 15% Participants with tracheostomy: 10% Ventilation group – high dependency Participants on NIV <16 hours per day: 5% Participants on NIV >16 hours per day: 15% Tracheostomy participants: 30% Ventilation group – home-based Participants on NIV <16 hours per day: 90% Participants on NIV >16 hours per day: 70% Tracheostomy participants: 60%	

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Study, country, currency (year)	Study design and aim	Population (sample size)	Cost valuations used in the study	Direct costs (medical/ non-medical)	Indirect costs	Total costs and drivers	Resource use	Applicability to clinical practice in England and for cost-effectiveness analysis
			medication, a weighted average of different formulations deemed suitable for the target population was used For resources related to laboratory tests, respiratory tests/evaluations, orthopaedic devices, surgeries and respiratory devices, several	Hospitalisations: £66,988 GP and Emergency: £423 Health material: £3,936 Social services: £27,896 Total: £104,377 Health state C (SMA Type 2) Drugs: £743 Medical tests: £311 Medical visits: £2,247 Hospitalisations: £37,420 GP and Emergency: £176				

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Study, country, currency (year)	Study design and aim	Population (sample size)	Cost valuations used in the study	Direct costs (medical/ non-medical)	Indirect costs	Total costs and drivers	Resource use	Applicability to clinical practice in England and for cost-effectiveness analysis
			published sources (NICE, NHS) were used	Health material: £2,046 Social services: £18,598 Total: £61,541 Health state B (SMA Type 3) Drugs: £939 Medical tests: £277 Medical visits: £1,899 Hospitalisations: £468 GP and Emergency: £71 Health material: £591 Social services: £2,952				

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Study, country, currency (year)	Study design and aim	Population (sample size)	Cost valuations used in the study	Direct costs (medical/ non-medical)	Indirect costs	Total costs and drivers	Resource use	Applicability to clinical practice in England and for cost-effectiveness analysis
				Total: £7,197 aE=permanent ventilation; D=not sitting; C=sits unassisted; B=walks unassisted.				
Lo 2022 Country UK	Design Survey Aim To quantify preferences of people with SMA and caregivers for different attributes of SMA treatments for Type	Adult people with SMA/caregiver survey respondents (N=84 adults with SMA and N=83 caregivers): Adult person with SMA (≥18 years) or	People with SMA and caregiver survey	NR	NR	Caregiver work attendance: Employed full time: 59% Employed part-time: 18% Homemaker: 23% Reduced working hours: 37% Changed jobs to improve	Reported CRU in paediatric cohort (N=83; proxy reporting) Breathing support Mechanical breathing support >16 hours daily: n=0 (0%) Mechanical breathing support for some of the day: n=43 (52%) No mechanical support: n=40 (48%) SMA treatment Nusinersen: n=54 (65%) Surgery: n=2 (2%) Other: n=1 (1%) None: n=29 (34%) Tools/equipment	Study reports relevant CRU data for adult and paediatric people with Type 2 and 3 non-ambulatory SMA in the UK which are likely to be relevant for infirming the economic evaluation The sample size is relatively large (N=84 participants with SMA, N=83 caregivers) with all participants based in the UK; the results can be considered

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Study, country, currency (year)	Study design and aim	Population (sample size)	Cost valuations used in the study	Direct costs (medical/ non-medical)	Indirect costs	Total costs and drivers	Resource use	Applicability to clinical practice in England and for cost-effectiveness analysis
	2 and non-ambulatory Type 3 SMA, and to estimate health utility values for SMA treatment outcomes from a UK general public sample	parent/caregiver of a child with SMA (<18 years) A self-reported or proxy-reported diagnosis of SMA Age of onset between 7 and 18 months (Type 2) or 18 months and 17 years (Type 3) Non-ambulatory				flexibility: 30% Stopped working due to caregiving: 23%	Breathing machine or mechanical ventilation: n=45 (54%) Feeding tube: n=0 (0%) Wheelchair use: n=81 (98%) Suction machine: n=79 (95%) Walking frame: n=39 (47%) Other: n=1 (1%) Reported CRU in adult participants with SMA (N=84) Breathing support Mechanical breathing support >16 hours daily: n=1 (1%) Mechanical breathing support for some of the day: n=22 (26%) No mechanical support: n=61 (73%) SMA treatment Nusinersen: n=1 (1%) Surgery: n=17 (20%) Other: n=13 (15%) None: n=58 (69%) Tools/equipment Breathing machine or mechanical ventilation: n=30 (36%) Feeding tube: n=9 (11%) Wheelchair use: n=84 (100%)	applicable to clinical practice in England

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Study, country, currency (year)	Study design and aim	Population (sample size)	Cost valuations used in the study	Direct costs (medical/ non-medical)	Indirect costs	Total costs and drivers	Resource use	Applicability to clinical practice in England and for cost-effectiveness analysis
							Suction machine: n=10 (12%) Walking frame: n=1 (1%) Other: n=22 (26)	
Pena-Longobardo, 2020 Country: UK, France, Germany Please note N is data for all countries and n is specific to the UK Currency: Euros, 2014 (Linked to Aranda-Reneo, 2020(203))	Design Cross-sectional study Aim To estimate the economic impact and HRQOL of people with SMA	Population Children/adolescents with SMA (N= 86; n=34)) and their caregivers (N= 41; n=11) SMA type Type 1, n = 7 Type 2, n = 20 Type 3, n = 7	People with SMA and caregiver survey The National Tarriff Payment system was used to evaluate performance by the NHS and calculate UK costs Zarit Interview and Barthel Index used to determine social impact	UK Data (annual costs €, 2014), mean (SD), % Drugs: 560 (2085), 1.03% Medical visits: 4569 (9908), 8.42% Hospitalisations: 2219 (5490), 4.09% GP and Emergency: 842 (3130), 1.55% Medical tests: 874 (1223), 1.61%	UK Data (annual costs €, 2014), mean (SD), % Social services: 2187 (6197), 4.03% Main informal carer: 27,012 (43,826), 49.75% Other informal carers: 13,516 (25,151), 24.89% Healthcare transporta: 58 (270), 0.11% aCosts associated with non-healthcare transport and housing and vehicle adaptation	UK Data (annual costs €, 2014), mean (SD), % Total costs: 54,295 (68,431), 100.00%	Caregiving time (daily hours), mean (SD) = 12.5 (5.96)	The data is applicable to that of clinical practice in the UK Additionally, the data is relevant to the population of interest (individuals with 5q SMA) and therefore are relevant to the model

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Study, country, currency (year)	Study design and aim	Population (sample size)	Cost valuations used in the study	Direct costs (medical/ non-medical)	Indirect costs	Total costs and drivers	Resource use	Applicability to clinical practice in England and for cost-effectiveness analysis
				Medical material: 1958 (2428), 3.61%				
Stewart, 2023 Country UK (Glasgow, Scotland) Currency NA Cost year NA	Design Retrospective, single-centre, chart review Aim To assess the clinical impact of nusinersen, risdiplam and OA on children with SMA	All children with SMA who had been treated with nusinersen, risdiplam or OA at a single centre (N=10) SMA Type Type 1: n=6 Type 2: n=4	NR	NR	NR	NR	Treatment type Nusinersen: n=7/10 OA: n=1/10 Two therapies (type NR): n=2/10 Ventilation use Mask ventilation required: SMA Type 1: n=4/6 SMA Type 2: attempted but not tolerated in n=1 Long-term tracheostomy ventilation required (unable to wean off ventilation): SMA Type 1: n=1/6 SMA Type 2: NR Hospital admissions Hospital admissions n=7/10 Multiple admissions: n=3/10 Gastrostomy use SMA Type 1: n=5/6	The study is based in the UK (Scotland); therefore HCRU results should be applicable to clinical practice in England. HCRU only data are reported, not costs, limiting applicability of the data for cost-effectiveness analysis

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Study, country, currency (year)	Study design and aim	Population (sample size)	Cost valuations used in the study	Direct costs (medical/ non-medical)	Indirect costs	Total costs and drivers	Resource use	Applicability to clinical practice in England and for cost-effectiveness analysis
Westrate 2021 Country: UK Currency: NA Cost year: NA	Design: Single-centre retrospective review of medical records Aim: To describe care provided and outcomes of 'treatment-naïve' individuals with SMA Type 1 prior to nusinersen availability, and of nusinersen-treated individuals with SMA Type 1	Individuals with SMA Type 1 (N=66) assessed at GOSH between 2008 – 2021 Treatment-naïve participants: n=38 Nusinersen treated participants: n=28	NR	NR	NR	NR	Treatment-naïve group: NIV: n=15 (41%) Cough assist: n=2 (6%) Enteral feeding: n=33 (92%) GT: n=2 (6%) NGT: n=31 (86%) Nusinersen treated group: NIV: n=26 (93%) Cough assist: n=25 (96%) Enteral feeding: n=24 (86%) GT: n=18 (64%) NGT: n=4 (14%) NGT + oral intake: n=2 (7%)	The study is based in the UK, therefore the HCRU results are applicable to practice in England. However, HCRU data only are reported, not costs, limiting the applicability of the data for cost-effectiveness analysis

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Study, country, currency (year)	Study design and aim	Population (sample size)	Cost valuations used in the study	Direct costs (medical/ non-medical)	Indirect costs	Total costs and drivers	Resource use	Applicability to clinical practice in England and for cost-effectiveness analysis
Cost and healthcare resource use studies identified in original SLR								
SMA UK 2019 Country: UK Currency: GBP Cost year: NR	Design: Prospective surveys (survey A and B) Aim: To assess how SMA impacts affected persons' and caregivers' lives	Survey A, n=125 (SMA Type 2, 39%; Type 3, 61%) Survey B, n=188 (SMA Type 1, 15%; Type 2, 57%; Type 3 28%)	NR	Mean out of pocket costs per person with SMA (survey B): £8,025	Mean annual cost for loss of productivity per unpaid caregiver (based on reducing their hours by 25 hours per week): £14,350	Total annual direct cost per person with SMA (survey A): £49,723	HCRU for people with SMA Type 1, 2 and 3 reported in the slide deck for the following: Average number of interventions and equipment per person with SMA The percentage of people with SMA who visit HCPs each year The average number of daily activities per people with SMA and the support needed to perform ADLs Total number of caregiver hours per person with SMA per week by level of mobility The number of unpaid caregivers providing support to one person with SMA Unpaid caregivers who support people with SMA each week	These findings should be used with caution; data from two un-published surveys that have not been peer-reviewed. Study reports CRU for SMA Types 1, 2 and 3 which would be useful for informing economic evaluation Study based in the UK; therefore, results are applicable to a UK setting
Ali 2019 Country: UK Currency, cost year: NA	Design: Retrospective analysis Aim: To establish the hospital utilisation	Paediatric individuals with SMA Type 1 who received nusinersen (n=9)	NR	NR	NR	NR	Resource use per paediatric individual with SMA Type 1 over a lifetime (assumed): Median number of nusinersen doses (range): 5 (4–6) Children who received BiPAP: n=7 Ventilated via tracheostomy: n=1	This study reports data relating to resource use associated with nusinersen treatment in paediatric individuals with SMA Type 1 which may be useful for informing economic evaluation

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Study, country, currency (year)	Study design and aim	Population (sample size)	Cost valuations used in the study	Direct costs (medical/ non-medical)	Indirect costs	Total costs and drivers	Resource use	Applicability to clinical practice in England and for cost-effectiveness analysis
	and associated costs for paediatric individuals treated with nusinersen						Number of days in hospital since diagnosis (range): 665 (4–177) days Median number of days in hospital since diagnosis: 64 days Total number of days in HDU (range): 52 (4–116) days Total number of days in PICU (range): 4 (0–103) days	This study is based in the UK, therefore the resource use reported would be applicable to a UK setting

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B.3.5.1 Intervention and comparators' costs and resource use

The list price per one 60 mg/80 ml vial of risdiplam is £7,900.

[redacted]

It is anticipated that the majority of patients will receive risdiplam via homecare, the cost for which will be covered by Roche. However, a small proportion of patients ([redacted]) (217) may choose to have risdiplam administered through the hospital instead of home delivery, in which case pharmacist time is required for the preparation of risdiplam. It is assumed that 5 minutes of pharmacist time (cost: £53 per hour, Band 6 pharmacist) (218) will be required to reconstitute one vial of risdiplam. For the purpose of economic modelling, patients with type 1 SMA were assumed to require a vial approximately every 44 days and 12 days, respectively, until they reach a bodyweight >20 kg. This assumption was based on risdiplam dosing and patient baseline characteristics in the risdiplam studies.

The list price per one 2.4mg/ml vial of nusinersen is £75,000 and the assumed price for onasemnogene abeparvovec is £1,600,080.58, which is assumed to include the drug and administration cost (NHS Ref Costs 2021/22: Onasemnogene Abeparvovec [HICD0587; High Cost Drugs]) (Appendix K).

Presymptomatic (RAINBOWFISH) and type 1 (FIREFISH) model

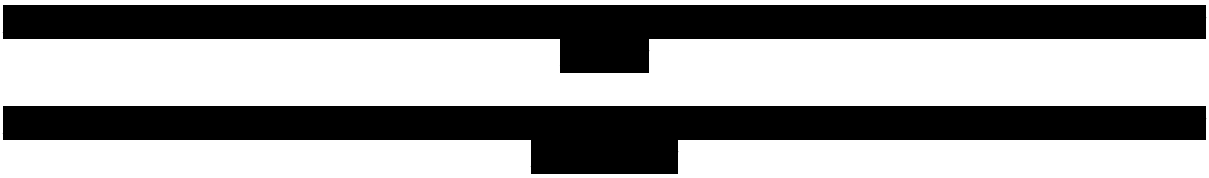
The acquisition costs for risdiplam were applied in the model in line with the age- and weight-based dosing table described in the SmPC (Section B.3.2.3). As the baseline age of patients was less than 2 years, weight-based dosing was applied.

The model is able to estimate the potential weight of a patient to ensure that a suitable monthly price is calculated. Data for patient weight, height and age were pooled from the TRO19622(219), OLEOS (220) SUNFISH (110), FIREFISH (108) and NatHis-SMA studies (221).

The results depicted in

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Figure 34 demonstrate that weight increases most rapidly in the early years, and then plateaus in early adulthood, with gender contributing to the changes. This resulted in two formulae to describe the weight estimation related to age and gender as follows:



These formulae were included in the model to calculate the relationship between patient age and weight.

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Figure 34: Weight algorithm for SMA patients

[redacted]

Within Part 2 of the FIREFISH trial, a relative dose intensity of [redacted]% was observed for the risdiplam arm.

It is anticipated that relative dose intensity will also not be 100% in clinical practice; therefore, this value has been applied to the acquisition costs for risdiplam accordingly.

For the acquisition costs of the comparators, for nusinersen the list price per one 12 mg/5 ml vial at £75,000 has been applied (222). For the dosing, 4 loading doses have been applied over the first two months and then a maintenance dose every 4 months, administered via intrathecal injection (222). As the administration takes place in hospital, NHSE currently funds a local annual tariff of £10,815 per individual on nusinersen, which has been applied within the model. For the cost of onasemnogene aberparvovec, a single cost to include both the administration and drug cost of £1,600,80.58 has been applied (223). There is no treatment acquisition cost associated with BSC. SMA-related costs for BSC are applied to each motor milestone health states in the economic models, and the derivation of resource use and costing for the model health states is described in Section B.3.5.2.

Type 2/3 (SUNFISH) model

The acquisition costs for risdiplam were applied in the model in line with the age- and weight-based dosing table described in the SmPC (Section B.3.2.3). Given that the baseline average age of patients in the SUNFISH trial exceeded 20 kg, it was assumed all patients would receive a daily dose of 5 mg. This was a conservative assumption, as it is expected that younger and lighter type 2/3 patients would receive a smaller dose of risdiplam in UK clinical practice, in line with the expected placement of risdiplam into the patient pathway.

Within Part 2 of the SUNFISH trial, a relative dose intensity of [redacted]% was observed for the risdiplam arm. It is anticipated that relative dose intensity will also not be 100% in clinical practice; therefore, this value has been applied to the acquisition costs for risdiplam accordingly.

The comparator costs for nusinersen and BSC as listed under presymptomatic and type 1 also apply to this model.

B.3.5.2 Health-state unit costs and resource use

Although an SLR was conducted to identify studies providing data for cost and resource use in SMA, the robust evidence was sparse, particularly in relation to indirect (non-medical) costs associated with SMA, despite patients' requirement for a substantial amount of care and support.

Although not specified in the risdiplam DCA, due to the uncertainty around previous costs published in SMA, feasibilities of different methodology types were explored to capture this data to inform the cost-effectiveness models. Initially, a database study feasibility assessment was conducted to understand if healthcare resource use data could be collected through Clinical Practice Research Datalink (CPRD) Gold, CPRD Aurum and Health Episode Statistics (HES), which are linked databases reporting data from a subset of primary care centres and secondary care data from all hospitals in England (224). An initial feasibility analysis indicated that estimates for important categories of HCRU, such as ventilation

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procedures, surgeries and respiratory tests, would be captured in these databases. Additionally, patients could be identified with available SMA-specific diagnosis codes (International Classification of Diseases, 10th Revision [ICD-10], Read or SNOMED). However, during the initial stages of the CPRD study, challenges arose in identifying patients belonging to the different health states. This was due to the defining of motor milestones in each health state not being explicitly recorded in the CPRD/HES routine care datasets. Alongside consulting clinical experts, multiple approaches were sought to determine how to define the motor milestone health states using the information provided within the database, via proxy variables. The challenges faced were issues around recursive analysis, inability to reliably differentiate between patients of different health states using individual HCRU items or recorded comorbidities and using an assumption of a linear, positive correlation between broader HCRU types such as hospital visits – which may in fact not be valid for all health states.

Due to the challenges of the database study, a *de novo* modified Delphi panel was conducted between November 2023 and March 2024 with the objective of collecting quantitative expert clinical opinion on the amount of healthcare resource use (HCRU) associated with the management of SMA types 1 and 2/3 in the United Kingdom (UK). The detailed methodology can be found in the report on file (225). In brief, a pre-specified protocol was designed outlining eligibility criteria for participation, methods of data collection and analysis of results. A lead consultant neurologist and expert in SMA, as well as two representative from SMA patient advocacy groups (PAG) were consulted on the scope and design of the questionnaire. The modified Delphi panel consisted of two rounds with the aim of trying to achieve consensus on the resource use estimates. In each round, geographically-spread invited participants individually responded to one of three questionnaires, respectively covering paediatric patients with SMA type 1, paediatric patients with SMA type 2/3 or adult patients with SMA type 2/3, to reflect expected differences in clinical practice and HCRU needs in these populations. In total, 34 out of 36 (97%) invited participants completed the Round 1 survey and 28 out of 34 (82%) invited participants completed the Round 2 survey. Following completion of the two Delphi rounds, the aggregate results were shared at a clinical expert advisory board meeting which took place in March 2024. Discussions centred around the results for items which had not reached consensus during the two preceding rounds, as well as providing interpretation and validation for consensus values achieved. The results were also contextualised and validated with the two PAG representatives, as informed by providing patients' real-world experiences. The results showed that healthcare resource use was high in patients with SMA, with frequent planned and unplanned healthcare visits, tests or procedures for the condition along with many costs around the funding and purchasing of equipment that is currently not accounted for. Unit costs were sourced from NHS reference costs (223) and applied to the proportion and frequencies (per cycle) of healthcare resource utilisation derived from the survey results. The resulting total costs for presymptomatic and type 1, and type 2/3 SMA are shown in Table 134 and Table 135, respectively.

Table 134. Modified Delphi panel HCRU results applied to presymptomatic and type 1 SMA (RAINBOWFISH and FIREFISH) model health states per monthly cycle (225)

Health state	Total costs per cycle		One-off costs
	Paediatric patient	Adult patient	

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Permanent ventilation	£1,557	£761	£15,834
Unable to sit	£1,966	£697	£15,547
Sitting	£1,504	£521	£12,964
Standing	£989	£189	£7,359
Walking	£414	£121	£3,702

Table 135. Modified Delphi panel HCRU results applied to type 2/3 SMA (SUNFISH) model health states per monthly cycle (225)

	Total costs per cycle		One-off costs
Health state	**Paediatric patient**	**Adult patient**	
Unable to sit	£1,581	£697	£15,586
Sitting with support	£1,315	£521	£9,456
Sitting without support	£1,315	£521	£9,456
Standing	£660	£189	£2,372
Walking	£222	£121	£715

As was the case with the utilities, during TA755 the preference of the committee was for the health state resource use to align with was preferred during the nusinersen appraisal for SMA (TA588) (18). Health state resource use was initially sourced from Bastida et al. 2017 (171) and later based on a real-world evidence study using Hospital Episode Statistics (HES) data (linked to motor milestones). The suitability of Bastida et al. 2017 was challenged by the ERG and the NICE committee in TA588, mainly due to the costs being underestimated. As such, these have not been included in this analysis. The ERG preferred the use of data from a real-world evidence study conducted by the manufacturer. Therefore these costs have been included as a scenario analysis. See Table 136 and Table 137, respectively for the health state costs applied in the risdiplam type 2/3 and type 1 models per monthly cycle. No data was collected for the permanent ventilation health state in the TA588 real-world evidence study, and an assumption needed to be made.

Table 136: Real-world study (TA588) applied to presymptomatic and type 1 SMA (FIREFISH) model health states per monthly cycle, with the one-off costs from the modified Delphi panel

Health state	Total costs per cycle* from TA588	One-off costs
Permanent ventilation[a]	N/A	£15,834
Not sitting	£13,284	£15,547
Sitting	£9,704	£12,964
Standing	£1,951	£7,359
Walking	£1,951	£3,702

Footnotes: *costs have been inflated from 2018/19 using NHSCII Pay and Price Index; [a]The permanent ventilation health state was calculated to be 175% of the 'not sitting' health state

Table 137: Real-world study (TA588) applied to type 2/3 SMA (SUNFISH) model health states per monthly cycle, with the one-off costs from the modified Delphi panel

Health state	Total costs per cycle* from TA588	One-off costs

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Not sitting	£13,284	£15,586
Sitting with support	£13,284	£9,456
Sitting without support	£9,704	£9,456
Standing	£1,951	£2,372
Walking	£1,951	£715

Footnotes: *costs have been inflated from 2018/19 using NHSCII Pay and Price Index

Due to the uncertainty and complexity in the costs presented for HST15, these have not been incorporated into the modelling analysis (152).

The results from the modified Delphi panel, in addition to the real-world evidence study considered in both TA588 and TA755, were both considered to inform the presymptomatic, type 1 and type 2/3 models for risdiplam. Upon review with clinicians and patients, the feedback was that overall at face value both cost scenarios presented were lower than expected, potentially because items such as specialised vehicles, certain wheelchair types (and their respective maintenance), homecare packages and personal assistances were not accounted for and are associated with significant cost. As such, the results from the modified Delphi panel were chosen to inform the base case, with the real-world evidence study from TA588 explored in a scenario analysis. The TA588 RWE study didn't collect a cost for the permanent ventilation health state and therefore requires imputation from other sources and assumptions, and also did not account for the one-off costs that have been collected as part of the Delphi panel study. The results from the modified Delphi panel study are a comprehensive resource, collected through a robust methodology.

B.3.5.3 Adverse reaction unit costs and resource use

As described in Section B.4.3.4, adverse events have not been included in any of the models due to the very low incidence (<5%) of adverse events experienced by patients that were considered to be related to treatment in the RAINBOWFISH, FIREFISH and SUNFISH trials, respectively (Section B.2.10).

B.3.5.4 Miscellaneous unit costs and resource use

Whilst it is acknowledged that the incorporation of VAT savings is not part of the NICE reference case, these have been explored in a scenario analysis to explore the true savings to NHSE that vary depending on the type of treatment administration, i.e. hospital versus homecare.

B.3.6 Severity

In line with the NICE Methods Manual, an adjustment to the value of a QALY can apply where there is a shortfall in QALYs for people living with a condition, compared with a person without the condition, over the remaining lifetime of the patients.

Baseline characteristics from the risdiplam trials were used to inform the expected total discounted QALYs for the general population (Total QALYs for patients living with SMA receiving current treatment) were informed by the discounted QALYs from the risdiplam cost-effectiveness models, respective to each patient population analysed. Under each base case, patients are expected to require treatment for the duration of their lifetime. The baseline characteristics informing general population QALYs can be seen in Table 138. The

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results from the QALY shortfall analysis can be seen below for presymptomatic, type 1 and type 2/3 in Table 139. Since the updated Methods Manual has been in place, no other evaluation in SMA has published this severity analysis. For all comparisons across all three populations, an adjustment to the value of risdiplam QALYs of 1.7 can apply, and has been included within the base case.

Table 138. Baseline characteristics informing general population QALYs

Patient population	Factor	Value (reference to appropriate table or figure in submission)	Reference to section in submission
Presymptomatic	Sex distribution	55.6% female	Section B.2.3 Patient demographics and baseline characteristics
	Starting age, years	0.075	Section B.2.6 Clinical effectiveness results of the relevant studies
Type 1	Sex distribution	57% female	Section B.2.3 Patient demographics and baseline characteristics
	Starting age, years	0.484	Section B.2.6 Clinical effectiveness results of the relevant studies
Type 2/3	Sex distribution	51% female	Section B.2.3 Patient demographics and baseline characteristics
	Starting age, years	10.00	Section B.2.6 Clinical effectiveness results of the relevant studies

Table 139. QALY shortfall analysis

Patient population	Expected total QALYs for the general population	Assumed current treatment	Total QALYs expected for people living with the condition, under current treatment	Absolute QALY shortfall	Proportional QALY shortfall
Presymptomatic	70.50	Nusinersen	20.83	49.67	0.70
		OA	20.83	49.67	0.70
		BSC	-4.98	75.48	1.07
Type 1	70.52	Nusinersen	-0.61	71.13	1.01
		OA	0.25	70.27	1.00

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		BSC	-5.96	76.48	1.08
Type 2/3	61.18	Nusinersen	1.45	59.73	0.98
		BSC	-4.83	66.01	1.08

B.3.7 Uncertainty

Due to the difficulty in collecting, analysing and subsequently evaluating technologies in a rare condition, there is inherent uncertainty within the efficacy estimates included within the economic model. Data sparsity within rare conditions is not a novel issue, but pragmatism should be taken into consideration when evaluating the evidence at hand.

For the consideration of risdiplam, comprehensive economic models have been presented with all available comparators included. However, as explained in Section B.2.9, it is difficult to provide indirect treatment comparisons for risdiplam to other available comparators due to issues in study eligibility criteria, baseline characteristics, endpoints measured, study assessment timepoints, single arm studies and small patient numbers.

More specifically in presymptomatic SMA patients, within the studies used to inform the comparative efficacy estimates, motor milestones were not reported using the same measurements. For example, RAINBOWFISH and NURTURE used the ulnar nerve for the CMAP amplitude measurement, while SPR1NT used the peroneal nerve; RAINBOWFISH assessed BSID-III item 22 in patients with 2 SMN2 copies at Month 12, whereas SPR1NT utiltised two endpoints based on SMN2 copy number: item 26 for 2 SMN2 copies and item 40 for 3 SMN2 copies, both assessed at 18 months. Moreover, the assessment schedules between the studies differed, as well as there being heterogeneous populations at baseline and small sample sizes (n=5-15 per arm), creating high levels of uncertainty within any comparison (quantitative and qualitative) of these treatments. As a result, equal efficacy has been assumed across the interventions (except BSC) and a cost-comparison has been provided for this population.

In type 1 SMA, considering the comparison to nusinersen, ENDEAR was an RCT and FIREFISH was a single arm trial – none of the ITC methods employed were able to adjust for these differences in study design. A robust, longer term comparison was not possible for risdiplam versus BSC as patients from the sham arm in ENDEAR switched to nusinersen after 13 months. Within the comparison of FIREFISH versus STR1VE (both EU and US studies), due to limited overlap between the populations due to differences in eligibility criteria and baseline characteristics, the results do not provide sufficient evidence to draw concrete conclusions on the relative efficacy between the two treatments with regards to survival outcomes, motor function, achievement of motor milestones, and the incidence of SAEs, after adjusting for differences in age and baseline motor function score.

For type 2/3 SMA, similar issues are observed. CHERISH and SUNFISH had different populations, as seen by the more restrictive eligibility criteria and therefore healthier baseline characteristics for CHERISH. Upon attempting to match the populations, the ESS was greatly reduced causing greater uncertainty in any estimates produced. Additionally, due to different primary endpoints for studies, comparative effectiveness was conducted using secondary endpoints, however the data is not clearly published or available for these

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causing further uncertainty in the interpretation of the data. The uncertainties of the relative efficacy estimates produced for all patient populations have been included within the models, and the extrapolations of these over time create more uncertainty in the overall results presented which should be taken into account.

On a similar note, during the period of the MAA, real-world data was collected to further understand how risdiplam would be used in routine clinical practice. However, as presented in Section B.2.6.4, the real-world data sample sizes are small, the population baseline characteristics are more severe than seen in the clinical trials and the follow-up periods are inconsistent. As a result no conclusions should be drawn from the data itself.

Taking all of the above into consideration highlights the issues with the differing patient populations. The risdiplam studies were much broader in their acceptance of patients compared with the other treatments in terms of severity, and that combined with being third to market resulted in a more severe patient population. Many patients (within a rare population) were already being treated with another intervention, reducing the eligible patient population and determining the characteristics of those available to receive risdiplam, either within a clinical trial or the real-world. As such, the presented treatment effect of risdiplam could be considered conservative, as risdiplam treatment has been observed in a more severe patient population versus those observed for comparators.

For completeness of the economic evaluation, BSC has been provided as a comparator in each SMA population presented. However, given the availability of DMT's for the treatment of SMA, there is a question around the relevance of BSC as a comparator in the context of current practice and the treatment landscape. Clinical experts do believe that BSC has a place in the pathway, but this is for patients who are either not eligible for an available DMT or choose not to receive active treatment, therefore raising a question in the head-to-head comparison of BSC with the other DMT's. Moreover, with the introduction of DMT's, SMA patients (particularly those with worse prognosis, i.e. type 1) are reaching milestones never seen before in natural history; clinicians are referring to these patients as a new phenotype - "treated type 1" patients. Whilst additional data has been collected for risdiplam since the start of the MAA, the trajectory of these patients in terms of outcomes, health-related quality of life and costs is still completely unknown. The economic models presented only provide a simplified version of what is expected to happen based on what is known now, but it is well accepted that it is unknown what the longer term outcomes for this new phenotype of patients will be. Further information would be needed to quantify this over time.

An additional challenge is quantifying patient utility data. Given the age demographics and the severity of the condition for this population it is difficult to obtain robust utility estimates for these patients, as can be seen by the multiple attempts provided over previous technology appraisals.

Likewise, multiple attempts across multiple appraisals have been made to try to capture the true costs of managing SMA. Within this submission, another *de novo* approach has been presented that has been developed in collaboration with both clinical and patient experts. It was acknowledged through expert discussion that it is extremely difficult to accurately reflect these costs, as even within types of SMA, the severity and therefore cost of all patient's condition will differ. . There is also geographical variability in the availability of resources and differences in approaching the overall management of SMA. The costs presented only consider the NHS PSS perspective as per the reference case, but there are significant costs

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unaccounted for that patients, families, communities and charities pay out of pocket for in order to manage SMA. These are not exceptional circumstances, but in fact apply to all patients, irrespective of their SMA type. It should be taken into consideration that the costs that have been previously presented and currently presented do not fully represent the picture of living with and managing SMA.

B.3.8 Managed access proposal

As this appraisal is considering risdiplam following entry to a managed access agreement, a proposal for a new MAA is not relevant.

B.3.9 Summary of base case analysis inputs and assumptions

B.3.9.1 Summary of base case analysis inputs

Table 140. Base case inputs: presymptomatic SMA (FIREFISH) model

Input	Value	Section
Patient characteristics		
Age, years	0.48	Section B.3.3.2
Female	57%	
Body weight, kg; mean	5	
Not sitting	100%	
Sitting	0%	
Standing	0%	
Walking	0%	
Non-permanent respiratory support	28%	
Severe scoliosis	0%	
Transition probabilities		
Motor milestone health states	Risdiplam, nusinersen and OA set to equal BSC using PNCR data	Section B.3.3.2
Permanent ventilation health state	Switch to BSC when no additional data is available	
Overall survival	General population mortality (ONS)	Section B.3.3.2
Discontinuation, patients per cycle	0	Section B.3.3.2
Disease related events		
% scoliosis	PNCR analysis (177)	Section B.3.3.1
% respiratory support		
% bulbar dysfunction		
Severity modifier		
QALY weight	1.7	Section B.3.6
Patient utilities		

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Permanent ventilation	-0.020	Section B.3.4.5
Not sitting	0.100	
Sitting	0.200	
Standing	0.700	
Walking	0.850	
Carer utilities		
Permanent ventilation	0.484	Section B.3.4.5
Not sitting	0.484	
Sitting	0.628	
Standing	0.771	
Walking	0.915	
Risdiplam costs		
Cost per 60 mg/80 ml vial	£7,900 (list price) [redacted] (net price)	Section B.3.5.1
Pharmacy time (cost per reconstitution of one vial) for proportion of patients not receiving via homecare	£4.42	
Relative dose intensity	[redacted]	
Health state costs		
One-off costs		
Permanent ventilation	£15,834	Section B.3.5.2
Not sitting	£15,547	
Sitting	£12,964	
Standing	£7,359	
Walking	£3,702	
Total costs per cycle: paediatric patient		
Permanent ventilation	£1,557	Section B.3.5.2
Not sitting	£1,966	
Sitting	£1,504	
Standing	£989	
Walking	£414	
Total costs per cycle: adult patient		
Permanent ventilation	£761	Section B.3.5.2
Not sitting	£697	
Sitting	£521	
Standing	£189	
Walking	£121	

PAS, patient access scheme

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Table 141. Base case inputs: type 1 SMA (FIREFISH) model

Input	Value	Section
Patient characteristics		
Age, years	0.48	Section B.3.3.2
Female	57%	
Body weight, kg; mean	5	
Not sitting	100%	
Sitting	0%	
Standing	0%	
Walking	0%	
Non-permanent respiratory support	28%	
Severe scoliosis	0%	
Transition probabilities		
Motor milestone health states	[redacted]	Section B.3.3.2
Permanent ventilation health state	[redacted]	
Overall survival	[redacted]	Section B.3.3.2
Discontinuation, patients per cycle	0	Section B.3.3.2
Disease related events		
% scoliosis	Wijngaarde et al. 2019	Section B.3.3.2
% respiratory support	Wadman et al. 2017	
% bulbar dysfunction	Van der Heul et al. 2019	
Severity modifier		
QALY weight	1.7	Section B.3.6
Patient utilities		
Permanent ventilation	-0.020	Section B.3.4.5
Not sitting	0.100	
Sitting	0.200	
Standing	0.700	
Walking	0.850	
Carer utilities		
Permanent ventilation	0.484	Section B.3.4.5
Not sitting	0.484	
Sitting	0.628	
Standing	0.771	
Walking	0.915	
Risdiplam costs		
Cost per 60 mg/80 ml vial	£7,900 (list price) [redacted] (net price)	Section B.3.5.1

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Pharmacy time (cost per reconstitution of one vial) for proportion of patients not receiving via homecare	£4.42	
Relative dose intensity	[redacted]	
Health state costs		
One-off costs		
Permanent ventilation	£15,834	Section B.3.5.2
Not sitting	£15,547	
Sitting	£12,964	
Standing	£7,359	
Walking	£3,702	
Total costs per cycle: paediatric patient		
Permanent ventilation	£1,557	Section B.3.5.2
Not sitting	£1,966	
Sitting	£1,504	
Standing	£989	
Walking	£414	
Total costs per cycle: adult patient		
Permanent ventilation	£761	Section B.3.5.2
Not sitting	£697	
Sitting	£521	
Standing	£189	
Walking	£121	

PAS, patient access scheme

Table 142: Base case inputs: type 2/3 SMA (SUNFISH) model

Input	Value	Section
Patient characteristics		
Age, years	10.0	Section B.3.3.1
Female (SE)	50.6%	
Type 2	71.1%	
Type 3	28.9%	
Not sitting	0%	
Sitting (supported)	13.0%	
Sitting (unsupported)	74%	
Standing	6.0%	
Walking	7.0%	
Respiratory support	39.89%	

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Severe scoliosis	31.67%	
Transition probabilities	*Various*	Section B.3.3.1
Type 2 OS	[redacted]	Section B.3.3.1
Type 3 OS	General population mortality (ONS)	
HR – mortality with risdiplam	0.75	
Discontinuation, patients per cycle	0	Section B.3.3.1
Disease related events		
% scoliosis	Natural history study (182)	B.3.3.3
% respiratory support		
% bulbar dysfunction		
Severity modifier		
QALY weight	1.7	Section B.3.6
Patient utilities		
Not sitting	−0.170	Section B.3.4.5
Sitting (supported)	0.040	
Sitting (unsupported)	0.040	
Standing	0.555	
Walking	0.555	
Carer utilities		
Not sitting	0.700	Section B.3.4.5
Sitting (supported)	0.772	
Sitting (unsupported)	0.843	
Standing	0.915	
Walking	0.915	
Risdiplam costs		
Cost per 60 mg/80 ml vial	£7,900 (list price) [redacted] (net price)	Section B.3.5.1
Pharmacy time (cost per reconstitution of one vial) for proportion of patients not receiving via homecare	£4.42	
Relative dose intensity	[redacted]	
Health state costs		
One-off costs		
Permanent ventilation	£15,586	Section B.3.5.2
Not sitting	£9,456	
Sitting	£9,456	
Standing	£2,372	
Walking	£715	

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Total costs per cycle: paediatric patient		
Permanent ventilation	£1,581	Section B.3.5.2
Not sitting	£1,315	
Sitting	£1,315	
Standing	£660	
Walking	£222	
Total costs per cycle: adult patient		
Permanent ventilation	£697	Section B.3.5.2
Not sitting	£521	
Sitting	£521	
Standing	£189	
Walking	£121	

HR, hazard ratio; ONS, Office for National Statistics; OS, overall survival; PAS, patient access scheme; SE, standard error

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B.3.9.2 Assumptions

Key assumptions made in the presymptomatic, type 1 and type 2/3 base case analyses

Model	Assumption	Justification	Section
Clinical efficacy			
All	Patients' improvement or deterioration in motor milestone achievement was sequential.	It was clinically validated that improvement or deterioration by greater than one milestone within the period of one month would not be expected in SMA patients of all types (226).	B.3.3.1 B.3.3.2 B.3.3.3
Presymptomatic	Efficacy for risdiplam, nusinersen and OA has been assumed to be equal and the assumption of no permanent ventilation/disease events occurrence for all treated patients.	Due to the challenges conducting the ITC for the presymptomatic population, the naïve comparisons suggest these technologies behave the same on the endpoints measured, and so a conservative assumption has been to assume equal efficacy. Moreover, no permanent ventilation/disease events were modelled due to a lack of observed events in RAINBOWFISH.	B.3.3.1
Type 2/3	After 24 months, the majority of type 2/3 patients treated with risdiplam may only improve or remain stable in terms of motor milestones gained, whilst patients treated with BSC may only remain stable or deteriorate.	These assumptions were consistent with the assumptions considered in the final NICE decision for TA588 (18). Furthermore, these assumptions were also validated by clinical experts at UK advisory boards and supported by findings from the literature, as described in Section B3.10.	B.3.3.3
Type 1	After 24 months, patients treated with risdiplam may only improve or remain stable in terms of motor milestones gained, whilst patients treated with BSC may only remain stable or deteriorate.	These assumptions were consistent with the assumptions considered in the final NICE decision for TA588 (18). Furthermore, these assumptions were also validated by clinical experts at UK advisory boards and supported by findings from the literature, as described in Section B.3.10.	B.3.3.2
Presymptomatic	A 10 year (120 month) treatment duration has been used	A 10 year assumption on treatment duration has been applied based on the rationale that much is not known about the long-term treatment and impact of these medicines. At the time that the interim data was completed (2021), the first DMT had been in trials since 2011, hence the 10 year assumption (227).	
All	Within the ITC it was not possible to generate comparative estimates for backwards transitions for the comparators, i.e. 'sitting' to 'not sitting'. Backwards transitions for all comparators were	This assumption was conservatively made in lieu of evidence and ITC data.	B.3.3.1 B.3.3.2 B.3.3.3

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	conservatively assumed to be the same as risdiplam.		
All	Mortality for patients with SMA type 3 and patients with SMA type 2 that reach the standing or walking health states is equal to general population mortality (192). Mortality for patients with SMA type 1 that reach the standing or walking health states becomes equal to type 2 mortality, informed by an SLR of mortality in type 2 patients. In presymptomatic patients, the overall survival is informed by general population mortality, due to a lack of events in the RAINBOWFISH study.	There is evidence from the literature that the overall survival of type 3 patients is similar to that of the general population (145). The approach for type 2 patients was informed by the approach taken in TA588, and UK clinical expert opinion (*Clinical exp section ref;* Section B.3.3.1). A similar approach was taken for type 1 patients reaching the highest health states, i.e. setting their mortality equal to type 2 patients, for consistency (B.3.3.2).	
Cost and resource use			
All	0.4% of patients choose to have risdiplam administered through the hospital instead of home delivery, for which pharmacist costs are required.	Real-world homecare data has been collected through the MAA, and 99.6% receive risdiplam via homecare.	B.3.5.1
All	One-off costs are applied at cycle 0, irrespective of the data source used to apply per cycle costs	As one-off costs were not collected in previous publications, the Roche HCRU study one-off costs have been applied to cycle 0 to try to more accurately reflect the cost of managing SMA.	B.3.5.2
Utilities			
All	For presymptomatic and type 1, the ERG early onset model, Biogen clinical advisor utility values were utilised. For type 2/3, the HSUVs sourced from Lloyd et al. 2019 were used. Both sources possessed the greatest clinical validity to represent each population.	These utility values are deemed as being clinically valid by expert clinicians to the risdiplam cost-effectiveness models.	B.3.4.5
All	For carer utilities, a HSUV was obtained from the study conducted by Bastida et al. 2017 (171) and assigned to the lowest health state in each model. General population utility was sourced for the highest health states, and intermediate values were calculated for the health states in between.	This approach aligns with that conducted by the manufacturer in TA588 (18).	B.3.4.5

BSC: best supportive care; ERG: evidence review group; HSUV: health-state utility values; ITC: indirect treatment comparison; NICE: National Institute for Health and Care Excellence; SMA: spinal muscular atrophy; SLR: systematic literature review.

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B.3.10 Base case results

Cost-effectiveness results for risdiplam at list price are presented below. Cost-effectiveness results at the PAS price are presented in Section B.3.10 (base case results) and in Appendix T. Dissaggregated results can be found in Appendix J.

The base case results for the presymptomatic analysis are presented in Table 143 and Table 144, with the list price and PAS price of risdiplam, respectively. As equal efficacy has been assumed between risdiplam, nusinersen and OA, a cost-comparison analysis has been provided and a cost-effectiveness analysis has been presented for risdiplam versus BSC. [redacted] For the BSC comparison, risdplam is associated with substantially greater quality-adjusted life years (QALYs), 14.51 QALYs for risdiplam versus -3.42 QALYs for BSC. This difference in QALYs reflects the improvements in HRQoL for both patients and carers associated with risdiplam treatment compared to BSC. Additionally, risdiplam extends patients' lives compared to BSC, as reflected in the life years gained (LYG), incremental LYG of 4.7 years, respectively. The incremental cost-effectiveness ratio (ICERs) were £125,936 and [redacted] at this list and with-PAS prices, respectively.

The base case results for the type 1 model are presented in Table 145 for the list price and Table 146 for the with-PAS price of risdiplam. For the comparison of risdiplam versus both nusinersen and OA, the application of the PAS results in [redacted]. Risdiplam results in greater improvements in HRQoL for both patients and carers in comparison to BSC, as reflected by the substantial gain in QALYs from -4.97 with BSC to 1.89 with risdiplam. Furthermore, risdiplam extends patients' lives compared to BSC, as shown by the increase in LYG of 6.79 with BSC and 13.48 with risdiplam. The ICERs were £242,519 and [redacted] at the list and with-PAS prices, respectively.

The base case results for the type 2/3 analysis are presented in Table 147 for the list price and Table 148 for the with-PAS price. At both list and PAS price, [redacted]. For the BSC comparison, risdiplam is associated with higher QALYs, 2.39 QALYs for risdiplam versus -4.79 QALYs for BSC. This difference in QALYs reflects the improvements in HRQoL for both patients and carers associated with risdiplam treatment compared to BSC. Additionally, risdiplam extends patients' lives compared to BSC, as reflected in LYG, 21.63 versus 20.29 years, respectively. The ICERs were [redacted] and [redacted] at the list and with-PAS prices, respectively.

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Table 143. Base case results for the presymptomatic SMA (RAINBOWFISH) model (list price), risdiplam versus comparator

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER incremental (£/QALY)
Risdiplam	£4,166,372	18.64	14.51	-	-	-	-
Nusinersen	£4,785,969	NA	NA	-£619,597	NA	NA	NA
OA	£1,747,146	NA	NA	£2,419,226	NA	NA	NA
BSC	£327,582	13.95	-3.42	£3,838,791	4.70	30.48	£125,936

ICER: incremental cost-effectiveness ratio; LYG: life years gained; QALYs: quality-adjusted life years

Table 144: Base case results for the presymptomatic SMA (RAINBOWFISH) model (PAS price), risdiplam versus comparator

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER incremental (£/QALY)
Risdiplam	[redacted]	18.64	14.54	-	-	-	-
Nusinersen	£4,785,969	NA	NA	[redacted]	NA	NA	NA
OA	£1,747,146	NA	NA	[redacted]	NA	NA	NA
BSC	£327,582	13.95	-3.42	[redacted]	4.70	30.48	[redacted]

ICER: incremental cost-effectiveness ratio; LYG: life years gained; QALYs: quality-adjusted life year

Table 145: Base case results for the type 1 SMA (FIREFISH) model (list price), risdiplam versus comparator

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER incremental (£/QALY)
Risdiplam	£3,048,405	13.48	1.89	-	-	-	-
Nusinersen	£2,915,805	11.26	-0.33	£132,600	2.22	3.77	£35,160
OA	£1,919,785	12.92	0.49	£1,128,620	0.56	2.38	£474,048
BSC	£219,069	6.79	-4.97	£2,829,336	6.69	11.67	£242,519

ICER: incremental cost-effectiveness ratio; LYG: life years gained; QALYs: quality-adjusted life years

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Table 146: Base case results for the type 1 SMA (FIREFISH) model (PAS price), risdiplam versus comparator

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER incremental (£/QALY)
Risdiplam	[redacted]	13.48	1.89	-	-	-	-
Nusinersen	£2,915,805	11.26	-0.33	[redacted]	2.22	3.77	[redacted]
OA	£1,919,785	12.92	0.49	[redacted]	0.56	2.38	[redacted]
BSC	£219,069	6.79	-4.97	[redacted]	6.69	11.67	[redacted]

ICER: incremental cost-effectiveness ratio; LYG: life years gained; QALYs: quality-adjusted life year

Table 147: Base case results for the type 2/3 SMA (SUNFISH) model (list price), risdiplam versus comparator

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER incremental (£/QALY)
Risdiplam	£4,504,435	21.63	2.39	-	-	-	-
Nusinersen	£4,599,047	21.51	1.55	-£94,612	0.13	1.44	Risdiplam is dominant
BSC	£305,448	20.29	-4.79	£4,198,986	1.34	12.22	£343,682

ICER: incremental cost-effectiveness ratio; LYG: life years gained; QALYs: quality-adjusted life years

Table 148: Base case results for the type 2/3 SMA (SUNFISH) model (PAS price), risdiplam versus comparator

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER incremental (£/QALY)
Risdiplam	[redacted]	21.63	2.39	-	-	-	-
Nusinersen	£4,599,047	21.51	1.55	[redacted]	0.13	1.44	[redacted]
BSC	£305,448	20.29	-4.79	[redacted]	1.34	12.22	[redacted]

ICER: incremental cost-effectiveness ratio; LYG: life years gained; QALYs: quality-adjusted life years

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B.3.11 Exploring uncertainty

B.3.11.1 Probabilistic sensitivity analysis

Probabilistic sensitivity analyses (PSA) were generated by assigning distributions to all input parameters and randomly sampling from these distributions over 2,000 iterations, in order to calculate the uncertainty in costs and outcomes. A summary of the distributions chosen for the probabilistic parameters in the presymptomatic, type 1 and type 2/3 models are provided in Appendix S.

The results of the probabilistic base case results for the presymptomatic, type 1 and type 2/3 models for risdiplam at list price are presented in Table 149, Table 150 and Table 151, respectively. For the presymptomatic model, the cost-effectiveness plane (with a willingness-to-pay threshold of £30,000 per QALY) shows that all iterations of the list price versus BSC and OA are above the cost-effectiveness threshold, and the iterations versus nusinersen are below the threshold, suggesting risdiplam is cost-effective against nusinersen (Figure 35). The PSA found that the probability of risdiplam being cost-effective at the willingness-to-pay threshold of £30,000 is [redacted] at list price for the presymptomatic population (Figure 36). For the type 1 model, the cost-effectiveness plane (with a willingness-to-pay threshold of £30,000 per QALY) demonstrates that risdiplam is above the cost-effectiveness threshold against BSC and for majority of the OA iterations. For the risdiplam comparison against nusinersen, these are distributed across the threshold with some iterations demonstrating that risdiplam is cost-effective at list price (Figure 37). The PSA found that the probability of risdiplam being cost-effective at the willingness-to-pay threshold of £30,000 is [redacted] at list price for the type 1 population (Figure 38). For the type 2/3 model, the cost-effectiveness plane (with a willingness-to-pay threshold of £30,000 per QALY) demonstrates that risdiplam is above the cost-effectiveness threshold against BSC and versus nusinersen iterations are distributed across the threshold with some iterations demonstrating that risdiplam is cost-effective at list price (Figure 39). The PSA found that the probability of risdiplam being cost-effective at the willingness-to-pay threshold of £30,000 is [redacted] at list price for the type 2/3 population (Figure 40). The with-PAS PSA results are presented in Appendix T.

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Table 149. Probabilistic base case results for the presymptomatic SMA (RAINBOWFISH) model (list price)

Average probabilistic results			Incremental results: risdiplam versus comparator		
Treatment	**Costs**	**QALYs**	**Costs**	**QALYs**	**ICER per QALY**
Risdiplam	£4,149,533	14.23	-	-	-
Nusinersen	£4,768,367	14.23	-£618,834	NA	NA
Onasemnogene abeparvovec	£1,754,558	14.22	£2,394,976	NA	NA
BSC	£336,678	-2.47	£3,812,855	28.38	£134,340

Table 150. Probabilistic base case results for the type 1 SMA (FIREFISH) model (list price)

Average probabilistic results			Incremental results: risdiplam versus comparator		
Treatment	**Costs**	**QALYs**	**Costs**	**QALYs**	**ICER per QALY**
Risdiplam	£3,335,374	3.48	-	-	-
Nusinersen	£3,461,649	2.02	-£126,274	2.50	-£50,596
Onasemnogene abeparvovec	£1,944,207	-2.11	£1,391,167	9.57	£145,391
BSC	£285,855	-6.25	£3,049,520	16.55	£184,258

Table 151. Probabilistic base case results for the type 2/3 SMA (SUNFISH) model (list price)

Average probabilistic results			Incremental - Risdiplam versus comparator		
Treatment	**Costs**	**QALYs**	**Costs**	**QALYs**	**ICER per QALY**
Risdiplam	£4,215,781	2.49	-	-	-
Nusinersen	£4,344,519	1.67	-£128,738	1.41	-£91,294
BSC	£309,195	-4.50	£3,906,587	11.87	£329,084

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Figure 35. Incremental cost-effectiveness plane for the presymptomatic SMA (RAINBOWFISH) model (list price)

Figure 36. Cost-effectiveness acceptability curve for the presymptomatic SMA (RAINBOWFISH) model (list price)

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Figure 37. Incremental cost-effectiveness plane for the type 1 SMA (FIREFISH) model (list price)

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Figure 38. Cost-effectiveness acceptability curve for the type 1 SMA (FIREFISH) model (list price)

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Figure 39. Incremental cost-effectiveness plane for the type 2/3 SMA (SUNFISH) model (list price)



Figure 40. Cost-effectiveness acceptability curve for the type 2/3 SMA (SUNFISH) model (list price)

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B.3.11.2 Deterministic sensitivity analysis

In the presymptomatic model, the inputs with the greatest impact on the ICER versus BSC is the cost of risdiplam itself, followed by the health state utility values for patients in the walking health state, caregivers of patients in the walking health state and the number of carers per patients (Figure 41). When compared to nusinersen and OA, across both the biggest drivers to the ICER are the carer utility values in the not sitting and sitting health states as well as the patient utility values in the not sitting and sitting health states (Figure 42 and

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Figure ***43***).

Figure 41. Deterministic sensitivity analysis results for the presymptomatic SMA (RAINBOWFISH) model (list price), ICER versus BSC (list price)



Figure 42. Deterministic sensitivity analysis results for the presymptomatic SMA (RAINBOWFISH) model (list price), ICER versus nusinersen (list price)



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Figure 43. Deterministic sensitivity analysis results for the presymptomatic SMA (RAINBOWFISH) model (list price), ICER versus OA (list price)



In the type 1 model, the inputs with the greatest impact on the ICER versus all three comparators is the risdiplam drug acquisition cost. When compared to BSC, the second biggest driver on the ICER is overall survival versus risdiplam in the not sitting health state, followed by event-free survival versus risdiplam (

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Figure ***44***). In the comparison against nusinersen, the second greatest impact to the ICER is the nusinersen drug acquistion cost, followed by the overall survival hazard ratio versus risdiplam in the not sitting health state and event-free survival (Figure 45). For the OWSA compared to OA, the patient utility value in the sitting health state followed by the drug acquisition cost of OA have the second and third greatest impacts on the ICER (

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Figure ***46***).

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Figure 44. Deterministic sensitivity analysis results for the type 1 SMA (FIREFISH) model (list price), ICER versus BSC (list price)



Figure 45. Deterministic sensitivity analysis results for the type 1 SMA (FIREFISH) model (list price), ICER versus nusinersen (list price)



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Figure 46. Deterministic sensitivity analysis results for the type 1 SMA (FIREFISH) model (list price), ICER versus OA (list price)



In the type 2/3 model, the inputs with the greatest impact on the ICER versus BSC are the caregiver utilities for patients in the sitting without support and not sitting health states, and the risdiplam drug acquisition cost (Figure 47). When compared to nusinersen, the drug acquisition costs for risdiplam and nusinersen are the greatest drivers of the ICER, followed by the mortality for type 2 patients for both risidplam and nusinersen (

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Figure ***48***).

Figure 47. Deterministic sensitivity analysis results for the type 2/3 SMA (SUNFISH) model (list price), ICER versus BSC (list price)



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Figure 48. Deterministic sensitivity analysis results for the type 2/3 SMA (SUNFISH) model (list price), ICER versus nusinersen (list price)



For the OWSA presented with the with-PAS price and for the incremental costs and QALYs, see Appendix T.

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B.3.11.3 Scenario analysis

The scenario analysis for the presymptomatic model are detailed in Table 152. The scenarios that have the greatest effect on the base case ICER versus BSC and impacts on the incremental cost versus nusinersen and OA are outlined below.

Changing the BSC efficacy source to the PNCR data with SMN2 copies matched to the RAINBOWFISH resulted in a change of +34.24%. The BSC outcomes in the base case is informed by the overall weighted PNCR analysis. The "matched" analysis explored in the scenario analysis below, however as the sample sizes are already small the matching of the cohorts creates an even smaller sample size increasing the uncertainty within the estimates. Moreover, within the matching there are other confounding factors that are not being taken into account. The preferred BSC data source is the PNCR weighted SMN2 copy as SMN2 is taken into account as an exploratory covariate within the model, unlike the matched cohort. The matched cohort can also not be used for the PSA due to lack of bootstraps being able to be generated for this analysis. Therefore, the overall population with the SMN2 weighted source is the most reliable efficacy source for BSC.

For the caregiver utility values, applying the UK Burden of Illness study values changed the base case ICER by +54.69%. This scenario was not supported in the original TA755 appraisal and is also not validated by most recently elicited UK clinical expert opinion, who indicated that there is not enough of a difference between utility values by health state – and does not make sense with what is seen in reality, thus lacking face validity (see Sections B.3.5.2 and B.3.14.1).

Whilst it is not part of the NICE reference case, the application of VAT savings has a notable impact on the incremental costs of risdiplam versus nusinersen and OA, +142.35% and -13.10%, respectively.

Furthermore, as an innovative, life-extending therapy, the scenario that explores a discount rate of 1.5% for benefits and 3.5% for costs lowers the ICER versus BSC by -21.16% in comparison to the base case.

Table 152. Scenario analysis results for the presymptomatic SMA (RAINBOWFISH) model (list price)

Scenario	ICER vs BSC	% ICER change from the base case	Incremental costs vs nusinersen	% change from base case	Incremental costs vs OA	% change from base case
Base case	£125,936	-	-£619,597	-	£2,419,226	-
Efficacy scenarios						
Comparative efficacy vs. BSC: Source for BSC set to PNCR data with SMN2 copies matched to RF	£169,061	+34.24%	-	-	-	-
Source for % scoliosis: change to Wijngaarde et al. 2019 (179)	£127,409	+1.17%	-£619,597	-	£2,419,226	-
Source for % bulbar dysfunction: change to Wadman et al. 2017 (180)	£129,267	+2.64%	-£619,597	-	£2,419,226	-

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Source for % respiratory support: change to van der Heul et al. 2019 (181)	£122,934	-2.38%	-£619,597	-	£2,419,226	-
HCRU scenarios						
Alignment with TA588 source for HCRU	£107,126	-14.94%	-£619,597	-	£2,419,226	-
Alignment with TA588 source for HCRU and PV health state costs: 175% increase from the “Not Sitting” health state	£99,501	-20.99%	-£619,597	-	£2,419,226	-
Utility values scenarios						
Source for patient utility values: EQ-5D-3L (18)	£130,745	+3.82%	-£619,597	-	£2,419,226	-
Source for patient utility values: EQ-5D-Y(169)	£132,444	+5.17%	-£619,597	-	£2,419,226	-
Source for caregiver utility values: Roche utility survey (173)	£135,930	+7.94%	-£619,597	-	£2,419,226	-
Source for caregiver utility values: UK Burden of Illness Study	£194,807	+54.69%	-£619,597	-	£2,419,226	-
Other Scenarios						
Inclusion of VAT saving from risdiplam homecare	£126,041	+0.08%	-£1,501,615	+142.35%	£2,102,422	-13.10%
Number of carers lowered to 2	£129,780	+3.05%	-£619,597	-	£2,419,226	-
Number of carers increased to 3	£112,595	-10.59%	-£619,597	-	£2,419,226	-
Discount rate for both costs and benefits is lowered to 1.5%	£131,466	+4.39%	-£608,745	+1.75%	£3,709,624	+53.34%
Discount rate for benefits is lowered to 1.5%, discount rate for costs remains 3.5%	£99,282	-21.16%	-£619,597	-	£2,419,226	-

BSC: best supportive care; EQ-5D-5L: EuroQoL 5 Dimensions 3 Levels; EQ-5D-Y: European Quality of Life-5 Dimensions – Youth version; ERG: Evidence Review Group; HCRU: healthcare resource use; ICER: incremental cost-effectiveness ratio; LY: life year; NICE: National Institute for Health and Care Excellence; PV: permanent ventilation; QALY: quality-adjusted life year; RF: RAINBOWFISH

The scenario analyses for the type 1 model are detailed in Table 153. The scenarios that have the greatest effect on the base case ICER are outlined below.

Changing the efficacy of OA to the STR1VE-US STC data source changes the base case ICER by -45.09%. Whilst the base case includes the STR1VE-EU unanchored MAIC analysis to inform the OA efficacy estimates, as explained in Section B.2.9.4, neither one of these data sources (EU or US) are suitable to inform decision making due to the high heterogeneity between the patient populations, issues with assessment visit matching and lack of similar motor milestone endpoints reported. This scenario analysis using the STR1VE-US dataset to inform OA should be considered alongside the base case to inform decision making.

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Exploring the HCRU data source with TA588 values impacts the ICERs for BSC, nusinersen and OA by +26.48%, +127.29% and -15.99%, respectively. This changes again if the PV health state takes on the assumption from TA755 that PV health state cost is 175% of non-sitting. However, in both TA588 and TA755 the costs were still thought to be too low and lack face validity. The methods in which the new costs have been generated through the Delphi panel are considered to be more robust, splitting out paediatric and adult costs as well as the collection of one-off costs. However, as mentioned in Section B.3.7, it is difficult to reflect the true cost of living and managing SMA, as shown by the multiple different attempts to capture this data.

The application of different patient utility values also has a notable effect on the ICER, the EQ-5L-3L (taken from the NICE ERG TA588 early onset model) and the Lloyd et al. EQ-5D-Y values at face value are both considered to have too low values for the poorer prognosis health states, stating that if a patient is either permanently ventilated, not sitting or sitting their health state is worse than death – and this is not thought to have face validity. The exploration of different caregiver utility values also impacts the ICERs; the Roche utility survey values were considered to have some validity given the increase from the permanent ventilation health state to walking but the UK Burden of Illness study lacked approval due to a lack of utility difference seen between health states.

Whilst it is not part of the NICE reference case, the application of VAT savings has a notable impact on the ICERs for nusinersen and OA, with risdiplam becoming dominant and a change of -28.16%, respectively.

Applying the SMA REACH UK baseline characteristics to the analysis increases each ICER by +18.58%, +329.90% and 42.89% versus BSC, nusinersen and OA. This drastic change in the ICER is due to the older patient population and poorer health condition of these real-world collected patients, as explained in Section B.2.6.4.

Furthermore, as an innovative, life-extending therapy, the scenario that explores a discount rate of 1.5% for benefits and 3.5% for costs lowers the ICERs by -20.67%, -22.30% and -24.24% in comparison to the base case against BSC, nusinersen and OA, respectively.

Table 153. Scenario analysis results for the type 1 SMA (FIREFISH) model (list price)

Scenario	ICER vs BSC	% ICER change from the base case	ICER vs nusinersen	% ICER change from the base case	ICER vs OA	% ICER change from the base case
Base case	£242,519	-	£35,160	-	£474,048	-
Efficacy scenarios						
Comparative efficacy vs. OA: Source for OA set to STC STR1VE-US	£242,519	0.00%	£35,160	0.00%	£260,283	-45.09%
Risdiplam transition probabilities informed by bootstrapped multi-state model 5	£243,454	+0.39%	£40,452	+15.05%	£481,238	+1.52%
Source for % scoliosis: based on fixed proportions over time based on FIREFISH	£235,254	-3.00%	£33,751	-4.01%	£490,166	+3.40%
Source for % respiratory support: on fixed	£246,889	+1.80%	£36,208	+2.98%	£489,014	+3.16%

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proportions over time based on FIREFISH						
Source for % bulbar dysfunction: on fixed proportions over time based on FIREFISH	£230,755	-4.85%	£33,704	-4.14%	£545,182	+15.01%
HCRU scenarios						
Alignment with TA588 source for HCRU	£306,734	+26.48%	£79,916	+127.29%	£398,253	-15.99%
Alignment with TA588 source for HCRU and PV health state costs: 175% increase from the “Not Sitting” health state	£191,731	-20.94%	Risdiplam is dominant	NA	£438,312	-7.54%
Utility values scenarios						
Source for patient utility values: EQ-5D-3L (NICE ERG TA588)	£365,978	+50.91%	£51,518	+46.52%	£493,180	+4.04%
Source for patient utility values: EQ-5D-Y (Lloyd et al, 2019)	£305,522	+25.98%	£45,654	+29.85%	£570,826	+20.42%
Source for caregiver utility values: Roche utility survey	£213,798	-11.84%	£32,063	-8.81%	£511,472	+7.89%
Source for caregiver utility values: UK Burden of Illness Study	£261,195	+7.70%	£38,753	+10.22%	£639,519	+34.91%
Other Scenarios						
Changing time horizon to 20 years	£244,034	+0.62%	Risdiplam is dominant	NA	£365,034	-23.00%
Changing time horizon to 40 years	£244,308	+0.74%	£53,673	+52.65%	£515,213	+8.68%
Inclusion of VAT saving from risdiplam homecare	£242,707	+0.08%	Risdiplam is dominant	NA	£340,557	-28.16%
Changing baseline characteristics to REACH UK patient population	£287,577	+18.58%	£151,152	+329.90%	£677,366	+42.89%
Number of carers lowered to 2	£244,026	0.62%	£25,280	-28.10%	£479,551	1.16%
Number of carers increased to 3	£236,673	-2.41%	£34,690	-1.34%	£453,244	-4.39%
Discount rate for both costs and benefits is lowered to 1.5%	£245,524	1.24%	£73,787	109.86%	£600,461	26.67%
Discount rate for benefits is lowered to 1.5%, discount rate for costs remains 3.5%	£192,384	-20.67%	£27,318	-22.30%	£359,154	-24.24%

BSC: best supportive care; EQ-5D-5L: EuroQoL 5 Dimensions 3 Levels; EQ-5D-Y: European Quality of Life-5 Dimensions – Youth version; ERG: Evidence Review Group; HCRU: healthcare resource use; ICER: incremental cost-effectiveness ratio; LY: life year; NICE: National Institute for Health and Care Excellence; PV: permanent ventilation; QALY: quality-adjusted life year; STC: simulated treatment comparison.

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The scenario analyses for the type 2/3 model are detailed in Table 154. The scenarios that have the greatest effect on the base case ICER are outlined below.

Overall, none of the scenarios applied have a significant impact to the comparison between risdiplam and nusinersen as the outcome remains the same.

Similar to presymptomatic and T1, altering the patient and caregiver utility sources has a notable impact to the ICER versus BSC. The SUNFISH EQ-5D patient utility values are considered to be overall too low and therefore lack face validity. Although a clinician preference was given to the Roche UK utility survey values, through discussion with clinicians it is thought that the burden of caring for type 2/3 patients is lower than what it would be for poorer prognosis patients (i.e. type 1). Therefore, as the Roche UK utility values do not differentiate between type 1 and type 2/3, it wouldn't be plausible to assume that caregiver utility would be the same for types 1 and types 2/3. For the UK Burden of Illness study caregiver values, these again lack face validity due to an absence of differentiation between utilities across health states.

Finally, as an innovative, life-extending therapy, the scenario that explores a discount rate of 1.5% for benefits and 3.5% for costs lowers the ICER versus BSC by -35.28% in comparison to the base case.

Table 154. Scenario analysis results for the type 2/3 SMA (SUNFISH) model (list price)

Scenario	ICER vs BSC	% ICER change from the base case	ICER vs nusinersen	% ICER change from the base case
Base case	£343,682	-	Risdiplam is dominant	-
Efficacy scenarios				
Comparative efficacy vs. BSC: set to Natural history study (182)	£393,879	14.61%	Risdiplam is dominant	-
Risdiplam efficacy informed by non-imputed 5-year SUNFISH (excl. Asia)	£343,018	-0.19%	Risdiplam is dominant	-
Risdiplam efficacy post follow-up set to the extrapolations as seen in the SUNFISH trial period	£348,773	1.48%	Risdiplam is dominant	-
Weibull used for Type 2 OS extrapolation	£344,337	0.19%	Risdiplam is dominant	-
Source for % scoliosis: change to Wijngaarde et al. 2019 (179)	£378,700	10.19%	Risdiplam is dominant	-
Source for % bulbar dysfunction: change to Wadman et al. 2017 (180)	£335,340	-2.43%	Risdiplam is dominant	-
Source for % respiratory support: change to van der Heul et al. 2019 (181)	£356,877	3.84%	Risdiplam is dominant	-
HCRU scenarios				
Alignment with TA588 source for HCRU	£301,478	-12.28%	Risdiplam is dominant	-
Utility values scenarios				

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Source for patient utility values: TA588 ERG clinical advisors	£323,424	-5.89%	Risdiplam is dominant	-
Source for patient utility values: EQ-5D-3L values from SUNFISH	£604,673	75.94%	Risdiplam is dominant	-
Source for caregiver utility values: Roche utility survey	£1,341,134	290.23%	Risdiplam is dominant	-
Source for caregiver utility values: UK Burden of Illness Study	£506,566	47.39%	Risdiplam is dominant	-
Other Scenarios				
Inclusion of VAT saving from risdiplam homecare	£343,989	0.09%	Risdiplam is dominant	-
Changing baseline characteristics to REACH UK patient population	£349,955	1.83%	Risdiplam is dominant	-
Number of carers lowered to 2	£345,580	0.55%	Risdiplam is dominant	-
Number of carers increased to 3	£336,296	-2.15%	Risdiplam is dominant	-
Discount rate for both costs and benefits is lowered to 1.5%	£340,647	-0.88%	£7,826	+111.91%
Discount rate for benefits is lowered to 1.5%, discount rate for costs remains 3.5%	£222,426	-35.28%	Risdiplam is dominant	-

BSC: best supportive care; EQ-5D-5L: EuroQoL 5 Dimensions 3 Levels; EQ-5D-Y: European Quality of Life-5 Dimensions – Youth version; ERG: Evidence Review Group; HCRU: healthcare resource use; ICER: incremental cost-effectiveness ratio; LY: life year; NICE: National Institute for Health and Care Excellence; PV: permanent ventilation; QALY: quality-adjusted life year.

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B.3.11.4 Threshold analysis

Where it is known that confidential discounts are in place for comparators, the NICE user manual for the submission template recommends presenting scenarios with a range of potential discounts to aid decision making. ICER ranges have been presented in the comparisons of risdiplam with PAS price versus nusinersen and OA for each patient population using the base case.

In the presymptomatic population, risdiplam becomes cost neutral versus nusinersen between a discount range of 75-80% when applied to the nusinersen list price. When compared to OA, risdiplam becomes cost neutral versus OA at a discount level between 20-25%.

Assuming a willingness-to-pay threshold of £30,000 per QALY gain, in the type 1 SMA population, risdiplam is cost-effective versus nusinersen between a discount range of 70-75% and risdiplam is cost-effective against OA between a discount range of 50-55%. In the type 2/3 SMA population, risdplam can be considered cost-effective versus nusinersen at a discount level between 70-75%.

Table 155. Comparator discount level threshold analysis in the presymptomatic SMA (RAINBOWFISH) model using the base case and with-PAS price

Discount	Nusinersen		OA	
	Discounted nusinersen price	Incremental costs vs nusinersen	Discounted OA price*	Incremental costs vs OA
0%	£75,000	[redacted]	£1,600.080.58	[redacted]
5%	£71,250	[redacted]	£1,520,076.55	[redacted]
10%	£67,500	[redacted]	£1,440,072.52	[redacted]
15%	£63,750	[redacted]	£1,360,068,49	[redacted]
20%	£60,000	[redacted]	£1,280,064,46	[redacted]
25%	£56,250	[redacted]	£1,200,060,44	[redacted]
30%	£52,500	[redacted]	£1,120,056.41	[redacted]
35%	£48,750	[redacted]	£1,040,052.38	[redacted]
40%	£45,000	[redacted]	£960,048.35	[redacted]
45%	£41,250	[redacted]	£880,044.32	[redacted]
50%	£37,500	[redacted]	£800,040.29	[redacted]
55%	£33,750	[redacted]	£720,036.26	[redacted]
60%	£30,000	[redacted]	£640,032.23	[redacted]
65%	£26,250	[redacted]	£560,028.20	[redacted]
70%	£22,500	[redacted]	£480,024.17	[redacted]
75%	£18,750	[redacted]	£400,020.15	[redacted]
80%	£15,000	[redacted]	£320,016.12	[redacted]
*Informed by NHS Ref Costs 2021/22: Onasemnogene Abeparvovec [HICD0587; High Cost Drugs]				

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Table 156. Comparator discount level threshold analysis in the type 1 SMA (FIREFISH) model using the base case and with-PAS price

Discount	Nusinersen		OA	
	Discounted nusinersen price	ICER vs nusinersen	Discounted OA price*	ICER vs OA
0%	£75,000	[redacted]	£1,600.080.58	[redacted]
5%	£71,250	[redacted]	£1,520,076.55	[redacted]
10%	£67,500	[redacted]	£1,440,072.52	[redacted]
15%	£63,750	[redacted]	£1,360,068,49	[redacted]
20%	£60,000	[redacted]	£1,280,064,46	[redacted]
25%	£56,250	[redacted]	£1,200,060,44	[redacted]
30%	£52,500	[redacted]	£1,120,056.41	[redacted]
35%	£48,750	[redacted]	£1,040,052.38	[redacted]
40%	£45,000	[redacted]	£960,048.35	[redacted]
45%	£41,250	[redacted]	£880,044.32	[redacted]
50%	£37,500	[redacted]	£800,040.29	[redacted]
55%	£33,750	[redacted]	£720,036.26	[redacted]
60%	£30,000	[redacted]	£640,032.23	[redacted]
65%	£26,250	[redacted]	£560,028.20	[redacted]
70%	£22,500	[redacted]	£480,024.17	[redacted]
75%	£18,750	[redacted]	£400,020.15	[redacted]
80%	£15,000	[redacted]	£320,016.12	[redacted]
*Informed by NHS Ref Costs 2021/22: Onasemnogene Abeparvovec [HICD0587; High Cost Drugs]				

Table 157. Comparator discount level threshold analysis in the type 2/3 SMA (SUNFISH) model using the base case and with-PAS price

Discount	Nusinersen	
	Discounted nusinersen price	ICER vs nusinersen
0%	£75,000	[redacted]
5%	£71,250	[redacted]
10%	£67,500	[redacted]
15%	£63,750	[redacted]
20%	£60,000	[redacted]
25%	£56,250	[redacted]
30%	£52,500	[redacted]
35%	£48,750	[redacted]
40%	£45,000	[redacted]

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45%	£41,250	[redacted]
50%	£37,500	[redacted]
55%	£33,750	[redacted]
60%	£30,000	[redacted]
65%	£26,250	[redacted]
70%	£22,500	[redacted]
75%	£18,750	[redacted]
80%	£15,000	[redacted]

B.3.11.4 Summary of sensitivity analyses results

The results of the probabilistic base case in both analyses were closely reflective of the deterministic analysis, demonstrating that the models are robust to variation in input parameters. This was mirrored in the results of the deterministic sensitivity analyses, where only a small number of inputs had a significant impact on the ICERs when varied to their limits.

The results of the sensitivity analysis demonstrate that the chosen utility values are a significant driver to the results. The full extent of the impact of the chosen utility values can be seen throughout B.3.11 and speaks to how difficult it is to quantify both patient and caregiver utility values, and also noting the significant impact the choice of values has on decision making. Moreover, the cost of risdiplam and comparators are influential parameters as demonstrated by the sensitivity analyses. This is addressed by the PAS that has been provided to NICE confidentially.

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B.3.12 Subgroup analysis

No subgroup analyses were performed.

B.3.13 Benefits not captured in the QALY calculation

Due to the simplification of economic modelling, it is not possible to reflect all of the benefits that patients experience whilst on treatment with risidiplam. Firstly, risdiplam is the only oral treatment for SMA and is not associated with the risks that come with intrathecal administration. Due to lumbar puncture being an invasive procedure, infants and young children with SMA require anaesthesia and sedation is known to potentiate adverse respiratory reactions, which can be extremely serious in SMA patients (87). Given these factors, the intrathecal administration procedure is likely to cause anxiety for SMA patients and their families. Whilst the costs of intrathecal administration are captured, the broader benefits of receiving oral treatment are not reflected within the economic analysis.

Secondly, the current tools available to measure motor function cover important items, but are widely thought to not be sensitive enough to capture small changes in SMA (such as HFMSE and RULM). Furthermore, currently available outcome measures do not capture other important features of life with SMA that are deemed to be important to patients and their families such as the ability to perform daily activities, respiratory function, swallowing, fatigue and endurance. A qualitative study examined how individuals with SMA, their caregivers and clinicians defined meaningful change, primarily in the type 2 and non-ambulant type 3 patient populations – where it is harder to identify significant changes in improvement (42). The study captured views of 96 individuals and themes that emerged were related to defining meaningful change in motor function. Respondents stated that meaningful change is relative to functional ability and so any changes observed should be considered on a spectrum, depending on the baseline for individual patients; the importance of avoiding a significant decline in function and recognising the ability to maintain existing abilities was more important than being able to develop new ones; and finally small improvements make a big difference to the ability of an individual to function and thrive (42). As described in earlier sections, the baseline for the patient populations assessed with risdiplam are notably worse than other clinical studies assessing DMTs, and so this should be taken into consideration, as overall the starting point for these patients is worse than those observed in other studies.

A separate study evaluated bulbar function in n=25 non-ambulatory adults with type 2 and type 3 SMA, who had advanced disease stage with severe motor deficits, before and after risdiplam treatment initiation, measured using the Sydney Swallow Questionnaire (SSQ) and the bulbar subscore of the Amyotrophic Lateral Sclerosis Functional Rating Scale Revised (b-ALSFRS-R), alongside measuring extremity function with HFSME and RULM (228). Interestingly, the SSQ found improved scores following 12 months of risdiplam therapy and the b-ALSFRS-R observed a trend towards improvement. Whereas whilst the RULM score did improve after 12 months, the HFMSE did not and neither correlated with the SSQ. The study highlighted the importance of recognising bulbar function in addition to established motor score measurements (228). Sitas et al conducted a real-world study observing type 2 and 3 SMA patients on risdiplam to collect motor function scores and patient reported

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outcomes such as quality of life (229). The study found that all patients had reported an increase in their quality of life. 59% of patients who had bulbar symptoms reported improvements in bulbar function, and one-third of patients were seen to have an increase in appetite and subjective improvement in digestion (229). This bulbar function data is lacking from the data package presented in this dossier due to not being listed in the clinical trial or the real-world data collection. Also the challenge of small sample sizes with a rare disease makes it difficult to capture enough data to fulfil modelling requirements. Nonetheless, this improvement in function is important and relevant to patients, families and their clinicians and the difficulty in capturing it with standardised motor function measures should be taken into consideration.

Anecdotal evidence from the clinical and patient community also speak to the opportunity that risdiplam treatment has afforded them to be able to attend school, become working tax payers and play roles within their own community. This change in patients and families quality of life is difficult to capture, and the impact to society that these patients will have is also not accounted for within the economic analysis.

B.3.14 Validation

B.3.14.1 Clinical expert opinion elicitation

In order to ensure assumptions within the economic models were aligned with clinical practice, we sought opinion from clinical experts who actively treat SMA patients (146). Topics covered:

- Comparators listed in the NICE scope for the appraisal and the relevance of these to current practice, i.e. the application of BSC for patients with the availability of DMTs.
- Most appropriate life expectancy for SMA patients, given that this has now changed with the availability of DMTs versus what was previously seen in natural history
- Understanding what happens in practice if a patient receiving risdiplam plateaus or deteriorates in their response to treatment i.e would they discontinue
- Real-life transitions between motor milestone developments
- Overall survival, event-free survival, utility values and resource use costs were also discussed.

B.3.14.2 Validation of cost-effectiveness analysis

All models have been built to align with the NICE reference case, adopting an NHS and PSS perspective, a lifetime time horizong to fully capture all costs and QALY gains associated with the interventions, and discount rates for costs and benefits of 3.5% (168). All models were subject to an external quality assurance procedure, which included technical validation of key model inputs and calculations. Any issues or errors were documented and addressed in the final version of the models. Patient and clinical expert opinion was sourced during model development to inform model assumptions, to ensure they were clinically valid and/or aligned with UK clinical practice for the treatment of SMA (see Section B.3.14.1).

The model designs have been based on the original model presented in TA755, which were rigourously tested. The initial model was discussed with several world-leading experts from various geographies around the world (see TA755: Section B.3.10.1 and Section B.3.10.2) and further validated with UK-based advisory boards (67) and see Appendix Q. As

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mentioned in Section B.3.2.2, an ad-board was run with academic health economics experts to discuss potential adaptations to the original model (177). It was discussed that an economic model cannot captured all aspects of SMA, (also mentioned in B.3.13), and is a well-documented challenge, particularly in the case of rare diseases.

B.3.15 Interpretation and conclusions of economic evidence

Cost-effectiveness of risdiplam in presymptomatic, type 1 and type 2/3 SMA patients

Across all populations modelled, the results of the cost-effectiveness analyses for risdiplam versus BSC illustrate that risdiplam is associated with substantially greater QALYs and LYGs compared to BSC. These results illustrate the benefits that risdiplam brings to SMA patients over and above what was considered BSC, in terms of gains in both HRQoL and survival for patients and HRQoL for carers of patients with SMA. Whilst BSC may be suitable for a subset of patients in each population, i.e. higher SMN2 copies in presymptomatic, or those who refuse/deny DMT treatment in type 1 and type 2/3 populations, the question does still remain how appropriate BSC is as a comparator for this appraisal. In the presymptomatic SMA base case analysis, risdiplam is associated with an ICER of [redacted] per QALY (with PAS) versus BSC.

Due to a limited published data, small sample sizes and high heterogeneity between risdiplam, nusinersen and OA, equal efficacy was assumed between all 3 interventions and a cost-comparison has been presented. In the presymptomatic population risdiplam versus nusinersen and OA demonstrates that incremental cost savings can be realised when considering the risidplam PAS price, and in the absence of knowing comparator confidential discounts, the threshold analysis shows that even with comparator discounts applied, risdiplam is still seen to demonstrate cost-savings. In the presymptomatic SMA base case analysis, risdiplam is associated with a cost-saving of [redacted] and [redacted] when compared to nusinersen and OA.

In the comparison of risdiplam to nusinersen across type 1 and 2/3, risdiplam offers benefits in both LYG and QALYs in the base case. This is further reinforced by the incremental QALY results from the probabilistic analysis. In both the type 1 and type 2/3 base case analyses, [redacted] when considering the ICER (with PAS). A similar story can be seen for risdiplam versus OA in the type 1 population, particularly when focussing on the QALY gains, and a slight benefit is also observed in LYG too. In the type 1 SMA base case, risdiplam dominates OA when considering the ICER (with PAS).

Importantly, as a disease-modifying therapy, risdiplam is anticipated to contribute to patient outcomes that are well beyond the natural history of patients with SMA. The incremental benefit that risdiplam brings is explicitly reflected in the motor milestones that patients may achieve across all three patient populations.

Strengths and limitations of the evaluation

The cost-effectiveness models developed for presymptomatic, type 1 and type 2/3 SMA are associated with a number of strengths:

- Firstly, thorough research was undertaken during the conceptualisation and development stage of the economic models to ensure that they are as reflective as possible of the natural history of SMA, without becoming overly complex. Literature

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searches on the natural history of SMA and treatment guidelines were conducted, and these were supplemented by consultations with UK-based and international clinical experts working routinely with SMA patients. The aim of these activities was to ensure that the health states are reflective of abilities SMA patients may feasibly achieve in their lifetimes and represent meaningful changes in patients' and carers' lives in terms of HRQoL. Furthermore, during model design, previous models developed for the treatment of SMA were carefully reviewed, including the cost-effectiveness models built for the NICE appraisal for nusinersen in early- and later-onset SMA (TA588), from which substantial learnings were taken into account based on the ERG and Committee's critique, as well as the model developed by ICER in the US for the same disease area (18). In the update of the models from TA755, both patients, clinicians and academic health economists were consulted on how the modelling could be adapted and improved to more accurately reflect the benefits SMA patients experience when on treatment (164).

- A comprehensive approach was taken for sourcing inputs for the cost-effectiveness models. Evidence was generated *de novo* where possible, and as required to address the uncertainties highlighted in the DCA as part of the MAA commitments. This evidence was supplemented by systematically searching for and considering existing data. Following collection of all potential data sources for inputs, precedent with prior NICE appraisals in SMA and ensuring clinical plausibility through consultation with both UK clinical experts and patient group representatives was prioritised. As the model has been based on the economic model presented in TA755, many of the clinical assumptions still held (see Appendix Q and Section B.3.14) on the validation of model inputs and assumptions to ensure they closely reflect clinical practice. The gaps identified in TA588 and TA755 have been acknowledged, and through addressing the commitments in the DCA, all possible efforts have been made to ensure our company base case is an appropriate basis for NICE decision making. Where areas of uncertainty do exist, these have been highlighted and thoroughly explored through extensive scenario and sensitivity analysis.

- Even though UK trial sites were not included in FIREFISH and SUNFISH, in TA755 UK clinical advisors confirmed that the clinical development programme of risdiplam is generally reflective of the prevalent SMA population seen in UK clinical practice. As there are very few presymptomatic patients in the UK, it is difficult to confirm how well the RAINBOWFISH trial mirrors patients seen in clinical practice, although UK clinicians have had no objections to this data. It is worth noting that the enrolment criteria for the -FISH studies are broader than those listed for other SMA studies evaluating DMTs (75, 76), and UK clinical experts have confirmed that the recruited populations resemble the global spectrum of disease, supporting the external validity of the trial results.

- All three models are fully aligned to the NICE final scope for this appraisal, with model populations and the comparator accurately reflecting the submission decision problem. Evidence sources and model settings were also aligned with the NICE

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reference case, with risdiplam and BSC evaluated from the NHS/PSS perspective, over a lifetime horizon, with costs and utilities discounted at 3.5% (168).

Nevertheless, the economic analysis is also associated with limitations:

- Whilst longer term data has been provided for both FIREFISH and SUNFISH, it is still uncertain as to how these SMA patients will progress over time with the introduction of DMTs. Clinicians are observing type 1 SMA patients reach ages, development and motor milestones never seen before the introduction of DMTs and it is still unpredictable how these paitents will progress over time. Whilst efforts have been made to seek validation from UK clinical experts on the likely long-term assumptions and trajectories for patients treated with either risdiplam, nusinersen or OA, it is still proving to be a challenging feat to make long-term predictions.

- The single-arm nature of the RAINBOWFISH, FIREFISH and post-12 months for SUNFISH trials can potentially be considered a limitation of the evidence base, as it necessitated an ITC to be conducted to generate comparative efficacy estimates and transition probabilities for all comparators. The RAINBOWFISH and FIREFISH studies were single arm in design, due to both the small prevalent and incident patient population in rare conditions such as SMA and the fact that it was not considered appropriate (unethical) to treat infants with SMA with placebo when it was thought there could be a clinical benefit of risdiplam treatment. It was not possible to conduct robust ITCs in the presymptomatic population due to small sample sizes, high heterogeneity and different endpoints. In type 1 SMA, a comparison with BSC was performed up to 12 months but not after this point due to a lack of appropriate BSC data to perform the comparison. The comparison in type 1 SMA of risdiplam to OA is confounded with uncertainty, and whilst it has been provided for the purposes of fulfilling the NICE scope, the high uncertainty as seen in the ITC outcomes presented in Section B.2.9.4 and in the sensitivity analyses provided in Section B.3.11 show that the comparisons are not valid and pragmatism needs to be taken when interpreting this data. In the type 2/3 SMA population, due to different primary endpoints between risdiplam and nusinersen, as well as a high heterogeneity between the populations, this led to high uncertainty within the generated comparative efficacy estimates. For all comparisons, both the naïve and populated-adjusted were provided and therefore the limitation of having single-arm evidence from the studies was addressed as comprehensively as possible.

- As highlighted by the expert clinicians as part of the UK advisory boards (Appendix Q), and discussed as part of TA588, TA755 and HST15, health economics cost-effectiveness models may not fully reflect the patient and carer experience of SMA, with some clinical manifestations of SMA and the impact on the carer community not being fully captured. This is a well-documented limitation of most economic models, which are a simplification of reality and cannot fully capture all elements of a disease process. From this perspective, however, the economic analysis in this evidence submission should be considered conservative, as it is likely that the full benefits that risdiplam offers to patients and carers are not fully captured and reflected. This could include benefits such as improvements to respiratory and bulbar function, and in

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particular to upper limb function, which can bring substantial independence in patients' lives. Importantly, particularly for older SMA patients the potential to maintain gained function is even considered to be prioritised over gaining new skills and functions – the importance of a plateau for patients is difficult to model without penalising the risdiplam arm for incurring costs without creating further benefits. A further likely benefit not captured is reduced hospitalisation, which will benefit the HRQoL of patients and carers alike. It is important that recognition of the fact that the broad and severe impact of SMA cannot be fully captured by the economic models or the NICE reference case, is taken into account in the NICE decision-making process. Additional considerations and NICE decision modifiers should be recognised for this appraisal, similarly to NICE's decision-making for nusinersen in TA588, risdiplam in TA755 and OA in HST15.

- Although the clinical development programme of risdiplam is generally reflective of the prevalent SMA population seen in UK clinical practice, the evaluated populations used for risdiplam versus nusinersen and OA are much broader, i.e. older patients and in poorer health condition, allowing for contractures and scoliosis. This results in difficulty comparing the populations and when compared through statistical methodologies, the output results are not reflective of the true efficacy of risdiplam. As previously mentioned, this is due to confounding factors such as small sample sizes and significant heterogeneity between populations. When attempts are made to match these populations, this notably reduces the estimated sample size further increasing the uncertainty in the results. Moreover, the real-world data collected via the MAA through the SMA REACH registries illustrates an older and poorer prognosis patient population, even when compared to the –FISH studies. This is likely due to patients in better health meeting the eligibility criteria's for nusinersen and OA. Patients ineligible for nusinersen and OA received risdiplam; the impact of this can be seen in the sensitivity analysis. The timing of introduction of the DMTs has such a critical role in both the real-world data collected and also in the clinical trial data, particularly in rare diseases. Within the type 2/3 model, the mean baseline age was 10 years. It is anticipated that in clinical practice, risdiplam would be initiated at a much younger age than this, such that patients start receiving the benefits of therapy as early as possible. Due to the mean starting age in the SUNFISH trial, it is anticipated that patients had a worse prognosis than UK patients that would be treated in clinical practice. This means that the clinical results informing the model are likely to be conservative.

- A final limitation of the economic analysis is the combination of type 2 and type 3 patients in one economic model, as it is such a heterogeneous group.. It should be noted that even with type 3 patients there are considerable differences in characteristics between ambulant and non-ambulant patients. Additionally, subgroups such as type 3a and type 3b patients could not be explored. Results of the type 2/3 economic model should be interpreted in light of the heterogeneous population of the SUNFISH trial.

Cost-effectiveness analysis conclusions

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Overall, since the majority of the key approaches and assumptions in the base case analysis of the economic evaluation are either conservative in nature, or in line with UK clinical expert opinion, or based on precedent from TA588 and TA755, we believe that the base case cost-effectiveness results presented in our submission are appropriate as a basis for NICE decision-making. The presymptomatic model results support the conclusion that risdiplam is a plausibly cost-effective and cost-saving treatment option versus BSC, nusinersen and OA, at PAS price. In the type 1 and type 2/3 SMA models, risdiplam is a cost-effective treatment option versus OA, at PAS price, and versus nusinersen risdiplam is also shown to be a cost-effective option at PAS price across both populations. Finally, risdiplam is associated with substantial improvements to patient and carer HRQoL, in addition to an extension to patients' lives, compared to BSC.

As demonstrated in our evidence submission, risdiplam is a therapy with statistically significant and clinically meaningful efficacy outcomes across patients with presymptomatic, type 1 and type 2/3 SMA. Based on the comprehensive economic analysis presented, it should also be considered a cost-effective treatment option compared to BSC, OA and nusinersen. Importantly, results of the economic analysis should also be seen in light of the fact that SMA is a severe and rare condition, with a broad impact on patients, many of whom are children and people with disabilities, and their carers. NICE decision modifiers to account for the rarity, severity and broad impact of SMA should therefore explicitly be applied in this appraisal, similarly to factors recognised in TA588, TA755 and HST15.

Currently, only OA is routinely funded for presymptomatic and type 1 SMA patients. There is currently no routinely funded therapy for type 2/3 SMA – both risdiplam and nusinsersen are only reimbursed through their respective MAAs, and there is a risk of high unmet need being present once again for these type 2/3 patients, in addition to presymptomatic and type 1 patients ineligible for treatment with OA. Risdiplam offers a valuable, efficacious and clinically relevant additional therapeutic option for all patients across the continuum of SMA (i.e., irrespective of the patient's age, type of SMA, or physical status), and, importantly, the only available treatment option for a proportion of patients who may not be eligible for OA or treatment with nusinersen through the existing MAA.

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Multiple Technology Appraisal

Nusinersen and risdiplam for treating spinal muscular atrophy (MA review of TA588 and TA755) [ID6195]

Addendum:
FIREFISH study – clinical data to month 60 (Part 2 patients, ITT)

July 2024

File name	Version	Contains confidential information	Date
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1. FIREFISH 60-month data update

1.1. Summary

CS Document B provided clinical data for the FIREFISH study (Part 2, ITT) up to month 48. The purpose of this Addendum is to provide updated Tables and Figures including clinical data for the final time point, month 60.

Clinicians, people living with SMA, and their parents or caregivers repeatedly cite that small improvements can make a significant difference in the ability of a person or their family to function and thrive (1). People with SMA and caregivers fear progressive loss of function, and being able to maintain those abilities (stabilisation) is a meaningful outcome. Risdiplam treatment for up to five years resulted in infants with type 1 SMA achieving major motor milestones that they would never be able to achieve without treatment. Infants treated with risdiplam maintained or continued to improve in their ability to sit without support, and several patients could stand alone by the end of the study.

The data in this Addendum show that long-term risdiplam treatment continues to maintain or increase the clinically meaningful improvement in patients with Type 1 SMA.

1.2. Primary efficacy endpoint

As detailed in CS Document B Section B.2.6.1.1, 12 of 41 patients (29.3%; 90% CI: 17.8%, 43.1%) in Part 2 were sitting without support at 12 months of treatment, as assessed by Item 22 of the BSID-III gross motor scale, 'sits without support for 5 seconds'. By 24 months, 25 patients (61%; 90% CI: 46.9%, 73.8%) were sitting without support for 5 seconds. The proportion of patients sitting without support for 5 seconds (BSID-III) was generally sustained through the open-label extension (OLE) phase, indicating long-term benefit for patients receiving risdiplam treatment. With the latest 60-month data, [redacted] patients ([redacted]; 90% CI: [redacted]) were sitting without support for 5 seconds. This proportion ([redacted] of patients sitting at Month 60) is significantly higher than the pre-defined performance criterion of 5% based on well-established natural history data (p<0.0001) (Table 1).

Table 1: Patients sitting without support for 5 seconds over time (ITT Population, FIREFISH Part 2)

Endpoint	Risdiplam n=41	Performance criterion	p-value
Number / proportion (90% CI) of patients sitting without support for 5 seconds (BSID-III) at Month 12	12/41 29.3% (17.8 – 43.1%)	5%	< 0.0001
Number / proportion (90% CI) of patients sitting without support for 5 seconds (BSID-III) at Month 24	25/41 61.0% (46.9% – 73.8%)	5%	<0.0001
Number / proportion (90% CI) of patients sitting without support for 5 seconds (BSID-III) at Month 36 (OLE)	[redacted]	[redacted]	[redacted]
Number / proportion (90% CI) of patients sitting without support for 5 seconds (BSID-III) at Month 48 (OLE)	[redacted]	[redacted]	[redacted]

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Number / proportion (90% CI) of patients sitting without support for 5 seconds (BSID-III) at Month 60 (OLE)	[redacted]	[redacted]	[redacted]

BSID-III, Bayley Scales of Infant and Toddler Development, third edition; CI, confidence interval
This Table is an update of Table 17 in CS Document B.

1.3. Secondary efficacy endpoints

1.3.1. Sitting without support for 30 seconds, standing alone and walking alone (BSID-III)

The proportion of patients sitting without support for 30 seconds was generally sustained through the OLE phase (Table 2). [redacted] patients ([redacted]; 90% CI: [redacted], [redacted]) were standing alone by the end of the OLE (month 60) compared with [redacted] patients ([redacted]; 90% CI: [redacted], [redacted]). While this is [redacted], infants with type 1 SMA developing the ability to stand independently is a clinically meaningful breakthrough for these families, given that without treatment these children would never be expected to even sit without support.

Table 2: A summary of patients sitting without support for 30 seconds, standing alone, and walking alone over time as assessed by the BSID-III gross motor scale (ITT population, FIREFISH Part 2)

Endpoint and time point	Risdiplam n=41	Performance criterion	p-value
Number (proportion) and (90% CI) of patients sitting without support for 30 seconds (BSID-III)			
Month 12	7 (17.1%) 8.3% – 29.7%	NA	-
Month 24	18 (43.9%) 30.6% – 57.9%	5%	<0.0001
Month 36 (OLE)	[redacted]	[redacted]	[redacted]
Month 48 (OLE)	[redacted]	[redacted]	[redacted]
Month 60 (OLE)	[redacted]	[redacted]	[redacted]
Number (proportion) and (90% CI) of patients standing alone (BSID-III)			
Month 12	0 (0%) 0% – 7.1%	NA	-
Month 24	0 (0%) 0.00% – 7.1%	5%	1.0000
Month 36 (OLE)	[redacted]	[redacted]	[redacted]
Month 48 (OLE)	[redacted]	[redacted]	[redacted]
Month 60 (OLE)	[redacted]	[redacted]	[redacted]
Number (proportion) and (90% CI) of patients walking alone (BSID-III)			
Month 12	0 (0%) 0% – 7.1%	NA	-

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Month 24	0 (0%) 0.00% – 7.1%	5%	1.0000
Month 36 (OLE)	[redacted]	[redacted]	[redacted]
Month 48 (OLE)	[redacted]	[redacted]	[redacted]
Month 60 (OLE)	[redacted]	[redacted]	[redacted]

BSID-III, Bayley Scales of Infant and Toddler Development, third edition; CI, confidence interval
This Table is an update of Table 18 in CS Document B.

1.3.2. CHOP-INTEND

As detailed in CS Document B Section B.2.6.1.2, 23 of 41 patients (56.1%; 90% CI: 42.1%, 69.4%) in Part 2 achieved a CHOP-INTEND total score of 40 or higher. The improvements in CHOP-INTEND scores seen at month 12 were further enhanced at month 24 and generally maintained through to month 48. The proportion of patients who achieved a CHOP-INTEND score of 40 or higher was generally maintained during the OLE phase. The proportion of patients who presented motor function improvement, as measured by an increase of at least 4 points from baseline in their CHOP-INTEND score, was maintained at month 24 and remained relatively stable in the OLE phase of the study up to month 60

Table **3**).

Table 3: CHOP-INTEND scores over time (ITT Population, FIREFISH Part 2)

Endpoint and time point	Risdiplam n=41	Performance criterion	p-value
Number (proportion) and (90% CI) of patients who achieve a score of 40 or higher in the CHOP-INTEND			
Month 12	23 (56.1%) 42.1–69.4%	17%	<0.0001
Month 24	31 (75.6%) 62.2–86.1%	NA	-
Month 36 (OLE)	[redacted]	[redacted]	[redacted]
Month 48 (OLE)	[redacted]	[redacted]	[redacted]
Month 60 (OLE)	[redacted]	[redacted]	[redacted]
Number (proportion) and (90% CI) of patients who achieve an increase of at least 4 points in their CHOP-INTEND			
Month 12	37 (90.2%) 79.1–96.6%	17%	<0.0001
Month 24	37 (90.2%) 79.1–96.6%	NA	-
Month 36 (OLE)	[redacted]	[redacted]	[redacted]
Month 48 (OLE)	[redacted]	[redacted]	[redacted]
Month 60 (OLE)	[redacted]	[redacted]	[redacted]

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		[redacted]		

CHOP-INTEND, Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders; CI, confidence interval. This Table is an update of Table 19 in CS Document B.

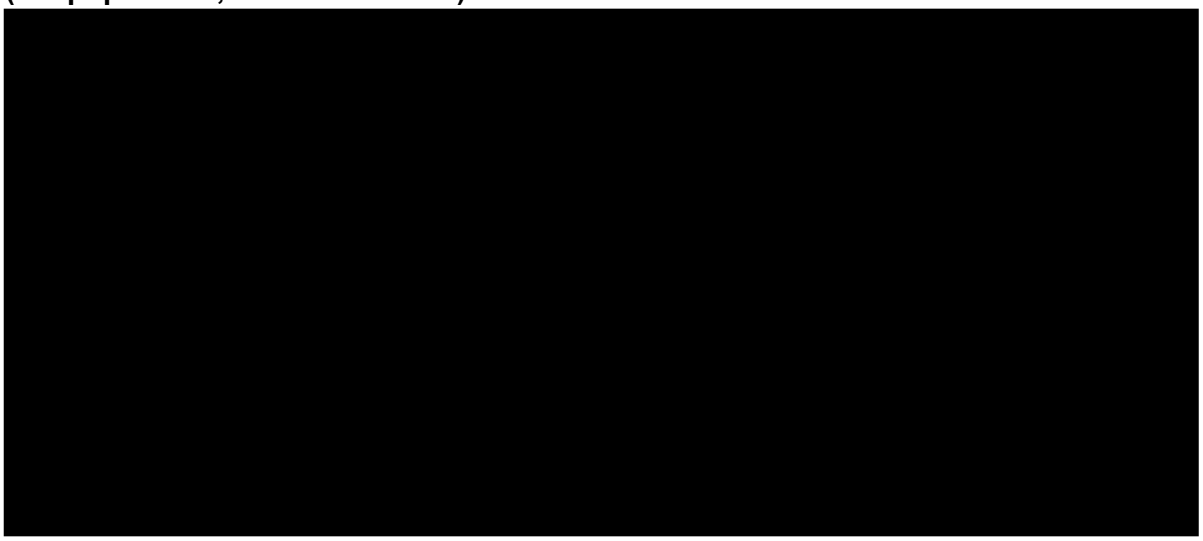
Data from the OLE phase of the study demonstrate that the mean change from baseline in the CHOP-INTEND score was generally maintained over time (

Figure **1**).

Note that the graph in CS Document B, Figure 3 showed data up to month 48 for pooled patients (Part 1 and Part 2) because the equivalent graph for only Part 2 patients was not available at the time of submission.

Figure 1 shows data for Part 2 patients only, in line with all data in this Addendum.

Figure 1: Mean change from baseline in the CHOP-INTEND Score and 90% CI by visit, (ITT population, FIREFISH Part 2)



1.3.3. HINE-2

As detailed in CS Document B Section B.2.6.1.2, 32 of 41 patients (78.0%; 90% CI: 64.8%, 88.0%) were classified as motor milestone responders, as assessed by HINE-2 at month 12. The proportion of patients classified as motor milestone responders per the HINE-2 assessment was increased or maintained during the OLE phase of the study through to month 60 (

Table **4**).

Table 4: Summary of motor milestone responders as assessed by HINE-2 over time (ITT Population, FIREFISH Part 2)

Endpoint and time point	Risdiplam n=41	Performance criterion	p-value
Number (proportion) and (90% CI) of motor milestone responders[a] as assessed by the HINE-2			

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Month 12	32 (78.0%) 64.8–88.0%	12%	<0.0001
Month 24	35 (85.4%) 73.2–93.4%	NA	-
Month 36 (OLE)	[redacted]	[redacted]	[redacted]
Month 48 (OLE)	[redacted]	[redacted]	[redacted]
Month 60 (OLE)	[redacted]	[redacted]	[redacted]

[a] An improvement in a motor milestone was defined as at least a 2-point increase in the ability to kick (or maximal score) or a 1-point increase in head control, rolling, sitting, or walking. Worsening was defined as a 2-point decrease in ability to kick (or lowest score) or a 1-point decrease in head control, rolling, sitting, crawling, standing or walking. Voluntary grasp was excluded from the definition. An infant was classified as a responder if more motor milestones showed improvement than showed worsening.
CI, confidence interval; HINE-2, Hammersmith Infant Neurological Examination Module 2.
This Table is an update of Table 20 in CS Document B.

The percentages of infants within the higher attainment response categories for HINE-2 were overall increased or maintained during the OLE phase (

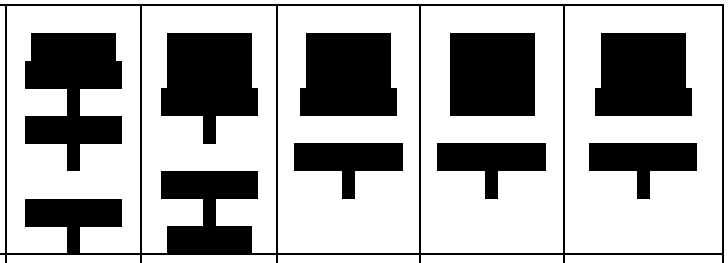
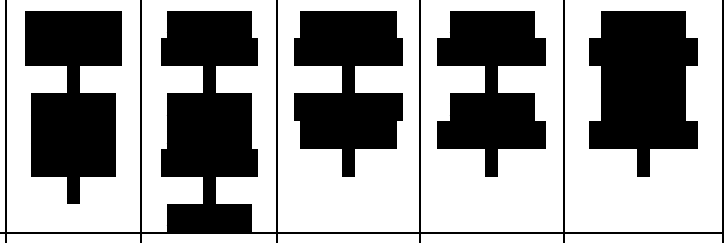
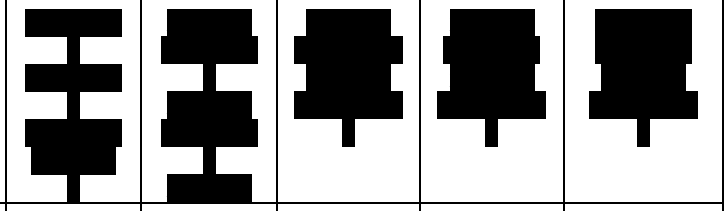
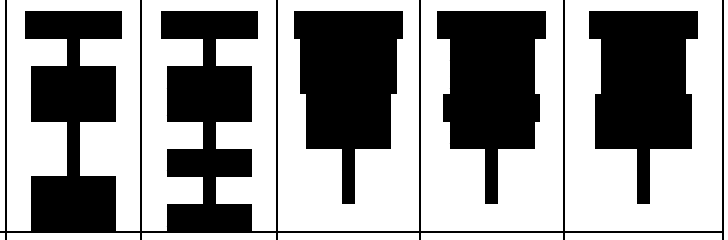
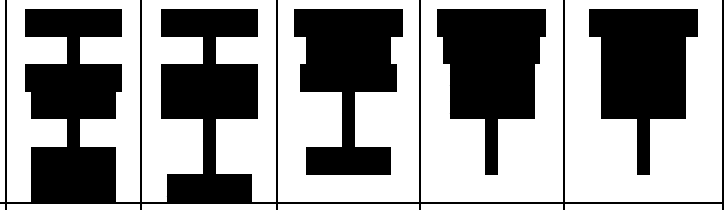
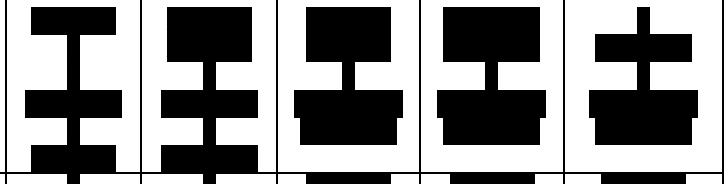
Table **5**). For example, at baseline, no patients could sit. At month 12, most of the patients (61.0%) achieved some level of sitting, which increased to 70.7% at month 24 and [redacted] at month 60. Data from the OLE phase demonstrated that children treated with risdiplam maintained or continued to achieve HINE-2 motor milestones.

As explained in CS Document B Section 2.6.1.2, natural history data demonstrates that at 12 months, infants achieved no motor milestones in voluntary grasping, kicking or rolling, and achieve no level of crawling, standing or walking at any time point (2). Therefore, the fact that after long-term treatment with risdiplam, a large proportion of infants achieved motor milestones with regards to grasping, kicking and rolling and some patients had even begun to crawl and show signs of standing shows clinically meaningful developments for these patients and their families.

Table 5: Summary of the infants within each attainment response category of the HINE-2 over time (ITT Population, FIREFISH Part 2)

n, (%)	Time point (risdiplam n=41)				
	Month 12	Month 24	Month 36 (OLE)	Month 48 (OLE)	Month 60 (OLE)
Head control Unable to maintain head upright Wobbles All the time maintained upright Not done	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Sitting Cannot sit Sits with support at hips Props Stable sit Pivots (rotates) Not done	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

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Voluntary grasp No grasp Uses whole hand Index finger and thumb but immature grasp Pincer grasp Not done					
Ability to kick (in supine) No kicking Kicks horizontally, legs do not lift Upward (vertically) Touches leg Touches toes Not done					
Rolling No rolling Rolling to side Prone to supine Supine to prone Not done					
Crawling Does not lift head On elbow On outstretched hand Crawling flat on abdomen Crawling on hands and knees Cannot test Not done					
Standing Does not support weight Supports weight Stands with support Stands unaided Cannot test Not done					
Walking Bouncing Cruising (walks holding on) Walking independently Cannot test Not done					
Withdrawal					
Death					
Missing					

Patients who reached the target date for a visit but did not perform the assessment by the clinical cut-off date are counted as missing.
This Table is an update of Table 21 in CS Document B.

1.3.4. Survival and ventilation-free survival

As detailed in CS Document B section 2.6.1.2, the proportion of infants alive without permanent ventilation at month 12 was 85.4% (35/41; 90% CI: 73.4%, 92.2%) Three infants died within the first 3 months following study enrolment, and 3 infants met the endpoint of permanent ventilation. At month 60, most patients were alive without permanent ventilation. A total of [redacted] patients had died and [redacted] patients had met the endpoint of permanent ventilation (

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Table 6).

[redacted]. The proportion of infants alive without permanent ventilation at month 24, 36, 48 and 60 were 82.9% (90% CI: 70.5%, 90.4%), 82.9% (90% CI: 70.5%, 90.4%), 77.9% (90% CI: 64.9, 86.6) and 77.9% (90% CI: 64.9, 86.6), respectively.

[redacted].
The median time to death or permanent ventilation was not evaluable.

Table 6: Time to death or permanent ventilation (ITT population, FIREFISH Part 2)

	Risdiplam n=41				
	Month 12	**Month 24**	**Month 36 (OLE)**	**Month 48 (OLE)**	**Month 60 (OLE)**
People with event, n (%)	6 (14.6)	7 (17.1)	[redacted]	[redacted]	[redacted]
Earliest contributing event, n Death Permanent ventilation	 3 3	 3 4	[redacted]	[redacted]	[redacted]
Median time to event, months (90% CI)	NE (NE, NE)	NE (NE, NE)	[redacted]	[redacted]	[redacted]
Patients remaining at risk Proportion event-free, % (90% CI)	35 85.37 (73.35, 92.24)	34 82.93 (70.54, 90.44)	[redacted]*	[redacted]	[redacted]**
Performance criterion	42%	NA	[redacted]	[redacted]	[redacted]
p-value (z-test)	<0.0001	-	[redacted]	[redacted]	[redacted]

This Table is an update of Table 22 in CS Document B.
*There were no events between 24 and 36 months – the change in the number of patients at risk is due to a discontinuation (this patient is censored in the analysis and the Kaplan-Meier estimate remains constant over this interval).
**The change in the number of patients at risk is due to some patients completing treatment before reaching exactly 60 months from enrolment.

1.3.5. Nutrition

Oral feeding abilities were maintained by the majority of infants in the OLE phase of the study (

Table **7**).

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Table 7: Summary of patients' ability to feed over time (ITT population, FIREFISH Part 2)

	Risdiplam n=41				
	Month 12	**Month 24**	**Month 36* (OLE)**	**Month 48 (OLE)**	**Month 60 (OLE)**
Able to feed orally, n (%) (90% CI)	34 (82.9) (70.3, 91.7)	35 (85.4) (73.2, 93.4)	[redacted]	[redacted]	[redacted]

*There was some missing data at month 36 as this data was initially not collected during the OLE period
This Table is an update of Table 23 in CS Document B.

1.3.6. Healthcare utilisation

There were a total of 51 hospitalisations by month 12, resulting in a rate of 1.30 (90% CI: 1.02, 1.65) hospitalisations per patient-year (please see Section 2 for detail on hospitalisation data correction). By month 48, [redacted]. The rate of hospitalisations (number of hospitalisations per patient-year) [redacted] through the OLE phase of the study. By month 60, [redacted]. For patients who were hospitalised, the median number of nights for which they were admitted [redacted] (

Table **8**). These numbers include planned / elective hospital admissions.

Table 8: Summary of hospitalisations over time; number of hospitalisations per patient-year and number of nights admitted to hospital per infant (ITT population, FIREFISH Part 2)

	Risdiplam n=41				
	Month 12	**Month 24**	**Month 36 (OLE)**	**Month 48 (OLE)**	**Month 60 (OLE)**
Number of hospitalisations	51	72	[redacted]	[redacted]	[redacted]
Number of hospitalisations per patient-year (90% CI)	1.33 (1.04, 1.68)	0.94 (0.76, 1.14)	[redacted]	[redacted]	[redacted]
Number of nights per infant Median (Min – Max)	17.00 (2.0 – 151.0)	15.00 (2.0 – 164.0)	[redacted]	[redacted]	[redacted]

This Table is an update of Table 24 in CS Document B.

1.4. Adverse reactions

1.4.1. Exposure to risdiplam

As detailed in CS Document B Section 2.10.1, In Part 2 of the FIREFISH study up to the CCOD of 22 November 2022, the median duration of exposure to risdiplam was

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[redacted]). All patients had received at least [redacted] of the total number of prescribed doses (dose intensity).

With the updated 5-year FIREFISH data cut, the median exposure to risdiplam in Part 2 patients at the final CCOD of 22 December 2023 was [redacted] months (range: [redacted] – [redacted]). The median dose intensity was [redacted] (range: [redacted] – [redacted]) (Table 9). All patients had received at least [redacted] of the total number of prescribed doses (dose intensity).

Table 9: Exposure to risdiplam (ITT population, FIREFISH Part 2)

	Risdiplam (n=41)
Treatment duration (months) Mean (SD) Median Min – Max	[redacted]
Treatment duration category (months) 0 - ≤ 6 months >6 - ≤ 12 months >12 - ≤ 18 months >18 - ≤ 24 months >24 - ≤ 30 months >36 - ≤ 42 months >54 - ≤ 60 months >60 months	[redacted]
Total number of doses Mean (SD) Median Min – Max	[redacted]
Missed doses n Mean (SD) Median Min – Max	[redacted]
Partial doses n Mean (SD) Median Min – Max	[redacted]
Overdoses n Mean (SD) Median Min – Max	[redacted]
Dose intensity, (%) Mean (SD) Median Min – Max	[redacted]

Treatment duration is the date of the last study drug administration minus the date of the first study drug administration plus one day. Dose intensity is the number of doses actually received divided by the expected number of doses. Partial dose: actual dose administered <90% of planned dose. Overdose: actual dose administered >110% of planned dose.
This Table is an update of Table 87 in CS Document B.

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1.4.2. Adverse events

Up to five years of treatment, risdiplam was well tolerated, and the safety remains consistent with its known safety profile. No new safety signals were identified. Three patients died during the first three months of risdiplam treatment due to SMA-related complications. There were no new deaths reported in the study after this point.

All patients reported at least one AE, but no patients withdrew from the study due to an AE (Table 10).

A summary of AEs by preferred term reported in more than 5% of the patients is provided in Table 11.

Table 10: Overview of adverse events by frequency (ITT population, FIREFISH Part 2)

n, (%)	Risdiplam (n=41)
Total number of people with at least one AE	[redacted]
Total number of AEs, n	[redacted]
Total number of deaths	[redacted]
Total number of people withdrawn from study due to an AE	[redacted]
Total number of people with at least one AE with fatal outcome Serious AE Serious AE leading to withdrawal from treatment Serious AE leading to dose modification/treatment interruption Related serious AE AE leading to withdrawal from treatment AE leading to dose modification/interruption Related AE Related AE leading to withdrawal from treatment Related AE leading to dose modification/interruption Grade 3–5 AE	[redacted]

Multiple occurrences of the same AE in one individual are counted only once except for "total number of AEs" row in which multiple occurrences of the same AE are counted separately.
This Table is an update of Table 88 in CS Document B.

Table 11: Adverse events reported in >5% of patients (FIREFISH Part 2)

Adverse event (n, %)	Risdiplam n=41
Pyrexia	[redacted]
Upper respiratory tract infection	[redacted]
Pneumonia	[redacted]
Constipation	[redacted]
Nasopharyngitis	[redacted]
Diarrhoea	[redacted]
Rhinitis	[redacted]
Vomiting	[redacted]
Bronchitis	[redacted]
COVID-19	[redacted]
Respiratory tract infection	[redacted]
Respiratory tract infection viral	[redacted]
Teething	[redacted]

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Urinary tract infection	[redacted]
Influenza	[redacted]
Gastroesophageal reflux disease	[redacted]
Cough	[redacted]
Respiratory distress	[redacted]
Respiratory failure	[redacted]
Cryptorchidism	[redacted]
Joint dislocation	[redacted]
Pharyngitis	[redacted]
Pneumonia viral	[redacted]
Rash	[redacted]
Rash maculo-papular	[redacted]
Bronchiolitis	[redacted]
Dehydration	[redacted]
Haematuria	[redacted]
Malnutrition	[redacted]
Miliaria	[redacted]
Urticaria	[redacted]

This Table is an update of Table 89 in CS Document B.

1.4.3. Serious adverse events

Overall, [redacted] patients ([redacted]) in Part 2 experienced at least one SAE throughout the study; this is an increase of [redacted] patients between month 48 and month 60. A summary of the types of SAEs is provided in Table 12.

Please see Section 2 for detail on 48-month SAE data correction.

Table 12: Serious adverse events (ITT population, FIREFISH Part 2)

Serious adverse events (n, %)	Risdiplam (n=41)
Total number of patients with at least one adverse event	[redacted]
Overall total number of events	[redacted]
Infections and infestations Total number of patients with at least one adverse event Total number of events	[redacted]
Respiratory, thoracic and mediastinal disorders Total number of patients with at least one adverse event Total number of events	[redacted]
Gastrointestinal disorders Total number of patients with at least one adverse event Total number of events	[redacted]
Metabolism and nutrition disorders Total number of patients with at least one adverse event Total number of events	[redacted]
Cardiac disorders Total number of patients with at least one adverse event Total number of events	[redacted]
Injury, poisoning and procedural complications Total number of patients with at least one adverse event Total number of events	[redacted]
Nervous system disorders Total number of patients with at least one adverse event Total number of events	[redacted]
Congenital, familial and genetic disorders Total number of patients with at least one adverse event	[redacted]

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Total number of events	[redacted]
Investigations Total number of patients with at least one adverse event Total number of events	[redacted]

This Table is an update of Table 90 in CS Document B.

1.5. Conclusion

Risdiplam treatment was well tolerated and the safety profile remained stable for up to 5 years in a symptomatic Type 1 SMA population of infants who, in their majority, started treatment after 3 months of age. No new safety signals were identified, no new deaths were reported in the study after the 24-month clinical cut-off, no patients withdrew from the study due to an AE, and there was an overall decline in AE rates and SAE rates, which stabilised in the fourth and fifth years of treatment.

Risdiplam efficacy data for people with Type 1 SMA demonstrated clinically meaningful improvements in complex motor function at 24 months. These improvements were generally maintained throughout the 60-month study duration, with some patients having further improvements. This indicates that a long-term benefit for patients receiving risdiplam treatment in improving and maintaining improvements in motor function outcomes. Clinicians, people living with SMA, and their parents or caregivers repeatedly cite that small improvements can make a significant difference in the ability of a person or their family to function and thrive (42). People with SMA and caregivers fear progressive loss of function, and being able to maintain those abilities (stabilisation) is a meaningful outcome.

Overall, efficacy and safety findings at the 60-month data cut were consistent with findings at the 48-month data cut. These longer-term efficacy and safety data provide important evidence of the continued benefit of risdiplam in patients with infantile-onset (Type 1) SMA, reducing uncertainty in longer-term safety and durability of longer-term efficacy.

2. Statement of correction – FIREFISH Month 48 data cut

In the FIREFISH study, HINE-2 scores for one Part 2 patient were provided to the company after the clinical cut-off date for the 48-month analysis. However, the data from this patient was included in the final 60-month analysis. Tables 20 (HINE-2 motor milestone responders) and 21 (HINE-2 scores) of CS Document B have been updated in this Addendum (Tables 4 and 5, respectively) to reflect this additional patient. The patient generally scored highly in the attainment response categories:

[redacted]

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As the patient scored highly in attainment response scores across the range of HINE-2 motor categories, the outcomes of the company Type 1 analysis could be considered somewhat conservative. The inclusion of this patient in the 48 month population would likely improve overall change from baseline and may provide an improvement in the MAIC adjusted HINE-2 motor milestone response hazard ratio.

Hospitalisation data for one patient was provided to the company after the clinical cut-off date for the primary analysis, and data for another patient was provided to the company after the clinical cut-off date for the 48-month analysis. The data from these patients was included in the final 60-month analysis. Table 24 of CS Document B (number and length of hospitalisations) has been updated in this Addendum (Table 8) to reflect this. As a result of the additional data, the number of hospitalisations at month 12 increased from [redacted] to [redacted] and the number of hospitalisations at month 48 increased from [redacted] to [redacted].

Please also note a decrease in the total number of SAEs in the 'Respiratory, thoracic and mediastinal disorders' category of Table 12 from [redacted] to [redacted]. This is due to an error in the month 48 data.

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3. References

1. McGraw S, Qian Y, Henne J, Jarecki J, Hobby K, Yeh WS. A qualitative study of perceptions of meaningful change in spinal muscular atrophy. BMC neurology. 2017;17(1):68.
2. Cances C, Vlodavets D, Comi GP, Masson R, Mazurkiewicz-Bełdzińska M, Saito K, et al. Natural history of Type 1 spinal muscular atrophy: a retrospective, global, multicenter study. Orphanet journal of rare diseases. 2022;17(1):300.

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NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Multiple Technology Appraisal

Nusinersen and risdiplam for treating spinal muscular atrophy (MA review of TA588 and TA755) [ID6195]

Summary of Information for Patients (SIP)

April 2024

File name	Version	Contains confidential information	Date
SMA NICE MTA SIP_Final	**V1.0**	**N**o	**1**8 April 2024

Summary of Information for Patients (SIP):

The pharmaceutical company perspective

What is the SIP?

The Summary of Information for Patients (SIP) is written by the company who is seeking approval from NICE for their treatment to be sold to the NHS for use in England. It is a plain English summary of their submission written for patients participating in the evaluation. It is not independently checked, although members of the public involvement team at NICE will have read it to double-check for marketing and promotional content before it is sent to you.

The **Summary of Information for Patients** template has been adapted for use at NICE from the Health Technology Assessment International – Patient & Citizens Involvement Group (HTAi PCIG). Information about the development is available in an open-access IJTAHC journal article

SECTION 1: Submission summary

Note to those filling out the template: Please complete the template using plain language, taking time to explain all scientific terminology. Do not delete the grey text included in each section of this template as you move through drafting because it might be a useful reference for patient reviewers. Additional prompts for the company have been in red text to further advise on the type of information which may be most relevant and the level of detail needed. You may delete the red text.

1a) Name of the medicine (generic and brand name):

Generic Name: Nusinersen Brand Name: Spinraza

1b) Population this treatment will be used by. Please outline the main patient population that is being appraised by NICE:

The main patient population being re-appraised by NICE for the treatment with nusinersen (Spinraza) encompasses individuals diagnosed with spinal muscular atrophy (SMA), specifically focusing on those with the 5q variant of the disease. This includes a wide range of patients across different age groups and SMA subtypes. NICE previously assessed nusinersen in 2019 and conditionally reimbursed its use subject to a managed access agreement (a temporary period of reimbursement whilst further data are collected to address key uncertainties [1]). The Managed access agreement (MAA) was initially set up for 5 years for 5qSMA patients with symptomatic type 1, 2 or 3 SMA; it also included pre-symptomatic patients with up to 4 copies of SMN2. Patients were able to access nusinersen subject to strict start and stopping criteria as outlined in the MAA protocol [1]. These populations will form the key populations in this re-appraisal and will be assessed based on clinical effectiveness data collected through a long-term extension study (SHINE) ongoing studies (presymptomatic,

NURTURE) and via real world evidence collected in UK clinical practice through multiple registries including SMA REACH and Adult SMA REACH.

It should be noted that certain subtypes within the marketing authorisation will not be included in the key populations being re-appraised; namely type 0 and type 4 5qSMA. Type 0 is extremely rare (<1% of diagnosed cases) and refers to infants that show symptoms of SMA before or immediately following birth, many of patients sadly do not survive more than a few months and clinical experts deem the treatment of such patients as futile [2].

Type 4 is another rare form of SMA (<5% of diagnosed cases) and is recognised as the least severe form. Symptom onset for type 4 patients is in adulthood and is associated with slowly progressive muscle weakness. The use of nusinersen in type 4 patients has not been tested in a clinical trial, furthermore real-world evidence is extremely limited and currently insufficient to meet the expectations of health technology assessment.

1c) Authorisation: Please provide marketing authorisation information, date of approval and link to the regulatory agency approval. If the marketing authorisation is pending, please state this, and reference the section of the company submission with the anticipated dates for approval.

Nusinersen has a marketing authorisation from the MHRA for the treatment of 5q SMA [3]. It was initially approved by the EMA on 30 May 2017 [4].

1d) Disclosures. Please be transparent about any existing collaborations (or broader conflicts of interest) between the pharmaceutical company and patient groups relevant to the medicine. Please outline the reason and purpose for the engagement/activity and any financial support provided:

Biogen would like to disclose the following collaborations with patient groups:

- SMA UK: Sponsorship has been provided for projects in 2016, 2021, 2022 and 2023 relating to SMA support UK outreach services, digital community outreach, educational resources in schools and patient story development. A grant was provided in 2020 in response to COVID-19 emergency funding needs. Biogen also supported the SMA UK Family Conference in 2018 via a grant.
- Muscular Dystrophy UK: Sponsorship has been provided for a number of conference between 2018 – 2022 including MD UK Care advisor, Neuromuscular Translational Research & Physiotherapy conferences. An educational grant was provided in 2022 towards MD UK Open-TACT, a website resource for physiotherapists.

Transparency is important to Biogen and details of funding of UK patient groups is disclosed on the Biogen UK website: https://transparency.biogen.com/en/united-kingdom.html

SECTION 2: Current landscape

Note to authors: This SIP is intended to be drafted at a global level and typically contain global data. However, the submitting local organisation should include country-level information where needed to provide local country-level context.

Please focus this submission on the **main indication (condition and the population who would use the treatment)** being assessed by NICE rather than sub-groups, as this could distract from the focus of the SIP and the NICE review overall. However, if relevant to the submission please outline why certain sub-groups have been chosen.

2a) The condition – clinical presentation and impact

Please provide a few sentences to describe the condition that is being assessed by NICE and the number of people who are currently living with this condition in England. Please outline in general terms how the condition affects the quality of life of patients and their families/caregivers. Please highlight any mortality/morbidity data relating to the condition if available. If the company is making a case for the impact of the treatment on carers this should be clearly stated and explained.
Spinal Muscular Atrophy (SMA) is a rare genetic disease that affects muscles and nerves, causing weakness and sometimes leading to serious health problems. It's estimated that around 1,340 people in the UK have SMA [5]. SMA is recognised by the European Medicines Agency (EMA) as an orphan disease and, without treatment, is the leading genetic cause of infant mortality globally [6]. People with SMA don't have enough of a protein called survival motor neuron (SMN), which is important for the health of nerve cells that control muscles. This lack of protein causes muscles to weaken over time, leading to difficulties with movement and breathing [6,7]. There are different types of SMA, ranging from severe to milder forms, depending on when symptoms start and how they progress: 1. Presymptomatic SMA: People who have the genetic mutation for SMA but haven't shown any symptoms yet. 2. Infantile-onset SMA (Type 1): The most severe form, appearing before 6 months of age, causing severe muscle weakness and breathing problems. It's often fatal if untreated [8]. 3. Later-onset SMA (Types 2 and 3): Less severe forms appearing after 6 months but before 18 years of age, with varying degrees of muscle weakness. People with Type 2 can't walk independently, while those with Type 3 may lose the ability to walk over time after achieving it [8]. 4. Adult-onset SMA (Type 4): Very rare, usually causing muscle weakness in adulthood, but with a slower progression compared to other types [8]. SMA happens because the body doesn't make enough of a protein called survival motor neuron (SMN). This is because there's something wrong with a gene called survival motor neuron gene (SMN1). Without enough SMN protein, the nerve cells that control muscles die, which makes the muscles weaker over time. SMA is passed down through genes [9,10]. If both parents pass on a faulty SMN1 gene to their child, the child will have SMA. If someone has only one faulty gene, they won't have SMA themselves, but they could pass it on to their children. If two people who carry the SMA gene have a child, there's a 1 in 4 chance the child will have SMA.

There's another gene called SMN2 that can partially make up for the missing or faulty SMN1 gene, but it only makes about 10% of the protein needed [11-13]. Everyone has at least one copy of SMN2, and some people have up to eight copies. Having more copies of SMN2 usually means a less severe form of SMA, but it's not the only thing that affects how severe the disease is.

Nusinersen is a treatment that can help slow down the progression of SMA, improve motor function, and enhance the quality of life for patients [14]. It's particularly beneficial for Type 1 SMA patients, often called non-sitters, where nusinersen can greatly reduce the need for invasive treatments and frequent hospital visits. But even with this improvement, patients may still need additional support like breathing machines and devices to help with coughing, especially in the early years.

For those with Type 2 and advanced Type 3 SMA, nusinersen can help lessen muscle weakness and breathing difficulties [15]. Studies have shown that it slows down how fast the disease gets worse and helps patients move better.

For people with Type 3 SMA, also known as walkers, nusinersen can increase their ability to move and be independent [15]. It also delays when they might start having more serious problems moving around.

2b) Diagnosis of the condition (in relation to the medicine being evaluated)

Please briefly explain how the condition is currently diagnosed and how this impacts patients. Are there any additional diagnostic tests required with the new treatment?

Doctors often suspect SMA if there's a family history of the disease or if a baby shows certain physical signs. The most reliable way to confirm if someone has SMA is through genetic tests that look at specific genes called SMN1 and SMN2. If they find that both copies of the SMN1 gene are missing, it confirms SMA. If there's only one copy of SMN1 and the child shows symptoms, they do more tests to check for mutations in that gene. However, if there are two complete SMN1 genes, SMA is unlikely unless there are strong symptoms or a family history of the disease.

It's important to know that although Newborn Screening (NBS) for SMA isn't widely available in the UK yet, it's being considered by the National Screening Committee (NSC), with some pilot programs happening [16]. This is important because finding and treating SMA early can greatly improve outcomes. The fact that the UK NSC are looking into newborn screening shows a possible shift towards earlier diagnosis and treatment, which is crucial for better patient care.

2c) Current treatment options:

The purpose of this section is to set the scene on how the condition is currently managed:

- What is the treatment pathway for this condition and where in this pathway the medicine is likely to be used? Please use diagrams to accompany text where possible. Please give emphasis to the specific setting and condition being considered by NICE in this review. For example, by referencing current treatment guidelines. It may be relevant to show the treatments people may have before and after the treatment under consideration in this SIP.
- Please also consider:

- if there are multiple treatment options, and data suggest that some are more commonly used than others in the setting and condition being considered in this SIP, please report these data.
- are there any drug–drug interactions and/or contraindications that commonly cause challenges for patient populations? If so, please explain what these are.

Before 2017, there were no treatments available for SMA, so people with the condition received supportive care to help manage their symptoms. Supportive care aims to make life easier for SMA patients and their caregivers by addressing issues like breathing problems, nutrition, bone health, and rehabilitation. However, it doesn't treat the root cause of SMA or slow down its progression.

Since 2017, there have been significant developments in SMA treatment in England. Several therapies have become available, which have changed how SMA is managed and improved outcomes for patients and their families.

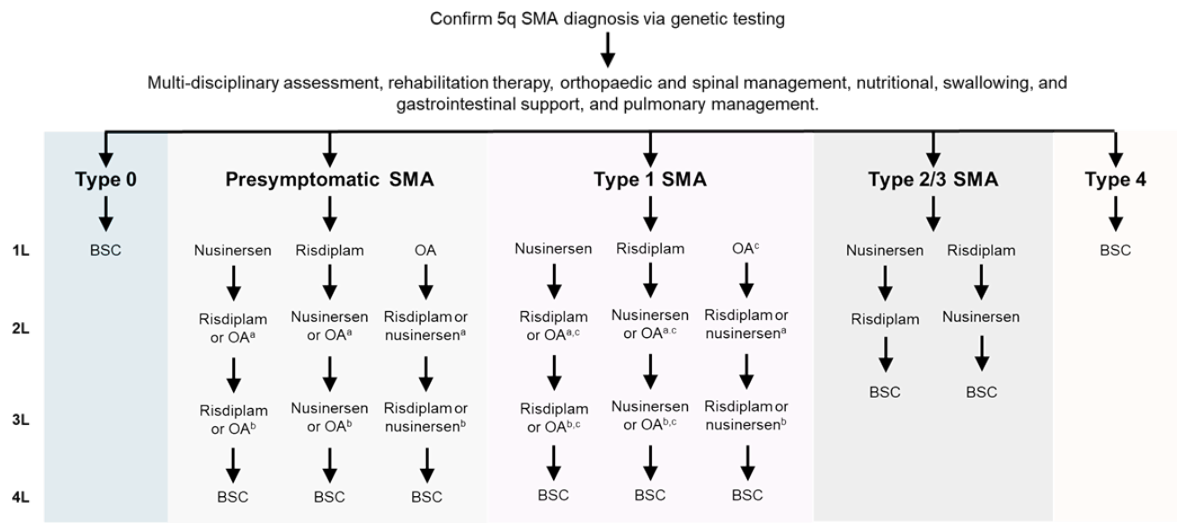
One of these therapies, nusinersen, became available in the UK through a special program in 2017 (known as the expanded access program [EAP]) [17]. It was initially offered for the most severe form of SMA (Type 1) and was provided for free by Biogen (the manufacturer of nusinersen). Later, in 2018, an urgent commissioning policy was implemented for NHS England to reimburse the administration costs for nusinersen provided by the EAP [18].

In 2019, NICE assessed nusinersen for people with types 1, 2, and 3 SMA and presymptomatic SMA. The clinical trial evidence showed that nusinersen improved a range of outcomes that are important to people with infantile- and later-onset SMA and, at the time, that there was some evidence that nusinersen is effective for presymptomatic SMA. However, there was no long-term evidence, so the long-term benefits were highly uncertain. As such, nusinersen was made available to people with type 1, 2 and 3 SMA and presymptomatic SMA as part of a 5-year MAA, while data to address the uncertainties about the benefits of nusinersen was collected [1].

In 2020, another treatment called onasemnogene abeparvovec (Zolgensma), was licensed. It's a gene therapy designed to help SMA patients who have certain genetic mutations. In 2021, NICE recommended it as an option for 5q SMA with a bi-allelic mutation in the SMN1 gene for type 1 SMA in babies aged 12 months and younger. NHS England expanded this eligibility criteria to include children of any age weighing up to 21 kg. In April 2023, NICE recommended onasemnogene abeparvovec for presymptomatic individuals with SMA [19,20].

Also in 2021, Risdiplam (Evrysdi), an oral medication, was licensed for SMA treatment. It's used for patients with Type 1, 2, or 3 SMA, as well as presymptomatic patients with 1-4 SMN2 copies. Similar to nusinersen, risdiplam was made available as part of an MAA for SMA types 1, 2, and 3 due to uncertainty in the long-term clinical effectiveness. Initially, there was an age restriction for use only in patients 2 months and older, but it was lifted in 2023 [21].

These treatments represent significant progress in SMA care and provide hope for better outcomes for patients and families affected by the condition. A schematic of the possible treatment pathway is shown in the figure below:



2d) Patient-based evidence (PBE) about living with the condition

Context:

- **Patient-based evidence (PBE)** is when patients input into scientific research, specifically to provide experiences of their symptoms, needs, perceptions, quality of life issues or experiences of the medicine they are currently taking. PBE might also include carer burden and outputs from patient preference studies, when conducted in order to show what matters most to patients and carers and where their greatest needs are. Such research can inform the selection of patient-relevant endpoints in clinical trials.

In this section, please provide a summary of any PBE that has been collected or published to demonstrate what is understood about **patient needs and disease experiences**. Please include the methods used for collecting this evidence. Any such evidence included in the SIP should be formally referenced wherever possible and references included.

Living with Spinal Muscular Atrophy (SMA) or caring for someone who does brings unique challenges and experiences. Recent research, especially on treatments like Nusinersen, has given us valuable insights into these experiences, aiming to make them a central part of scientific discussions and healthcare improvements.

- Talking and Listening: By conducting interviews and surveys, researchers have gathered detailed stories and experiences from patients and their families. This qualitative method helps understand the personal and emotional aspects of living with SMA.
- Measuring and Assessing: Using tools like the PedsQ™ Family Impact Module and the EuroQol EQ-5D, researchers quantitatively measure the quality of life and the impact of SMA on both patients and caregivers. These tools help turn personal experiences into data that can guide improvements in care.
- Patients and caregivers have contributed to multiple studies that explored the impact of SMA on health-related quality of life, using tools such as the PedsQL and EQ-5D, and these have shown the debilitating impact of the disease. For example, a study by Pena-Longobardo and colleagues analysed the quality of life of 34 people in the UK with types 1 to 3 SMA[22]. The study quantified the impact of the disease by measuring utility, which is an assessment of health-related quality of life that uses a scale of 0 to 1 (in which 0 is equivalent to death and 1 is equivalent

to perfect health). The average utility score in the study was 0.167 and this indicates the large negative impact that SMA can have on those with the disease.

What You and Your Families Have Shared

- The Impact on Families: Caregiving for someone with SMA can be more than a full-time job[23] and it often involves grandparents and extended families. Caregivers who have shared their stories describe the physical and emotional strain, financial challenges, and how the severity of SMA affects their lives.
- The Role of Treatments Like Nusinersen: While treatments offer hope, they also come with their own challenges. Families have noted both potential benefits and difficulties, especially regarding how these treatments affect the well-being of caregivers.

Caregivers' Experiences

- Beyond Full-Time Care: The amount of time and effort caregivers dedicate is immense, often surpassing the demands of many other conditions. This dedication underlines the necessity for stronger social support networks to help caregivers maintain their employment and participate in social activities[24].
- Quality of Life: Caregivers often experience a significant impact on their own health and well-being, with many facing challenges that exceed those seen in other severe illnesses. The stories you have shared highlight the deep emotional and physical toll of caregiving in SMA, emphasizing the need for comprehensive support systems.

SECTION 3: The treatment

Note to authors: Please complete each section with a concise overview of the key details and data, including plain language explanations of any scientific methods or terminology. Please provide all references at the end of the template. Graphs or images may be used to accompany text if they will help to convey information more clearly.

3a) How does the new treatment work?

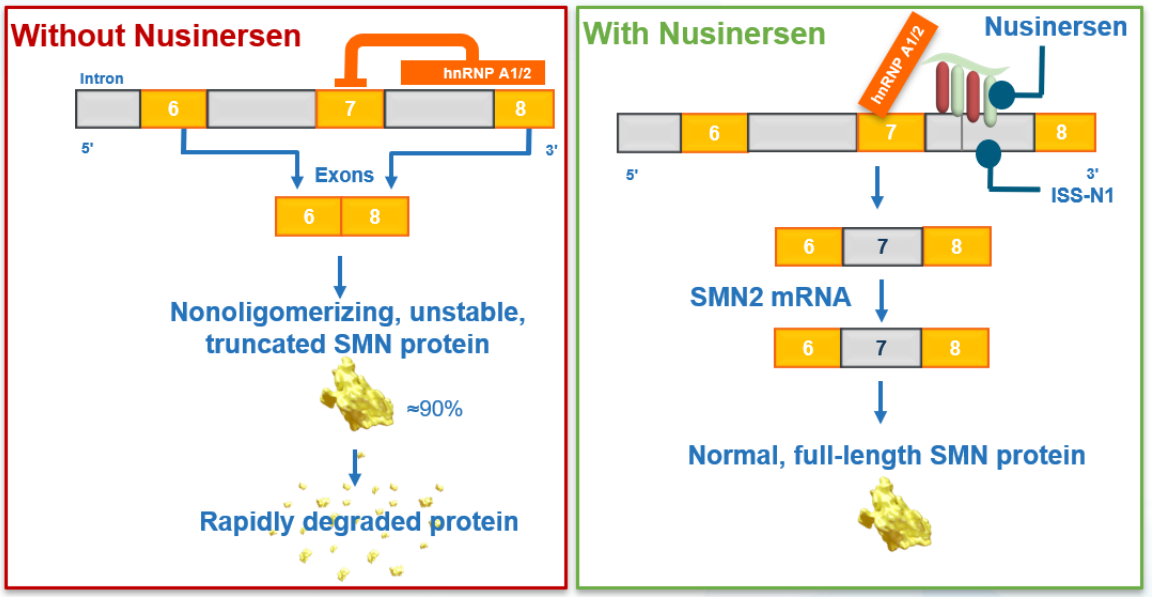
What are the important features of this treatment?

Please outline as clearly as possible important details that you consider relevant to patients relating to the mechanism of action and how the medicine interacts with the body

Where possible, please describe how you feel the medicine is innovative or novel, and how this might be important to patients and their communities.

If there are relevant documents which have been produced to support your regulatory submission such as a summary of product characteristics or patient information leaflet, please provide a link to these.

Mechanism:
Nusinersen, an antisense oligonucleotide (ASO), alters SMN2 pre-mRNA splicing, thereby increasing functional SMN protein production, crucial for motor neuron function and survival. SMA arises from SMN1 gene mutations, leading to insufficient SMN protein. Although all SMA patients have at least one SMN2 gene copy, it inherently produces insufficient functional protein. Nusinersen enhances SMN production from SMN2, partly offsetting the SMN1 loss and providing therapeutic benefits like improved motor function and potentially extended survival[25].



Key Aspects of Nusinersen:

- Nusinersen increases SMN production by targeting the SMN2 gene production of SMN protein.
- The therapy is applicable to a wide SMA patient range, covering presymptomatic to various onset forms of the disease.
- Nusinersen is administered via intrathecal injections.
- Its effectiveness is supported by comprehensive clinical trials, showing positive impacts on motor milestones, survival rates, and hospitalisation reduction for SMA patients.

Significance:
Nusinersen introduced a novel therapeutic approach, shifting from solely symptomatic management to addressing the genetic basis of SMA. This shift not only enhanced motor function and survival prospects but also reshaped the treatment landscape for SMA when it was introduced, offering a potentially life-altering option for affected individuals and families. Its broad applicability and the possibility of early intervention underscore nusinersen's role in transforming SMA management, aligning with better patient outcomes and quality of life improvements.

Additionally, the summary of product characteristics can be found at:
https://www.medicines.org.uk/emc/product/2715

The patient information leaflet can be found at:
https://www.medicines.org.uk/emc/files/pil.2715.pdf

3b) Combinations with other medicines

Is the medicine intended to be used in combination with any other medicines?

- Yes / No

If yes, please explain why and how the medicines work together. Please outline the mechanism of action of those other medicines so it is clear to patients why they are used together.

If yes, please also provide information on the availability of the other medicine(s) as well as the main side effects.

If this submission is for a combination treatment, please ensure the sections on efficacy (3e), quality of life (3f) and safety/side effects (3g) focus on data that relate to the combination, rather than the individual treatments.

No, the marketing authorisation for nusinersen doesn't include using it with other treatments for SMA. However, it's essential to recognise that SMA management is continuously evolving. Studies like RESPOND and ASCEND are looking into whether using Nusinersen in combination with, or after, other treatments could have benefits for patients.

- The RESPOND study is investigating the use of nusinersen in patients who have received gene therapy with onasemnogene abeparvovec (Zolgensma®) but show suboptimal clinical progress. It explores whether adding Nusinersen treatment could help these patients further, aiming to see how the two treatments work together when gene therapy alone isn't enough [26].
- Similarly, the ASCEND study investigates the use of higher doses of Nusinersen in patients who have previously been treated with risdiplam (Evrysdi®), another SMA medication. This research aims to understand if sequencing different SMA treatments can lead to better results, especially for patients with later-onset SMA who are non-ambulatory [27].

3c) Administration and dosing

How and where is the treatment given or taken? Please include the dose, how often the treatment should be given/taken, and how long the treatment should be given/taken for.

How will this administration method or dosing potentially affect patients and caregivers? How does this differ to existing treatments?

How Nusinersen Is Given [28]:
Nusinersen is given by injecting it directly into the cerebrospinal fluid (CSF) through a procedure called intrathecal bolus injection via lumbar puncture. This means the medication is delivered directly to the nervous system through a needle inserted in the lower back during a lumbar puncture.

Treatment Schedule [28]:
At the start, patients receive four loading doses of nusinersen on days 0, 14, 28, and 63. After that, they get a maintenance dose every 4 months. Each dose, whether during the loading phase or for maintenance, is 12 mg (5 ml).

How It Affects Patients and Caregivers:
Using intrathecal administration means patients need to go to clinics for lumbar puncture procedures, which might be inconvenient. While it's less frequent than daily treatments, it still requires regular visits to medical facilities.

Comparison to Other Treatments:
Unlike pills or injections into the vein, giving nusinersen through the spine may seem more invasive, but it ensures the drug goes straight to the central nervous system, targeting the motor neurons directly. This differs from other treatments like risdiplam, which is taken by mouth, or onasemnogene abeparvovec, a gene therapy given in a one-time infusion into the vein. Each treatment has its pros and cons, so choosing the right one depends on what works best for each patient and their lifestyle.

3d) Current clinical trials

Please provide a list of completed or ongoing clinical trials for the treatment. Please provide a brief top-level summary for each trial, such as title/name, location, population, patient group size, comparators, key inclusion and exclusion criteria and completion dates etc. Please provide references to further information about the trials or publications from the trials.

Two completed pivotal trials; ENDEAR and CHERISH in addition to a long-term extension study, SHINE (Note earlier phase studies e.g. CS3A, CS1, CS10, CS2 and CS12 are not documented here).

ENDEAR Study Overview

- Sites: Conducted in 31 sites 13 countries, including the US, UK, Canada, among others.
- Design: This Phase III trial tested nusinersen against a placebo (sham procedure) in infants with Type I SMA, using a double-blind method where neither participants nor researchers knew who received the actual treatment.
- Key inclusion criteria: a confirmed diagnosis of SMA with two SMN2 gene copies, symptom onset before 6 months of age, adequate nutrition, adherence to SMA care guidelines, and absence of central nervous system complications
- Key exclusion criteria: low oxygen levels during screening, early onset of SMA symptoms, brain or spinal cord diseases affecting assessments and prior history of gene therapy or similar treatments.
- Intervention: Participants received nusinersen through spinal injections, following an initial loading phase and subsequent maintenance doses (n=80).
- Control Group: A sham procedure mimicking the treatment was performed on a separate group for comparison (n=41).
- Duration: The trial spanned 13 months.
- Primary Objectives: Evaluations focused on motor function improvements and survival without permanent ventilation.
- Secondary Objectives: Included survival rates, need for permanent ventilation, and other health indicators.

Further information on ENDEAR can be found at:
https://www.clinicaltrials.gov/study/NCT02193074

CHERISH Study Overview

- Sites: Conducted in 24 sites in 10 countries, including the US, Japan, and several in Europe.
- Design: This Phase III trial tested nusinersen against a placebo (sham procedure) in patients with Type 2 or 3 SMA, using a double-blind method where neither participants nor researchers knew who received the actual treatment.
- Inclusion criteria: confirmed genetic diagnosis of 5q SMA, onset of symptoms after 6 months of age, age between 2 to 12 years, ability to sit independently but never walk independently, HFMSE score ≥10 and ≤54 or lower, estimated life expectancy of over 2 years, and adequate contraception for reproductive-age patients.
- Exclusion criteria: respiratory insufficiency, the need for gastric feeding tube, severe contractures or scoliosis, recent hospitalization or planned surgery, history of brain/spinal cord disease, prior nusinersen dosing, and history of other disease modifying therapies.
- Intervention: Nusinersen was administered through spinal injections, with an initial loading phase followed by a maintenance dose (n=84).

- Control Group: A sham procedure mimicking the treatment was performed on a separate group for comparison (n=42).
- Duration: Planned for 15 months.
- Primary Objectives: The study primarily looked at changes in motor function as measured by the HFMSE score.
- Secondary Objectives: These included achieving new motor milestones and improvements in other health-related quality of life measures.

Further information on CHERISH can be found at:
https://www.clinicaltrials.gov/study/NCT02292537

Both studies aimed to assess the effectiveness of nusinersen in improving outcomes for SMA patients, with ENDEAR focusing on infantile-onset SMA and the CHERISH on later-onset forms of the disease.

SHINE Study Overview

- Sites: Conducted in 46 sites across 14 countries worldwide, including Australia, Canada, Japan, and the US, among others. These sites had previously participated in at least one other related study.
- Design: This is an open-label extension study, meaning all participants are aware they are receiving the treatment.
- Patient Population: Participants are individuals with SMA who previously took part in other studies like ENDEAR, CHERISH, EMBRACE, CS3A, or CS12.
- Inclusion Criteria: Eligible participants must have completed the previous specified study within the last 16 weeks, have supportive psychosocial circumstances, and consent from parents or legal guardians.
- Exclusion Criteria: Exclusions include new or worsening conditions that may interfere with study participation, significant abnormalities in certain health parameters, and inability or unwillingness to comply with study procedures.
- Intervention: Participants receive nusinersen at a dose of 12 mg via a spinal injection every four months. A loading dose may be required for patients transitioning from previous studies on sham control.
- Permitted and Disallowed Concomitant Medication: Participants may receive supportive care medications as needed, but other experimental SMA treatments are prohibited during the study.
- Efficacy Analyses: The study included a number of secondary efficacy endpoints including assessments such as survival rates, achievement of motor milestones, changes in motor function, growth parameters, and quality of life assessments.
- Safety Analyses: The study was primarily a safety study with assessments involve monitoring adverse events, physical examinations, vital signs, and laboratory tests.
- Pre-planned Subgroups: Analysis includes separate evaluation of infantile-onset and later-onset populations, with subgroup analyses based on age at first dose and disease duration.

Further information on SHINE can be found at:
https://www.clinicaltrials.gov/study/NCT02594124

Four ongoing studies; NURTURE, DEVOTE, RESPOND & ACSEND

Study Name: NURTURE

- Sites: Conducted at 15 sites across 7 countries including the US, Germany, Italy, and others.
- Objective: The study aimed to evaluate the impact of nusinersen, on pre-symptomatic infants diagnosed with SMA.

- Study Design: This is an open-label study, meaning all participants are aware they are receiving the treatment.
- Inclusion Criteria: Infants under 6 weeks old with genetically diagnosis and presymptomatic SMA, who were in good health and meeting growth milestones, were eligible.
- Exclusion Criteria: Infants with certain health conditions or prior treatments were not eligible for participation.
- Intervention: Nusinersen was administered through spinal injections, with an initial loading phase followed by a maintenance dose (n=25).
- Primary Objectives: The main focus was to determine the duration without serious respiratory intervention or death.
- Secondary Objectives: Other aspects studied included survival rates, motor skill development, growth, and general health changes.

Further information on NURTURE can be found at:
https://www.clinicaltrials.gov/study/NCT02386553

DEVOTE Trial

- Sites: Conducted at 66 sites across 26 countries including the US, UK, Canada among others
- Design/ Intervention: Escalating dose, randomised, controlled study.
    - Part A (complete):
        - Open-label study in later-onset SMA.
        - Evaluates safety and tolerability of higher dosing regimen of nusinersen.
        - Patients receive 3 loading doses of intrathecal 28 mg nusinersen at 14-day intervals, followed by 28 mg maintenance doses every 4 months.
        - Safety data indicates adequate tolerability of higher dose.
        - Although efficacy was not the primary focus, most patients showed motor function improvement or stabilisation.
    - Part B:
        - Pivotal, randomised, double-blind, active-controlled study.
        - Enrollment complete, with 126 patients having infantile- or later-onset SMA.
        - Randomized (1:2) to receive either approved 12 mg dose or higher dose of nusinersen.
        - Higher dose consists of two loading doses (50 mg) 14 days apart, followed by maintenance doses (28 mg) every 4 months.
    - Part C:
        - Initiated based on favorable safety findings from Part B.
        - Evaluates safety of transitioning from approved maintenance dose (12 mg) to higher loading dose (50 mg) and maintenance dose (28 mg).
- Primary Objectives:
    - Assess the safety and tolerability of higher doses of intrathecal nusinersen in SMA patients (Parts A and C).
    - Evaluate the clinical efficacy of higher doses of intrathecal nusinersen in SMA patients, measured by change in CHOP-INTEND total score (Part B).
- Secondary Objectives:
    - Examine the clinical efficacy of higher doses of intrathecal nusinersen in SMA patients (Parts A, B, and C).

- Investigate the effects of higher doses of intrathecal nusinersen in SMA patients (Parts A and C).
- Evaluate the safety and tolerability of higher doses of intrathecal nusinersen in SMA patients.
- Compare the effects of higher doses of intrathecal nusinersen with the currently approved dose in SMA patients (Part B).

Further information on DEVOTE can be found at:
https://www.clinicaltrials.gov/study/NCT04089566

RESPOND Study

- Sites: Conducted at 15 sites across 5 countries including the US, Germany and Italy among others
- Design: A phase 4 study among patients with SMA who previously received onasemnogene abeparvovec (Zolgensma)
- Intervention: Nusinersen was administered through spinal injections, with an initial loading phase followed by a maintenance dose
- Key inclusion criteria: genetic confirmation of 5q SMA, SMN2 copy number of at least 1, age up to 36 months at the first nusinersen dose, prior receipt of onasemnogene abeparvovec at least 2 months before the first nusinersen dose, and suboptimal clinical status as determined by the investigator.
- Key exclusion criteria: prior exposure to nusinersen, severe side effects from onasemnogene abeparvovec, recent use of investigational drugs, biological agents, or devices, and any previous treatments for SMA except onasemnogene abeparvovec given as part of an investigational study.
- Primary objective: evaluate the clinical outcomes in terms of total HINE-2 score.
- Secondary objective: evaluate the safety and tolerability, clinical outcomes and pharmacodynamics in terms of adverse events, changes in clinical laboratory parameters, electrocardiograms, and vital signs. Additionally, participants' achievement of motor milestones and changes in motor function scores (CHOP INTEND, HFMSE, RULM) and time to death or need for permanent ventilation.

Further information on RESPOND can be found at:
https://www.clinicaltrials.gov/study/NCT04488133

ASCEND Trial

- Sites: Conducted at 29 sites across 5 countries including the US, Germany and Italy among others
- Design: A phase 4 study among patients with SMA who previously received risdiplam (Evrysdi)
- Intervention: Two loading doses of 50 mg each, around 2 weeks apart, followed by maintenance doses of 28 mg every 4 months during the core study. After this period, they may have the option to continue receiving 28 mg maintenance doses every 4 months for up to 2 years in the optional long-term extension.
- Key inclusion criteria: Participants must have genetic confirmation of 5q SMA, later-onset SMA with symptom onset after 6 months of age, aged 15 to 50 years, body weight >20 kg, nusinersen-naive participants must have had prior treatment with risdiplam for ≥6 months before enrollment, nusinersen-experienced participants must have stopped nusinersen for ≥16 months and must have been on risdiplam for ≥12 months before enrollment and able to perform the age-appropriate functional assessments in the study..
- Key exclusion criteria: Participants with recent major illness, history of bacterial meningitis, viral encephalitis, tracheostomy or permanent ventilation, noninvasive ventilation necessity, certain medical histories or conditions, pregnancy or

breastfeeding, recent investigational treatment, or prior gene therapy for SMA are excluded.

- Primary objective: Evaluate the clinical outcomes in terms of total change its total revised upper limb module (RULM) score.
- Secondary objective: evaluate the safety and tolerability, clinical outcomes and pharmacodynamics and pharmacokinetics.

Further information on ASCEND can be found at:
https://www.clinicaltrials.gov/study/NCT05067790

3e) Efficacy

Efficacy is the measure of how well a treatment works in treating a specific condition.

In this section, please summarise all data that demonstrate how effective the treatment is compared with current treatments at treating the condition outlined in section 2a. Are any of the outcomes more important to patients than others and why? Are there any limitations to the data which may affect how to interpret the results? Please do not include academic or commercial in confidence information but where necessary reference the section of the company submission where this can be found.

The summary of efficacy results from the ENDEAR, CHERISH, SHINE, and NURTURE studies demonstrates the effectiveness of nusinersen in treating Spinal Muscular Atrophy (SMA) across different patient populations, from early symptomatic to later-onset forms, and even presymptomatic infants. A summary highlighting the key findings is provided below:

ENDEAR (Infantile-Onset SMA) [14]

- Significant Findings: Demonstrated that 51% of nusinersen-treated infants met the primary endpoint of motor milestone response, compared with 0% in the sham group, and there was a significant 47% reduction in the risk of death or permanent ventilation compared to sham treatment.
- Patient Impact: The results indicate improved survival without permanent ventilation and enhanced motor functions, directly affecting the quality of life and independence compared with no treatment.

CHERISH (Later-Onset SMA) [15]

- Significant Findings: Showed improved motor functions in patients, with a mean improvement in HFMSE and RULM scores significantly higher in the nusinersen group compared to sham.
- Patient Impact: The improvements in HFMSE and RULM scores suggest enhanced physical abilities and potential for greater independence in daily activities compared with no treatment.

SHINE (Open-Label Extension) [29,30]

- Significant Findings: Continued nusinersen treatment led to sustained improvements in survival, motor milestones, and other functional measures over the long term for both infantile-onset and later-onset SMA patients. Earlier initiation of nusinersen following symptom onset was associated with superior outcomes.
- Patient Impact: The long-term data support the enduring benefits of nusinersen, reinforcing its role in managing SMA and the importance of early and sustained treatment.

NURTURE (Presymptomatic Infants) [31]

- Significant Findings: None of the presymptomatic infants treated with nusinersen required permanent ventilation, and some patients achieved WHO motor

milestones within normal developmental timeframes, with improvements in CHOP INTEND and HFMSE scores.
- Patient Impact: The results underscore the potential for nusinersen to alter the disease course dramatically when initiated before symptoms develop, potentially allowing children to achieve normal motor milestones.

Importance of Outcomes to Patients:
The results from studies show that nusinersen may have a positive impact on patients' lives by helping them live longer, improving their ability to move, and making their daily life better. For families dealing with SMA, treatments that boost movement abilities, reduce hospital visits, and increase life expectancy are important because they mean more independence and a better quality of life.

Limitations of Data:
Even though the data support the effectiveness of nusinersen, there are some limitations. It can be hard to measure how well treatments work in diseases that get worse over time. Also, there might be biases in open-label studies where everyone knows who is getting the treatment, and we still need more long-term data to know how well the treatment works over many years. Plus, what works in clinical studies might not always be the same in a real-world clinical setting because of differences in treatment access, healthcare provision and patient characteristics.

Interpretation of Results:
While nusinersen shows benefits for different types and stages of SMA, not everyone responds the same way. This means treatments should be tailored to each person. The data also highlight how important it is to start treatment early, ideally even before symptoms show up, to get the best results.

3f) Quality of life impact of the medicine and patient preference information

What is the clinical evidence for a potential impact of this medicine on the quality of life of patients and their families/caregivers? What quality of life instrument was used? If the EuroQol-5D (EQ-5D) was used does it sufficiently capture quality of life for this condition? Are there other disease specific quality of life measures that should also be considered as supplementary information?

Please outline in plain language any quality of life related data such as **patient reported outcomes (PROs).**

Please include any **patient preference information (PPI)** relating to the drug profile, for instance research to understand willingness to accept the risk of side effects given the added benefit of treatment. Please include all references as required.

Quality of Life Instruments Used
- Various tools, including the Paediatric Quality of Life Inventory (PedsQL) and Assessment of Caregiver Experience with Neuromuscular Disease (ACEND), were used to understand how SMA affects daily life, function, and caregiver burden [29].
- The PedsQL was specifically used in the SHINE study to gauge quality of life in patients with infantile-onset and later-onset SMA, focusing on children's health-related quality of life.
- It is important to note that obtaining an accurate measure of Quality of Life (QoL) in children, particularly those with conditions like Spinal Muscular Atrophy (SMA), presents unique challenges. Children's ability to articulate their experiences and feelings can vary significantly by age, developmental stage, and the severity of their condition. Additionally, SMA impacts patients in ways that are broad and multifaceted, affecting physical capabilities, emotional well-being, and social participation. These nuances make it difficult for any single instrument, such as the EQ-5D, to fully capture the comprehensive effects of SMA on a child's life.

Recognising these challenges is crucial in understanding the selection and application of the following instruments:

Quality of Life Related Data

- In SHINE, ongoing treatment with nusinersen showed potential to maintain or improve daily life and function over time, with caregivers reporting better caregiving and emotional well-being through ACEND scores.

Disease-Specific Quality of Life Measures

- While the EQ-5D is a generic instrument for assessing health outcomes, SMA-specific measures such as the Hammersmith Functional Motor Scale Expanded (HFMSE) and the CHOP INTEND (for infantile onset) provide more detailed insights into the physical capabilities and progression, which directly impacts quality of life. These disease-specific tools, combined with broader QoL instruments like PedsQL and ACEND, offer a more comprehensive view of the treatment's impact.

3g) Safety of the medicine and side effects

When NICE appraises a treatment, it will pay close attention to the balance of the benefits of the treatment in relation to its potential risks and any side effects. Therefore, please outline the main side effects (as opposed to a complete list) of this treatment and include details of a benefit/risk assessment where possible. This will support patient reviewers to consider the potential overall benefits and side effects that the medicine can offer.

Based on available data, please outline the most common side effects, how frequently they happen compared with standard treatment, how they could potentially be managed and how many people had treatment adjustments or stopped treatment. Where it will add value or context for patient readers, please include references to the Summary of Product Characteristics from regulatory agencies etc.

Most Common Side Effects [28]:

- Headache, vomiting, and back pain are the most common adverse events associated with the administration of nusinersen. These adverse events are considered related to lumbar puncture and mostly occur within 72 hours after the procedure. For a more detailed overview of safety data, please see the summary of product characteristics for nusinersen [insert link/ref to SmPC]
- Among the presymptomatic SMA population, no adverse events (AEs) were considered to be related to nusinersen over a median follow-up of 4.9 years. In symptomatic patients with early-onset and later-onset SMA who entered the long-term SHINE extension study, nusinersen was well tolerated and no specific safety concerns were detected in the study. AEs were generally consistent with underlying SMA or with the lumbar puncture procedure.

3h) Summary of key benefits of treatment for patients

Issues to consider in your response:

- Please outline what you feel are the key benefits of the treatment for patients, caregivers and their communities when compared with current treatments.
- Please include benefits related to the mode of action, effectiveness, safety and mode of administration
-

Key Benefits of Nusinersen:

For Patients:

- Mode of Action: Nusinersen was the first approved treatment which targeted the underlying cause of SMA, helping produce a vital protein for motor neuron health, which can slow or stop progression of the disease.
- Effectiveness: Clinical trials show nusinersen can improve motor function, survival rates, and achievement of milestones in SMA patients, offering greater independence and quality of life.
- Safety profile: nusinersen has demonstrated an acceptable safety profile across all SMA types. . The most common adverse events associated with the administration of nusinersen were considered related to the lumbar puncture procedure.

For Caregivers and Families:

- Quality of Life: Improvements in motor function may reduce caregiver stress, enhancing life quality for both patients and families.

For Communities:

- Healthcare Resource Utilisation: It may lower the need for hospitalisations and intensive care, reducing healthcare resource usage over time.

Compared with Current Treatments:

- Innovative Mechanism: Unlike symptom management, nusinersen targets the underlying cause of SMA.
- Broad Applicability: Effective across various SMA types and stages, it provides a versatile treatment option.
- Long-term Benefits: Extension studies show sustained benefits, offering hope for continued disease control.

In summary, the introduction of disease modifying therapies like nusinersen has led to a change in thinking in the management of SMA, benefiting patients, caregivers, families, and communities by improving disease management and reducing burden.

3i) Summary of key disadvantages of treatment for patients

Issues to consider in your response:

- Please outline what you feel are the key disadvantages of the treatment for patients, caregivers and their communities when compared with current treatments. Which disadvantages are most important to patients and carers?
- Please include disadvantages related to the mode of action, effectiveness, side effects and mode of administration
- What is the impact of any disadvantages highlighted compared with current treatments

Side Effects:

- Procedure-Related Risks: Receiving nusinersen involves spinal injections, which can cause headaches, back pain, or rare issues like meningitis.
- Serious Side Effects: Bleeding problems and kidney damage have been observed after administration of other antisense oligonucleotide therapies. Further testing may be required if your doctor is concerned about this.

Mode of Administration:

- Spinal Injections: These injections can be unpleasant, especially for young children or those with spinal issues, making treatment more complicated.
- Hospital Visits: Patients need to visit hospitals for these injections, which can be inconvenient for families.

Summary:

- The main downsides come from the injection process and side effects related to the injection procedure.. While other SMA treatments might be less invasive or more long-lasting, there are different benefits and risks associated with each therapy and the choice depends on each patient's needs and discussions with their doctors.

3i) Value and economic considerations

Introduction for patients:

Health services want to get the most value from their budget and therefore need to decide whether a new treatment provides good value compared with other treatments. To do this they consider the costs of treating patients and how patients' health will improve, from feeling better and/or living longer, compared with the treatments already in use. The drug manufacturer provides this information, often presented using a health economic model.

In completing your input to the NICE appraisal process for the medicine, you may wish to reflect on:

- The extent to which you agree/disagree with the value arguments presented below (e.g., whether you feel these are the relevant health outcomes, addressing the unmet needs and issues faced by patients; were any improvements that would be important to you missed out, not tested or not proven?)
- If you feel the benefits or side effects of the medicine, including how and when it is given or taken, would have positive or negative financial implications for patients or their families (e.g., travel costs, time-off work)?
- How the condition, taking the new treatment compared with current treatments affects your quality of life.

Three separate health economic models were created to cover different populations of SMA: presymptomatic SMA, SMA Type 1, and a combined model for SMA Types 2 and 3. This distinction is crucial because SMA's progression and impact can vary widely across these types. The models are Markov state transition models.

For this case, the models include various states representing SMA progression, based on gross motor function milestones defined by the World Health Organization (not sitting, sitting without support, standing with assistance and walking independently). Permanent ventilation (PV) is also included as a state, reflecting severe respiratory issues, particularly in presymptomatic and Type 1 SMA. Death is considered a final state across all models. By structuring the model this way, it aims to realistically capture the SMA experience and the potential impact of treatments like nusinersen on altering disease progression.

Nusinersen has been shown to extend life in some SMA subtypes. This extension of life is achieved primarily by delaying the progression of the disease, reducing the severity of the disease and its complications, and enabling the attainment of motor milestones that are not typically experienced in the natural history of SMA. The ability of patients to reach these milestones indicates a significant alteration in the disease's typical trajectory, directly impacting longevity and quality of life.

The economic model incorporates outcomes from several pivotal trials to assess the effectiveness of these treatments

- NURTURE trial data (ongoing) was used up to 5 years, focusing on the presymptomatic stage of SMA.
- ENDEAR and SHINE trials provided data for up to 6 years for Type 1 SMA patients.

- CHERISH and SHINE trials, offering insights into the effects of treatment over a period of 7 years for SMA Types 2 and 3.
- The model uses HINE-2 scores, WHO motor milestones, PV, and survival rates from trials up to 7 years to assess treatment impacts on motor function and lifespan.
- Post-trial, it calculates long-term effects, aligning with SMA's natural progression, to estimate life-long benefits despite limited direct data.
- The treatment improves quality of life (QoL) by enabling patients to achieve or maintain motor milestones beyond what is observed in the natural progression of SMA, as indicated by published EQ-5D data. To capture the full scope of benefits, including those not fully represented by WHO motor milestones like enhanced upper limb movements in patients who can sit without support, an "on-treatment" utility increment is assumed. This method acknowledges the direct impact on QoL, although it may not encompass every aspect of the condition or its treatment effects on patients' lives.
- The new treatment introduces both positive and negative cost implications for the healthcare service, fully encapsulated within the model. This encompasses direct healthcare costs like drug acquisition, administration, specialist visits, and hospitalisations. Differences in how the medicine is administered compared to existing treatments could also impact patient experience and the associated costs.
- These aspects are considered in evaluating the overall cost-effectiveness of the treatment, ensuring a comprehensive view of its financial impact on the health service.

Cost-Effectiveness Results: The model predicts improvements in overall survival and quality-adjusted life years (QALYs), with the incremental cost-effectiveness ratio (ICER) suggesting nusinersen is a cost-effective option for a subset of patients with 5q SMA. Specific figures for survival, QALY gains, and ICER were derived from the model, reflecting the drug's value in extending life and improving quality of life within accepted cost thresholds.

3j) Innovation

NICE considers how innovative a new treatment is when making its recommendations.
If the company considers the new treatment to be innovative please explain how it represents a 'step change' in treatment and/ or effectiveness compared with current treatments. Are there any QALY benefits that have not been captured in the economic model that also need to be considered (see section 3f)

The introduction of nusinersen into the therapeutic landscape has addressed an unmet need by providing the first disease-modifying treatment for SMA, targeting the underlying cause of the disease rather than merely managing symptoms. Below are key points that highlight its innovative impact and potential QALY (Quality-Adjusted Life Year) benefits that might not be fully captured in economic models.

Innovation in Treatment and Effectiveness

- Targeted Genetic Mechanism: Nusinersen's mechanism of action directly targets the underlying cause of SMA by modifying the splicing of the SMN2 gene to increase the production of functional SMN protein, essential for motor neuron survival. As the first disease modifying treatment for SMA, nusinersen offered hope for patients with this condition.

- Broad Applicability Across SMA Types: nusinersen is licensed for use in a wide range of patients, from infants to adults, and across all types of SMA, making it a versatile treatment option.
- Evidence of Effectiveness: Clinical trials have demonstrated improvements in motor milestones, survival rates, and motor function across different SMA types and stages, including presymptomatic, infantile and later-onset SMA. These benefits represent a substantial improvement over supportive care, which was the standard treatment before nusinersen.
-

3k) Equalities

Are there any potential equality issues that should be taken into account when considering this condition and this treatment? Please explain if you think any groups of people with this condition are particularly disadvantaged.
Equality legislation includes people of a particular age, disability, gender reassignment, marriage and civil partnership, pregnancy and maternity, race, religion or belief, sex, and sexual orientation or people with any other shared characteristics

More information on how NICE deals with equalities issues can be found in the NICE equality scheme
Find more general information about the Equality Act and equalities issues here

Geographic Location and Socioeconomic Status

- Access to Treatment Centres: The requirement for intrathecal administration of nusinersen may disadvantage individuals living in remote areas or those with limited access to specialized healthcare facilities capable of administering the treatment. Additionally, socioeconomic factors may influence an individual's ability to travel for treatment, potentially creating disparities in access based on geographic location and economic status.

SECTION 4: Further information, glossary and references

4a) Further information

Feedback suggests that patients would appreciate links to other information sources and tools that can help them easily locate relevant background information and facilitate their effective contribution to the NICE assessment process. Therefore, please provide links to any relevant online information that would be useful, for example, published clinical trial data, factual web content, educational materials etc.
Where possible, please provide open access materials or provide copies that patients can access.

Response:

Further information on NICE and the role of patients**:**

- Public Involvement at NICE Public involvement | NICE and the public | NICE Communities | About | NICE
- NICE's guides and templates for patient involvement in HTAs Guides to developing our guidance | Help us develop guidance | Support for voluntary and community sector (VCS) organisations | Public involvement | NICE and the public | NICE Communities | About | NICE

- EUPATI guidance on patient involvement in NICE: https://www.eupati.eu/guidance-patient-involvement/
- EFPIA – Working together with patient groups: https://www.efpia.eu/media/288492/working-together-with-patient-groups-23102017.pdf
- National Health Council Value Initiative. https://nationalhealthcouncil.org/issue/value/
- INAHTA: http://www.inahta.org/
- European Observatory on Health Systems and Policies. Health technology assessment - an introduction to objectives, role of evidence, and structure in Europe: http://www.inahta.org/wp-content/themes/inahta/img/AboutHTA_Policy_brief_on_HTA_Introduction_to_Objectives_Role_of_Evidence_Structure_in_Europe.pdf

SMA specific resources

- SMA UK: https://smauk.org.uk/
- MDUK: https://www.musculardystrophyuk.org/
- TreatSMA: https://treatsma.uk

4b) Glossary of terms

Response:

SIP (Summary of Information for Patients): A plain English summary provided by companies seeking NICE approval for their treatments, aimed at patients participating in the evaluation. It summarizes the company's submission to NICE and is checked for marketing content by NICE's public involvement team.

NICE (National Institute for Health and Care Excellence): An executive non-departmental public body of the Department of Health in England that publishes guidelines in four areas: the use of health technologies within the NHS, clinical practice, guidance for public sector workers on health promotion, and guidance for social care services and users.

Health Technology Assessment International (HTAi) Patient & Citizens Involvement Group (PCIG): A group focused on involving patients and the public in health technology assessment processes.

IJTAHC (International Journal of Technology Assessment in Health Care): A journal publishing research on the methods and findings from health technology assessments.

Generic Name: The standard name of a medicine without any brand name.

Brand Name: The trade name the manufacturer gives a medicine, distinguished from the medicine's generic name.

Spinal Muscular Atrophy (SMA): A genetic disorder that causes muscle weakness and atrophy due to the loss of motor neurons in the spinal cord and brainstem.

5q SMA: A form of spinal muscular atrophy that involves the 5q chromosomal region, affecting the SMN1 gene. It's the most common form of SMA.

Nusinersen (Spinraza): A medication used to treat spinal muscular atrophy, approved based on its ability to increase the production of the SMN protein.

Marketing Authorisation: Approval given by regulatory bodies like MHRA or EMA to market a medicine after assessing its safety, efficacy, and quality.

MHRA (Medicines and Healthcare products Regulatory Agency): The UK government agency responsible for ensuring that medicines and medical devices work and are acceptably safe.

EMA (European Medicines Agency): The agency of the European Union in charge of the evaluation and supervision of medicinal products.

Managed Access Agreement (MAA): An arrangement that allows patients to access treatments not yet fully approved for routine NHS use, under specific conditions and usually while more data is being collected.

SMN (Survival Motor Neuron) Protein: A protein essential for the survival of motor neurons, with insufficient levels leading to SMA.

SMN1 and SMN2 Genes: Genes that produce SMN protein. Mutations in SMN1 cause SMA, while the number of SMN2 copies can influence disease severity.

Orphan Disease: A condition that affects a small percentage of the population, often providing special status for drug development and approval.

Phenotypic Modifier: A genetic or environmental factor that alters how a disease presents in an individual.

Genetic Tests: Procedures used to identify genes and their mutations, including those related to diseases like SMA. They are crucial for diagnosing genetic conditions.

Newborn Screening (NBS): The process of testing newborn babies for certain diseases, including genetic conditions like SMA, to enable early detection and treatment.

National Screening Committee (NSC): A UK body responsible for advising policymakers on aspects of screening policy and the implications for the health care system.

Best Supportive Care (BSC): Medical care provided to improve the quality of life for patients with serious or life-threatening diseases, focusing on symptom management and psychosocial support rather than treating the underlying disease.

Expanded Access Programme (EAP): A programme that allows patients to gain access to investigational or unapproved treatments outside of clinical trials when no comparable or satisfactory alternative therapy options are available.

Onasemnogene Abeparvovec (Zolgensma): A gene therapy treatment for SMA that introduces a functional copy of the SMN1 gene to compensate for the genetic mutation causing the disease.

Risdiplam (Evrysdi): An orally administered medication that modifies the splicing of the SMN2 gene, increasing the production of functional SMN protein for the treatment of SMA.

Drug-Drug Interactions: A situation in which one drug affects the activity of another drug when both are administered together, potentially leading to decreased effectiveness or increased risk of adverse effects.

Contraindications: Conditions or factors that serve as reasons to withhold a certain medical treatment due to the harm it could cause the patient.

Patient-Based Evidence (PBE): Information derived from patient experiences, preferences, and outcomes, often used to inform healthcare decisions and policy-making.

PedsQL™ Family Impact Module: A tool designed to measure the impact of paediatric chronic health conditions on patients and their families in terms of physical, emotional, social, and cognitive functioning.

EuroQol EQ-5D-5L: A standardized instrument used as a measure of health outcome, providing a simple descriptive profile and a single index value for health status.

Antisense Oligonucleotide (ASO): A short, synthetic piece of nucleic acid designed to bind to specific RNA sequences, thereby affecting the expression of genes. Used in treatments like Nusinersen to alter RNA splicing and increase the production of a functional protein.

Intrathecal Injection: A method of delivering medication directly into the cerebrospinal fluid (CSF) surrounding the brain and spinal cord, usually via lumbar puncture.

Cerebrospinal Fluid (CSF): A clear, colourless body fluid found in the brain and spinal cord, which acts as a cushion for the brain's cortex, providing basic mechanical and immunological protection to the brain inside the skull.

Loading Dose: An initial higher dose or schedule of doses of a drug given to quickly achieve a therapeutic level in the bloodstream.

Maintenance Dose: A dose of a drug that maintains or keeps the drug's blood levels within the therapeutic range.

Bolus Injection: A method of drug delivery that involves injecting a medication, typically a liquid, into the body rapidly to immediately raise the concentration of the substance in the bloodstream.

Lumbar Puncture: A medical procedure that involves inserting a needle into the lower part of the spinal column to collect cerebrospinal fluid for diagnostic testing or to deliver medication directly into the CSF.

Gene Therapy: A technique that modifies a person’s genes to treat or prevent disease. In the context of SMA, gene therapy aims to introduce a functional copy of the SMN1 gene to compensate for the genetic mutation causing the disease.

Suboptimal Clinical Progress: A condition where the patient's response to treatment does not meet the expected level of improvement or stabilization as anticipated by clinical standards.

Phase III Trial: A late-stage clinical trial intended to gather more information about the effectiveness and safety of a medication in a larger population, comparing the new treatment against a current standard treatment or a placebo to assess its overall value in clinical practice.

Double-Blind: A study design in which neither the participants nor the researchers know who is receiving the experimental treatment and who is receiving a placebo or control treatment, to prevent bias in the results.

Sham Procedure: A simulated treatment that mimics the actual medical procedure in all ways except for the inclusion of therapeutic intervention. It is used as a control to study the effectiveness of a treatment without the influence of the placebo effect.

Hammersmith Functional Motor Scale Expanded (HFMSE): A scale used to assess motor abilities in individuals with SMA, measuring changes in motor function that may result from treatment.

Open-Label Extension Study: A continuation of a clinical trial where all participants, including those previously on placebo, receive the active treatment. It allows for the collection of additional data on effectiveness and long-term safety.

Open-Label Study: A type of clinical trial in which both the researchers and participants know which treatment is being administered. This approach is often used when it is not feasible to disguise the treatment, such as when comparing the effect of a drug to a surgical procedure.

Phase IV Trial: Post-marketing studies conducted after a treatment has been approved for use by the regulatory authorities. These trials gather additional information on the drug's risks, benefits, and optimal use.

Non-Ambulatory Patients: Individuals who are unable to walk. In the context of SMA clinical trials, this term refers to patients who have lost the ability to walk independently and assesses the efficacy of treatments in improving or stabilizing their condition.

Efficacy: The ability of a product to provide a beneficial effect (as measured in controlled clinical trials) on the disease or condition being treated.

Motor Milestone Response: A measure of significant improvement in motor functions, such as sitting, crawling, or walking, which are critical developmental targets for infants and children.

Primary Endpoint: The main result that is measured at the end of a study to see if the treatment worked (e.g., survival rate, improvement in health condition).

HFMSE (Hammersmith Functional Motor Scale Expanded): A tool used to assess motor function in individuals with SMA, focusing on abilities like sitting, standing, and walking.

World Health Organization (WHO) Motor Milestones: Standard developmental milestones that include physical activities and abilities such as sitting without support, standing, and walking, used to assess the development of infants and children.

CHOP INTEND (Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders): An assessment tool used to measure motor skills in infants with neuromuscular disorders, including those too young or too weak to perform voluntary movements.

Permanent Ventilation: The use of mechanical assistance to support or control breathing for an extended period, often required for individuals with severe respiratory muscle weakness.

Open-Label Extension: A continuation of a clinical trial where all participants, including those previously on placebo, receive the active treatment. It allows for the collection of additional data on the treatment's long-term efficacy and safety.

Sustained Improvements: Ongoing positive changes or benefits from a treatment over an extended period, indicating long-term efficacy.

Durability of Treatment Effects: The length of time the benefits of a treatment last after the treatment is completed.

Functional Measures: Tests or assessments that evaluate an individual's ability to perform tasks or activities that are part of daily living.

Real-World Applicability: The effectiveness and practicality of applying study findings to general clinical practice outside the controlled conditions of clinical trials.
Paediatric Quality of Life Inventory (PedsQL): A standardized tool used to measure the health-related quality of life in children and adolescents across physical, emotional, social, and school functioning.

Assessment of Caregiver Experience with Neuromuscular Disease (ACEND): A questionnaire designed to evaluate the impact of neuromuscular diseases on caregivers, covering aspects such as emotional, physical, and financial burdens.

Quality of Life (QoL): The general well-being of individuals and societies, outlining negative and positive features of life. It is a broad concept encompassing emotional, physical, material, and social well-being.

Patient Reported Outcomes (PROs): Direct reports from patients about how they feel or function in relation to a health condition and its therapy, without interpretation by healthcare professionals or anyone else.

Patient Preference Information (PPI): Data on patient values or preferences regarding specific treatment options, which can inform healthcare decisions and policy making.

Markov Model: A type of statistical model used in health economics to simulate the long-term costs and health outcomes of different treatments over time, based on transitions between health states.

Quality-Adjusted Life Year (QALY): A measure of disease burden, including both the quality and the quantity of life lived. It is used to assess the value of medical interventions.

Incremental Cost-Effectiveness Ratio (ICER): A statistic used in cost-effectiveness analysis to summarize the cost-effectiveness of a healthcare intervention. It represents the additional cost per additional unit of benefit (e.g., QALYs gained) of one intervention over another.

Health Economic Model: A mathematical framework designed to compare the health and economic outcomes of different healthcare interventions over time, often used to inform policy decisions and clinical guidelines.

Health Outcomes: The changes in health resulting from measures or specific health care investments or interventions, including changes in health status, health behaviour, and knowledge.

Utility Increment: An increase in the utility value (reflecting a patient's preference for a particular health state) attributed to treatment effects not directly captured by traditional measures.

Cost-Effectiveness: A measure of the relative costs and outcomes (effects) of two or more courses of action, typically expressed in terms of cost per QALY gained.

Direct Healthcare Costs: Expenses for medical services that result directly from treatment or intervention, such as medication, hospital care, and outpatient visits.

Equalities Issues: Considerations related to ensuring that all individuals have equal opportunity to benefit from treatments, regardless of age, disability, gender, race, or other characteristics.

4c) References

Please provide a list of all references in the Vancouver style, numbered and ordered strictly in accordance with their numbering in the text:

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NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Multiple Technology Appraisal

Nusinersen and risdiplam for treating spinal muscular atrophy (MA review of TA588 and TA755) [ID6195]

Summary of Information for Patients (SIP)

April 2024

File name	Version	Contains confidential information	Date
ID6195_Risdiplam for SMA_SIP	1.0	No	19 April 2024

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Summary of Information for Patients (SIP):

The pharmaceutical company perspective

What is the SIP?

The Summary of Information for Patients (SIP) is written by the company who is seeking approval from NICE for their treatment to be sold to the NHS for use in England. It is a plain English summary of their submission written for patients participating in the evaluation. It is not independently checked, although members of the public involvement team at NICE will have read it to double-check for marketing and promotional content before it is sent to you.

The **Summary of Information for Patients** template has been adapted for use at NICE from the Health Technology Assessment International – Patient & Citizens Involvement Group (HTAi PCIG). Information about the development is available in an open-access IJTAHC journal article.

SECTION 1: Submission summary

1a) Name of the medicine (generic and brand name):

Generic name: Risdiplam **Brand name:** Evrysdi®

1b) Population this treatment will be used by. Please outline the main patient population that is being appraised by NICE:

Patients with a clinical diagnosis of spinal muscular atrophy (SMA) type 1, type 2, or type 3 or with one to four *SMN2* copies

1c) Authorisation: Please provide marketing authorisation information, date of approval and link to the regulatory agency approval. If the marketing authorisation is pending, please state this, and reference the section of the company submission with the anticipated dates for approval.

European Union (EU): Evrysdi® was designated an 'orphan medicine' (a medicine used in rare diseases) on 26 February 2019. Further information on the orphan designation can be found here: ema.europa.eu/medicines/human/orphan-designations/eu3192145. Evrysdi® received a marketing authorisation valid throughout the EU on 26 March 2021. Further information can be found on the agency's website: ema.europa.eu/medicines/human/EPAR/evrysdi. **United Kingdom (UK):** Evrysdi® received a marketing authorisation valid from the Medicines and Healthcare Products Regulatory Agency (MHRA) on 20 May 2021 (1). In December 2023, the MHRA approved a licence extension for Evrysdi® to include people of all ages. This was granted based on the RAINBOWFISH presymptomatic SMA (<2

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months of age) patient population. Before the December 2023 licence extension, risdiplam was indicated only for people 2 months and over.

1d) Disclosures. Please be transparent about any existing collaborations (or broader conflicts of interest) between the pharmaceutical company and patient groups relevant to the medicine. Please outline the reason and purpose for the engagement/activity and any financial support provided:

The following grants were provided to patient groups by Roche relevant to SMA:

- In December 2023, a grant of £3,075 was provided to SMA UK to support their attendance at the SMA Europe conference.
- In September 2023, a grant of £42,350 was given to SMA UK to support their community engagement events. This involved peer to peer events to support different subgroups within SMA (e.g. a family day, an adult day etc.,) with different activities to bring together people living with SMA.
- In September 2023, £2,750 was given to MDUK as a sponsorship for an SMA webinar, which was held in January 2024.
- In June 2023, a £50,000 grant was given to MDUK to support the employment of a project manage to steer forward the newborn screening alliance who are campaigning for SMA newborn screening in the UK.
- In June 2023, a £67,354 grant was provided to SMA UK to support the SMA Care project. For this project, SMA UK have put together a working group of leading SMA consultants and people living with SMA to review current standards of care in the UK, and develop an updated version, in line with the international standards of care for SMA, over the next three years.

SECTION 2: Current landscape

2a) The condition – clinical presentation and impact

Please provide a few sentences to describe the condition that is being assessed by NICE and the number of people who are currently living with this condition in England.

Please outline in general terms how the condition affects the quality of life of patients and their families/caregivers. Please highlight any mortality/morbidity data relating to the condition if available. If the company is making a case for the impact of the treatment on carers this should be clearly stated and explained.

Condition that the medicine plans to treat:

SMA is a recessive genetic disorder. The survival motor neuron 1 (*SMN1)* gene produces the SMN protein. In SMA this gene does not function correctly, so people with SMA do not have adequate SMN protein. This causes symptoms such as severe weakness of the limbs, trunk, bulbar and respiratory muscles secondary to failure to gain and maintain functional motor nerve innervation of skeletal muscles (2). Respiratory failure accounts for the majority of deaths in people with SMA (3).

SMA subtypes and clinical course

SMA is a disease continuum with its subtypes defined by age at onset and the most advanced motor milestone achieved during development, classified as types 0 through 4,

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where type 1 (infantile-onset) and types 2 and 3 (later- onset) represent approximately 99% of all patients.

Type	Onset	Motor function achieved without treatment	Lifespan if untreated
0	Prenatal/foetal	Nil	< 6 months
1	<6 months	Sit with support only	<2 years
2	≥6–<18 months	Sit independently	>2 years
3	≥18–<36 months	Stand and walk	Normal
4	Adult (2nd or 3rd decade)	Walk during adulthood	Normal

How many people have the condition:

The incidence of SMA in Europe is approximately one in every 3,900 to 16,000 births, with type 1 SMA accounting for approximately 60% of cases (4-7). It is estimated that 68 children were born with SMA in the UK in 2022, with an estimated 675 – 1,350 children and adults living with SMA (6).

Effects on quality of life on patients, families and carers:

When left untreated SMA is a devastating and debilitating disease, and is life threatening for individuals with the most severe types. There are a wide range of symptoms and complications that can have detrimental effects on the day-to-day lives of people with SMA and their families (8-12). The progressive nature of the disease with loss of function over the course of months and years requires almost constant adaptation of the environment and leads to increasing disability and handicap for people with SMA. Minor viral respiratory infections or aspiration episodes may become life threatening and require intensive care and significant pulmonary rehabilitation (13-15).

Patients with type 1 SMA require repeated visits to hospital or medical providers in addition to prolonged use of home and palliative care such as diet provision via feeding tubes, frequent pneumonia treatment and chronic ventilatory support, which often place a significant emotional and social burden on patients and caregivers.

For patients with type 2 or 3 SMA, the inability or loss of activities of daily living (ADL) can have a major impact on individual well-being. Independence and the ability to perform basic personal tasks has been described by patients with type 2 or 3 SMA as a priority (16), with the preservation of or small improvements in upper extremity function being of particular importance to maintaining independence, social participation and quality of life (17).

Caring for people with SMA places a significant burden on caregivers, both from a detrimental impact on their own well-being and quality of life as well as from a financial perspective, for example loss of earnings.

2b) Diagnosis of the condition (in relation to the medicine being evaluated)

Please briefly explain how the condition is currently diagnosed and how this impacts patients. Are there any additional diagnostic tests required with the new treatment?

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How the condition is diagnosed:

If a person presents with the typical symptoms of SMA, a genetic blood test can be done to confirm the condition.

Type 1 SMA

People with infantile onset (type 1) SMA most commonly have two *SMN2* gene copies and typically present symptomatically before the age of 6 months. At diagnosis, these infants demonstrate reduced motor function compared with age matched normal infants, and will uniformly and rapidly lose motor function over time as assessed with a standard instrument for infants with SMA (18).

Type 2 SMA

People with type 2 SMA most commonly have three *SMN2* gene copies, and typically present symptomatically between the ages of 6–18 months. Consistent with all SMA subtypes, children with type 2 SMA have proximal greater than distal limb weakness and lower limb greater than upper limb weakness. These children will likely be able to sit and possibly stand but never walk independently given the greater amount of weakness in their lower limbs (2).

Type 3 SMA

Type 3 SMA is a less severe phenotype compared to type 1 and type 2 SMA. People with type 3 SMA most commonly have three or four *SMN2* gene copies, and typically present symptomatically between the ages of 18–36 months. Consistent with all SMA subtypes, children with type 3 SMA have proximal greater than distal limb weakness and lower limb greater than upper limb weakness. These children are able to sit, stand, and walk independently (2).

Newborn screening and genetic testing

If a family already has a child with SMA then genetic testing can be performed for subsequent siblings during pregnancy in order to diagnose and treat the child presymptomatically.

In the UK, SMA is currently not part of the newborn blood spot (NBS) screening programme, which supports the early identification, referral and treatment of babies with serious, rare conditions (19). Unfortunately, when patients are diagnosed through symptoms a lot of neuronal damage has already been done and motor function has been lost that will often never be regained. There is currently a pilot project, run by Oxford University Hospital, to screen newborn babies (20). If babies are diagnosed and treated presymptomatically, their prognosis is improved significantly (21), and therefore UK patient groups are advocating for this to be included in the screening programme (19).

2c) Current treatment options:

The purpose of this section is to set the scene on how the condition is currently managed:

- What is the treatment pathway for this condition and where in this pathway the medicine is likely to be used? Please use diagrams to accompany text where possible. Please give emphasis to the specific setting and condition being considered by NICE in this review. For example, by referencing current treatment guidelines. It may be relevant to show the treatments people may have before and after the treatment under consideration in this SIP.

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- Please also consider:+
    - if there are multiple treatment options, and data suggest that some are more commonly used than others in the setting and condition being considered in this SIP, please report these data.
    - are there any drug–drug interactions and/or contraindications that commonly cause challenges for patient populations? If so, please explain what these are.

What treatment are currently used:

There are currently two other approved disease-modifying treatments for SMA in the UK. Nusinersen (Spinraza®) is approved for the treatment of 5q SMA in paediatric and adult patients. Nusinersen is intrathecally administered (via an injection into the spinal cord), thus largely limiting the effects to the central nervous system (CNS). Nusinersen is available as an option for people with pre-symptomatic SMA or people with type 1, type 2 and type 3 SMA, excluding those unsuitable for intrathecal administration, on permanent ventilation or requiring a tracheostomy at baseline, and have a diagnosis of severe scoliosis and/or severe contractures. Onasemnogene abeparvovec (Zolgensma®) is an intravenously administered gene therapy to deliver a functional copy of the *SMN1* gene. Zolgensma is recommended as an option for treating type 1 and presymptomatic 5q SMA with a biallelic mutation in the *SMN1* gene and up to 3 copies of the *SMN2* gene in babies aged 12 months and under.

Best supportive care (BSC) requires a multidisciplinary approach and is tailored for individual patients. This includes the monitoring and support of patients in the absence of active disease modifying treatment and relies on the prevention and treatment of co-morbidities such as swallowing and feeding difficulties, scoliosis and thoracic deformity, contractures, and respiratory insufficiency.

Limitations of current treatments and unmet need:

While the approval of disease-modifying treatments (DMTs) has been a welcome breakthrough for people with SMA, there is a continued unmet need for those who are ineligible for Nusinersen or Zolgensma, as well as for those individuals for whom these treatment options are less than ideal.

Nusinersen
Intrathecal administration is an invasive procedure that is associated with risks and may not be feasible for all SMA patients, especially those who develop severe scoliosis, joint contractures or undergo a spinal surgery procedure (22-24). The intrathecal procedure may be causing anxiety for SMA patients, and anaesthesia is often required for many young children, which carries its own risks, especially in patients with respiratory challenges. Furthermore, there are questions surrounding the efficacy given the delivery of SMN protein is largely limited to the CNS and wearing-off effects have been reported (25-28).

Zolgensma
While this treatment choice is often a preference for parents whose children are eligible, parents struggle with uncertainty associated with the lack of knowledge of long-term

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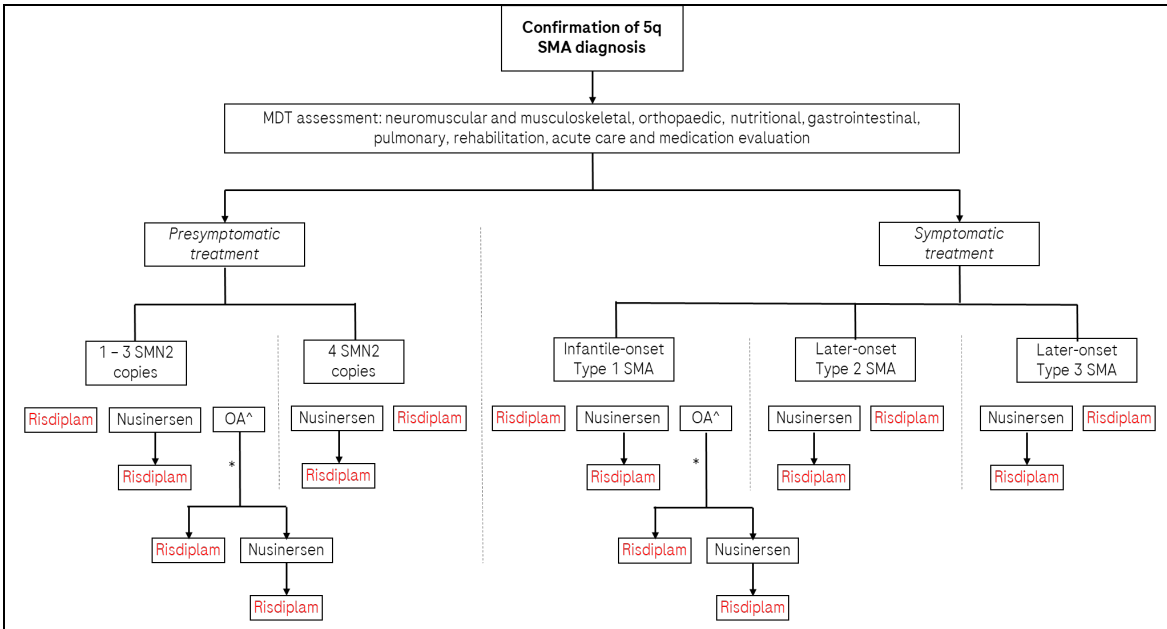
outcomes and whether the therapeutic effect will eventually fade (29). Furthermore, neuromuscular experts have raised concerns surrounding patient selection, safety considerations and the need for long-term monitoring (30-32). On the topic of patient selection, experts agreed that: age at onset, disease duration and baseline motor function status are the most important predictors of treatment response in symptomatic patients and *SMN2* copy number is the most important consideration in presymptomatic patients. In addition, the European experts agreed that gene therapy may not reduce risk of severe disability in patients presenting symptoms at birth, treated after a long disease duration, or with already severe evolution; and patients above 13.5 kg should only be treated in specific circumstances. Meanwhile, on the topic of safety considerations and long-term monitoring, it is important families understand the need for prednisolone tapering and monitoring of adverse events, given the potential long-term steroid use required to control liver abnormalities in some patients.

Proposed position for risdiplam in the SMA treatment pathway:

As an efficacious treatment in all people with SMA, risdiplam has the potential to significantly contribute towards addressing the continuing unmet need of people with SMA. Moreover, as an orally administered treatment, risdiplam provides a sustainable treatment option that can be administered at home and used for a life-long condition. The eligible population for risdiplam will include those patients who choose not to receive or are unsuitable for nusinersen or Zolgensma. Therefore, risdiplam is anticipated to provide an additional therapeutic option for all patients across the continuum of SMA (i.e., irrespective of the patient's age, type of SMA, or physical status), but in some of those cases it will be the only available treatment option. The proposed treatment pathway for risdiplam is summarised below (Figure 1).

Figure 1: Proposed position of risdiplam in pharmacological treatment pathway for SMA

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^Babies under 12 months of age *If OA is considered a treatment failure

2d) Patient-based evidence (PBE) about living with the condition

Context:

- **Patient-based evidence (PBE)** is when patients input into scientific research, specifically to provide experiences of their symptoms, needs, perceptions, quality of life issues or experiences of the medicine they are currently taking. PBE might also include carer burden and outputs from patient preference studies, when conducted in order to show what matters most to patients and carers and where their greatest needs are. Such research can inform the selection of patient-relevant endpoints in clinical trials.

In this section, please provide a summary of any PBE that has been collected or published to demonstrate what is understood about **patient needs and disease experiences**. Please include the methods used for collecting this evidence. Any such evidence included in the SIP should be formally referenced wherever possible and references included.

Results from a large online survey of patients and caregivers on early experiences with nusinersen (33)

A 54-item online survey was administered to adult patients and caregivers of paediatric patients diagnosed with SMA, to examine the early experience of nusinersen from the patient and caregiver perspective. One hundred and one patients with SMA were eligible and completed the study, of whom nearly half had type 2 SMA, while most of the remaining patients had type 1 of type 3. The results are summarised below:

Patient and caregiver reported experience with nusinersen

- With regard to specific attributes of treatment, adult patients considered changes in “energy and stamina” (58%), “respiratory function” (56%), and “motor function” (47%) to be their top three areas of satisfaction. Caregivers of pediatric patients reported the highest rates of satisfaction with regard to changes in “energy and stamina” (73%), “motor function” (61%), and “social functioning” (61%)
- Adult patients reported the lowest level of satisfaction with the following attributes, “treatment effect sustained over time” (50%), changes in “other symptoms (eg, pain, constipation)” (44%), and “medication administration” (39%). Caregivers of pediatric patients reported lowest satisfaction with changes in “activities of daily

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living" (37%), "time commitment to treatment" (34%), and "medication administration" (29%). Contrary to adult patients, a higher proportion of caregivers of pediatric patients (54%) reported high satisfaction with treatment effect being sustained over time compared to adult patients (22%)
- Patients reported a substantial level of discomfort during their treatment administration. With adult patients reporting a higher average discomfort compared to caregivers of pediatric patients

Reasons for not receiving nusinersen

- The first and second most frequent reason for not receiving treatment included "challenging route of administration" (58%) and "waiting for new treatment options" (46%)

Attributes of future SMA treatments

- Patients ranked safety (88%, n = 89), efficacy (87%, n = 88), and route of administration (59%, n = 60) as the most important attributes when considering future SMA treatments
- While safety and efficacy were consistently ranked as top considerations, adult patients ranked efficacy as the number one factor, while caregivers ranked safety as the most important factor for their younger patients

Overall, this study identified that efficacy, safety and route of administration were the key attributes considered by patients for medications to treat SMA.

A discrete choice experiment (DCE) survey on patient and caregiver treatment preferences for type 2/3 SMA (34)

A DCE survey was developed to elicit the preferences of adult patients and caregivers regarding different treatment aspects of SMA. The aim of the study was to examine treatment preferences of patients and caregivers of patients with type 2 and non-ambulatory type 3 SMA in the Netherlands, Belgium, Finland, Ireland and Portugal. A total of 65 participants completed the survey; most patients had type 2 SMA (by reported SMA type: 66%, by reported age of symptom onset: 69%), and a minority had non-ambulatory type 3 SMA (31-32%). The results are summarised below:

Patient and caregiver treatment preferences

- Participants were 4.8 and 8.1 times more likely to choose a treatment associated with stable or improved motor function, respectively
- Participants were 4.3 and 5.8 times more likely to choose a treatment associated with stable or improved breathing function, respectively
- Treatment administration, treatment risks and side effects, and demonstrated evidence in SMA types (Types 1, 2 and 3 SMA vs Types 1 and 2 SMA vs Type 1 SMA only) had a smaller influence on choice
- Participants were 1.8 times less likely to choose a treatment administered via an intrathecal injection in hospital every 4 months than a treatment taken orally once daily at home
- Participants were equally likely to prefer the oral therapy or the one-time intravenous treatment
- Participants preferred to avoid adverse events; they were 1.6 times less likely to choose a treatment associated with a risk of liver injury, and fatigue, headache

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and/or nausea compared with a treatment associated with a risk of diarrhoea and rash
- Participants considered treatments associated with headache, vomiting and/or body pain every 4 months as equally bad as a treatment with a risk of diarrhoea and rash
- Participants were 2.3 times less likely to choose a treatment for which effectiveness had been demonstrated in Type 1 SMA only compared with a treatment with demonstrated effectiveness in Types 1, 2 and 3 SMA
- Participants were no more or less likely to choose a treatment with demonstrated effectiveness in Types 1 and 2 SMA compared with a treatment with demonstrated effectiveness in Types 1, 2 and 3 SMA

Overall, this study demonstrates the importance patients place on treatments that can improve motor and breathing function, but also that they place considerable value on maintaining these functions. Furthermore, while considered less important than efficacy, patients would choose to avoid an intrathecal injection and treatments that involve a risk of liver injury or those that have only demonstrated effectiveness in type 1 SMA.

SECTION 3: The treatment

3a) How does the new treatment work?

What are the important features of this treatment?

Please outline as clearly as possible important details that you consider relevant to patients relating to the mechanism of action and how the medicine interacts with the body

Where possible, please describe how you feel the medicine is innovative or novel, and how this might be important to patients and their communities.

If there are relevant documents which have been produced to support your regulatory submission such as a summary of product characteristics or patient information leaflet, please provide a link to these.

Risdiplams's key features and how it works:

SMA is caused by a deficiency in the SMN protein, which is expressed systemically. SMN is crucial for the development and maintenance of motor neurons, but also has been shown to be involved with multiple other pathways (35-37). In humans, two genes, *SMN1* and *SMN2*, are involved in the production of the SMN protein. Patients affected by 5q SMA carry a mutation in chromosome 5q, causing the *SMN1* gene to produce insufficient levels of functional SMN protein. In turn, they have to depend on the *SMN2* gene to produce SMN protein. However, the *SMN2* gene alone produces an unstable version of the SMN protein that does not work as well as the full-length protein.

Risdiplam is a small molecule, orally administered, DMT that enables the *SMN2* gene to produce the full-length protein, leading to an increased production in functional and stable SMN protein. Risdiplam has good distribution into both the central nervous system (CNS) and systemically throughout the body, increasing levels of functional SMN protein in both the CNS and periphery to a similar magnitude (38, 39). In other words, risdiplam treats SMA by increasing and sustaining functional SMN protein levels throughout the body. This is expected to increase survival of motor neurons, thereby reducing current symptoms of the disease and slowing down its progression.

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3b) Combinations with other medicines

Is the medicine intended to be used in combination with any other medicines? • Yes / No If yes, please explain why and how the medicines work together. Please outline the mechanism of action of those other medicines so it is clear to patients why they are used together. If yes, please also provide information on the availability of the other medicine(s) as well as the main side effects. **If this submission is for a combination treatment, please ensure the sections on efficacy (3e), quality of life (3f) and safety/side effects (3g) focus on data that relate to the combination, rather than the individual treatments.**
Risdiplam is not used in combination with other medicines.

3c) Administration and dosing

How and where is the treatment given or taken? Please include the dose, how often the treatment should be given/taken, and how long the treatment should be given/taken for. How will this administration method or dosing potentially affect patients and caregivers? How does this differ to existing treatments?
Risdiplam is taken orally once a day using the re-usable oral syringe provided, at approximately the same time each day. If the patient is unable to swallow and has a feeding tube, risdiplam can be administered via the tube. The recommended once daily dose of risdiplam is determined by age and body weight. ● <2 months of age: 0.15 mg/kg ● 2 months to < 2 years of age: 0.20 mg/kg ● ≥2 years of age (<20 kg): 0.25 mg/kg ● ≥2 years of age (≥20 kg): 5 mg

3d) Current clinical trials

Please provide a list of completed or ongoing clinical trials for the treatment. Please provide a brief top-level summary for each trial, such as title/name, location, population, patient group size, comparators, key inclusion and exclusion criteria and completion dates etc. Please provide references to further information about the trials or publications from the trials.
Evidence for the clinical effectiveness of risdiplam is sourced from the broadest clinical trial development programme in SMA, which confirms that risdiplam offers a clinical benefit to a broad and heterogeneous population of people with SMA, reflective of that seen in clinical practice, without restrictions or limitations on their physical conditions. Two pivotal studies, **FIREFISH** [NCT02913482 (40)] and **SUNFISH** [NCT02908685 (41)], deliver robust and long-term clinical evidence confirming the efficacy and safety of risdiplam treatment for SMA over the course of 5-years, in infants with type 1 SMA and in paediatric and adult patients with type 2 or 3 SMA, respectively. FIREFISH is a phase 2/3, open-label, single arm, multicentre study (with 14 investigational sites across 10 countries) to investigate the safety, tolerability and efficacy of risdiplam in patients with type 1 SMA. The study consisted of an exploratory dose-finding part (Part 1) and a confirmatory part

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(Part 2) where patients could receive risdiplam at the dose selected for a treatment period of 24 months, and then enter an open-label extension (OLE) for 3-years. A total of 41 patients were enrolled in part 2 and completed the study. SUNFISH is a phase 2/3 two-part, seamless, multicentre (with 42 investigational sites across 14 countries), randomised, double-blind, placebo-controlled study to investigate the safety, tolerability and efficacy of risdiplam in patients with type 2/3 SMA. Like FIREFISH, SUNFISH consisted of a dose-finding part (Part 1) and a confirmatory part (Part 2) to assess the efficacy and safety of treatment with risdiplam at the selected dose level from Part 1. A total of 180 patients were randomized (2:1) to receive either risdiplam or placebo, which was stratified by age group. Patients enrolled in Part 2, who initially received placebo, were switched to active treatment at week 52, and the initial treatment assignment remained blinded to patients and clinical site staff until all patients completed the week 104 study visit. After week 104, all patients had the opportunity to join OLE for 3 years, which is now complete.

In addition to these two pivotal studies, **RAINBOWFISH** [NCT03779334 (42)] is an open-label, single-arm, multicentre (with 7 sites across 7 countries) study to investigate the efficacy and safety of risdiplam in patients aged from birth to 6 weeks (at first dose) who have been genetically diagnosed with SMA (*SMN1* deletion and any *SMN2* copies) but are not yet presenting with SMA symptoms. All patients will receive risdiplam orally once daily for 2 years at a dose selected to achieve the targeted exposure range (the dose may be adapted as patients grow and mature), following by an open-label extension phase of at least 3 years and a follow-up, for a total treatment duration of at least 5 years for each infant enrolled. Enrolment in this ongoing study is complete with 26 patients enrolled. The primary analysis has been conducted, corresponding with the data when the last patients enrolled had completed 12 months of treatment.

The pivotal studies are also supported by **JEWELFISH** [NCT03032172 (43)], an open-label, non-comparative study in people with type 1, 2 and 3 SMA (6 months to 60 years old) who had received previous treatment for SMA. The primary objective of JEWELFISH was to assess safety. Enrolment in this ongoing study is complete with 174 patients enrolled. Primary analysis has been conducted, corresponding with the data when the last patients enrolled had completed 24 months of risdiplam treatment.

3e) Efficacy

Efficacy is the measure of how well a treatment works in treating a specific condition.

In this section, please summarise all data that demonstrate how effective the treatment is compared with current treatments at treating the condition outlined in section 2a. Are any of the outcomes more important to patients than others and why? Are there any limitations to the data which may affect how to interpret the results? Please do not include academic or commercial in confidence information but where necessary reference the section of the company submission where this can be found.

Risdiplam efficacy:

Due to the different populations and age ranges of patients included in the studies (as a consequence of the different age of onset of symptoms across the different SMA types), the studies utilise different assessment scales for motor function and, hence, efficacy data have not been pooled. Instead, the efficacy results of each study are summarised separately.

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FIREFISH primary outcome measure:

Risdiplam treatment was associated with a clear gain of clinically important motor milestones, including the primary endpoint of sitting without support. After 12 months of treatment with risdiplam, 29.3% of patients were sitting without support, as assessed by Item 22 of the BSID-III gross motor scale (a scale to assess infants attainment of motor milestones such as sitting, crawling and walking). In comparison with natural history studies, this proportion is significantly higher than the expected performance criterion of 5% ($p<0.0001$).

FIREFISH secondary outcome measures:

The results of the secondary and exploratory efficacy endpoints supported the primary endpoint, showing that risdiplam treatment was associated with clinically meaningful improvements in motor and bulbar functions in patients with type 1 SMA. Furthermore, at Month 12, 85.4% of patients were alive without permanent ventilation. In comparison with natural history studies, this proportion is significantly higher than the expected performance criterion of 42% ($p<0.0001$).

The long-term efficacy data from the open-label extension phase of the study support the analysis results at 12 months of treatment. Infants treated with risdiplam for up to 4 years maintained or continued to improve in their motor abilities, achieving motor milestones that type 1 SMA patients would never be able to achieve without treatment. For further details please see section B.2.6.1 of the NICE submission.

SUNFISH primary outcome measure:

The improvement in motor function seen in patients treated with risdiplam at month 12 was clinically meaningful and statistically significantly better than the placebo control data ($p=0.0156$). In the analysis of the MFM32 total score (a motor scale used to assess functional ability in neuromuscular diseases), the mean change from baseline at month 12 was 1.36 in patients receiving risdiplam and -0.19 in patients receiving placebo.

SUNFISH secondary outcome measures:

Risdiplam treatment for up to 5 years resulted in an improvement or stabilisation in motor function in a broad an heterogeneous population of patients with later-onset, type 2 and 3 SMA. Stabilisation of motor function is clinically meaningful for these patients, particularly over this long time frame, given a yearly decline would be expected without treatment. For further details on these results see section B.2.6.2 of the NICE submission.

RAINBOWFISH primary outcome measure:

After 12 months of risdiplam treatment, the primary endpoint of sitting without support for 5 seconds as assessed by Item 22 of the BSID-III gross motor scale (a scale to assess infants attainment of motor milestones such as sitting, crawling and walking) was met with a statistically significant and clinically meaningful proportion of patients (80% of the primary efficacy population) achieving this milestone. In comparison with natural history studies, this proportion is significantly higher than the expected performance criterion of 5% ($p<0.0001$).

RAINBOWFISH secondary outcomes measures:

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The efficacy data show that, overall, patients who completed 12 months of risdiplam treatment achieved important motor milestones and high levels of motor function (as assessed by several motor function scales). All patients were alive without the need for permanent ventilation during the first year of treatment. Additionally, all patients were able to feed orally and swallow.

3f) Quality of life impact of the medicine and patient preference information

What is the clinical evidence for a potential impact of this medicine on the quality of life of patients and their families/caregivers? What quality of life instrument was used? If the EuroQol-5D (EQ-5D) was used does it sufficiently capture quality of life for this condition? Are there other disease specific quality of life measures that should also be considered as supplementary information?

Please outline in plain language any quality of life related data such as **patient reported outcomes (PROs).**

Please include any **patient preference information (PPI)** relating to the drug profile, for instance research to understand willingness to accept the risk of side effects given the added benefit of treatment. Please include all references as required.

Type 1 SMA

The Infant Toddler Quality of Life Questionnaire – 47-item short-form version (ITQOL-SF47) was used to capture parent / caregiver reported outcomes on patients health related quality of life (HRQoL) in FIREFISH and RAINBOWFISH. In FIREFISH, patients treated with risdiplam for 12 months showed no change in median score across 4 domains (patient impact – overall health, growth and development, temperament and modd, and parental impact – time limitation), an improvement in median score for one domain (parent impact – emotional health), and a decline in the median score for four domains (patient impact – physical abilities, general health perceptions, bodily pain and discomfort, and parent impact – family cohesion). In RAINBOWFISH, patients treated with risdiplam for 12 months showed improvement or no change in HRQoL, as evidenced by an increase of no change in median scores from baseline in each domain on the ITQOL-SF47, with the exception of one domain (general health perceptions). The changes in HRQoL observed in these trials are difficult to interpret, given the lack of natural history data across this measure, and given some items could not be assessed due to the young age of the patients enrolled.

Type 2/3 SMA

In SUNFISH, patients and caregivers reported continuous improvement or stabilisation in the level of help needed for activities of daily living. Independence and the ability to perform basic personal tasks has been described by patients as a priority for type 2 and 3 SMA patients (16). SMAIS-ULM items focus on upper limb related activities of daily living with higher scores indicating greater independence in completing activities such as writing, using a touchscreen, dressing and washing the upper body, particularly relevant for the recruited population who are non-ambulant and wheelchair bound. These results indicate important improvements in patients' everyday lives with regards to increased independence.

3g) Safety of the medicine and side effects

When NICE appraises a treatment, it will pay close attention to the balance of the benefits of the treatment in relation to its potential risks and any side effects. Therefore, please outline the main side effects (as opposed to a complete list) of this treatment and include details of a benefit/risk

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assessment where possible. This will support patient reviewers to consider the potential overall benefits and side effects that the medicine can offer.

Based on available data, please outline the most common side effects, how frequently they happen compared with standard treatment, how they could potentially be managed and how many people had treatment adjustments or stopped treatment. Where it will add value or context for patient readers, please include references to the Summary of Product Characteristics from regulatory agencies etc.

When all of the data across all of the clinical trials is taken together, risdiplam has a favourable safety profile in pre-symptomatic, paediatric and adult treatment-naïve and pre-treated patients with all types of SMA. Both FIREFISH and SUNFISH studies demonstrated that the rate of adverse events (AEs) and serious adverse events (SAEs) declined over 48 months of risdiplam treatment and then stabilised. RAINBOWFISH showed that risdiplam was well tolerated in presymptomatic patients with SMA below the age of 2 months. JEWELFISH demonstrated that risdiplam was well tolerated in adult and adolescent patients who had received previous treatments (including Nusinersen and Zolgensma). The nature and incidence of AEs observed across SMA populations were consistent with the known safety profile of risdiplam and were as would be expected for patients with SMA. Overall, with up to 5 years exposure, the evidence demonstrates a clearly positive benefit/risk profile for risdiplam.

While being generally well tolerated, risdiplam did have a safety profile showing these most common adverse events:

In infantile-onset SMA patients, the most common adverse reactions observed in risdiplam clinical studies were:

- Pyrexia (fever) (54.8%)
- Rash (29.0%)
- Diarrhoea (19.4%)

In later-onset SMA patients, the most common adverse reactions observed in risdiplam clinical studies were:

- Pyrexia (21.7%)
- Headache (20.0%)
- Diarrhoea (16.7%)
- Rash (16.7%)

3h) Summary of key benefits of treatment for patients

Issues to consider in your response:

- Please outline what you feel are the key benefits of the treatment for patients, caregivers and their communities when compared with current treatments.
- Please include benefits related to the mode of action, effectiveness, safety and mode of administration

Risdiplam is an effective and safe disease modifying therapy available for all people with SMA. The comprehensive clinical development programme provides robust evidence that risdiplam offers a clinical benefit to a broad and heterogeneous population of people with SMA, reflective of that seen in clinical practice, without restrictions or limitations on

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their physical conditions. The inclusion criteria for clinical studies of risdiplam allowed for the enrolment of older patients and those with more advanced disease, compared to nusinersen clinical trials, which is important since the concept of clinical benefit differs by age and disease severity. Taken together, the robust efficacy results observed across clinical trials demonstrate that risdiplam provides a substantial treatment benefit in patients across the SMA disease spectrum, representing and important advancement in the treatment of SMA. Risdiplam treatment resulted in substantial divergence from the natural history of disease in patients with type 1, 2 and 3 SMA when assessing patient's survival, achievement of critical motor development milestones and improvement / stabilisation in motor function.

Risdiplam offers patients sustainable self- or caregiver-assisted treatment at home. Risdiplam's oral route of administration and liquid formulation presents a significant advantage over intrathecal injections for people with SMA, irrespective of age, physical status, or disease severity. It is a sustainable treatment option due to its daily home administration, given orally or via feeding tube by the patient or a caregiver, without requiring hospital clinic visits, invasive procedures or concomitant use of additional medicines. Furthermore, as an oral formulation with selected dosing regimens that ensure similar risdiplam exposure across the wide age and body weight range in the SMA population, risdiplam is the only disease modifying therapy that can be initiated within hours of diagnosis to rapidly increase functional SMN protein and allow patients to benefit from treatment as early as possible.

3i) Summary of key disadvantages of treatment for patients

Issues to consider in your response:

- Please outline what you feel are the key disadvantages of the treatment for patients, caregivers and their communities when compared with current treatments. Which disadvantages are most important to patients and carers?
- Please include disadvantages related to the mode of action, effectiveness, side effects and mode of administration
- What is the impact of any disadvantages highlighted compared with current treatments

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While being generally well tolerated, risdiplam did have a safety profile showing these most common adverse events:

In infantile-onset SMA patients, the most common adverse reactions observed in risdiplam clinical studies were:

- Pyrexia (fever) (54.8%)
- Rash (29.0%)
- Diarrhoea (19.4%)

In later-onset SMA patients, the most common adverse reactions observed in risdiplam clinical studies were: Pyrexia (21.7%)

- Headache (20.0%)
- Diarrhoea (16.7%)
- Rash (16.7%)

Male and female patients of reproductive potential should adhere to the following contraception requirements:

- Female patients of childbearing potential should use highly effective contraception during treatment and for at least 1 month after the last dose.
- Male patients, and their female partners of childbearing potential, should both ensure that highly effective contraception is achieved during treatment and for at least 4 months after the last dose.

Risdiplam is not recommended during pregnancy and in women of childbearing potential not using contraception.

Another disadvantage to using risdiplam is the need to keep it refrigerated once reconstituted; it can be stored at room temperature (below 40°C) for no more than a total of 120 hours. This may make travelling more difficult as risdiplam needs to be dosed every day.

The disadvantages listed above may make risdiplam less suitable than other available treatments for some patients.

3j) Value and economic considerations

Introduction for patients:

Health services want to get the most value from their budget and therefore need to decide whether a new treatment provides good value compared with other treatments. To do this they consider the costs of treating patients and how patients' health will improve, from feeling better and/or living longer, compared with the treatments already in use. The drug manufacturer provides this information, often presented using a health economic model.

In completing your input to the NICE appraisal process for the medicine, you may wish to reflect on:

- The extent to which you agree/disagree with the value arguments presented below (e.g., whether you feel these are the relevant health outcomes, addressing the unmet needs and issues faced by patients; were any improvements that would be important to you missed out, not tested or not proven?)

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- If you feel the benefits or side effects of the medicine, including how and when it is given or taken, would have positive or negative financial implications for patients or their families (e.g., travel costs, time-off work)?
- How the condition, taking the new treatment compared with current treatments affects your quality of life.

How the model reflects the condition

- The economic case presented in this submission is based on an analysis assessing the use of risdiplam compared to nusinersen, onasemnogene abeparvovec and best supportive care (BSC) for the treatment of the following patient populations: presymptomatic, type 1, type 2 and 3 spinal muscular atrophy.
- The approach taken to model costs and health benefits is done by splitting patients into different health states, according to the SMA type:
    - Presymptomatic and type 1 SMA: “Permanent ventilation”, “Not sitting”, “Sitting”, “Standing”, “Walking” and “Death”
    - Type 2 and 3 SMA: “Not sitting”, “Sitting with support”, “Sitting without support”, “Standing”, “Walking” and “Death”
- The risdiplam and comparator trial data, in combination with real-world evidence data, are used to predict how long patients on each treatment remain in each health state, and the amount of costs and health gains they accrue.

Modelling how much a treatment extends life and improves quality of life

- Quality of life in the economic model is determined by the health state a patient is in and whether or not they are receiving treatment. The economic model accounts for both patients’ and their respective caregivers’ quality of life. The quality of life values assigned to each health state are based on previously reviewed appraisals and newly collected values, informed with the help of clinicians and patient groups.
- In the comparison of risdiplam versus BSC, across all SMA populations evaluated, it is predicted that people living with SMA treated with risdiplam will live longer with a higher quality of life than those treated with BSC. These gains mostly occur from delaying disease progression. When comparing risdiplam to nusinersen, increased gains in life years and the quality of those years can be seen in those receiving risdiplam, particularly for type 1 SMA patients, with a slightly smaller gain in type 2 and 3 patients. For patients who receive onasemnogene abeparvovec, a smaller difference is observed but a gain in quality of life is predicted for risdiplam patients. In the presymptomatic patients, due to limitations with data, equal efficacy has been observed between risdiplam nusinersen and onasemnogene abeparvovec. It should be noted that these results are based on the data inputted and the modelling structure.
- Data on event-free survival (i.e. ventilation), overall survival, time on treatment, quality of life, disease-related events and resource use all feed into the economic model. Observed data from the risdiplam studies, comparators studies and real-world data is used to predict long-term outcomes. The amount of observed data available to inform these predictions varies by treatment, with 1-year, 4-year and 5-year data available for risdiplam in presymptomatic, type 1 and type 2/3 SMA, respectively, along with 12-18 months for onasemnogene, 2-4 year data for nusinersen and 1-year for best supportive care. All three models predict disease progression, costs and health outcomes over the lifetime of all patients in the model,

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30 years for presymptomatic and type 1 SMA patients and 90 years for type 2 and 3 patients.

Modelling how the costs of treatment differ with risdiplam treatment

- The total costs of treatment related to risdiplam is expected to be greater than that of BSC. This is driven by the drug acquisition costs as there are none associated with what was considered as BSC, in lieu of active treatment. Compared to nusinersen and onasemnogene abeparvovec, risdiplam is expected to be cost saving due to lower administration costs and particularly in type 1, keeping patients in better health states for longer.

Uncertainty

- Due to the difficulty in collecting, analysing and subsequently evaluating technologies in a rare condition, there is inherent uncertainty within the efficacy estimates included within the economic model.
- As a result of significant differences between patient populations across risdiplam and comparator studies, it is difficult to provide indirect treatment comparisons for risdiplam versus other available comparators (nusinersen, onasemnogene aberparvovec and BSC) due to differences in study eligibility criteria, patient clinical characteristics, endpoints measured, study assessment timepoints, single arm studies and small patient numbers.
- As this appraisal is a re-evaluation of risdiplam following entry to a managed access agreement, real-world data was collected during this period to further understand how risidplam would be used in routine clinical practice. However, due to small sample sizes, more severe clinical characteristics at treatment initiation and inconsistent follow-up periods, the data is not robust enough to draw conclusions from.
- The risdiplam studies were much broader in their acceptance of patients compared with the other treatments in terms of severity, and that combined with being third to market resulted in a more severe patient population. Many patients (within a rare population) were already being treated with another intervention, reducing the eligible patient population and determining the characteristics of those available to receive risdiplam, either within a clinical trial or the real-world.
- For completeness of the economic analysis, BSC has been provided as a comparator in each SMA population presented. However, as active therapies such as nusinersen, onasemnogene abeparvovec and risdiplam are available for the treatment of SMA, there is a question around how relevant BSC is as a comparator in the context of current practice and the treatment landscape. Clinical experts do believe that BSC has a place in the pathway, but this is for patients who are either not eligible for an available active treatment or choose not to receive active treatment, therefore raising the question whether a head-to-head comparison for the entire population being evaluated is relevant. With the introduction of new active treatments, SMA patients (particularly those with worse prognosis, i.e. type 1) are reaching milestones never seen before in natural history; clinicians are referring to these patients as a new type of SMA: “treated type 1” patients. Whilst every effort has been made to collect additional data for risdiplam during the managed access agreement period, the trajectory of these treated patients in terms of outcomes, quality of life and costs is completely unknown. The economic models presented

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only provide a simplified version of what is expected to happen based on what is currently known, but it is well accepted that longer term outcomes for these patients is unknown.

- An additional challenge is collecting quality of life data for people living with SMA. Given the age demographics and the severity of the condition for this population, it is difficult to obtain robust quality of life estimates for these patients, as can be seen by the multiple attempts to try to collect this over previous technology appraisals.
- The same situation can be said for capturing the true costs of managing SMA. This evidence submission presents another *de novo* approach that has been developed in collaboration with both clinical and patient experts. It was acknowledged through expert discussion that it is extremely difficult to accurately reflect the entire cost of SMA, as even within the type of SMA the patient's condition can differ. There is also geographical variability in the availability of resources and differences in approaching the overall management of SMA. The costs presented only consider the NHS and personal social services perspective, as per the NICE reference case, but there are significant costs that are unaccounted for that patients, families, communities and charities pay out of pocket for in order to manage SMA. These are not exceptional circumstances, but in fact apply to all patients, irrespective of their SMA type. It should be taken into consideration that the costs that have been previously presented and currently presented do not fully represent the picture of living with and managing SMA.

Cost-effectiveness results

- In the company's base case analysis, risdiplam is shown to be cost-saving versus nusinersen and onasemnogene abeparvovec (versus list price) and plausibly cost-effective versus best supportive care in the presymptomatic SMA population. In type 1 and type 2/3 populations, risdiplam is shown to be dominant, providing more QALYs and costing less, compared to nusinersen and onasemnogene abeparvovec (versus list price). When compared to BSC in type 1 and type 2/3 populations, whilst risdiplam costs more, patients on risdiplam experience improved quality of life and increased life years are gained.. These results do not take into account any confidential commercial discounts for the comparator treatments, or the committee's preferred assumptions which may differ to those applied in the base-case analysis.

Additional factors

- All three indications (presymptomatic, type 1, type 2 and 3) are expected to meet the criteria to make adjustments to the value of a QALY, in line with the NICE Methods Manual, in the comparisons of nusinersen, onasemnogene abeparvovec and BSC. An adjustment to the value of risdiplam QALYs (x1.7) can apply for these comparisons.

3k) Innovation

NICE considers how innovative a new treatment is when making its recommendations.
If the company considers the new treatment to be innovative please explain how it represents a 'step change' in treatment and/ or effectiveness compared with current treatments. Are there any QALY benefits that have not been captured in the economic model that also need to be considered (see section 3f)

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SMA results from mutations in the SMN1 gene leading to low levels of SMN protein expression (44). SMN protein is expressed in all cells, with motor neurons shown to be very susceptible to low levels of functional SMN protein (45); however, accumulating evidence indicates that SMA is a multisystem disease that also affects peripheral tissues. Reduced levels of SMN protein throughout the whole body is thought to play a vital role in disease pathophysiology (36). Therapies for SMA aim to increase the levels of SMN protein. Effective disease intervention for SMA may therefore require a body-wide correction of SMN protein levels to reverse or slow disease progression. Risdiplam is a centrally and peripherally distributed, oral SMN2 pre-mRNA splicing modifier. It crosses the blood-brain barrier and is distributed throughout the body, increasing levels of functional SMN protein in both the CNS and periphery to a similar magnitude (38, 39). Therefore, treatment with risdiplam is expected to improve outcomes in many patients by preventing or delaying disease progression, both from a motor function perspective and a systemic perspective.

3l) Equalities

Are there any potential equality issues that should be taken into account when considering this condition and this treatment? Please explain if you think any groups of people with this condition are particularly disadvantaged.
Equality legislation includes people of a particular age, disability, gender reassignment, marriage and civil partnership, pregnancy and maternity, race, religion or belief, sex, and sexual orientation or people with any other shared characteristics

More information on how NICE deals with equalities issues can be found in the NICE equality scheme
Find more general information about the Equality Act and equalities issues here

SMA is both a rare and a very serious condition, and that any treatment benefits are highly valued by patients and families. In addition, the SMA patient population, for which risdiplam will be a treatment option, includes babies, children and young people, as well as adults with disabilities.

In the current funding situation, SMA patients who are permanently ventilated or have a tracheostomy are not eligible to receive risdiplam. This decision was made as there was little to no experience of treating permanently ventilated patients with DMTs and therefore no clearly known benefits. The situation has developed in the last few years and clinicians in the UK do report an improvement in quality of life of slowing of expected deterioration of motor / respiratory function.

Overall, pragmatism should be taken during the decision making process for this rare and seriously debilitating condition.

SECTION 4: Further information, glossary and references

4a) Further information

Feedback suggests that patients would appreciate links to other information sources and tools that can help them easily locate relevant background information and facilitate their effective contribution to the NICE assessment process. Therefore, please provide links to any relevant online information that would be useful, for example, published clinical trial data, factual web

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content, educational materials etc.
Where possible, please provide open access materials or provide copies that patients can access.

SMA specific information:

- SMA UK, International Standards of Care for SMA https://smauk.org.uk/support-information/about-sma/standards-of-care-for-sma/
- SMA UK, Information on Risdiplam (Evrysdi) https://smauk.org.uk/treatments-research/risdiplam/
- SMA UK, Access to Treatment https://smauk.org.uk/treatments-research/uk-access-to-treatment/

Risdiplam clinical trials

- FIREFISH https://pubmed.ncbi.nlm.nih.gov/36244364/ and https://pubmed.ncbi.nlm.nih.gov/33626251/
- SUNFISH https://pubmed.ncbi.nlm.nih.gov/34942136/ and https://pubmed.ncbi.nlm.nih.gov/36735057/
- RAINBOWFISH https://www.sciencedirect.com/science/article/abs/pii/S0960896623002742
- JEWELFISH https://pubmed.ncbi.nlm.nih.gov/36780114/

Further information on NICE and the role of patients:

- Public Involvement at NICE Public involvement | NICE and the public | NICE Communities | About | NICE
- NICE's guides and templates for patient involvement in HTAs Guides to developing our guidance | Help us develop guidance | Support for voluntary and community sector (VCS) organisations | Public involvement | NICE and the public | NICE Communities | About | NICE
- EUPATI guidance on patient involvement in NICE: https://www.eupati.eu/guidance-patient-involvement/
- EFPIA – Working together with patient groups: https://www.efpia.eu/media/288492/working-together-with-patient-groups-23102017.pdf
- National Health Council Value Initiative. https://nationalhealthcouncil.org/issue/value/
- INAHTA: http://www.inahta.org/
- European Observatory on Health Systems and Policies. Health technology assessment - an introduction to objectives, role of evidence, and structure in Europe: http://www.inahta.org/wp-content/themes/inahta/img/AboutHTA_Policy_brief_on_HTA_Introduction_to_Objectives_Role_of_Evidence_Structure_in_Europe.pdf

4b) Glossary of terms

ADL	Activities of Daily Living
AE	Adverse Event
BSC	Best Supportive Care
BSID-III	Bayley Scale of Infant Development (third edition)
CNS	Central Nervous System

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DCE	Discrete Choice Experiment
DMT	Disease Modifying Therapy
EU	European Union
HRQoL	Health Related Quality of Life
ITQOL-SF47	The Infant Toddler Quality of Life Questionnaire – 47 Item Short Form Version
MFM-32	Motor Function Measure 32
MHRA	Medicines and Healthcare products regulatory agency
OLE	Open-label extention
SAE	Serious Adverse Event
SMA	Spinal Muscular Atrophy
SMAIS-ULM	SMA Independence Scale – Upper Limb Module
SMN	Survival Motor Neuron

4c) References

Please provide a list of all references in the Vancouver style, numbered and ordered strictly in accordance with their numbering in the text:

1. Roche Products Ltd. Evrysdi 0.75 mg/mL powder for oral solution 2023.
2. Finkel R, Bertini E, Muntoni F, Mercuri E. 209th ENMC International Workshop: Outcome Measures and Clinical Trial Readiness in Spinal Muscular Atrophy 7-9 November 2014, Heemskerk, The Netherlands. Neuromuscular disorders : NMD. 2015;25(7):593-602.
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NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Multiple Technology Appraisal

Nusinersen for treating spinal muscular atrophy – (MA review of TA588)

Clarification questions

March 2025

File name	Version	Contains confidential information	Date
ID6195 EAG Biogen clarification letter SMA for MTA_Biogen_Final_[redacted]	1a	No	25/03/2025

Section A: Clarification on effectiveness data

A1. Document B Section B.2.6. Adverse reactions: Could the company provide a detailed list of the key reasons for treatment discontinuation observed in the clinical trials? How did these reasons vary across different SMA subtypes?

Pivotal Studies

Presymptomatic SMA – NURTURE[1]

As of the 15th February 2021 datacut, no patients discontinued nusinersen treatment.

Type 1 SMA – ENDEAR [2]

ENDEAR (CS3B) was stopped prematurely due to improved efficacy observed in the nusinersen treated group compared to the control group during an interim analysis. Of the 121 subjects who received treatment, 89 (74%) completed the study (81% of subjects in the nusinersen group and 59% of subjects in the control group). Overall, the rate of treatment discontinuation was lower in the nusinersen group (59%) than the control group (63%). Thirty two out of 80 subjects (40%) in the nusinersen group and 10 out of 41 subjects (24%) in the control group discontinued treatment due to early study closure.

Thirteen out of 80 subjects (16%) in the nusinersen group and 16 out of 41 subjects (39%) in the control group experienced an adverse event with a fatal outcome. [redacted] deaths were due to respiratory disorders (nusinersen vs. control: [redacted]% vs. [redacted]%), such as respiratory failure ([redacted]% vs. [redacted]%), acute respiratory failure ([redacted]% vs. [redacted]%), respiratory arrest ([redacted]% vs. [redacted]%), and respiratory distress ([redacted]% vs. [redacted]%). Two subjects in nusinersen group and 3 subjects in the control group ([redacted]% vs. [redacted]%) died of cardiorespiratory arrest. [redacted] subjects in the nusinersen group died of nervous system disorders; [redacted] due to hypoxic brain injury after cardiorespiratory arrest and

[1] Crawford TO, Swoboda KJ, De Vivo DC, Bertini E, Hwu WL, Finkel RS, et al. Continued benefit of nusinersen initiated in the presymptomatic stage of spinal muscular atrophy: 5-year update of the NURTURE study. Muscle Nerve. 2023;68(2):157-70.

[2] Biogen and IONIS Pharmaceuticals data on file. A study to assess the efficacy and safety of nusinersen (ISIS 396443) in infants with spinal muscular atrophy (ENDEAR). 2017

[redacted] due to hypoxic-ischemic encephalopathy after aspiration. [redacted] subject in each group died of unknown causes. [redacted] in the nusinersen group died due to general physical health deterioration.

The types of events leading to death in both groups are consistent with causes of death observed in the context of SMA and none were considered by the Investigator to be related to study treatment.

[redacted] additional subjects in the nusinersen group were withdrawn from the study and discontinued treatment. [redacted] in the control group was withdrawn from the study after undergoing all the scheduled sham procedures.

Type 2/3 SMA – CHERISH[3]

CHERISH (CS4) was stopped prematurely due to improved efficacy observed in the nusinersen treated group compared with the control group during the interim analysis. Of the 126 subjects who received treatment, all 126 subjects (100%) completed the study and 125 subjects (99%) completed treatment (99% in the nusinersen group and 100% in the control group). One subject in the nusinersen group discontinued treatment. The subject received the Day [redacted] doses, but the dosing could not be completed on Day [redacted] and the subject did not receive the fourth dose before the decision was made to terminate the study early.

Open Label Extension – SHINE[4]

<u>Infantile onset</u>

Participants with infantile-onset SMA entered SHINE (Study CS11) following the completion of either the sham-controlled Study CS3B or the open-label Studies CS3A and EMBRACE (SM202 Part 2).

[3] Biogen and IONIS Pharmaceuticals data on file. CS4 (CHERISH). A phase 3, randomized, double-blind, sham-procedure controlled study to assess the clinical efficacy and safety of ISIS 396443 administered intrathecally in patients with later-onset spinal muscular atrophy [CHERISH]. Clinical study report. Study number: 396443-CS4. Interim. February 3, 2017.
[4] Biogen and IONIS Pharmaceuticals data on file. A study for participants with spinal muscular atrophy (SMA) who previously participated in nusinersen (ISIS 396443) investigational studies (SHINE). Identifier: NCT02594124. In: ClinicalTrials.gov [internet]. Bethesda: US National Library of Medicine: 2021. Available from https://www.clinicaltrials.gov/ct2/show/NCT02594124.

A total of 137 participants with infantile-onset SMA received nusinersen in the index study and/or Study CS11 and were included in the integrated analyses, of whom 100 participants were screened at ≤ 7 months of age and 37 participants were screened at > 7 months of age.

Of the 137 participants with infantile-onset SMA who received nusinersen in the index study and/or Study CS11:

- [redacted] participants ([redacted]%) completed treatment in the index study and/or Study CS11.
- [redacted] participants ([redacted]%) discontinued treatment in the index study or Study CS11 for the following reasons: AE ([redacted] participants [redacted]%]), voluntary withdrawal ([redacted] participants [redacted]%]), transition to commercial drug (nusinersen) ([redacted] participants [redacted]%]), Investigator judgment ([redacted] participants [redacted]%]), and other ([redacted] participants [redacted]%]).
- [redacted] participants ([redacted]%) completed treatment in the index studies but did not enrol in Study CS11.

Figure 1 Disposition of Participants: Infantile-Onset SMA.



Later onset

Participants with later-onset SMA entered SHINE (Study CS11) following the completion of either the sham-controlled CHERISH (Study CS4), the open-label

Studies CS2/CS12, or EMBRACE (Study SM202). Data from participants in Study CS1 is included in safety analyses but not in efficacy analyses. Of the 190 participants with later-onset SMA who received nusinersen in the index study and/or Study CS11 and were included in the integrated analyses:

- [redacted] participants ([redacted]%) completed treatment in the index study and/or Study CS11.
- [redacted] participants ([redacted]%) discontinued treatment in the index study or Study CS11 for the following reasons: voluntary withdrawal ([redacted] participants [[redacted]%]), transition to commercial drug (nusinersen) ([redacted] participants [[redacted]%]), AE ([redacted] participants [[redacted]%]), other ([redacted] participants [[redacted]%]), and Investigator judgment ([redacted] participants [[redacted]%]).
- [redacted] participants ([redacted]%) completed treatment in the index studies but did not enrol in Study CS11.

Figure 2.Disposition of Participants: Later-Onset SMA



The AEs that led to discontinuation of treatment were consistent with the underlying complications of SMA. All AEs that led to discontinuation of treatment were considered not related or unlikely related to study drug.

Section B: Clarification on cost-effectiveness data

Pre-symptomatic economic model

B1. Document B Section 3.2.2. Can the company clarify why the economic model for the pre-symptomatic population is informed by WHO motor milestones given the availability of HINE-2 data from the NURTURE and ENDEAR trials, particularly given the population? Which of the two measures has a better clinical validity for the pre-symptomatic population?

HINE-2 was developed specifically for neuromuscular conditions and is a more granular instrument than WHO motor milestones. HINE-2 is only applicable to and validated in children aged up to 24 months old[5]. HINE-2 cover 8 milestones including voluntary grasp, ability to kick, head control, rolling, sitting, crawling, standing, and walking. Within each milestone are intermediate steps of attaining the full milestone, for example, it has four levels of sitting: sits with support at hips, props self-up, stable sitting and pivots, alongside the corresponding developmental age population norm. In contrast, the WHO instrument measures six gross motor milestones: sitting without support, hands-and-knees crawling, standing with assistance, standing alone, walking with assistance and walking alone, also with corresponding developmental age population norms.[6] The WHO instrument has clear, quantitative definitions of motor milestones, with respect to the physician's method of administration and interpretation of the child's performance. For example, sitting without support is defined as the ability to sit up straight unaided for at least 10 seconds which is not a criterion in the HINE-2.

In NURTURE (presymptomatic SMA) HINE-2 was administered up to day 778, thereafter the WHO motor milestone questionnaire was administered. In the 5-year update of the NURTURE study, all children with three SMN2 copies (n=10) achieved all WHO motor milestones within normal developmental timeframes, apart from

[5] Haataja L, et al. Optimality score for the neurologic examination of the infant at 12 and 18 months of age. J Pediatr. 1999 Aug;135(2 Pt 1):153-61.
[6] De Sanctis R, Coratti G, Pasternak A, Montes J, Pane M, Mazzone ES, Young SD, Salazar R, Quigley J, Pera MC, Antonaci L, Lapenta L, Glanzman AM, Tiziano D, Muntoni F, Darras BT, De Vivo DC, Finkel R, Mercuri E. Developmental milestones in type I spinal muscular atrophy. Neuromuscul Disord. 2016 Nov;26(11):754-759. doi: 10.1016/j.nmd.2016.10.002. Epub 2016 Oct 5. PMID: 27769560; PMCID: PMC5091285.

walking with assistance in one child (this child later went onto achieve standing alone and walking alone within normal developmental timeframes). In children with two SMN2 copies (n=15), all achieved sitting without support and standing with assistance, 14 achieved hands and knees crawling and walking with assistance, and 13 achieved standing alone and walking alone, with some attaining milestones within normal developmental timeframes. As all patients at least achieved the ability to sit without support and were > 2 years of age, the WHO instrument should be considered the most clinically valid for the pre-symptomatic population.

In ENDEAR (symptomatic type 1 SMA), participants were younger than 24 months at the end of the trial and, therefore, WHO motor milestones were not gathered (although this instrument was used in SHINE if the patient was > 2 years of age and able to sit without support). Furthermore, prior to the advent of disease modifying therapies in SMA, type 1 patients would never achieve the ability to sit without support. It is therefore more clinically valid to use the HINE-2 in this population to monitor development progress in a more granular manner, this is aligned with UK clinical practice.

To make best use of the extensive follow-up data available for nusinersen in the economic model it was necessary to use HINE-2 up to 24-months old, and WHO thereafter, when assessing the achievement of gross motor milestones. If equivalence between the two instruments was not assumed then it would have been necessary to disregard data from either HINE-2 or WHO. This would have meant that a substantial proportion of relevant efficacy data for nusinersen would have been excluded from the economic model and it was judged that this would have reduced the robustness of the available data pool. It could also be argued that the exclusion of this data would have led to misleading efficacy estimates being presented as part of the company submission.

B2. [Priority question] Document B Section 3.3.1. Presymptomatic model: Would it be possible for the company to share the results from the HINE-2 analysis as one of the clinical endpoints of NURTURE?

In NURTURE, HINE motor milestones are only assessed and reported in the study up to Day 778, after which motor milestone development is based on WHO motor milestones criteria.

The latest available clinical study report (CSR) is from November 2020 and based on a datacut from 19th February 2020. The information for the HINE-2 outcomes presented below are based on this datacut. A later datacut from 15th February 2021 is presented after with WHO motor milestones.

Total motor milestone scores[7]

The mean HINE total motor milestone score at baseline for the 25 participants in the Efficacy Set was [redacted] points, ranging from [redacted] to [redacted] points. Baseline scores were lower for participants with 2 *SMN2* copies (mean [redacted] points, range: [redacted] to [redacted] points) than for participants with 3 *SMN2* copies (mean [redacted] points, range: [redacted] to [redacted] points).

The mean HINE total motor milestone score increased steadily over time up to Day 659 and remained stable thereafter (Figure 3). No participant experienced worsening in HINE total motor milestone score compared to baseline at any subsequent visit up to Day 778 or the last study visit.

Figure 3. Mean HINE Total Motor Milestones Over Time – Efficacy Set



[7] Biogen and IONIS Pharmaceuticals. A study of multiple doses of nusinersen (ISIS 396443) delivered to infants with genetically diagnosed and presymptomatic spinal muscular atrophy (NURTURE). Identifier: NCT02386553. In: ClinicalTrials.gov [internet]. Bethesda: US National Library of Medicine: 2021.

Response in expected and selected motor milestones[8]

In this February 2020 datacut, all 25 participants achieved the maximum level for head control (i.e., all the time upright), sitting (i.e., stable sit or pivot), voluntary grasp (i.e., pincer grasp), rolling (i.e., supine to prone), and kicking (i.e., touches toes). Eleven of 15 participants (73%) with 2 *SMN2* copies and all 10 participants (100%) with 3 *SMN2* copies achieved the maximum level for crawling and standing on study, and 10 of 15 participants (67%) with 2 *SMN2* copies and all 10 participants (100%) with 3 *SMN2* copies achieved the maximum level for walking on study. Participants with 3 *SMN2* copies achieved milestones at ages similar to what is expected in healthy infants without SMA. Participants with 2 *SMN2* copies either achieved milestones at similar ages or were delayed in the achievement of milestones as compared with children without SMA.

As would be expected, participants with 3 *SMN2* copies generally achieved motor milestones faster than participants with 2 *SMN2* copies, particularly for the milestones of standing independently and walking. The median age for achieving standing independently was [redacted] months for participants with 2 *SMN2* copies and [redacted] months for participants with 3 *SMN2* copies. The median age for achieving walking independently was [redacted] months for participants with 2 *SMN2* copies and [redacted] months for participants with 3 *SMN2* copies. Most participants maintained the motor milestones they had achieved at every visit following the time they first achieved them. Loss of motor milestones was infrequent and often transient.

WHO motor milestones

After day 778, milestones were assessed using the WHO instrument and in the 5-year update, 100% of the 3 SMN2 copy cohort maintained the ability to walk independently and 87% of the 2 SMN2 copy cohort also achieved this milestone.[9]

[8] Biogen and IONIS Pharmaceuticals. A study of multiple doses of nusinersen (ISIS 396443) delivered to infants with genetically diagnosed and presymptomatic spinal muscular atrophy (NURTURE). Identifier: NCT02386553. In: ClinicalTrials.gov [internet]. Bethesda: US National Library of Medicine: 2021.

[9] Crawford TO, Swoboda KJ, De Vivo DC, Bertini E, Hwu WL, Finkel RS, et al. Continued benefit of nusinersen initiated in the presymptomatic stage of spinal muscular atrophy: 5-year update of the NURTURE study. Muscle Nerve. 2023;68(2):157-70.

B3. [Priority question] Document B Section 3.3.1. Presymptomatic model: Can the company clarify how HINE-2 and WHO motor milestone data were pooled together to inform model state occupancy for nusinersen for patients younger than 2 years old in the NURTURE study?

As described in the response to question B1, HINE-2 was administered until patients were aged 24 months, which is the standard approach with this instrument. From 24 months and older, the WHO instrument was administered. Therefore, it was necessary to assume equivalence across the two instruments in terms of achieving each gross motor milestone (i.e. a patient achieving 'sitting without support' using the WHO instrument would also obtain a score of 3 or 4 when measured for sitting using HINE-2). More details on this are included on pages 131 and 132 of the company submission, including Table 34 which has been replicated below.

Table 1. Definitions of health states for HINE-2 section 2 and WHO measures of motor skills

	HINE-2 section 2 definition	WHO motor milestone definition
Sitting without support	Score 3-4 in sitting ability (stable sitting or pivot achievement) and a score of less than 2 in standing ability.	Sits up straight with head erect for 10 seconds without support from hands.
Standing with support	Score of 2 in standing ability. Any score in other items except walking ability.	Stands in an upright position on both feet holding onto a stable object with support from hands only for 10 seconds. The body does not touch the stable object.
Walking independently	Score of 3 in walking ability. Any score in other items.	5 steps independently. One leg moves while the other supports weight.

B4. [Priority question] Document B Section 3.3.1.2. BSC effectiveness:

a) Can the company clarify whether WHO motor milestone were data collected for ENDEAR?

WHO motor milestone data were not collected in ENDEAR as participants were <24 months old in the trial and, therefore, the HINE-2 instrument was used to assess motor function for the full time horizon. However, once participants entered the open-label extension SHINE study then WHO motor milestone data were collected, from the age of 24 months and once the patient was able to sit without support.

b) How was ENDEAR data used to inform state occupancy in the BSC arm?

HINE-2 data reported for the placebo arm of ENDEAR was used to inform health state occupancy for BSC during the first 4 cycles in the type 1 model (up to 12 months). This data also informed the effectiveness of BSC in the pre-symptomatic model, as described in more detail in the response to question B4c.

c) Were any of the HINE-2 data from ENDEAR used to inform the BSC arm in the presymptomatic model?

As described in Section B.3.3.1.3 of the company submission, the NURTURE study did not include a control arm and, therefore, there was no direct data to inform the efficacy of BSC from this study.

Instead, control arm data from the ENDEAR (type 1) and CHERISH (type 2 and type 3) were used to inform the effectiveness of BSC in the pre-symptomatic model. This was achieved by estimating a weighted average of the proportion of patients that achieved each motor milestone with BSC in the type 1 population (described in Section B.3.3.2) and the type 2/3 population (described in Section B.3.3.3). The weighted average was information by the distribution of the total SMA population by SMA sub-type, based on a worldwide epidemiology study conducted by Calucho et al (more details in Document B)[10].

B5. Document B Section B.3.2.1 Economic analysis: did the company consider results from the RAINBOWFISH study to inform the risdiplam arm in the nusinersen evidence submission, and consider the feasibility of an ITC or similar approach between this study and NURTURE?

Yes, the feasibility of undertaking an ITC using data from NURTURE and RAINBOWFISH was considered. At the time of completing the updated clinical SLR (October 2023), very limited published data from the RAINBOWFISH study were available. This is because only one poster publication from March 2022 was

[10] Calucho M et al. Correlation between SMA type and SMN2 copy number revisited: An analysis of 625 unrelated Spanish patients and a compilation of 2834 reported cases. Neuromuscul Disord. 2018 Mar;28(3):208-215.

identified, which reported preliminary safety and efficacy data from the study[11]. This poster did report data on motor milestone attainment but this was for only 7 patients and very limited information on baseline characteristics was included in the publication, including potential treatment effect modifiers, making it challenging to estimate the comparability of the populations, leading to potential bias of unknown size and direction. Therefore, due to the combination of a very small sample size and limited reporting of study information, it was judged not feasible to incorporate data from RAINBOWFISH into an ITC.

B6. Document B Section B.3.2.1 Economic analysis: Were additional clinical endpoints such as event-free survival or permanent ventilation-free survival considered for the ITC between nusinersen and OA?

There were no permanent ventilation or death events in either the NURTURE or SPR1NT clinical trials[12, 13]. As such, there were insufficient events to undertake an ITC between nusinersen and OA for these outcomes.

B7. Document B Section 3.3.1. Presymptomatic model: Was a cost-comparison between nusinersen, risdiplam, and OA considered?

No head-to-head data is available to compare the effectiveness of nusinersen, risdiplam, and OA. As described in Section B.2.5 of Document B, an indirect comparison of nusinersen versus OA was attempted in the pre-symptomatic population but the outputs from this analysis were disregarded due to the very high levels of bias associated with the ITC. Additionally, as described in the response to question B5, an ITC of nusinersen versus risdiplam in the pre-symptomatic population was judged to not be feasible due to a small sample size (n=7) and lack of reporting for the RAINBOWFISH study. Overall, this meant there was insufficient evidence to support a position of equal treatment effect for all interventions, which is a requirement for a cost-comparison.

[11] Servais L, et al. RAINBOWFISH: preliminary efficacy and safety data in risdiplam-treated infants with presymptomatic spinal muscular atrophy. In: 17th International Congress on Neuromuscular Diseases. Brussels. J Neuromuscul Dis. 2022.9(Suppl 1):S114-15.
[12] Crawford T, et al. Continued benefit of nusinersen initiated in the presymptomatic stage of spinal muscular atrophy: 5-year update of the NURTURE study. Muscle Nerve. 2023 Aug;68(2):157-170.
[13] Strauss K, et al. Onasemnogene abeparvovec for presymptomatic infants with two copies of SMN2 at risk for spinal muscular atrophy type 1: the Phase III SPR1NT trial. Nat Med. 2022 Jul;28(7):1381-1389.

B8. Document B Section 3.3.1. Presymptomatic model, Table 37:

The company submission shows the results from Mercuri et al. 2018 as the difference (95% CI): [redacted] but the estimates reported in the publication were 14 (−7 to 34). Could the company clarify this difference?

There is an error in the company submission as a "-" is missing from the confidence interval. Therefore, the company submission should have read as follows:

[redacted]

All other differences are related to rounding.

B9. [Priority question] Document B Section 3.3.1. Presymptomatic model, Table 37: The average long-term risk of motor milestone decline for nusinersen is a composite measure of the probability of treatment response from the ENDEAR and CHERISH trials.

a) **ENDEAR data uses HINE-2 data, while CHERISH uses WHO motor milestones. Did the company consider the limitations of pooling data with different clinical definitions?**

As described in the response to question B1, the HINE-2 and WHO instruments do not use exactly the same definitions for each motor milestone. In particular, the WHO instrument tends to use a more strict definition, such that it may be harder for an individual to reach a specific motor milestone when measured using the WHO, rather than HINE-2. The assumption of equivalence was necessary in order to maximise the amount of motor milestone attainment data that was available to assess the effectiveness of nusinersen and BSC.

b) **Risk of decline is derived as the inverse of the probability of treatment response. Did the company consider the limitations of equating no treatment response with motor milestone decline?**

Natural history data shows that people with SMA types 1 to 3 will ultimately experience a decline in their motor function if they are not receiving active therapy

(i.e. BSC), with the rate of decline affected by the SMA type. Therefore, natural history data from Wadman et al was used to model long-term decline with BSC[14].

In terms of nusinersen, current evidence from clinical trials indicates that motor milestones are maintained with this treatment. However, there is an absence of long-term evidence available to inform treatment effects and it may be overly optimistic to assume motor milestones would be maintained indefinitely. Additionally, in the advisory board that was undertaken, clinical experts highlighted that they would eventually expect to see decline with disease modifying therapies albeit at a slower rate compared with BSC.

In an absence of evidence to inform long-term decline for those receiving nusinersen, an assumption was required. It was judged preferable to use an assumption based upon available evidence, as much as possible. Therefore, the treatment effect for nusinersen versus BSC, as measured within the clinical trials, was applied to natural history data for long-term decline, regardless of whether that initial treatment effect was based on milestone attainment or milestone decline.

The uncertainty around the long-term effectiveness of nusinersen was acknowledged in the original submission via investigation in the scenario analysis by (a) halving the rate of decline and (b) removing the rate of decline so people maintained stable throughout their lifetimes.

c) For the CHERISH relative effectiveness estimate, why is an Odds Ratio formula applied to the probabilities of improvement in WHO motor milestones?

Thank you for your question. Upon review of the available data, it is apparent that it was an error to treat the relative effectiveness estimates from CHERISH as an odds ratio. In fact, there reported data was a relative risk and, as such, it was unnecessary to apply the odds ratio formula. This means that there was a small error in the relative risk of decline for nusinersen versus best supportive care that was applied in the later-onset model. More details are provided below.

[14] Wadman R, et al. Muscle strength and motor function throughout life in a cross-sectional cohort of 180 patients with spinal muscular atrophy types 1c-4. Eur J Neurol. 2018 Mar;25(3):512-518.

The relative long-term effectiveness of nusinersen versus BSC was based on the proportion of people who gained at least one WHO motor milestone in CHERISH. At 15 months, which was the final follow-up, [redacted] and [redacted] of people on nusinersen and BSC, respectively, achieved this outcome. This equates to a relative risk of [redacted] ([redacted]). However, as described above, in the original company submission this was incorrectly labelled as an odds ratio and was subsequently converted to a relative risk. Instead the relative risk of [redacted] should have been used directly. This could then be converted to a relative risk of motor milestone maintenance or decline, which equates to a value of [redacted] (1 ÷ [redacted]). This value is lower than the relative risk of [redacted] that was applied in the original company submission and indicates a higher level of long-term effectiveness with nusinersen.

The later-onset model has been updated to include the new relative risk estimate. This is based on the models that were created for the addendum that was provided to NICE in September 2024. The results for the total later-onset population in that addendum are replicated below.

Table 2: Deterministic Results from the Type 2/3 Model – Sept 2024 addendum

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)	NHB at £30,000 / QALY
Nusinersen	[redacted]	19.00				
BSC	[redacted]	15.21	[redacted]	3.79	[redacted]	[redacted]

The results following the inclusion of the updated relative risk value are presented below. By comparing the two tables, it can be seen that the update to the model has led to a reduction in the ICER of approximately [redacted]

Table 3: Deterministic Results from the Type 2/3 Model – following updated relative risk

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)	NHB at £30,000 / QALY
Nusinersen	[redacted]	19.15				
BSC	[redacted]	15.21	[redacted]	3.95	[redacted]	[redacted]

The relative risk described above also affects the pre-symptomatic model, so this model has also been updated. In the original submission, an average (mean) of the long-term effectiveness estimates from the type 1 and type 2/3 models was used, which equated to a relative risk of decline of [redacted] for nusinersen versus BSC (that is for the full pre-symptomatic population). Following the changes described above, an average relative risk of [redacted] has been estimated for the total pre-symptomatic population. This is based on the updated relative risk of [redacted] from the type 2/3 model and the relative risk of [redacted] from the original type 1 model (as described on p152 of Document B).

The pre-symptomatic model has been updated to include the new relative risk estimate described above. This is based on the models that were created for the addendum that was provided to NICE in September 2024. The results for the total pre-symptomatic population in that addendum are replicated below.

Table 4: Deterministic Results from the Pre-symptomatic model – Sept 2024 addendum

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)	NHB at £30,000 / QALY
Nusinersen	[redacted]	16.85				
BSC	[redacted]	8.75	[redacted]	8.10	[redacted]	[redacted]

The results following the inclusion of the updated relative risk value are presented below. By comparing the two tables, it can be seen that the update to the model has led to a reduction in the ICER of approximately [redacted]

Table 5: Deterministic Results from the Pre-symptomatic model – following updated relative risk

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)	NHB at £30,000 / QALY
Nusinersen	[redacted]	17.08				
BSC	[redacted]	8.75	[redacted]	8.32	[redacted]	[redacted]

d) **For the CHERISH relative effectiveness estimate, since the difference in improvements in WHO motor milestones was not statistically significant between nusinersen and BSC, was this uncertainty included in the economic model?**

Yes. The relative risk was varied in the PSA assuming a standard error of 0.07% and a log-normal distribution.

B10. Document B Section 3.3.1. Presymptomatic model: Has the company considered further motor milestones data from the REACH registries to inform long-term effectiveness assumptions in the model?

At the time of submission, there was only data available for 5 patients with pre-symptomatic SMA from the REACH registry. Alternatively, the NURTURE study provides data for 25 patients over 5 years of follow-up. Therefore, it was judged that NURTURE was a substantially more robust data source to inform the effectiveness of nusinersen in the pre-symptomatic model.

Type-1 SMA economic model

B11. [Priority question] Document B Section 3.3.2. Infantile-onset (type 1) model:

a) **Can the company clarify how were data from the ENDEAR trial (using HINE-2) and data from the SHINE study (using WHO motor milestones) pooled to inform state occupancy?**

As described in responses to questions B1 and B3, HINE-2 is only administered to children aged up to 24 months. The total follow-up period in ENDEAR was 13 months with the mean age at baseline approximately 6 months. Therefore, HINE-2 data was collected for the duration of ENDEAR. Once patients moved into the open-label extension SHINE study the HINE-2 was replaced with WHO motor milestone instrument to track the impact of treatment on motor function. Therefore, within the model, health state occupancy was informed by HINE-2 data from ENDEAR for the first four cycles in the model (up to 12 months) and WHO data was used for all subsequent cycles up to month 60 for nusinersen.

b) **Is state occupancy for the first 12 months informed by HINE-2 outputs, and WHO motor milestones subsequently?**

Yes this is correct, as described in the response to question B11a above.

c) **Can the company comment on the potential limitations of pooling the patient populations from ENDEAR with SHINE?**

SHINE is an open-label extension study that enrolled patients once the follow-up period for ENDEAR had ended. Therefore, given the same cohort was included in both studies, it was deemed relevant to pool data from ENDEAR and SHINE in order to maximise the time horizon from which nusinersen efficacy data were available to inform the cost-effectiveness model. There are not expected to be any major limitations from this approach.

d) **Can the company comment on the potential limitations of pooling HINE-2 and WHO motor milestones data together?**

Please see responses to questions B1 and B9.

B12. Document B Section 3.3.2.4 Infantile-onset (type 1) model, survival:

a) **Can the company clarify whether the SHINE data used to inform the nusinersen arm cover all of the ITT population in the SHINE study or is it only those patients previously treated with nusinersen before the baseline of SHINE?**

The SHINE data that was used to inform the nusinersen arm in the economic model was based on those patients previously treated with nusinersen during ENDEAR (i.e. not the full ITT population of SHINE). Theoretically, all type 1 SMA patients who received nusinersen during SHINE could have been analysed. However, this includes patients who received placebo for 13 months during the ENDEAR study. In clinical practice, the aim is to administer active therapy as soon as possible after diagnosis. Therefore, for those participants who received placebo during ENDEAR, the delay in receiving active therapy does not reflect current clinical practice. Therefore, it was judged appropriate to base the efficacy of nusinersen on only those patients who received that intervention from the baseline of ENDEAR.

b) **Was a RPSFTM model used to pool SHINE and ENDEAR data for the analysis of permanent ventilation data?**

Yes that is correct, an RPSFTM was used to pool SHINE and ENDEAR data for permanent ventilation data.

c) **Can the company provide clarification on how some of the datapoints in the survival data for BSC from ENDEAR extend beyond the follow-up points of the trial?**

RPSFTM was used to adjust the survival of people in the control arm of ENDEAR. As described in Section B.3.3.2.4 of Document B, this method is designed to estimate what would have happened to the control arm from the ENDEAR study if they did not switch treatments (to nusinersen) at the start of the open-label extension SHINE. This provided additional follow-up data for the control arm. The process meant that if participants who received placebo during ENDEAR then died during SHINE the RPSFTM method predicted when they would have died if they did not switch to nusinersen and this is reflected in the presented Kaplan-Meier curves. In other words, the KM curves include placebo patients who switched to nusinersen during SHINE but then adjusted using the RPSFTM methods, which is why the curves extend beyond the final 13-month follow-up visit in ENDEAR.

Health Related Quality of Life

B13. Document B Section 3.4.5. Health-related quality-of-life data: Did the company consider using utility estimates from either the MAA or the systematic review as scenario analyses in the economic model at the time of writing the submission? Would it be a useful approach using a more current data-cut from the MAA data to inform quality of life in the economic model?

As described in pages 170 and 171 of Document B of the company submission, the systematic review identified 17 primary studies reporting potentially relevant data on the impact of SMA on health-related quality of life. However, only 3 studies reported data that matched the health states in the models. The use of data from these 3

studies was ultimately disregarded for reasons described in Document B (namely issues with generalisability, face validity and non-use of EQ-5D).

It was judged that it would not be beneficial to incorporate the health-related quality of life data from the MAA into the model. For the paediatric MAA, EQ-5D data was only captured for two patients, which is insufficient data to inform the model.

For the adult MAA, data were available from up to 51 patients. However, data was only reported for the full cohort, which means there was no data by health state and this would be required to inform the model. Therefore, specific data analysis requests would have been necessary to generate health state utilities that could be used to inform the model.

B14. Document B Section 3.4.4. Adverse reactions:

a) **Can the company expand on potential implications from assuming that the impact of treatment-related adverse effects are already captured by baseline utility values?**

The approach to exclude adverse events from the cost-effectiveness models is aligned with the previous NICE submissions related to SMA, including TA588, TA755 and HST24. As noted in the company submission from HST24 “it is difficult to separate utilities due to treatment from the complications associated with SMA, which are already accounted for in the health state.” Therefore, if the impact of specific adverse events were included in the model, via the inclusion of disutilities, this may lead to the double counting of certain negative health effects.

The uncertainty associated with health state utilities was addressed by the provision of several scenario analyses. These included using different sources of utility data, and excluding caregiver and on-treatment utility increments.

b) **Did the company explore if there was any disutility associated with intrathecal administration of Nusinersen?**

Adverse reactions considered related to the lumbar puncture procedure are headache, vomiting and back pain which largely occur within 72 hours of the

procedure and are short-lived and transient in nature.[15] Therefore any impact on health-related quality of life is expected to be negligible so it was not considered. As described above, given the nature of SMA it is difficult to separate utilities due to treatment from the complications associated with SMA, which are already accounted for in the health state utility values.

The current approach to exclude any disutilities associated with adverse events aligns with the previous NICE submissions related to SMA and is consistent across treatments.

[15] EMC. Spinraza 12 mg solution for injection. 2023. Available from: https://www.medicines.org.uk/emc/product/2715.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Multiple Technology Appraisal

Nusinersen for treating spinal muscular atrophy – (MA review of TA588)

Additional clarification questions

April 2025

File name	Version	Contains confidential information	Date
ID6195 SMA MTA Biogen clarification questions (Set 2)_Biogen response_Final_[redacted]	1a	No	09/04/2025

Section A: Clarification on effectiveness data

Presymptomatic

A1. [Priority question] What risk of bias if any might be associated with using the unanchored MAIC results on HINE-2 milestones (from NURTURE and SPR1NT or NURTURE and RAINBOWFISH) to inform relative effectiveness between disease modifying therapies? Is it appropriate to assume equivalence in effectiveness on average between therapies in the absence of better evidence?

As noted in the Company submission, Biogen's position is that, due to the major limitations associated with the indirect comparisons (ITCs) that were attempted in order to compare nusinersen with risdiplam and OA, there is a substantial risk of bias associated with the outputs from those ITCs. Therefore, it is not possible to make any kind of reliable comparison between these interventions and this includes assuming equivalence. If such an assumption is made it would be associated with a very high level of uncertainty that may cause misleading conclusions to be drawn. Therefore, it is judged that the only reasonable and appropriate approach is to compare nusinersen with BSC alone, as it is possible to generate reasonable comparative efficacy estimates against this comparator.

The limitations associated with the ITCs were covered in Section B.2.5 of the Company submission and are summarised below, for the pre-symptomatic population:

- A comparison of nusinersen with risdiplam was not possible due to the limited published data from the RAINBOWFISH study that were available at the time (notably, data were only available for 7 patients and very limited information on baseline characteristics were reported – this is discussed further in the response to question B5 from the clarification questions sent to Biogen on 7th March).

- The effective sample size (ESS) for the matching adjusted indirect comparison (MAIC) was very low. The original sample size for the nusinersen population in NURTURE was 25 and this was reduced to an ESS of 8.78 after weighting. Therefore, the ITC was based on very small patient numbers.

- The World Health Organisation (WHO) motor milestone instrument states that the upper limit for achieving walking independently within a normal timeframe is 18 months. However, in the NURTURE study, data were not reported at 18 months and so, to complete the MAIC, data were extracted from the last WHO assessment that occurred before a participant turned 18 months of age. The exact timepoint for data collection is unclear from the OA SPR1NT trial but it is noted that children were reported up to 18 months. Therefore, if assessments of motor milestone achievement were made at different timepoints this will bias the indirect comparisons (as a child will have a greater chance of achieving a milestone if the follow-up visit occurred when they were older). Additionally, different instruments were also used across trials: WHO milestones in NURTURE vs. Bayley-III in SPR1NT with definitions of milestone attainment varying between them. In order to make a comparison, it was necessary to assume equivalence between these definitions which introduced further bias into the analysis.

It should be noted that small differences in inclusion/exclusion criteria and baseline characteristics impact both motor and nonmotor clinical outcomes within the presymptomatic population. For example, a subgroup analysis was undertaken on patients in NURTURE with 2 SMN2 copies who did not have CMAP <2mV and who were not areflexic at baseline (criteria used in the SPR1NT trial of OA - SPR1NT only reported peroneal CMAP values whereas ulnar CMAP values were presented for NURTURE). Eight children met these criteria, were of similar age at first nusinersen dose, had similar baseline HINE-2 score and their baseline CHOP-INTEND scores were higher versus all children with 2 SMN2 copies in NURTURE (n=15). No child in this subgroup received respiratory intervention of gastrostomy tube placements vs. 4 and 5 children, respectively, among all children with 2 SMN2 copies. One child met the protocol-specified criteria for SMA symptoms vs 8/15 among all children with 2 SMN2 copies. Furthermore, a higher proportion in this subgroup achieved WHO motor milestones within normal developmental milestones[1]. The differences between this subgroup and the main NURTURE population illustrates the impact of baseline status on the efficacy outcomes.

[1] Crawford T et al., Continued benefit of nusinersen initiated in the presymptomatic stage of spinal muscular atrophy: 5-year update of the NURTURE study. Muscle Nerve. 2023 Aug;68(2):157-170. doi: 10.1002/mus.27853. Epub 2023 Jul 6.

Type 1

A2. [Priority question] What risk of bias if any might be associated with using the unanchored MAIC results on HINE-2 milestones (from ENDEAR and STR1VE or ENDEAR and FIREFISH) to inform relative effectiveness between disease modifying therapies?

Please see the response to question A1 – it is Biogen's position that the ITC data should not inform the relative effectiveness of all disease modifying therapies due to the substantial risk of bias associated with these comparisons.

A summary of the major limitations associated with the ITCs, for the type 1 population, are provided below:

- As with the pre-symptomatic analysis, the ESS was very low for the type 1 population which may indicate widely imbalanced variables or little overlap between baseline characteristics, leading to low statistical power to detect differences between treatment. For example, for the analysis of the achievement of sitting without support at 18 months, the ESS for nusinersen was 12.61 (reduced from the study cohort of 46).

- As described in the response to question A1, there is a risk that the timepoints for the final follow-up visits were misaligned across the relevant studies. This would cause the indirect comparisons to be biased in favour of the intervention with the latest follow-up visit.

- For the comparison of nusinersen versus OA, the achievement of motor milestones was based on BSID-III and HINE-2 for OA and nusinersen, respectively. However, clinical experts noted that it is not appropriate to assume that these two instruments can be assumed to be equivalent in the way motor milestone attainment is captured. In particular, it is likely easier for someone to achieve 'sitting without support' when using BSID-III because this instrument incorporates upper limb function, which is not the case with HINE-2.

Additionally, Jiang and colleagues previously completed a critical appraisal of three published MAICs comparing disease modifying interventions for both infantile-onset and later-onset SMA and their findings are relevant here[2]. In particular, the article included the following two conclusions that emphasised the issues associated with indirect comparisons for the current SMA treatments (including nusinersen, risdiplam and OA):

- "Various sources of bias in the MAICs were identified, including lack of control for key confounders and effect modifiers, inconsistency in outcome definitions across trials, imbalances in important baseline characteristics after weighting, and lack of reporting key elements."

- "Findings from a MAIC can be misleading because of cross-trial differences in inclusion/exclusion criteria, baseline characteristics, definitions and assessment schedules of outcomes, and key baseline confounders not balanced after weighting, especially in the context of SMA."

The issues described by Jiang and colleagues are, on the whole, also relevant to the ITCs that were undertaken as part of the company submission (as they were based on the same data sources). Therefore, that critical appraisal further emphasises the major risk of bias associated with ITCs related to nusinersen, risdiplam and OA, much of which are of unknown magnitude and direction which would introduce significant added uncertainty into the decision problem.

[2] Jiang T., et al. A Critical Appraisal of Matching-Adjusted Indirect Comparisons in Spinal Muscular Atrophy. Adv Ther. 2023 Jul;40(7):2985-3005. doi: 10.1007/s12325-023-02520-2.

A3. [Priority question] What risk of bias, if any, might be associated with using the MAIC results on Permanent Ventilation (from ENDEAR and FIREFISH) to inform relative effectiveness between disease modifying therapies? Is it appropriate to assume relative equivalence on average between therapies in the absence of better evidence?

Please see the response to question A2. The issues described in that response also apply to a MAIC for permanent ventilation. It should be also noted that there are important differences exclusion criteria between trials regarding pulmonary events and pulmonary function, which are key factors influencing outcomes such as permanent ventilation and overall survival. FIREFISH included more restrictive exclusion criteria than ENDEAR (e.g., excluded patients with hospitalisation for pulmonary event within the last 2 months; with invasive ventilation or tracheostomy; requiring non-invasive ventilation or hypoxemia with or without ventilator support; and history of respiratory failure or severe pneumonia and had not fully recovered their pulmonary function at time of screening vs. excluded patients with hypoxemia at screening). Incomparable exclusion criteria used in FIREFISH and ENDEAR may have enriched for a population in FIREFISH with less pulmonary burden compared to patients in ENDEAR that cannot be resolved through MAIC weighting.

Type 2/3

A4. [Priority question] What risk of bias if any might be associated with using the STC results on motor milestones (from CHERISH and SUNFISH) to inform relative effectiveness between disease modifying therapies?

Please see the response to question A1 – it is Biogen's position that the ITC data should not inform the relative effectiveness of all disease modifying therapies due to the substantial risk of bias associated with these comparisons.

It was not possible to undertake any indirect comparison directly related to motor milestones for the type 2/3 population. This was due to a lack of data on the attainment of motor milestones using instruments such as WHO or MFM-32 for comparators. Instead, as reported in section B.2.5 of the Company submission, within this population two STCs were completed related to HFMSE and RULM.

The major issues with these STCs were described in the paragraph below, which is taken from the Company submission:

“For the comparison of nusinersen versus risdiplam in the type 2/3 population, a simulated treatment comparison (STC) was completed to compare RULM and HFMSE scores. An STC was necessary because the attempt to complete a MAIC failed, likely due to a poor overlap for the age at screening and age at symptom onset for the nusinersen and risdiplam trials, which were judged to be key covariates. However, the differences in age between the study population still had a major impact on the STC outputs. In particular, the median age at screening was 108 months and 49.2 months within the risdiplam and nusinersen studies, respectively. Additionally, the maximum age of screening for nusinersen patients was 101.8 months. Therefore, to enable a comparison, the STC was estimating nusinersen patient outcomes that were beyond the observed data for this covariate (i.e. it was estimating the efficacy of nusinersen for patients with a median age of 108 months but the oldest patient in the nusinersen study had an age of 101.8 months at screening).”

Additionally, the critical appraisal undertaken by Jiang and colleagues, as described in the response to question A2, included a MAIC for the later-onset population. Therefore, the conclusions from that critical appraisal also apply to the Biogen ITCs in the type 2/3 population, which reemphasises the major risk of biases associated with those ITCs and lack of comparability in the underlying populations. For example, there were importance differences in exclusion criteria for CHERISH vs. SUNFISH (e.g. excluded patients with severe scoliosis or contractures vs. excluded patients who had surgery for scoliosis or hip fixation in the 1 year preceding screening or planned within next 18 months)

Section B: Clarification on cost-effectiveness data

Decision problem

B1. [Priority Question] Are the licenced indications for each of these interventions: risdiplam, nusinersen, and Onasemnogene abeparvovec (OA) comparable for each population Type?

Section B.1.3.2 of the submission document discusses the spectrum of subtypes of 5q SMA. Type 0 SMA often causes mortality due to respiratory distress within a few weeks.

Nusinersen

As per the SmPC, nusinersen is indicated for the treatment of 5q Spinal Muscular Atrophy. Clinical trial data for nusinersen currently reflects the presymptomatic population, as well as type 1, type 2 and type 3 SMA.

Nusinersen is the only treatment with a marketing authorisation for type 4 SMA. Evidence on the use of nusinersen in type 4 SMA is predominantly available from the SMArtCARE registry, which included 9 (4%) patients with type 4 SMA.

In England and Wales, NICE has recommended nusinersen for people with pre-symptomatic SMA, or SMA types 1, 2 or 3, under the terms of a managed access agreement (MAA).

Risdiplam

As per the SmPC, risdiplam is indicated for the treatment of 5q Spinal Muscular Atrophy with a clinical diagnosis of SMA Type 1, Type 2 or Type 3 or with one to four SMN2 copies.. Clinical trial data for risdiplam currently reflects the presymptomatic population, as well as type 1, type 2 and type 3 SMA.

In England and Wales, NICE has recommended risdiplam for people with pre-symptomatic SMA, or SMA types 1, 2 or 3, under the terms of a managed access agreement (MAA).

Onasemnogene abeparvovec (OA)

As per the SmPC, onasemnogene abeparvovec is indicated for the treatment of:

- People with 5q SMA with a bi-allelic mutation in the SMN1 gene and a clinical diagnosis of SMA Type 1, or
- People with 5q SMA with a bi-allelic mutation in the SMN1 gene and up to 3 copies of the SMN2 gene.

The safety and efficacy OA has not been established in people aged 2 years of age and older or with body weight above 13.5 kg. Furthermore, the Food and Drug Administration (FDA) have approved OA in the paediatric population who have reached gestational age and are aged less than 2 years.

In England and Wales, NICE has recommended OA in paediatric, type 1 SMA population aged under 6 months. Those between 7 and 12 months may also have access to OA, however, this is dependent upon agreement by a national multidisciplinary team. In the paediatric population with presymptomatic 5qSMA, OA is recommended for those aged less than 12 months under a managed access agreement. Clinical expert statements in HST15 highlighted that the side effects of OA appear to be more frequent in heavier and/or older paediatrics.

Are there any patient subgroups who are more likely to be given one treatment or the other based on the available evidence?

It is important that patients and clinicians have the option to prescribe any of the available SMA therapies and to tailor treatment choice based on individual characteristics and the preference of patients, balancing multiple factors such as efficacy, safety, route and frequency of administration and lifestyle factors.

Children with specific comorbidities, such as pre-existing liver damage, or children with high levels of antibodies against the AAV9 virus (which is used to deliver the gene therapy) may not be suitable candidates for treatment with OA. Indeed, after clinical screening, SMA UK estimated that 5 in 100 children do not meet the clinical requirements for OA. Furthermore, some people may opt against gene therapy for personal reasons.

People with SMA in England and Wales who are ineligible for, or decide against, treatment with OA currently have access (via MAAs) to nusinersen and risdiplam.

Clinical experts stated that, the choice of first-line treatment (between nusinersen and risdiplam) depends upon (1) baseline clinical assessment and (2) clinician/family decision. For example, if the clinician anticipates compliance issues with a daily medication, nusinersen may be recommended over risdiplam. Administration with nusinersen is only required three times a year during the maintenance phase. However, there could be logistical reasons people may opt for risdiplam (for example, access to specialist hospitals).

As per terms of the nusinersen MAA, intrathecal injection must be technically feasible in the opinion of the treating clinician and not contraindicated. Furthermore, patients must not have received spinal fusion surgery following a diagnosis of scoliosis which, in the opinion of the treating clinician, prohibits safe administration of nusinersen. Whilst it is technically feasible for nusinersen to be administered to patients with severe scoliosis, via CT-guided or ultrasound-guided intrathecal injection[3,4], most centres in England and Wales NHS do not currently have the infrastructure/resources to allow for these modes of administration.

Are there any trial populations that may have characteristics such that effectiveness evidence may not be fully generalisable to the population type?

Clinical experts highlighted that the population in CHERISH, at baseline, was more representative of a type 2 SMA population, rather than a total later onset population. However, those who achieved and maintained the ability to walk independently in CHERISH and SHINE (3 of 39 people at day 750) were more indicative to a type 3 population (by definition).

[3] Rosiak G, Lusakowska A, Milczarek K, Konecki D, Fraczek A, Rowinski O, Kostera-Pruszczyk A. Ultra-low radiation dose protocol for CT-guided intrathecal nusinersen injections for patients with spinal muscular atrophy and severe scoliosis. Neuroradiology. 2021 Apr;63(4):539-545. doi: 10.1007/s00234-021-02643-9. Epub 2021 Jan 29. PMID: 33512541; PMCID: PMC7965851.

[4] Wei C, Liang Z, Wu Y, Liu S, Qiu J, Meng L, Li C, Li S, Bao X, Wang Z, Chen L, Xiong H. Ultrasound-guided interlaminar approach for nusinersen administration in patients with spinal muscular atrophy with spinal fusion or severe scoliosis. Orphanet J Rare Dis. 2023 Feb 17;18(1):30. doi: 10.1186/s13023-023-02630-8. PMID: 36800969; PMCID: PMC9936713.

CHERISH exclusion criteria excluded people with severe contractures or severe scoliosis evident on the x-ray examination at screening[5]. Under the terms of the nusinersen MAA, it is stated that people can enter the MAA if "they have not received spinal fusion surgery following a diagnosis of scoliosis which, in the opinion of the treating clinician, prohibits safe administration of nusinersen". This is likely because of the lack of infrastructure in the NHS. Therefore, the CHERISH population is representative of the population eligible for nusinersen in the England and Wales NHS.[6]

B2. Why was 4 months considered an appropriate model cycle length? Is it appropriate to consider shorter cycle lengths like 1 month?

It was assumed that people could only transition by a maximum of one motor milestone in each cycle (See Section B.3.2.2 of the company submission). Therefore, a key consideration when determining cycle length was that this cycle length should be granular enough to capture meaningful changes in motor milestones. Table 1 (Wadman et al. (2017)[7]) and Table 2 (WHO[8]) show the average age at which the untreated SMA population and general population, respectively, will achieve WHO motor milestones. Based upon the age at which motor milestones are achieved or lost, as presented in these tables, it is highly unlikely that several motor milestones would be gained or lost within a 4-month period. Clinical experts also confirmed that a 4-month cycle length would allow for changes in motor milestones to be captured appropriately.

[5] Biogen and IONIS Pharmaceuticals data on file. CS4 (CHERISH). A phase 3, randomized, double-blind, sham-procedure controlled study to assess the clinical efficacy and safety of ISIS 396443 administered intrathecally in patients with later-onset spinal muscular atrophy [CHERISH]. Clinical study report. Study number: 396443-CS4. Interim. February 3, 2017.

[6] National Institute for Health and Care Excellence (NICE). Nusinersen for treating spinal muscular atrophy. TA588. Variation 2 to the Managed Access Agreement. May 2021. Available at: https://www.nice.org.uk/guidance/ta588/resources

[7] Wadman RI, Wijngaarde CA, Stam M, Bartels B, Otto LAM, Lemmink HH, Schoenmakers MAGC, Cuppen I, van den Berg LH, van der Pol WL. Muscle strength and motor function throughout life in a cross-sectional cohort of 180 patients with spinal muscular atrophy types 1c-4. Eur J Neurol. 2018 Mar;25(3):512-518. doi: 10.1111/ene.13534. Epub 2018 Feb 2. PMID: 29194869.

[8] World health organisation. Motor development milestones. Percentiles and mean in days and months for six gross motor milestones. Accessed April 2025. Available at: https://www.who.int/tools/child-growth-standards/standards/motor-development-milestones

Additionally, the model structure is inherently memoryless. This means that, in theory, a 1-month cycle length could allow for a percentage of the cohort to transition from not sitting, to sitting, to standing with support to walking independently in consecutive cycles. Given the information above, this would not be reflective of the real world. Therefore, a 4-month cycle is more appropriate.

Finally, the 4-month cycle length aligned with the modelled treatment regimen described by the SmPC[9]. This is: four loading doses administered on study days 0, 14, 28 and 63, followed by maintenance dosing once every 4 months. The model included half cycle correction to account for the fact that events and transitions can occur at any point during the cycle, not necessarily at the start or end of each cycle.

Table 1. Average age (years) at which WHO motor milestones are achieved in untreated SMA as per Wadman et al. (2017)

Motor milestone	Sitting without support	Standing with assistance	Walking independently
Motor milestone attainment			
Type 1c	N/A	N/A	N/A
Type 2a	1.2 (0.4 - 6.3)	N/A	N/A
Type 2b	0.7 (0.3 - 1.5)	1.3 (0.5 - 6.5)	N/A
Type 3a	0.7 (0.5 - 1.5)	1.0 (0.6 - 2.0)	2.2 (0.9 -10.4)
Type 3b	0.6 (0.5 - 0.8)	0.9 (0.7 - 1.0)	1.3 (0.8 -1.5)
Motor milestone deterioration			
Type 1c	N/A	N/A	N/A
Type 2a	8.7 (0.7-29.1)	N/A	N/A
Type 2b	16.5 (13.0-16.5)	6.5 (1.1-46)	N/A
Type 3a	25 (15.5- 40.5)	15.3 (3.5-49.5)	11.8 (2.5-34.5)
Type 3b	N/A	34.3 (6.5-60.5)	34.1 (6.5-65.7)

Table 2. Average age (months) at which WHO motor milestones are achieved in the general population

Motor milestone	5th percentile	50th percentile	95th percentile
Sitting without support	4.3 (4.2, 4.4)	5.9 (5.8, 6.0)	8.0 (7.9, 8.2)
Standing with assistance	5.5 (5.4, 5.6)	7.4 (7.3, 7.5)	10.1 (9.9, 10.3)
Walking independently	9.4 (9.2, 9.6)	12.0 (11.9, 12.1)	15.3 (15.0, 15.6)

[9] Electronic medicines compendium (emc). Spinraza 12 mg solution for injection. Last revision: March 2025. Accessed March 2025. Available at: https://www.medicines.org.uk/emc/product/2715/smpc

Presymptomatic and Type 1

B3. Is it feasible and likely in clinical practice for nusinersen patients to start other disease modifying therapies after discontinuation of nusinersen (risdiplam or OA) due to: different mechanisms of action; treatment effectiveness (or lack of); treatment-related adverse effects or other reasons?

Clinical experts consulted by Biogen during an advisory board highlighted that the freedom to switch between treatments should be left as open as possible. Therefore, it is feasible for people to switch from nusinersen to risdiplam or OA after discontinuation, but the opposite is also true (i.e. switching to nusinersen after discontinuation from risdiplam or due to a lack of benefit from OA).

The best evidence for discontinuation rate associated with nusinersen is from the MAAs. Under the terms of the nusinersen MAA, people can discontinue nusinersen to another treatment if one of the following criteria are met[10]:

1. There is a deterioration of symptoms, as indicated by a worsening in either HINE-2, CHOP-INTEND, RHS or RULM over 2 consecutive measurements in the absence of any stability or improvement in other scales.

2. Permanent ventilation, defined as ≥16 hours/day for 21 consecutive days in the absence of acute reversible infection, or requirement of insertion of permanent tracheostomy.

3. Inability to administer nusinersen by intrathecal administration because of spinal fusion surgery.

If criteria (1) or (3) are met, the person may be able to switch to another treatment depending upon eligibility. Additionally, under the terms of the nusinersen MAA, people can enter the MAA if they have had a “non-successful” treatment with OA. “Non-successful” treatment is defined as total worsening in scale score corroborated by two consecutive measurements (HINE, CHOP-INTEND, RHS) without maintaining stability or improvement on another scale and/or a deterioration in

[10] National Institute for Health and Care Excellence (NICE). Nusinersen for treating spinal muscular atrophy. TA588. Variation 1 to the Managed Access Agreement. July 2019. Available at: https://www.nice.org.uk/guidance/ta588/resources

respiratory function, defined as an increasing requirement for respiratory support overnight and/or, for that patient, an uncharacteristic increase in respiratory infections requiring hospital treatment that cannot be accounted for by aspiration or intrinsic lung disease[11]. Whilst these criteria are perhaps representative of a lack of treatment response, they do not capture sub-optimal response to OA, restricting treatment choice for some patients.

The paediatric MAA showed a relatively high discontinuation rate from nusinersen to OA and risdiplam, particularly in type 1, in which 45.65% and 65.71% of type 1 people (on the early access programme [EAP] and not on the EAP [non-EAP], respectively) discontinued. However, it is expected that these rates are not reflective of true clinical practice today. This is because, during the MAA study period, OA became available as a treatment option in this population and people who are eligible for OA are expected to have this treatment as first line (potentially after bridging with nusinersen or risdiplam). Therefore, switching on this large scale would not happen now that both treatments are available. Discontinuation to risdiplam over the 3.5 years was 14% in people with type 1 SMA (EAP and non-EAP combined) and 23% in people with later-onset SMA combined. Only 1 person discontinued because of spinal surgeries.

Given the issues described above for the paediatric MAA, data from the adult MAA may be more reflective of discontinuation patterns with nusinersen. Data from the adult MAA indicates that 4% discontinued and, of these patients, 0% discontinued due to a lack of apparent clinical benefit. Discontinuation is more likely due to perceived issues with the procedure to administer nusinersen (i.e. the need for an intrathecal administration).

[11] National Institute for Health and Care Excellence (NICE). Nusinersen for treating spinal muscular atrophy. TA588. Variation 2 to the Managed Access Agreement. January 2022. Available at: https://www.nice.org.uk/guidance/ta588/resources

Presymptomatic

B4. [Priority question] Given the availability of new therapies for presymptomatic patients, is it likely that patients receive BSC in clinical practice?

There is currently no newborn screening programme for SMA. People with pre-symptomatic SMA are typically identified if a sibling has SMA. Therefore, a proportion of the pre-symptomatic population will be unaware they have the disease and this means they will receive no active treatment (equivalent to BSC). Additionally, nusinersen and risdiplam are not currently available under routine commissioning for the pre-symptomatic population, and not all patients will receive OA, so BSC is necessary in this group.

It should be reemphasised that, due to the major limitations associated with the indirect comparisons of nusinersen versus risdiplam and OA (as described in detail within the response to questions A1 to A4), a comparison of nusinersen against BSC is most appropriate.

B5. Is it reasonable to expect a treatment effect duration of 6 years for risdiplam and OA as well as nusinersen? After 6 years, patients cannot improve motor milestones and can only maintain or decrease their milestone improvements. What feasible alternative scenarios could capture uncertainty in the rate of decline?

As stated in Section B.3.7 of the company submission, follow-up data on the efficacy of nusinersen in the pre-symptomatic population is available for up to 72 months from the NURTURE study[12]. This data shows a durable treatment effect with nusinersen. Published efficacy data is available for up to 2 years for both risdiplam (RAINBOWFISH[13]) and OA (SPR1NT[14]). Therefore, the information on the treatment effect with risdiplam and OA is based on shorter follow-up. It would be inappropriate

[12] Biogen and IONIS Pharmaceuticals. A study of multiple doses of nusinersen (ISIS 396443) delivered to infants with genetically diagnosed and presymptomatic spinal muscular atrophy (NURTURE). Identifier: NCT02386553. In: ClinicalTrials.gov [internet]. Bethesda: US National Library of Medicine: 2021.
[13] Clinicaltrials.gov. A Study of Risdiplam in Infants With Genetically Diagnosed and Presymptomatic Spinal Muscular Atrophy (Rainbowfish). Accessed Match 2025. https://clinicaltrials.gov/study/NCT03779334
[14] Strauss KA et al., Onasemnogene abeparvovec for presymptomatic infants with three copies of SMN2 at risk for spinal muscular atrophy: the Phase III SPR1NT trial. Nat Med. 2022 Jul;28(7):1390-1397. doi: 10.1038/s41591-022-01867-3.

for Biogen to comment on the potential efficacy of risdiplam and OA beyond the available follow-up data from the pivotal clinical studies.

There are no longer-term data (beyond 72 months) to show the impact of treatment on motor milestones over a person's lifetime. Given the progressive nature of SMA, clinical experts consulted by Biogen expected a decline in motor function to occur over the long-term. However, it was not possible to estimate the point at which this would happen. Overall, a conservative assumption was adopted so that, after 72 months, the cohort receiving nusinersen could only maintain or decline in terms of their gross motor milestones (i.e. no additional motor milestone achievement was possible). This may not reflect clinical practice, and the point and rate of decline in motor milestones is uncertain.

One scenario reported in Section B.3.10.3 assumed there was no long-term decline for nusinersen to examine the impact this had on the cost-effectiveness results.

Type 1 SMA

B6. Is it reasonable to expect a treatment effect duration of 5 years for risdiplam and OA as well as nusinersen?

Please see the response to question B5 – it is not appropriate for Biogen to comment on whether the treatment effect of risdiplam and OA extends beyond the available follow-up data from the pivotal trials for these treatments.

B7. How likely is the percentage discontinuation in Type 1 for those "walking independently" appropriately reflected by 1%?

While it is possible for people on nusinersen to achieve walking independently and standing with support, these people were not observed in the MAA (a key reason for this is the follow-up time, 3.5 years for the MAA and 5-years in SHINE) Therefore, there was a paucity of data to inform discontinuation and this meant an assumption was required for the model.

In the paediatric MAA for nusinersen (see Appendix E in the company submission), 3 of 30 walkers discontinued over the 3.5 years (10.5 model cycles). Using the same calculations as per Section B.3.3.1.6 of the Company Submission, the per-cycle probability of a walker discontinuing nusinersen was 1.00% (see Equation 1).

In the absence of any discontinuation data specific to type 1 walkers, this assumption is reasonable.

Equation 1. Derivation of a per-cycle discontinuation probability for later-onset walkers

$$\text{Per cycle rate (r)} = \frac{\ln(1 - \frac{3}{30})}{10.5}$$

$$\text{Per cycle probability (p)} = 1 - e^{-r}$$

Type 2/3 SMA

B8. Document B, Section B.3.3.3 Later-onset model: "To incorporate the data from CHERISH and SHINE into the model for the type 2 sub-population, it was assumed that all BSC patients in the 'walking independently' health state should be defined as 'standing with support' and were allocated accordingly. To avoid biasing the model in favour of nusinersen, the same assumption was also applied to the nusinersen data." Can the company further clarify why were all type 2 patients "walking independently" in both the BSC and Nusinersen arms assumed equivalent to those "standing with support"?

Is it feasible for these patients to be distinguished in the economic model submitted? Is this likely to be a conservative or favourable assumption for nusinersen?

This assumption was required because, as outlined in Section B.3.3.3.2 in the company submission, clinical experts advised that the people enrolled in the CHERISH trial were more indicative of a type 2 population than a type 2/3 population[15]. Therefore, it was not appropriate to use CHERISH and SHINE data to

[15] Biogen and IONIS Pharmaceuticals data on file. CS4 (CHERISH). A phase 3, randomized, double-blind, sham-procedure controlled study to assess the clinical efficacy and safety of ISIS 396443 administered intrathecally in patients with later-onset spinal muscular atrophy [CHERISH]. Clinical study report. Study number: 396443-CS4. Interim. February 3, 2017.

inform motor milestone attainment for the total type 2/3 SMA population. CHERISH and SHINE data was, however, appropriate to inform the type 2 population.

One participant in the sham arm (which represents BSC) was able to walk at 92 days. As per the definition of type 2 SMA, it is clinically implausible for people with type 2 SMA to achieve walking independently without disease modifying treatment. Indeed, in natural history studies, (Wadman et al. [2018][16]), the maximum motor milestone attained by people with type 2 SMA was walking with support. Therefore, it was thought that the participant who achieved walking in the control arm had type 3 SMA, rather than type 2.

Biogen investigated the individual patient-level data (IPD), however, the IPD did not contain a variable that allowed for those with type 3 SMA to be accurately identified and censored. It would not be appropriate to remove the one participant who achieved "walking independently" from the data, without biasing towards nusinersen. The alternative was to allocate that those who achieved "walking independently" to "standing with support" for both BSC and nusinersen. This helped to avoid biasing the model in favour of nusinersen. However, it should also be considered a conservative assumption for nusinersen. This is because outcomes from ENDEAR and SHINE showed that those with type 1 SMA achieved the ability to walk independently after treatment with nusinersen. Therefore, it seems unlikely that those with type 2 SMA would not have the ability to achieve the same milestone with nusinersen (given that type 1 SMA is associated with a worse overall prognosis than type 2 SMA).

[16] Wadman RI, Wijngaarde CA, Stam M, Bartels B, Otto LAM, Lemmink HH, Schoenmakers MAGC, Cuppen I, van den Berg LH, van der Pol WL. Muscle strength and motor function throughout life in a cross-sectional cohort of 180 patients with spinal muscular atrophy types 1c-4. Eur J Neurol. 2018 Mar;25(3):512-518. doi: 10.1111/ene.13534. Epub 2018 Feb 2. PMID: 29194869.

Health Related Quality of Life

B9. Is there any reason to think that the utility estimate for a specific motor milestone may be higher when receiving risdiplam, nusinersen or OA than when not receiving such treatment for the same motor milestone?

If yes, is there any reason to believe there is a difference between risdiplam, nusinersen or OA?

The models contained an assumed utility increment to reflect the additional benefits of treatment on HRQoL. The model used health states based on the attainment of gross motor milestones, with the justification for this approach provided in Section B.3.2.2 of the company submission. However, fine motor milestones which have a meaningful impact on daily living activities and independence may not be explicitly captured under this structure.

A post-hoc analysis of CHERISH was conducted, including only patients who did not gain or lose a gross motor milestone at month 12 vs. baseline (e.g. including only those who could sit without support at both baseline and month 12). Mean change from baseline in both HFMSE and RULM were higher for those receiving nusinersen vs. sham control (HFMSE: [redacted] vs. [redacted]; RULM: [redacted] vs [redacted]).[17] Patients and caregivers consider a 1 point change in HFMSE to be a meaningful change and 2 point change in RULM is considered clinically meaningful. [18,19] A 1 point change can have a meaningful impact on daily living activities and maintaining independence e.g. it could mean a child can lift a drink to their mouth independently, self-operate the joystick on a powered wheelchair or roll from supine.

Therefore, any improvements in each of these outcomes, due to treatment with nusinersen, would not be quantified within the model. A utility increment associated

[17] Biogen. Data on file.
[18] Pera MC, Coratti G, Forcina N, Mazzone ES, Scoto M, Montes J, Pasternak A, Mayhew A, Messina S, Sframeli M, Main M. Content validity and clinical meaningfulness of the HFMSE in spinal muscular atrophy. BMC neurology. 2017 Dec;17:1-0.
[19] Pera MC, Coratti G, Mazzone ES, Montes J, Scoto M, De Sanctis R, Main M, Mayhew A, Muni Lofra R, Dunaway Young S, Glanzman AM. Revised upper limb module for spinal muscular atrophy: 12 month changes. Muscle & Nerve. 2019 Apr;59(4):426-30.

with active treatment has been incorporated to explore the potential impact of this plausible assumption.

There is currently no evidence to indicate whether there is a difference in this utility increment for nusinersen versus risdiplam and OA.

Disease complications

B10. Could the economic model better capture the impact of SMA by explicitly including the following disease-related events (rather than treatment-related events) using literature estimates: time to scoliosis? Time to respiratory support (not permanent)? Time to bulbar disfunction?

Is there evidence showing a difference in treatment-related risk for any of these disease-related events for nusinersen versus risdiplam or OA?

The decision was made to develop a model with health states that were defined based on the achievement of gross motor milestones. This approach is largely aligned with cost-effectiveness models for previous NICE appraisals of technologies related to SMA, including nusinersen [TA588], risdiplam [TA755] and OA [HST24]. The general consensus from these previous appraisals is that the use of modelling approach based on gross motor milestones is appropriate to capture the cost and health implications of the disease.

The main issue with incorporating the proposed disease related events (for example, bulbar dysfunction) within this model structure is the difficulty in disentangling the consequences of these events from the health state costs and utilities that are already captured in the model. For example, bulbar dysfunction is associated with a reduction in quality of life. However, the risk of this event is also greater in people with more severe forms of the disease and those with greater levels of motor dysfunction[20, 21]. This means that bulbar dysfunction is more prevalent in people residing in the ‘not sitting’ and ‘sitting’ health states and, as such, the negative health impact of the event may already be captured in the health state utilities associated

[20] Dunaway Young S et al., Assessing Bulbar Function in Spinal Muscular Atrophy Using Patient-Reported Outcomes. J Neuromuscul Dis. 2023 Mar 7;10(2):199–209. doi: 10.3233/JND-221573.
[21] Chen YS et al., Prevalence and risk factors for feeding and swallowing difficulties in spinal muscular atrophy types II and III. J Pediatr. 2012 Mar;160(3):447-451.e1. doi: 10.1016/j.jpeds.2011.08.016. Epub 2011 Sep 15.

with those states. Therefore, adding separate disutilities associated with these events makes it likely that double counting has taken place. The same could also be said with the costs associated with these events.

A separate issue is the difficulty in obtaining specific definitions for each event in a way that allows for their inclusion with a cost-effectiveness model framework. For example, bulbar dysfunction is a broad term that covers multiple potential symptoms. In particular, this event can be associated with difficulties with chewing, swallowing and speech but these are not the only potential symptoms. Due to the broad nature of the events, as well as a general paucity of data related to SMA, it is expected to be difficult to obtain reliable data on the cost and quality of life implications of each event within the SMA population.

As described in response to questions A1 to A4, due to the substantial risk of biases associated with an indirect comparison of nusinersen with risdiplam and OA, it is the position of Biogen that it is not appropriate to compare these interventions. This argument also holds for a comparison of the disease-related events listed in this question.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Multiple Technology Appraisal

Risdiplam for treating spinal muscular atrophy (MA review of TA755)

Clarification questions

March 2025

File name	Version	Contains confidential information	Date
ID6195 Risdiplam SMA clarification letter	1a	No	07/03/2025

Notes for company

Highlighting in the template

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Section A: Clarification on effectiveness data

A1. Document B Section B.2.9 Indirect and mixed treatment comparisons: Based on assumptions the sham control and placebo are sufficiently similar to serve as a common comparator. Could the company provide further justification for this assumption and explain how it impacts the reliability of the ITC findings?

The company applied the assumption of equivalence between oral placebo (SUNFISH) and sham procedure (CHERISH) after checking in a systematic and methodologically appropriate manner for which endpoints it holds true. Our peer-reviewed publication of the indirect treatment comparison (ITC) of risdiplam versus nusinersen published by Aponte Ribeiro et al (Roche's 1-year matching adjusted indirect comparisons [MAICs] of risdiplam vs nusinersen in T1 [FIREFISH vs. ENDEAR] and T2/3 [SUNFISH subpopulation vs. CHERISH])[1] outlines how we:

1. Undertook all feasible steps to minimise the differences in study populations and ensure comparability between the studies (i.e. by including a subset of SUNFISH patients, defined by CHERISH inclusion criteria)

2. Conducted all necessary analyses to ensure the validity of the assumption of equivalence between oral placebo (SUNFISH) and sham procedure (CHERISH), explicitly for each of the common endpoints

to understand whether a connected network and anchored comparison was feasible or not.

For Revised Upper Limb Module (RULM), upon matching, the control arms of SUNFISH and CHERISH showed similar responses with comparable improvements in RULM scores over the same time span. Indicating a good match of patients for this endpoint and appropriateness of applying the equivalence assumption.

For Hammersmith Functional Motor Scale (HFMSE), robust conclusions on the comparative efficacy on the HFMSE endpoints could not be drawn. Despite successful matching of baseline characteristics to CHERISH, the anchors did not show comparable improvements in HFMSE scores over time. Changes from baseline in HFMSE score were diverging for placebo versus sham control over time (see Supplementary Table 11 of Aponte Ribeiro et al). Indicating that the equivalence assumption for the placebo and sham arms does not hold true for this endpoint and therefore an ITC could not be performed for HFMSE.

A similar systematic approach was also undertaken in the 4-year update of our ITC of risdiplam versus nusinersen in patients with Type 2 / 3 SMA2, which was included in our submission dossier to NICE in April 2024. At 4 years of follow-up, an anchored MAIC was not feasible as there was no longer a common comparator (e.g. a placebo group) between the trials with the additional data collected. Patients in the placebo arm of SUNFISH were switched to active treatment at Week 52, and patients assigned in sham arm in the CHERISH trial switched to nusinersen arm from Year 2 onwards, which means the control arms in SUNFISH and CHERISH, SHINE/CHERISH were not anymore comparable as they were after 1 year of follow-up. Therefore, in the absence of common comparators, an unanchored MAIC was an appropriate approach to indirectly assess the relative efficacy of risdiplam versus nusinersen. Unanchored matching was not however performed for the HFMSE endpoint (and serious adverse events [SAEs]). This was because the anchored MAIC analysis was not successful on the HFMSE (and SAEs) as illustrated by differences in responses in the control arms, suggesting that matching for these endpoints was not successful. Therefore, an updated ITC of risdiplam vs nusinersen could only be performed for RULM. Results are included in submission dossier.

A2. Document B Section B.2.9.1. Systematic literature review: Roche had an SLR update of the SLR run in 2020. Would it be possible for the company provide a report or a link to the SLR done in 2020 as the statement was not appropriately referenced?

The was provided in Appendix D of the 2020 submission. However, the company have submitted the full report (Roche data on file_ Risdiplam_Spinal Muscular Atrophy (SMA)_SMA SLR-FA Update_Report (vFinal)_29th Jun '20 [CON]), for reference.

A3. Document B Section B.2.10.3 JEWELFISH (Previously treated SMA patients): In JEWELFISH (pre-treated population), were there signs of waning efficacy or diminishing benefit over time in those who switched from other treatments?

JEWELFISH's primary endpoints assessed the safety and PK of risdiplam in patients previously enrolled in the MOONFISH trial or previously treated with olesoxime, nusinersen or onasemnogene abeparvovec, the safety outcomes from this trial can be found in Document B Section B.2.10.3. Please note that the efficacy outcomes looked at in this trial were only exploratory.

All of the efficacy outcomes provided below are pooled for all previous treatments. It is worth noting that, without treatment, the expectation for this patient population is deterioration. The broad patient population in this study should also be taken into account when considering

the results, where the median age was 14.0 years with a range of 1-60. Of particular interest in these characteristics is the high proportion of patients with a baseline HFMSE score of <10 (63%), this is relevant because the HFMSE scale is not sensitive enough to detect a change in people with a baseline score <10.[2] A summary of the baseline characteristics can be found in this response in Table 1.

3 patients in JEWELFISH were treatment-naive, recruited from the placebo arm of the MOONFISH trial.

Table 1: JEWELFISH Population Baseline Characteristics

	All patients (n=174)
Age at enrolment, years, median (range)	14.0 (1-60)
≥18 years, n(%)	63 (36)
Gender, n (%)	
Male	95 (55)
SMA type, n(%)	
1	15 (9)
2	108 (62)
3	51 (29)
SMN2 copy number, n (%)	
1	3 (2)
2	13 (8)
3	136 (78)
4	22 (13)
Motor function at baseline*, n(%)	
Non-sitter	59 (34)**
Sitter	99 (57)**
Walker	16 (9)
Baseline HFMSE total score <10, n(%)	
Yes	105 (63)#
Scoliosis, n(%)	
Yes	139 (83)#
>40 degrees curvature	66 (39)#
Hip subluxation or dislocation, n(%)	
Yes	51 (30)#

*Non-sitters are defined as scoring 0 on Item 9 of the MFM while sitters scored ≥1 on Item 9 of the MFM but did not qualify as ambulant. Ambulant patients are defined as walkers.
**For patients aged <2 years, baseline motor milestones were evaluated by the HINE-2.
#Only reported for patients aged 2-60 years, N=168.

JEWELFISH Exploratory Efficacy Outcomes

MFM-32

A stabilisation in motor function as shown by the mean 32-item Motor Function Measure (MFM-32) total score was observed in the intention-to-treat (ITT) population from baseline to Month 24.

At Month 24, the mean change from baseline in MFM-32 total score was 0.17 points (95% confidence interval [CI]: 1.03, 0.68, n=137).

The majority of patients (54.7%) achieved an MFM-32 total score equal to or greater than their baseline score at Month 24.

Table 2: Summary of MFM32 Total Score and Change from Baseline by Visit, Patients Aged 2 to 60 Years, Intent-to-Treat Patients

	All patients (N=168)	
Visit	**Value at visit**	**Change from baseline**
Baseline		N/A
N	163	
Mean (SD)	39.93 (18.51)	
Median	40.63	
Min-Max	1.0-90.6	
95% CI for Mean	(37.07, 42.80)	
Week 52		
N	142	138
Mean (SD)	40.41 (18.75)	-0.35 (4.15)
Median	42.71	0.00
Min-Max	0.0-89.6	-12.5 - 18.8
95% CI for Mean	(37.30, 43.52)	(-1.05, 0.35)
Week 104		
N	140	137
Mean (SD)	40.67 (18.38)	-0.17 (5.08)
Median	41.67	0.00
Min-Max	0.0-87.5	-18.8 - 25.0
95% CI for Mean	(37.60, 43.74)	(-1.03, 0.68)

RULM

A stabilization in upper limb function as shown by the mean RULM total score was observed in the ITT population from baseline to Month 24.

At Month 24, the mean change from baseline in RULM total score was 0.71 points (95% CI: 0.17, 1.26, n=133).

The majority of patients (68.4%) achieved a change from baseline equal to or greater than 0 points in the RULM total score at Month 24 of treatment with risdiplam.

Table 3: Summary of RULM Total Score and Change from Baseline by Visit, Patients Aged 2 to 60 Years, Intent-to-Treat Patients

	All patients (N=168)	
Visit	**Value at visit**	**Change from baseline**
Baseline		N/A
N	165	
Mean (SD)	16.60 (9.19)	
Median	17.00	
Min-Max	0.0-37.0	
95% CI for Mean	(15.19, 18.01)	
Week 52		
N	149	146
Mean (SD)	16.48 (9.81)	0.16 (2.89)
Median	17.00	0.00
Min-Max	0.0-37.0	-12.0 - 12.0
95% CI for Mean	(14.89, 18.07)	(-0.32, 0.63)
Week 104		
N	136	133
Mean (SD)	17.49 (9.61)	0.71 (3.18)
Median	17.00	0.00
Min-Max	0.0 - 37.0	-7.0 - 16.0

95% CI for Mean	(15.86, 19.12)	(0.17, 1.26)

HFMSE

On average, the HFMSE total score was stable at Month 24 compared to baseline.

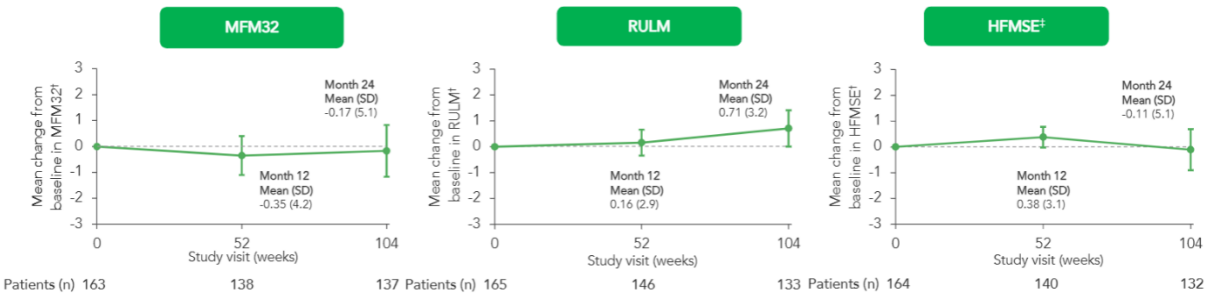
At Month 24, the mean change from baseline in HFMSE total score was 0.11 points (95% CI: 0.98, 0.76, n =132).

The majority of patients (62.9%) achieved a change from baseline equal to or greater than 0 points in the HFMSE total score after 24 months of treatment with risdiplam.

Table 4: Summary of HFMSE Total Score and Change from Baseline by Visit, Patients Aged 2 to 60 Years, Intent-to-Treat Patients

	All patients (N=168)	
Visit	**Value at visit**	**Change from baseline**
Baseline		N/A
N	164	
Mean (SD)	12.13 (14.74)	
Median	6.00	
Min-Max	0.0 - 60.0	
95% CI for Mean	(9.86, 14.41)	
Week 52		
N	142	140
Mean (SD)	12.83 (15.41)	0.38 (3.05)
Median	7.00	0.00
Min-Max	0.0 - 60.0	-10.0 - 12.0
95% CI for Mean	(10.27, 15.39)	(-0.13, 0.89)
Week 104		
N	134	132
Mean (SD)	12.71 (15.72)	-0.11 (5.05)
Median	7.00	0.00
Min-Max	0.0 - 61.0	-32.0 - 13.0
95% CI for Mean	(10.02, 15.39)	(-0.98, 0.76)

Figure 1: Summary of MFM-32, RULM and HFMSE mean change from baseline over 2 years for the total study population as detailed in Tables 1, 2 and 3.



Following 24 months of risdiplam treatment, the exploratory efficacy data show stabilisation in motor function as assessed by the MFM-32 and RULM in this broad and heterogeneous

population of patients aged 2 to 60 years. Additionally, the HFMSE total score was stable as compared to baseline.[3] Although direct comparisons with published data cannot be made, longitudinal studies of untreated patients consistently showed negative changes in measures of motor function. For example, a natural history cohort of patients aged 6–30 years showed a decline of –2.66 points in the MFM after 24 months.[4]

Section B: Clarification on cost-effectiveness data

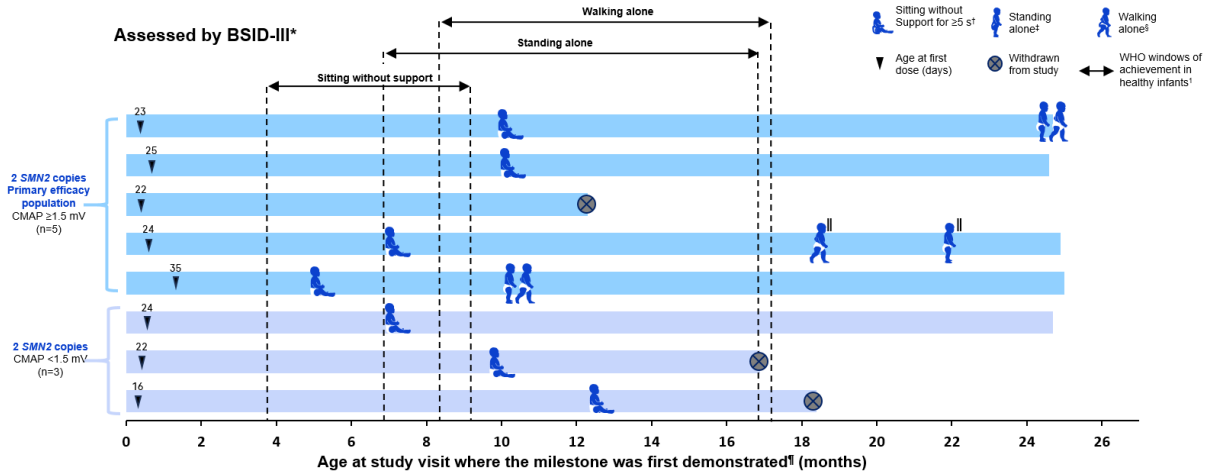
Presymptomatic SMA

B1. Document B Section B.3.2.1 Economic analysis: Could the company clarify whether it is possible to generate WHO motor milestone data from the RAINBOWFISH trial? Alternatively, is it possible to assume equivalence between HINE-2 and WHO motor milestone health outcomes?

In the RAINBOWFISH trial the Bayley Scales Of Infant and Toddler Development, third edition (BSID-III) was used as the primary outcome measure. The milestones achieved by patients, as measured by BSID-III were compared to the WHO windows for healthy children which are presented below in Figure 2, Figure 3 and Figure 4. Attainment of the maximum milestone within each domain (e.g. standing alone, walking unaided) may align well to the relevant WHO motor milestone. We strongly suggest that clinical expert advice is sought for the appropriateness of comparing HINE-2 or BSID-III milestones with WHO milestones in this patient group. It is worth noting that in the RAINBOWFISH trial, patients were not assessed formally with the WHO milestones until 48 months as patients may be too young to be able to complete this milestone scale.

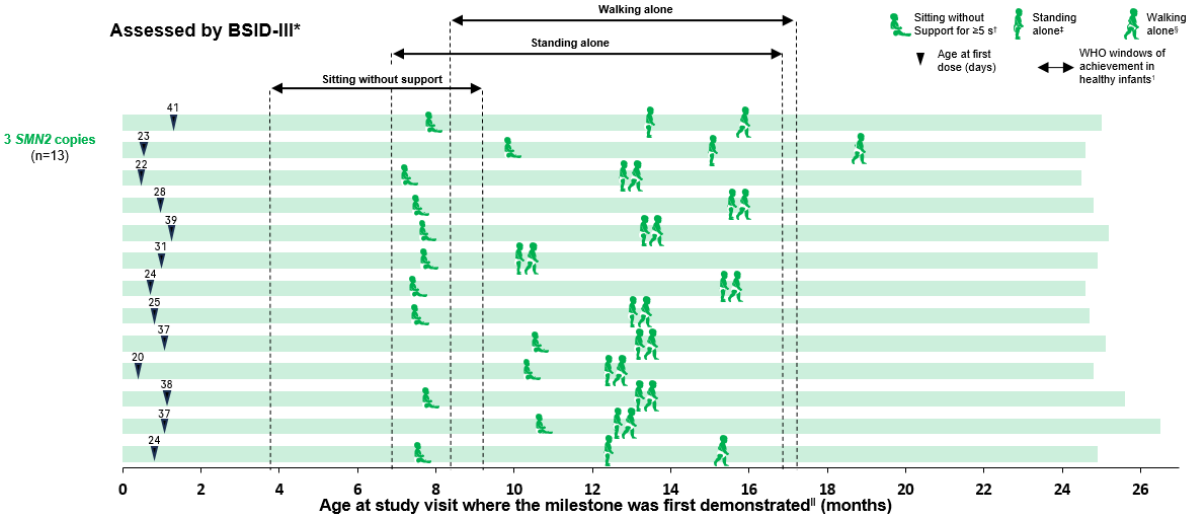
The data in Figure 2, Figure 3 and Figure 4 are taken from the 24-month results as these show a more complete picture of the milestone attainment for these patients. Unfortunately, due to a lack of a formal CSR being created for this study readout, we do not have tabulated results available. If tabulated results are required, please refer to Document B, Table 36 for the 12-month results.

Figure 2: BSID-III motor outcomes for infants with 2 SMN2 copies over 24 months with WHO windows of achievement in healthy infants overlaid



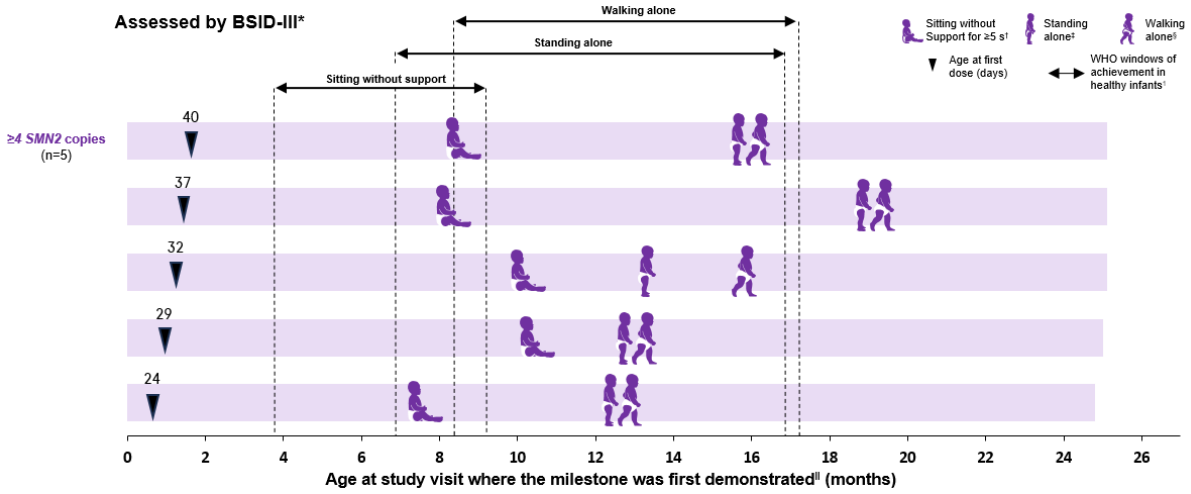
Key: *Data reported as assessed by the BSID-III Gross Motor Scale by two independent central readers. †Assessed using Item 22. ‡Assessed using Item 40. §Assessed using Item 42. ‖For this infant, there was disagreement between the independent central readers and the site clinical evaluator at the Week 78 visit for standing alone but walking alone was confirmed. Standing alone was not confirmed until the Week 92 visit. ¶The icons represent the age (months) of the patient at the visit where they were first able to demonstrate the corresponding motor milestone. Infants may have achieved the milestone between study visits. Some study visits were delayed by the COVID-19 pandemic. Data cut-off: 27 Mar 2024.
CMAP, compound muscle action potential; mV, millivolt; SMN, survival of motor neuron
WHO MGRS. Acta Paediatr Suppl. 2006; 450:86–95.[5]

Figure 3: BSID-III motor outcomes for infants with 3 SMN2 copies over 24 months with WHO windows of achievement in healthy infants overlaid



Key: *Data reported as assessed by the BSID-III Gross Motor Scale by two independent central readers. †Assessed using Item 22. ‡Assessed using Item 40. §Assessed using Item 42. ‖The icons represent the age (months) of the patient at the visit where they were first able to demonstrate the corresponding motor milestone. Infants may have achieved the milestone between study visits. Some study visits were delayed by the COVID-19 pandemic. Data cut-off: 27 Mar 2024.
SMN, survival of motor neuron; WHO, World Health Organization.
WHO MGRS. Acta Paediatr Suppl. 2006; 450:86–95.[5]

Figure 4: BSID-III motor outcomes for infants with ≥4 SMN2 copies over 24 months with WHO windows of achievement in healthy infants overlaid



Key: *Data reported as assessed by the BSID-III Gross Motor Scale by two independent central readers. †Assessed using Item 22. ‡Assessed using Item 40. §Assessed using Item 42. ‖The icons represent the age (months) of the patient at the visit where they were first able to demonstrate the corresponding motor milestone. Infants may have achieved the milestone between study visits. Some study visits were delayed by the COVID-19 pandemic.
Data cut-off: 27 Mar 2024.
SMN, survival of motor neuron
WHO MGRS. Acta Paediatr Suppl. 2006; 450:86–95.[5]

While HINE-2 milestone attainment could plausibly align with WHO motor milestones in the presymptomatic cohort, equivalence between the two scales has not been explored. Extreme caution should be taken in extrapolating the same connection for any symptomatic cohorts.

B2. Document B Section B.3.2.2. Model structure: Can the company clarify the following questions around the health-state definitions in the economic model based on HINE-2 data:

a) Are transitions between motor milestones defined by the highest score in either the walking, standing or sitting dimensions from the HINE-2 in a hierarchical order?

In order to estimate the probability of transition between health states, a continuous time multi-state model was fitted to the data. Continuous time models are a natural way of modelling chronic diseases, and assume that movements between health states can occur outside of the observation time points. As acquisition or loss of motor milestones is considered to be a continuous process and deemed potentially feasible in shorter time intervals, a continuous time model was considered to be appropriate in this setting.

Transitions between motor milestones, as measured by HINE-2, follow a sequential order. This means patient progression through motor milestones is assumed to occur in steps, moving from not sitting to sitting to standing to walking sequentially, without skipping any states. Correspondingly, the continuous time multi-state model used to derive transition probabilities was specified so that movements between non-adjacent health states were not allowed, i.e. if a patient was observed at a worse motor function (e.g. not sitting) during one

visit and at a better motor function (e.g. standing) during the next visit, it was assumed that the patient was capable of the intermediate motor function (e.g. sitting), even if it was not explicitly observed. This was applied to both improvement and deterioration of motor function.

While the cost-effectiveness model was specified to only allow transitions to adjacent health states instantaneously, the calculated monthly transition probability matrices from the multi-state Markov model may still provide probabilities for non-adjacent health states, since the fitted model may predict transitions to occur within a month. However, as we made the assumption that progression was always sequential, non-sequential transitions were ignored when incorporated into the cost-effectiveness model.

As such, transitions between motor milestone-based health states were not necessarily defined by the highest observed HINE-2 scores but also further adjusted as needed to adhere to the assumption of sequential transitions.

b) Are the motor milestones defined using the HINE-2 mutually exclusive? (i.e. Are patients reaching a high walking score counted separately from patients who are not able to reach a walking milestone) And do they cover the whole ITT population?

The company can confirm that, in line with the essential properties of the applied Markov modelling approach, motor milestone-based health states (defined using the HINE-2) are mutually exclusive.

The company can further confirm that the multi-state model used to derive transition probabilities was based on data from the entire RAINBOWFISH ITT population.

B3. [Priority question] Document B Section B.3.3.1. Presymptomatic SMA (RAINBOWFISH) model: Can the company clarify the following questions around the transition probabilities in the economic model based on HINE-2 data:

a) Can the company provide the proportion of patients at each HINE-2 defined motor milestone (not sitting, sitting, standing, walking) at baseline and at each RAINBOWFISH follow-up timepoint?

The RAINBOWFISH trial reported HINE-2 outcomes at baseline, and 12 months in the primary study readout. The 12-month HINE-2 outcomes can be found in Table 37 of Document B. For completeness and ease of reference, we have provided the tables below which show 12-month outcomes and 24-month outcomes for the requested milestones.

The baseline data has not been tabulated as 0 patients had reached the HINE-2 definition of sitting, standing or walking at baseline. Please see Table 9 in Document B for other baseline data used to contextualise this cohort of patients.

The 24-month data was first presented at the World Muscle Society (WMS) Congress in October 2024, so was not included in our original submission. It is worth noting that a formal CSR has not been produced for the 24-month RAINBOWFISH results, hence why no addendum of the data was provided to the EAG.

For simplicity, only the milestones in question are presented here (sitting, standing and walking) but the data is available for baseline and 12 months on head control, voluntary grasp, ability to kick, rolling and crawling if needed.

Considering the importance of survival motor neuron 2 (SMN2) copy number on outcomes in this population, we have provided a breakdown of each SMN2 copy number cohort as well as all patients.

Table 5: Summary of requested HINE-2 milestones achieved in the RAINBOWFISH trial at 12 months.

n, (%)	*SMN2* copy number			
	2 (N=8)	3 (N=13)	≥4 (N=5)*	All patients (N=26)
Sitting				
Cannot sit	1 (12.5)	0	0	1 (4.0)
Sits with support at hips	0	0	0	0
Props	0	0	0	0
Stable sit	1 (12.5)	0	0	1 (4.0)
Pivots (rotates)	6 (75.0)	13 (100.0)	4 (100.0)	23 (92.0)
Standing				
Does not support weight	4 (50.0)	0	0	4 (16.0)
Supports weight	0	0	0	0
Stands with support	3 (37.5)	3 (23.1)	2 (50.0)	8 (32.0)
Stands unaided	1 (12.5)	10 (76.9)	2 (50.0)	13 (52.0)
Walking				
Bouncing	2 (25.0)	0 (2.4)	0	2 (8.0)
Cruising (walks holding on)	0	3 (23.1)	1 (25.0)	4 (16.0)
Walking independently	1 (12.5)	9 (69.2)	2 (50.0)	12 (48.0)
Cannot test	4 (50.0)	1 (7.7)	1 (25.0)	6 (24.0)
Not done	1 (12.5)	0	0	1 (4.0)

* One patient could not be assessed as they were crying

Table 6: Summary of requested HINE-2 milestones achieved in the RAINBOWFISH trial at 24 months.

n, (%)	*SMN2* copy number			
	2 (N=5*)	3 (N=13)	≥4 (N=5)	All patients (N=23*)
Sitting				
Cannot sit	0	0	0	0
Sits with support at hips	0	0	0	0
Props	0	0	0	0
Stable sit	0	0	0	0
Pivots (rotates)	5 (100.0)	13 (100.0)	4 (100.0)	23 (100.0)
Standing				
Does not support weight	1 (20.0)	0	0	1 (20.0)
Supports weight	0	0	0	0
Stands with support	1 (20.0)	0	0	1 (4.3)
Stands unaided	3 (60.0)	13 (100.0)	5 (100.0)	21 (91.3)

Walking				
Bouncing	0	0	0	0
Cruising (walks holding on)	2 (40.0)	0	0	2 (8.7)
Walking independently	2 (40.0)	13 (100.0)	5 (100.0)	20 (87.0)
Cannot test	1 (20.0)	0	0	1 (4.3)
Not done	0	0	0	0

*Excludes 3 infants who withdrew before the Year 2 assessment to switch to onasemnogene abeparvovec.

b) How was goodness of fit from the continued time Markov multi-state model assessed?

The selection of the multi-state Markov model to be used in the cost-effectiveness models was determined by considering the predictive power and goodness of fit for each of the 4 alternative models considered. The statistical goodness of fit was assessed based on AIC criteria. Models with no or different covariates were implemented. Based on Akaike Information Criterion (AIC), the model with the lowest AIC was selected. In this case, Model 4 with SMN2 copy number and all forward transitions constrained to be equal included as covariates.

AIC criteria and likelihood ratio statistics for all models can be found in Table 7 and Table 8, respectively. Table 7 shows that Model 4 (SMN2 copy number, all forward transitions constrained to be equal) was the best fitting and most appropriate multi-state Markov model to derive transition probabilities, by AIC statistical fit. Table 8 indicates that the additional parameters of Model 4 significantly improve the model fit over the null Model 1 with no covariates.

Table 7: Goodness of fit statistics for multi-state Markov models

	Model	df	AIC (rank)	Log-Likelihood
1	Model 1 (No Cov)	5	246.135 (3)	-118.068
2	Model 2 (SMN2 copy number, Not Sitting->Sitting)	6	247.198 (4)	-117.599
3	Model 3 (SMN2 copy number, Not Sitting->Sitting, Standing->Walking)	7	243.784 (2)	-114.892
4	Model 4 (SMN2 copy number, all forward transitions constrained to be equal)	6	237.309 (1)	-112.655

Key: AIC, Akaike Information Criterion; cov, covariates; df, degrees of freedom; SMN2, survival of motor neuron 2.

Table 8: Likelihood ratio statistics for multi-state Markov models

	Model	df	Likelihood ratio statistic	p
1	Model 2 versus Model 1	1	0.9371082101	0.3330226473
2	Model 3 versus Model 1	2	6.351108327	0.04177094974
3	Model 4 versus Model 1	1	10.82557112	0.0010010781

Key: df, degrees of freedom.

c) How was predictive ability of the multi-state model to the data assessed?

Multi-state model predictions were compared with observed frequencies in RAINBOWFISH. Figure 5 presents the observed and predicted prevalence of patients in each motor milestone health state from the selected multi-state Markov model (MSM4) used in the cost-effectiveness model. This shows that MSM4 appropriately reflects the course of mobility for patients in the RAINBOWFISH study.

Figure 5: Observed versus multi-state Markov model predicted prevalence for RAINBOWFISH motor milestones – MSM 4 (Overall SMN2 copy number, all forward transitions constrained to be equal)



d) How was uncertainty in the transitions between motor milestones implemented in the model?

For multi-state Markov model-generated transition probabilities associated with risidiplam from the RAINBOWFISH study, as well as transition probabilities and time-to-event data for best supportive care (BSC) from the Paediatric Neuromuscular Clinical Research Network (PNCR) study, probabilistic values were randomly drawn from 5,000 bootstrap samples.

In the cost-effectiveness model, uncertainty around each set of dependent health state transitions (i.e. all possible transitions from one particular health state) was accounted for as part of the probabilistic sensitivity analysis via the application of a Dirichlet distribution. For the purpose of the calculation, the Dirichlet distribution itself applies separate gamma distributions to hypothetical patient numbers derived from the respective deterministic base case transition probabilities (e.g. a transition probability of 0.9 would equate to 90 patients within a hypothetical cohort of 100) in each set; the proportions of the thus sampled numbers

(relative to the total sum) subsequently inform the probabilistically sampled transition probabilities. Scenario analyses were provided for MSM4 by SMN2 copy number.

These assumptions were used and accepted in the cost-effectiveness models originally submitted in 2020. For consistency and to account for the heterogenous nature of different evidence sources across the three separate models (RAINBOWFISH, SUNFISH, FIREFISH), the same approach was applied across all three models.

B4. [Priority question] Document B Section B.3.3.1. Presymptomatic SMA (RAINBOWFISH) model: Is there likely to be a higher risk of mortality for patients at the not sitting and sitting health states for SMA-related causes other than permanent ventilation? Was this considered explicitly in the economic analysis?

There are no events of death or permanent ventilation in the current data from RAINBOWFISH, which pertain to presymptomatic patients with SMA treated with risdiplam. Therefore, an exploratory statistical analysis to estimate the risk of mortality based on various health states was not feasible at this stage. Data-driven assumptions or conclusions cannot be drawn from the existing trial population. Due to the limited evidence base available to inform the RAINBOWFISH model, reflected in the application of general population mortality across all of the disease-modifying treatment arms, no further assumptions around a potentially higher mortality risk in selected health states were considered.

It is important to continue monitoring these patients and their progression as they grow older. As more mature data from the trial becomes available, it might be feasible in the future to re-examine the hypothesis of potential associations between mortality risk and health state.

Even if a higher mortality risk in worse health states could be considered likely, the application of this in the model would only have a negligible impact, due to the general assumption of equal efficacy across the main comparators (nusinersen and onasemnogene abeparvovec) and risdiplam in the pre-symptomatic population.

From a purely clinical perspective, this assumption is not straightforward. The examples below provide cases where the assumption would change based on the circumstances of the patient and treatment timings.

1. If a truly presymptomatic patient was treated early enough with a disease-modifying treatment, then they would move through these health states as they develop. This patient's time in the not sitting and sitting health state would be unlikely to come with an increased mortality risk.

2. If a presymptomatic patient was treated after some physiological, and subclinical, damage has been done then there is a chance that they could remain in the milestones mentioned. In this case, there may be an increased risk of mortality due to the overall progression of the condition, including respiratory weakness. However, there is no evidence to substantiate this impact numerically. This is considerably

more likely to be a realistic scenario for patients with only 2 copies of the SMN2 gene.

Type 1 SMA

B5. [Priority question] Document B Section B.3.3.2 Type 1 SMA (FIREFISH) model: Can the company clarify the following questions around the transition probabilities in the economic model based on HINE-2 data:

a) **Can the company provide the proportion of patients at each HINE-2 defined motor milestone (not sitting, sitting, standing, walking) at baseline and at each FIREFISH follow-up timepoint?**

A summary of the infants within each attainment response category of the HINE-2 over time was presented in CS Document B Table 21 for the Part 2 population. Table 5 of the supplementary FIREFISH 60-month addendum includes the proportion of patients at each HINE-2 defined motor milestone up to 5 years. We do not have HINE-2 data for Month 0. CS Document B Table 6 includes the current and highest level of motor function achieved at baseline, where all patients could be classed as not sitting.

FIREFISH is an open-label, two-part, phase II/III dose-escalation/single-arm study. Part 1 is a dose-escalation study, while Part 2 is confirmatory as the dose selected is based on the results from Part 1. Clinical data from the population who received the final confirmatory dose of risdiplam in the FIREFISH trial in the 48 months follow-up (N=58) were utilised to develop transition probabilities between motor milestone health states for the risdiplam arm in the Type 1 cost-effectiveness model. Only the high dose cohort (Cohort 2; N=17) from Part 1 were pooled with Part 2 (N=41) for these analyses. The decision was made to incorporate Part 1 patients (who achieved the final risdiplam dose) so that the transition probabilities would be informed by a greater number of patients, and results would have greater robustness and statistical power. A summary of the infants within each attainment response category of the HINE-2 over time for the pooled Part 1 and Part 2 population is provided in Table 9.

Table 9: Summary of HINE-2 motor milestones by visit (ITT population, pooled FIREFISH Part 1 Cohort 2 and Part 2 patients)

n, (%)	Time point (risdiplam n=58)				
	Month 12	Month 24	Month 36 (OLE)	Month 48 (OLE)	Month 60 (OLE)
Head control					
Unable to maintain head upright	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Wobbles					
All the time maintained upright	27 (46.6)	37 (63.8)	37 (63.8)	40 (69.0)	40 (69.0)
Not done	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Sitting					
Cannot sit					
Sits with support at hips					
Props					
Stable sit	12 (20.7)	16 (27.6)	5 (8.6)	7 (12.1)	8 (13.8)
Pivots (rotates)	4 (6.9)	15 (25.9)	25 (43.1)	27 (46.6)	26 (44.8)
Not done					
Voluntary grasp					
No grasp					
Uses whole hand					
Index finger and thumb but immature grasp					
Pincer grasp					
Not done					
Ability to kick (in supine)					
No kicking					
Kicks horizontally, legs do not lift					
Upward (vertically)					
Touches leg					
Touches toes					
Not done					
Rolling					
No rolling					
Rolling to side					
Prone to supine					
Supine to prone	6 (10.3)	23 (39.7)	24 (41.4)	27 (46.6)	29 (50.0)
Not done					
Crawling					
Does not lift head					
On elbow					
On outstretched hand					
Crawling flat on abdomen					
Crawling on hands and knees					
Cannot test					
Not done					
Standing					
Does not support weight					
Supports weight					
Stands with support	2 (3.4)	7 (12.1)	9 (15.5)	5 (8.6)	3 (5.2)
Stands unaided	0	0	0	4 (6.9)	4 (6.9)
Cannot test					
Not done					
Walking					
Bouncing					
Cruising (walks holding on)	0	1 (1.7)	2 (3.4)	7 (12.1)	6 (10.3)
Walking independently	0	0	0	0	0
Cannot test					
Not done					
Withdrawal	0	1 (1.7)	2 (3.4)	3 (5.2)	3 (5.2)
Death	4 (6.9)	5 (8.6)	5 (8.6)	5 (8.6)	5 (8.6)
Missing					

Patients who reached the target date for a visit but did not perform the assessment by the clinical cut-off date are counted as missing. This Table is an update of Table 21 in CS Document B.

b) How was goodness of fit from the continued time Markov multi-state model assessed?

The selection of the multi-state Markov model to be used in the cost-effectiveness models was determined by considering the predictive power and goodness of fit for each of the 5 alternative models considered. The statistical goodness of fit was assessed based on AIC criteria. Models with no or different covariates were implemented. Based on AIC criteria, the model with the lowest AIC was selected. In this case, Model 5 with HINE-2 included as a covariate.

AIC criteria and likelihood ratio statistics for all models can be found in Table 10 and Table 11, respectively. Table 10 shows that Model 5 (HINE total score) was the best fitting and most appropriate multi-state Markov model to derive transition probabilities, by AIC statistical fit. Table 11 indicates that the additional parameters of Model 5 significantly improve the model fit over null Model 1 with no covariates.

Table 10: Goodness of fit statistics for multi-state Markov models

	Model	df	AIC (rank)	Log-Likelihood
1	Model 1 (No Cov)	5	493.881 (2)	-241.940
2	Model 2 (Age Group 20w)	6	495.879 (5)	-241.940
3	Model 3 (Age Group 5m)	6	495.581 (4)	-241.790
4	Model 4 (Symptom Dur Group 3m)	6	491.528 (3)	-239.764
5	Model 5 (HINE Total Score)	6	479.474 (1)	-233.737

Key: AIC, Akaike Information Criterion; cov, covariates; df, degrees of freedom; HINE, Hammersmith Infant Neurological Examination; m, months; w, weeks.

Table 11: Likelihood ratio statistics for multi-state Markov models

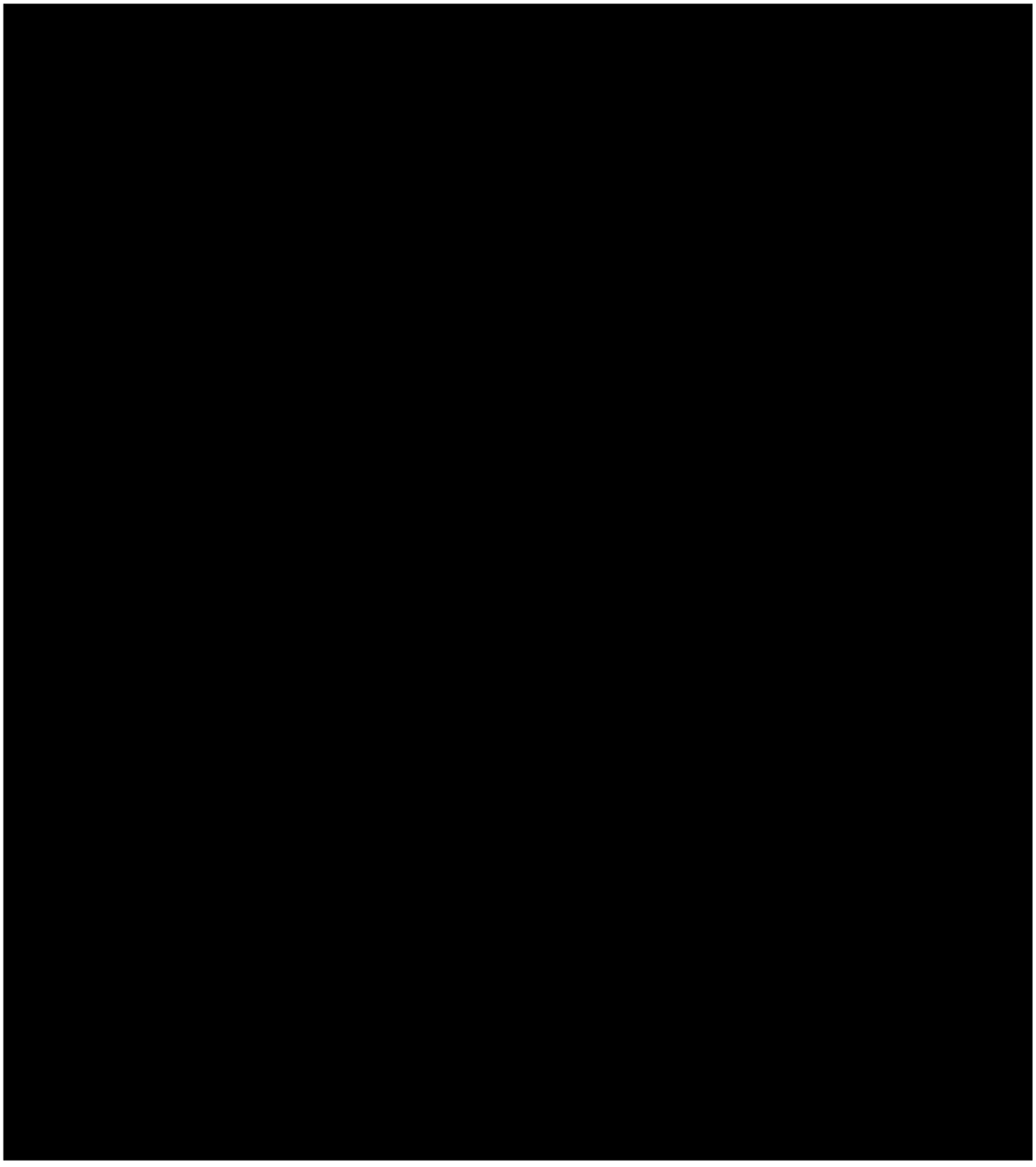
	Model	df	Likelihood ratio statistic	p
1	Model 2 versus Model 1	1	0.00173	0.967
2	Model 3 versus Model 1	1	0.300166	0.584
3	Model 4 versus Model 1	1	4.352604	0.037
4	Model 5 versus Model 1	1	16.407	0.0000511

Key: df, degrees of freedom.

c) How was predictive ability of the multi-state model to the data assessed?

Multi-state model predictions were compared with observed frequencies over the 4-year FIREFISH period. Figure 6 presents the observed and predicted prevalence of patients in each motor milestone health state used in the cost-effectiveness model. This shows that the selected multi-state Markov model (MSM5) appropriately reflects the course of mobility for patients in the FIREFISH study.

Figure 6: Observed versus multi-state Markov model predicted prevalence for FIREFISH motor milestones – MSM 5 (HINE-2)



d) How was uncertainty in the transitions between motor milestones implemented in the model?

As explained in Question B3d, probabilistic values were randomly drawn from bootstrap samples to assess the uncertainty across all estimates pertaining to the multi-state model, and uncertainty around each set of dependent health state transitions in the cost-effectiveness model was accounted for as part of the probabilistic sensitivity analysis via the application of a Dirichlet distribution. Scenario analyses were provided for MSM1 and MSM5 with or without bootstrapping.

These assumptions were used and accepted in the cost-effectiveness models originally submitted in 2020. For consistency and to account for the heterogenous nature of different evidence sources across the three separate models (RAINBOWFISH, SUNFISH, FIREFISH), the same approach was applied across all three models.

e) **Why was HINE-2 baseline score used as a covariate in some but not all probabilities? Did this follow a health economics analysis plan or a statistical analysis plan?**

Yes, a health technology assessment (HTA) statistical analysis plan (SAP) was followed.

The HTA SAP explains that covariates were to be investigated in the model if sufficient transitions between health states have been observed (≥10 observations). Due to the sparsity of data, it was anticipated that covariates may only be assessed for the transitions from "not sitting" to "sitting (with or without support)" and "sitting" to "not sitting (with or without support)". We have provided the HTA SAP for completeness.

B6. Document B Section B.3.3.2 Type 1 SMA (FIREFISH) model: Can the company clarify what was the risk rate of improving a motor milestone beyond 48 months for disease-modifying interventions (i.e. risdiplam)?

In line with the general assumption of treatment effect plateauing for the disease-modifying treatments, risk rates of improving a motor milestone were zero for all disease-modifying treatments from Month 66 onwards (for the remainder of the model time horizon). Please see CQ A4 from the June 2024 clarification stage for full description of the model treatment effect settings.

For Months 48 to 66, the monthly risk rates of improving a motor milestone can be calculated from the respective per-cycle transition probabilities (based on Year 4 FIREFISH data for risdiplam, the subsequent application of ITC-derived odds ratios for nusinersen and onasemnogene abeparvovec) and are summarised in Table 12.

Table 12: Monthly risk rates of improving a motor milestone (Months 48–66)

	Risdiplam	Nusinersen	Onasemnogene abeparvovec
Not sitting to sitting	[redacted]	[redacted]	[redacted]
Sitting to standing	[redacted]	[redacted]	[redacted]
Standing to walking	[redacted]	[redacted]	[redacted]

B7. Document B Section B.3.3.2 Type 1 SMA (FIREFISH) model, permanent ventilation: was independent patient data collected for permanent ventilation from FIREFISH that could be used for the time-to event analysis or was this just a

composite measure of EFS and OS? What are the potential pros and cons of the approach chosen?

The occupancy of the permanent ventilation health state is informed by the time-to event endpoints of event-free survival and overall survival.

Ventilation-free survival is a secondary efficacy endpoint in the FIREFISH study. It is a composite endpoint of time to death or permanent ventilation and is defined as the time in months from the date of enrolment into the study until the date of death from any cause or date of permanent ventilation, whichever event occurs first (See CS Doc B Section B.3.3.2). The date of permanent ventilation is the first of the >21 days of non-invasive ventilation support or intubation required for the endpoint to be confirmed, or the date of tracheostomy.

Then, to isolate transitions to the 'permanent ventilation' health state only, it was necessary to subtract the ventilation-free survival curves from the overall survival curves.

- To confirm, event/ventilation-free survival was a secondary efficacy endpoint in the FIREFISH study and was defined as the time to death from any cause or permanent ventilation (whichever occurred first); as such, it was required to subtract EFS from OS within the economic model in order to determine the probability of permanent ventilation in the alive patient population (represented by the area between the two survival curves)
    - Whilst this should be unproblematic when applied to the matched survival data from FIREFISH, the incorporation of additional mortality assumptions or relative treatment effects separately for OS may result in counterintuitive outcomes (e.g. if EFS were to be higher than OS at selected timepoints), requiring the application of corresponding technical safeguards in the model
- Whilst time-to-permanent ventilation (only) data was indeed collected as part of the FIREFISH trial, only 'time-to-death or permanent ventilation' data was available from relevant comparator trials (ENDEAR, STR1VE); as such, this outcome was the only appropriate choice in order to allow for essential indirect comparisons needed to inform efficacy in the economic model
    - Even if time-to-permanent ventilation (only) were to be implemented in the model, this would likely still require application of the corresponding probability of permanent ventilation to only the alive population in each cycle, the resulting final outcomes could therefore be expected to be similar between this and the current approach

Type 2/3 SMA

B8. Document B Section B.3.3.2 Type 1 SMA (FIREFISH) model and Section B.3.3.3 Type 2 SMA (SUNFISH) model: The economic model assumes there is a risk of decline in motor mobility for BSC patients over the long-term. Was the

estimate used for the rate of decline backed up by expert opinion and was there any further published evidence backing this assumption?

The company can confirm that the long-term risk of decline in motor milestones for patients in the BSC arm is based on a simple extrapolation of the transition probabilities (informed by FIREFISH and SUNFISH trial data) over the entire model time horizon.

As explained in CS Section B.1.3.1, it is well accepted that clinical decline can manifest differently for each SMA type depending on functional level, age, disease duration and clinical severity, demonstrated by natural history data. With regards to clinical expert validation, the original company submission (TA755) noted that UK clinical experts agreed that the majority of patients with SMA type 2 or 3, when receiving active treatment, are expected to experience a favourable trajectory compared to BSC. Patients on active treatment are likely to maintain or improve their health states in the long term. CS Doc B Section B.2.1.2 explains that clinical opinion confirmed that the initial improvement in motor function with risdiplam, followed by long-term stabilisation is the trajectory they would expect to see for patients receiving a DMT. Furthermore, they believe this represents a halting of disease, which over 5 years is clinically meaningful, versus the continued decline in ability they would expect to see in these patients before treatments became available. Furthermore, input from clinicians, in line with precedence from the original NICE appraisal of nusinersen (TA588), confirmed that patients receiving BSC are not expected to achieve improvement in the long term. Justification for assumptions regarding BSC extrapolation in the Type 2/3 model, along with cited data sources are summarised in CS Doc B Table 103.

The assumption of continued, long-term decline is further supported by Coratti et al. 2022, who observed overall negative 24-month changes in a cohort of 107 type 2 and 3 SMA patients assessed with the RULM tool.[6]

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NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Multiple Technology Appraisal

Risdiplam for treating spinal muscular atrophy – (MA review of TA755)

Additional clarification questions

April 2025

File name	Version	Contains confidential information	Date
ID6195 EAG Roche clarification responses set 2 090425 [REDACTED]	1.0	Yes	09/04/2025

Section A: Clarification on effectiveness data

Presymptomatic

A1. [Priority question] Risk of bias in the naïve comparison using evidence on presymptomatic patients:

a. **What risk of bias if any might be associated with using the point estimate results from a naïve comparison on HINE-2 milestones (from RAINBOWFISH and SPR1NT or RAINBOWFISH and NURTURE) to inform relative effectiveness between disease modifying therapies?**

The company faced significant challenges in evaluating the current therapies for SMA in presymptomatic children due to small sample sizes in the trials. Using naïve comparisons of point estimates from different trials to inform relative effectiveness between therapies can introduce several risks of bias. Selection bias arises from differences in baseline characteristics between trial populations, leading to biased estimates if these differences are not accounted for. Confounding variables, which are unevenly distributed across treatment groups, can distort the true effect of the treatments.

Given the small sample sizes in the presymptomatic population, the uncertainty of the estimates is high, as reflected in the broad 95% confidence intervals. This high uncertainty makes it challenging to draw reliable conclusions about the relative effectiveness of the treatments. We considered applying match-adjusted multiple comparison analyses (MAIC) to mitigate these biases. However, due to the small sample sizes, the effective sample size became too small to perform meaningful adjustments, with a ~50% reduction compared to the original sample size when attempting to match for predictive and prognostic factors.

Therefore, it was not feasible to generate evidence of differences between the two treatments from the existing presymptomatic trials due to the high uncertainty and small sample sizes. While our naïve comparisons showed better point estimates for one treatment at each visit, the large 95% confidence intervals indicate substantial uncertainty. Consequently, we refrained from making any assumptions of superiority for the presymptomatic population based on these comparisons.

b. Was risk of bias the reason why point estimates from the naïve comparison not used in the economic model?

Yes. In the company comparison versus nusinersen, risdiplam was systematically better when comparing the point estimate for each visit. However, the uncertainty around estimates does not allow us to make conclusions about treatment superiority in the presymptomatic population from the two trials.

c. If there is a significant risk of bias associated with population characteristics effect modifiers, does this mean that the evidence for one treatment is more generalisable to the population type than that for the other treatments?

In our analysis, the small sample sizes across the three clinical trials and the high uncertainty (broad 95% confidence intervals) complicate the generalisability of the findings. The risk of bias introduced by population characteristics or effect modifier imbalances, which could not be adjusted for, may distort the true effect of the treatments. Therefore, it is prudent to avoid making any assumptions or generalisations regarding the presymptomatic populations from the RAINBOWFISH, SPR1NT, and NURTURE trials.

d. Was uncertainty further tested around the assumption of equivalent effectiveness between risdiplam, nusinersen, and OA?

The statistical tests conducted in the naive comparisons examined the trials for non-inferiority using two-sided tests. These tests were not statistically significant, meaning they were unable to reject the null hypothesis that efficacy is consistent across trials for the current efficacy outcomes in the presymptomatic population of the RAINBOWFISH, NURTURE, and SPR1NT studies.

As detailed in Section B.3.3.1 of the company submission, an ITC was attempted in order to estimate comparator efficacy data. However, due to the small sample size, numerical differences in baseline characteristics, and the infeasibility of conducting MAIC to match for confounding variables, we must be cautious not to overinterpret the results in the presymptomatic populations.

The naïve comparison demonstrated non-statistically significant results for risdiplam in comparison to nusinersen and OA when evaluating mean changes in motor milestones. As caution is advised not to overinterpret the results in the presymptomatic populations, an assumption of equal efficacy between risdiplam, nusinersen and OA was used for the presymptomatic patient population.

The key takeaway is that there is insufficient evidence to determine whether there are differences in relative treatment efficacy based on the data from the aforementioned presymptomatic trials. Further analyses, including additional data sources, are necessary to investigate whether such differences exist for the case of the presymptomatic population.

In the economic model, uncertainty around the categorical assumption of equal motor milestone progression has been tested to some degree by allowing for the independent sampling of treatment-specific transition probabilities, assumed equal across all disease-modifying treatments in the deterministic base case, as part of the probabilistic sensitivity analyses (please also refer to the response to the previous March 2025 CQ B3d for details on how this was implemented in the model).

No further scenario analyses have been performed in addition to this, as these would have been reliant on applying assumed hazard ratios, in the absence of robust evidence as outlined above, so would have been likely to only introduce additional uncertainty.

Type 1

A2. [Priority question] What risk of bias if any might be associated with using the unanchored MAIC results on HINE-2 milestones (from FIREFISH and

STR1VE or FIREFISH and ENDEAR) to inform relative effectiveness between disease modifying therapies?

Naïve indirect comparisons use absolute values from clinical trial data without adjusting for the study population or methodological differences between clinical trials. This can carry a high risk of bias, as absolute values are influenced by the prognostic factors and effect modifiers unique to each trial population. It is important to adjust for study and population differences as far as possible to reduce the risk of bias.

Matching-adjusted Indirect Comparison (MAIC) is a methodology that reduces risk of bias in indirect treatment comparisons resulting from differences in prognostic factors and effect modifiers across different clinical trials.

While ENDEAR and FIREFISH were similar in terms of enrolment overall, considering age at first dose and disease duration of infants at baseline. In addition, no patients were on permanent ventilation at baseline in FIREFISH or ENDEAR. However, infants in FIREFISH had more severe disease at baseline as illustrated by the differences with 22.5 mean baseline CHOP-INTEND score for risdiplam (N=58) vs. 26.6 for nusinersen (N=80). Finally, the studies differed in design where ENDEAR was an RCT and FIREFISH was a single-arm study. Therefore, as FIREFISH was a single arm study, unanchored indirect comparisons were needed to compare the two treatments.

Roche undertook a formal feasibility assessment to understand whether an unanchored MAIC would be feasible against these studies. This included consideration of study design, comparability of baseline characteristics, sample sizes, outcome definitions, assessment of prognostic and predictive factors for matching. The company's feasibility assessment to indirect treatment comparison is detailed in CS Doc B.2.9.2. In short, the enrolled populations were similar enough to enable a comparison of the efficacy and safety of the two treatments using MAIC methodology and an unanchored MAIC was used to compare outcomes between FIREFISH and ENDEAR (1).

The company's MAIC methods are detailed in CS Doc B.2.9.3. To summarise, MAIC methodology was applied to reduce bias due to differences in prognostic factors and

effect modifiers across the study populations. Patients in FIREFISH (high dose N=58) were matched to the average characteristics of the nusinersen arm in ENDEAR (N=80). Characteristics used as matching factors in the MAIC analysis were mean age at first dose, disease duration at screening, and baseline CHOP-INTEND score.

The average risdiplam post-matching baseline characteristics were identical to the average ENDEAR baseline characteristics for all three matching factors (age at first dose: 5.4 months; disease duration: 13.2 months; CHOP-INTEND score: 26.6). An imbalance was introduced into gender (67% vs. 57%) after matching; however, gender has not been identified as a prognostic or effect-modifying factor, so this imbalance is not expected to impact results. Scenario analyses were performed in order to assess the stability of the matching algorithm and the sensitivity of outcomes. For this purpose, gender, ventilatory support, nutritional support, and HINE-2 at baseline were included as additional matching factors. Results remained consistent with the base case analysis and the effective sample size remained comparably the same, indicating that our initial selection captured the important prognostic and predictive factors with the highest contribution to population imbalances at baseline.

Results of the MAIC of FIREFISH and ENDEAR after 1 year of follow-up suggest a statistically significant and superior results for risdiplam compared with nusinersen across multiple outcomes, including survival, motor function and the likelihood of serious adverse events. This was supported by results from the updated MAIC analyses over 2 years, 3 years and 4 years of follow-up of risdiplam (FIREFISH) with nusinersen (SHINE/ENDEAR). Results suggest that infants with Type 1 SMA treated with risdiplam may see sustained long-term improvements in motor function response, lower risk of death or permanent ventilation and lower risk of serious adverse events compared with infants treated with nusinersen.

It was not feasible to conduct analyses on binary endpoints (Milestones achievement) using 2+ years follow up, as these were only reported for a subset of patients that reached the specific time point. Therefore, comparisons versus nusinersen were only possible for the outcomes for which there are published information and important outcomes may have been excluded. In addition,

comparisons versus BSC could not be performed at 4 years because patients in the sham arm in ENDEAR switched to nusinersen after 13 months of placebo. There was also a lack of information to compare other outcomes that may be relevant for treatment decision making (e.g. bulbar function, fatigability, patient-reported outcomes, and specific adverse events). The remaining risk of bias, as well as other limitations of unanchored MAIC as an approach are outlined in CS Doc B.2.9.5.

Even after applying best practice methods to match populations, there will still likely be underlying risk of bias remaining with these methodologies, especially in rare disease populations with small trial populations. Realistically, since FIREFISH is a single arm study, the only methodologically appropriate option in order to compare would be via an unanchored MAIC (or STC). The alternatives would be either a naive comparison between risdiplam and nusinersen (methodologically inappropriate) or no comparative efficacy at all.

As explained in CS Doc B.2.9.4 and B.2.9.5, the ITC between risdiplam and onasemnogene abeparvovec, even with the comparison to the two different STR1VE studies, does not provide sufficient evidence to draw concrete conclusions on the relative efficacy or safety between the two treatments. Despite only including three matching factors in the comparison of FIREFISH and STR1VE-US/EU, a MAIC was not feasible due to limited overlap in age and baseline CHOP-INTEND score. Hence, for the STR1VE comparison, STC was explored as an alternative method to derive relative effect estimates. The comparison of risdiplam to onasemnogene abeparvovec was limited by the short follow-up data publicly available for STR1VE studies. An indirect comparison between risdiplam and onasemnogene abeparvovec was deemed not feasible or appropriate to be updated after Month 12.

A3. [Priority question] What risk of bias if any might be associated with using the unanchored MAIC results on event free-survival (EFS, free from permanent ventilation or death) from ENDEAR and FIREFISH to inform relative effectiveness between disease modifying therapies?

Please see response to A2.

Type 2/3

A4. [Priority question] What risk of bias if any might be associated with using the unanchored MAIC results on motor milestones (from SUNFISH and CHERISH) to inform relative effectiveness between disease modifying therapies?

Naïve indirect comparisons use absolute values from clinical trial data without adjusting for the study population or methodological differences between clinical trials. This can carry a high risk of bias, as absolute values are influenced by the prognostic factors and effect modifiers unique to each trial population. It is important to adjust for study and population differences as far as possible to reduce the risk of bias.

MAIC is a methodology that reduces risk of bias in indirect treatment comparisons resulting from differences in prognostic factors and effect modifiers across different clinical trials. The company has responded to a similar clarification question (March 2025 CQ A1); please see our response there for details of the feasibility assessment and indirect comparison methods. In short, an anchored MAIC was possible for Year 1 assuming equivalence between oral placebo (SUNFISH) and sham procedure (CHERISH) (1), then only an unanchored MAIC was feasible for later data cuts (see CS Doc B.2.9.2).

While CHERISH and SUNFISH trials are both multicentre RCTs, there were some important differences in the inclusion/exclusion criteria which resulted in substantial differences in the baseline patient characteristics. For example:

- SUNFISH allowed patients ≤25 years of age to enrol, while in CHERISH only patients ≤12 years of age were eligible (the maximum age finally enrolled was 9 years)
- Restrictions on HFMSE total score were applied to CHERISH (scores ranged from 10 to 54), while no such restrictions were made with SUNFISH (where 41% of patients had a HFMSE score of <10)

- CHERISH excluded patients with severe scoliosis or severe contractures; however, these exclusion criteria were not applied in SUNFISH (where 32% of patients had severe scoliosis at baseline).

For the Type 2/3 population, given the differences in eligibility criteria between the studies, the company analysis included, as a starting point for the ITC, a subset from SUNFISH Part 2 to be representative of a CHERISH-like subpopulation. This included age 2-9, no patients with HFMSE <10 and no patients with severe contractures or severe scoliosis.

Following matching adjustment, imbalances from SUNFISH to CHERISH in terms of mean age at screening, mean baseline motor function score and mean SMN2 copy number were reduced, with some small numerical differences remaining. Differences to CHERISH were also reduced for other characteristics that were not directly matched for, such as age at symptom onset and symptom duration.

As with all methodologies, it is associated with limitations, detailed within CS Doc B.2.9.2, B.2.9.4 and B.2.12. When patients who would not have been enrolled in the CHERISH trial were excluded from the SUNFISH analysis population, only 68 patients remained in the analysis set (38% of the total sample size of 180). Regarding the unanchored MAIC specifically, the unanchored approach requires that effect modifiers and prognostic factors are in balance (or matched) between the populations. Attempts were made to align SUNFISH and CHERISH populations, but there may be further potential prognostic factors and effect modifiers in imbalance. For example, evidence of severe contractures was an exclusion criterion in CHERISH but not in SUNFISH and contractures information was not systematically captured in SUNFISH, so some patients with contractures may have remained in the CHERISH-like subset post-matching.

As explained in the response to A2, there will still likely be underlying risk of bias remaining with these methodologies with rare disease evidence bases. Realistically, in the absence of a common comparator between SUNFISH and CHERISH after Year 1, the only methodologically appropriate option to compare would be via an unanchored MAIC. The alternatives would be either a naïve comparison (methodologically inappropriate) or no comparative efficacy at all.

Section B: Clarification on cost-effectiveness data

Decision problem

B1. [Priority Question] Are the licenced indications for each of these interventions: risdiplam, nusinersen, and Onasemnogene abeparvovec (OA) comparable for each population Type?

Risdiplam is indicated for the treatment of 5q spinal muscular atrophy (SMA) in patients with a clinical diagnosis of SMA Type 1, Type 2 or Type 3 or with one to four SMN2 copies.

Onasemnagene abeparvovec is licenced in a more restricted population, for the treatment of:

- patients with 5q SMA with a bi-allelic mutation in the SMN1 gene and a clinical diagnosis of SMA Type 1, or
- patients with 5q SMA with a bi-allelic mutation in the SMN1 gene and up to 3 copies of the SMN2 gene.

Nusinersen is indicated in the broadest population of the three available treatments, for the treatment of 5q SMA.

As detailed above, the treatments are licensed in different indications. In addition, as part of the managed access agreement all patients who are permanently ventilated are currently ineligible for treatment. Separate to this appraisal process, patient groups are advocating for the expansion of the risdiplam license in line with the nusinersen broad indication to address the inequity for patients with Type 0 and 4.

a. **Are there any patient subgroups who are more likely to be given one treatment or the other based on the available evidence?**

As discussed above, the licenses for these therapies differ. Below we discuss other reasons certain subgroups may be more likely to receive a certain therapy.

Presymptomatic population

In February 2025, clinical experts on behalf of the SMA REACH registry advocated starting early ('bridging') treatment with risdiplam or nusinersen for presymptomatic babies with 2 SMN2 copies before onasemnogene abeparvovec can be administered if gene therapy is the choice of the family. General consensus of the clinical community is that children with presymptomatic SMA with 2 SMN2 copies are more likely to receive onasemnogene abeparvovec gene therapy if they are suitable for this treatment. As the UK does not have an SMA newborn screening programme, the only infants identified presymptomatically will include those who have a family history of SMA and have prenatal or early postnatal testing conducted. This is a very small cohort of infants in the UK. It is important to note that this is often down to patient preference rather than a strong clinical drive related to efficacy or based on available evidence.

Symptomatic type 1 SMA

In their letter to the clinical community in February 2025, SMA REACH recommended that bridging therapy represents the best approach for treating newly diagnosed symptomatic SMA type 1 patients with up to three SMN2 copies. We are aware that most, though not all, families choose onasemnogene abeparvovec gene therapy when a clinical diagnosis of type 1 SMA is made, and the urgency and clinical benefit of starting an SMN2 targeted therapy is discussed with the family. REACH registry data suggests that the vast majority of this cohort are initiated on risdiplam treatment while the baby is being assessed and optimised for gene therapy. The ease of risdiplam treatment initiation very quickly after diagnosis, rapid increase in SMN protein without a need for loading doses, the oral route of administration which is much less invasive than intrathecal administration, and minimal washout required before gene therapy (risdiplam treatment is typically stopped the day before onasemnogene abeparvovec infusion) can be postulated as reasons for this preference.

Due to the evolving phenotype and increased scientific and clinical knowledge of SMA, there are evidence gaps around outcomes such as bulbar function, cognition fatigability and patient reported outcomes within the registrational trials. These are

particularly pertinent in the Type 1 patients who had historically passed away before these challenges became apparent. As we learn more about these outcomes, they may become a differentiating factor for treatment choice across the breadth of SMA types.

Type 2/3 SMA

Risdiplam and nusinersen are both indicated for types 2 or 3 SMA. From the company's conversations with clinical experts, the treatment decision for a new patient in Type 2 or 3 are most often down to patient preference and lifestyle considerations. There is minimal to no clinical drivers suggesting a preference either way for any certain subgroups of patients based on efficacy. We of course suggest that clinical expert advice is also sought on this topic.

The treatment dynamic in the UK is currently skewed away from the expectation based on clinical expert insights. As nusinersen was made available in the UK before the other two therapies, any patients who were eligible for the treatment were largely initiated on it then. Therefore, the main cohort of patients not on nusinersen when risdiplam was made available were those with more severe disease progression and scoliosis which limited lumbar puncture access. The Managed Access Agreement discourages patients (and their HCP) from switching therapies unless there is a strong clinical need to do so which means that the treatment landscape has been more static than other countries. The company advises that if the REACH baseline characteristics are taken into account for patient demographics on each treatment, these nuances are taken into account.

b. **Are there any trial populations that may have characteristics such that effectiveness evidence may not be fully generalisable to the population type?**

Outcomes from different studies should be carefully considered and any unmatched comparisons should be considered with extreme caution. A few crucial baseline characteristics which are known to have an effect on outcomes are; age at symptom onset, disease duration, baseline function, and treatment duration. All studies demonstrate improved outcomes in patients with the shortest disease duration, with

a dramatic difference between treatment initiated before symptom onset and afterwards.

Tables 1-3 provide the inclusion and exclusion criteria from each of the key trials for each population with the company's comments on how those variables may affect the evidence's generalisability to the larger patient population.

Table 1: Inclusion and exclusion criteria from key trials in pre-symptomatic SMA

Pre-symptomatic SMA clinical trials		**Risdiplam (RAINBOWFISH)**	**Nusinersen (NURTURE)**	**Onasemnogene Abeparvovec (SPRINT)**
Key inclusion criteria	SMA diagnosis	Genetic diagnosis of SMA		
	Age	⩽6 weeks at first dose		
	SMN2 copy number	No eligibility limitations on *SMN2* copy number	2 or 3 copies of the *SMN2* gene	
	CMAP	No eligibility limitations on CMAP amplitude	Baseline ulnar CMAP amplitude ⩾1mV	Baseline CMAP amplitude ⩾2mV
	Nutrition	Receiving adequate nutrition and hydration at the time of screening	Not specified	Ability to tolerate thin liquids
Key exclusion criteria	Symptoms	Any clinical signs or symptoms suggestive of SMA		
	SMA therapy	Concomitant or previous administration of an SMA treatment or gene therapy		
	Oxygen levels	Hypoxemia		
	Respiratory support	Requiring invasive ventilation, tracheostomy or awake non-invasive ventilation	Not specified	Tracheostomy or current prophylactic use or requirement of non-invasive ventilatory support
	Laboratory results	Clinically significant abnormalities in laboratory test results		
	Weight	Weight-for-age is below the 3rd percentile on WHO Child Growth Standards	Not specified	Weight-for-age is below the 3rd percentile on WHO Child Growth Standards
Baseline characteristics that may reduce generalisability of study population		A wider population of infants with SMA has been enrolled in the RAINBOWFISH trial compared with NURTURE or SPR1NT.		
		SMA REACH recommend that pre-symptomatic cases with 2 *SMN2* copies are initiated on risdiplam or nusinersen at the time of diagnosis while the child is being assessed and optimised for gene therapy.		NICE recommendation for OA as an option for treatment of pre-symptomatic 5q SMA with a biallelic mutation

			in the *SMN1* gene and up to 3 copies of the *SMN2* gene in babies aged 12 months and under. However this study in pre-symptomatic infants only investigated babies 6 weeks and under, and treatment within the NHS is not always possible within this timeframe.
Overall comments	The absence of newborn screening in the UK means that outside the pilot NBS areas, the only possibility of pre-symptomatic infants being identified and treated early is those who have siblings affected by SMA and for whom pre-natal diagnosis (or very early postnatal diagnosis) is conducted.		

Table 2: Inclusion and exclusion criteria from key trials in Type 1 SMA

Type 1 (early onset) trials		**Risdiplam (FIREFISH)**	**Nusinersen (ENDEAR)**	**Onasemnogene Abeparvovec (STRIVE)**
Key inclusion criteria	SMA diagnosis	Clinical history, signs or symptoms attributable to Type 1 SMA with onset after 28 days but prior to the age of 3 months & confirmed 5q SMA genetic diagnosis	Medically diagnosed with spinal muscular atrophy (SMA)	SMA Type 1 diagnosis based on gene mutation analysis with biallelic *SMN1* mutations (deletion or point mutations)
	Age	1-7 months old	⩽7 months (210 days) at age of screening	<6 months (<180 days) of age at the time of OA infusion
	SMN2 copy number	Two *SMN2* gene copies		1 or 2 copies of *SMN2*
	Weight	Bodyweight ⩾3rd percentile for age		
Key exclusion criteria	SMA treatment	Treatment with another SMA treatment within 90 days of screening	Treatment with another SMA therapy within 30 days of screening	Receipt of an investigational or commercial compound, product or therapy administered with the intent to treat SMA at any time prior to screening
	Respiratory support	Requirement of invasive	Hypoxemia	Invasive ventilation, or

		ventilation or tracheostomy, or awake non-invasive ventilation or awake hypoxemia with or without ventilator support		non-invasive for ⩾12 (EU) or 6 (US) hours daily in the 2 (EU) or 1 (US) week/s prior to dosing
	Infection	Febrile illness within one week prior to screening and up to first dose administration	Presence of an active infection requiring systemic antiviral or antibacterial treatment during screening	Upper/lower respiratory tract infection. Serious non-respiratory tract illness requiring systemic treatment and/or hospitalisation within 2 weeks prior to screening; active viral infection/positive serology
	Aspiration	Not reported	Not reported	Signs of aspiration or whose weight-for-age falls below the 3rd percentile based on World Health Organization (WHO) Child Growth Standards and unwilling to use an alternative method to oral feeding.
Baseline characteristics that may reduce generalisability of study population		The standards of care for SMA have improved over the time that clinical trials investigating disease-modifying therapies in SMA type 1 have been conducted, with nutritional, respiratory and orthopaedic support optimised.		
		The SMA REACH registry enrolment demographics have been reported recently in the Lancet: Between Jan 1, 2019, and Nov 1, 2024, 507 patients with SMA (213 [42%] with SMA type 1, 188 [37%] with SMA type 2, and 106 [21%] with SMA type 3) were registered in the SMA REACH UK database. The mean age at diagnosis was 0·5 years (SD 0·4) for those with SMA type 1. However, this five-year period has witnessed increased awareness of SMA and it could be postulated that diagnosis more recently is earlier in most children with SMA type 1. The outcomes in clinical trials conducted in previous years might be different to those in children diagnosed and treated rapidly.		
		FIREFISH was conducted from December 2016 with the first patient enrolled in Part 1 (7 sites in 5 countries, all international centres of	ENDEAR was a randomised double blind sham controlled trial that started in August 2014.	Treatment naive infants were enrolled in the OA trials (STR1VE US started in October 2017 and STR1VE EU commenced in August 2018);

		excellence) followed by Part 2 beginning with the first patient enrolled in March 2018. Ten countries, with 17 sites recruited into Part 2, with varied standards of care, increasing the diversity and generalisability of the sites.		SMA REACH recommend that symptomatic type 1 SMA cases are now initiated on risdiplam or nusinersen at the time of diagnosis while the child is being assessed and optimised for gene therapy.
		The age at treatment initiation (6.7 months in Part 1 and 5.2 months in Part 2) is similar to that reported recently in the Lancet.	Infants were younger when they started treatment, and presented with a better motor function compared with the FIREFISH trial.	NICE recommendation for OA as an option for treatment of 5q SMA with a bi-allelic mutation in the SMN1 gene and a clinical diagnosis of SMA type 1 in babies only if they are 6 months of age or younger, or they are 7 to 12 months and their treatment is agreed by the national MDT.
Overall comments	There is a small cohort of individuals with SMA type 1 who have tracheostomy or require ⩾16 hours non-invasive ventilation who are currently accessing treatment through company supported schemes. A Delphi consensus process will develop guidance to establish the clinical benefit that these individuals receive from disease modifying therapies.			

Table 3: Inclusion and exclusion criteria from key trials in Type 2/3 SMA

Type 2/3 (later onset) SMA clinical trials		**Risdiplam (SUNFISH)**	**Nusinersen (CHERISH)**
Key inclusion criteria	SMA diagnosis	Confirmed diagnosis of 5q SMA	Clinically diagnosed with SMA with onset of symptoms after 6 months of age
	Age	2-25 years	2-12 years
	Function	Part 1 included both ambulant and non-ambulant SMA type 2 and people with SMA type 3 - there was no functional inclusion criteria. Part 2 was limited to non-ambulant type 2 SMA and type 3 SMA and all subjects had to be able to sit	Able to sit independently, but never had the ability to walk independently. Have motor function score (HFMSE) ⩾10 and ≤54 at screening.

		independently (item 9 of the MFM).	
	Scoliosis		Able to complete all study procedures; due to the intrathecal administration of nusinersen no child had severe scoliosis at baseline (Cobb angle >40 degrees). Presence of scoliosis, surgery for scoliosis or contractures was not reported.
Key exclusion criteria	SMA treatment	Concomitant or previous administration of a *SMN2*-targeting antisense oligonucleotide, *SMN2* splicing modifier or gene therapy either in a clinical study or as part of medical care.	Dosing with IONIS-SMN Rx in any previous clinical study, or treatment with another investigational drug.
	Surgery	Surgery for scoliosis or hip fixation in previous 12 months or planned within following 18 months.	Severe contractures or severe scoliosis; hospitalisation for any surgery, pulmonary event, nutritional support within 2 months of screening or planned during the duration of the study.
	Infection	Any major illness within one month before the screening examination or any febrile illness within one week prior to screening and up to first dose administration.	Presence of an untreated or inadequately treated active infection requiring systemic antiviral or antimicrobial therapy at any time during the screening period.
Baseline characteristics that may reduce generalisability of study population		The SUNFISH trial was recruited during the early period of nusinersen availability, which impacts on the baseline demographics of those who were enrolled - the mean symptom duration of the SUNFISH Part 2 was over 100 months with mean age at baseline around 10 years of age (around 3x more than in CHERISH).	The mean age at baseline was 3.7 years with symptoms being present for 36 months before treatment commenced.
		Part 2 SUNFISH enrolled patients with scoliosis (66.7%) with 32% of the enrolled population presenting with severe scoliosis (Cobb angle >40 degrees). One quarter of the patients had confirmed scoliosis surgery before screening. Additionally, over 40% of patients had contractures at baseline, which has an impact on	HFMSE scores were higher than those at baseline in the SUNFISH study (21.6 vs 16 in SUNFISH). Presence of scoliosis and contractures have an impact on the outcomes physically possible to achieve in individuals enrolled in clinical trials.

		achievement of motor function parameters. Baseline HFMSE was low (16) with 41% enrolling with a very low score (<10).	
		SUNFISH included a broader patient population (age and motor function) compared to CHERISH. The SUNFISH cohort is representative of non-ambulant individuals typically seen in clinics, including teenagers, adults and patients with reduced motor function - this population is under-represented in other clinical trials.	
Overall comments	There is a small cohort of individuals with SMA type 2 who have tracheostomy or require ⩾16 hours non-invasive ventilation who are currently accessing treatment through company supported schemes. A Delphi consensus process will develop guidance to establish the clinical benefit that these individuals receive from disease modifying therapies.		

B2. Why was 1 month considered an appropriate model cycle length? Is it appropriate to consider alternate cycle lengths like 4 months?

The model cycle length is selected to be monthly. A cycle length of one month was considered sufficiently granular to capture changes in patient outcomes and costs. The company's cost-effectiveness models had previously been deemed appropriate by NICE as part of the first evidence submission in 2021 and had undergone EAG critique in 2024 as part of this managed access review, where the monthly cycle length was accepted. As part of these various evidence submissions, model structures and inputs (including cycle length) were validated with experts.

State transition models assume that transitions from one health state to another occur at the beginning of each cycle. In reality, however, patient transition is a continuous process, which may occur any time during the cycle. By applying a short cycle length of one month, the difference between the actual transition time and the model predicted time is reduced. This allows for more accurate estimation of the length of time patients remain in the health states and also allows flexibility and accuracy in costing and dosing calculations, since the administration cycles of the

different treatments assessed in the model vary. Half-cycle correction was applied to the model in order to account for mid-cycle transitions.

In addition to the above general modelling principles, the pre-symptomatic and Type 1 cost-effectiveness models consider paediatric patient populations where children receiving disease modifying therapy for SMA would be expected to pass through developmental milestones on a monthly, weekly and sometimes daily basis (as babies and children without SMA do). Roche feels that a more granular cycle length of one month is more appropriate.

Presymptomatic and Type 1

B3. Is it feasible and likely in clinical practice for risdiplam patients to start other disease modifying therapies after discontinuation of risdiplam (nusinersen or OA) due to: different mechanisms of action; treatment effectiveness (or lack of); treatment-related adverse effects or; other reasons?

Roche would advise the EAG to consult with their clinical experts.

For the presymptomatic and Type 1 patients in question, there are multiple reasons to initiate risdiplam treatment. The reason for initiation of treatment with risdiplam will determine whether another DMT would be considered after risdiplam discontinuation. The paragraphs below outline the different scenarios.

Bridging

Some presymptomatic patients will opt for OA as their DMT. While the process for getting started on OA has been streamlined over time in the UK, it still often takes around 2 weeks to receive the AAV-9 seropositivity results, which are required before dosing. During this period, significant neuronal damage can occur. Physicians are choosing to bridge patients, most often with risdiplam, to their OA dose in order to preserve neuronal function.

In symptomatic patients who opt for OA, the UK consensus is now to ‘optimise’ patients on risdiplam or nusinersen before initiating OA.

In both of these scenarios, OA would technically be used following the discontinuation, albeit planned discontinuation, of risdiplam.

Patients who choose risdiplam over nusinersen/OA

The majority of patients will be offered any of the 3 DMTs when diagnosed with SMA, some of whom will choose risdiplam over nusinersen and OA. Similarly, some patients will choose to switch from nusinersen to risdiplam, driven more by patient/carer preference than a strong clinical need. In both of these scenarios, if a patient discontinued risdiplam then they would likely have the option to initiate nusinersen and potentially OA.

Patients whose only option is risdiplam

In the presymptomatic and Type 1 cohorts, patients may be ineligible for nusinersen due to scoliosis or spinal access issues. They may also be ineligible for OA due to AAV-9 seropositivity, weight or age. In these scenarios, risdiplam may be the only treatment option for these patients. In this scenario, neither nusinersen nor OA would be available after risdiplam discontinuation. That being said, risdiplam discontinuation is extremely unlikely in this scenario. To determine how unlikely, the EAG could consider approaching the paediatric REACH registry to ask for numbers.

Presymptomatic

B4. [Priority question] Given the availability of new therapies for presymptomatic patients, is it likely that patients receive BSC in clinical practice?

Does that include presymptomatic patients with a missed presymptomatic diagnosis?

Roche would advise the EAG to consult with their clinical experts.

As there is no newborn screening for SMA in the UK, the only patients that could be considered 'truly' presymptomatic would be those who are specifically tested prenatally or at birth as they have parents or siblings with SMA. Even then, there is clinical theory that SMA-related damage could occur *in utero*. This population is extremely small in the UK and likely less than one incident patient per year. Therefore, for the majority of the 'presymptomatic' population, by nature of their presymptomatic state and lack of a diagnosis, patients would not be aware of their SMA until they become symptomatic and are diagnosed. Upon diagnosis, it is highly

unlikely that any patient would opt for BSC. All patients would then likely start treatment with disease modifying treatments in line with the Type 1 or Type 2/3 models.

For the few patients who are diagnosed presymptomatically, physicians would not recommend BSC as an option and it is highly unlikely that parents would opt for it. In the future, when newborn screening becomes available, this stance will not change.

The company understands that this general assumption can be extended beyond the presymptomatic population to the Type 1 and Type 2/3 symptomatic populations. Where REACH registry data, as well as clinical opinion and Roche market forecasting data indicates that the vast majority of patients with SMA are receiving treatment with disease modifying therapies. For example, clinical opinion to the company backed up by data gathering in key treatment centres in the UK from October 2024 indicated that 0 eligible paediatric patients receive BSC over disease modifying therapies (Table 5). This is also supported by patient and carer advocacy groups who promote early intervention with disease modifying therapy.

For the adult population, data gathered through clinical conversations, presented in Table 5, suggests that only [redacted] of [redacted] ([redacted]%) patients sampled were receiving BSC instead of a disease modifying therapy and, when accounting for those who had previously discontinued a disease modifying therapy, this number shrinks to [redacted] of [redacted] ([redacted]%). Furthermore, the June 2024 REACH report, presented in Table 4, indicated that only 33 of 426 (7.7%) are still classed as 'natural history', which the company interprets to relate to BSC. The REACH data covered more sites than the Roche gathered data, but there was strong alignment in rates of BSC in centres that featured in both datasets.

Therefore, for the overall population sampled in Roche data gathering, only [redacted] of [redacted] ([redacted]%) people with SMA were receiving BSC instead of disease modifying therapy at first line (Table 5). This indicates the importance of intervention with disease modifying therapies to patients, carers and their clinicians. It also calls into question the relevance of a cost-effectiveness comparison to BSC when it is not a reasonable treatment option for over 95% of the eligible population.

Table 4: Risdiplam Adult REACH Report – June 2024 (Data cut: 4/6/2024)

	Total	Birmingham	Leeds	Bristol	Cardiff	Glasgow	King's	Newcastle	Nottingham	Salford	Sheffield	Southampton	St. George's	The Walton	UCLH	Cambridge	Oswestry	Swansea	Oxford
Total risdiplam	**289 (67.8%)**	24	5	19	2	11	5	22	15	27	23	15	18	5	45	20	10	3	20
Total natural history	**33 (7.7%)**	2	1	1	0	0	1	2	2	4	4	0	1	0	9	0	1	0	5
All patients enrolled	**426**	37	6	23	2	11	6	28	21	47	54	23	30	5	68	20	15	3	27

Note: REACH natural history doesn't account for discontinued or ineligible patients; Inferred nusinersen: 104 pts (24.4%)

Table 5: Roche UK data gathering – October 2024

Centre	Adults/Paeds	Total Patients	Patients on BSC	Proportion on BSC	Eligible and BSC first only	Eligible BSC proportion
Sheffield	Adults	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Nottingham	Adults	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
St Georges	Adults	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Leeds	Adults	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Newcastle	Adults	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Salford	Adults	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Oswestry	Adults	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
GOSH	Paeds	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Leeds	Paeds	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Liverpool	Paeds	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total	**Adults**	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total	**Paeds**	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
					Overall	[redacted]

B5. Assumptions of treatment effectiveness duration over the long-term:

a. **Is it reasonable to assume a treatment effectiveness duration of 6 years after the start of treatment for risdiplam, for nusinersen, and for OA?**

b. **Does the model assume treatment effectiveness stops after 6 years of starting treatment?**

c. **Is there evidence or mechanisms of action reasons for treatment effect waning or not waning?**

d. **Was the assumption of a risk of losing motor milestones over the long term considered?**

Roche would advise the EAG to consult with their clinical experts.

However, the company strongly refutes any treatment effectiveness duration for risdiplam. There is no evidence to suggest that the treatment effect of risdiplam stops or reduces over time. The company, along with the clinical community, consider that these DMTs are providing treatment effectiveness for as long as they are given by increasing the SMN protein needed for neuronal development and maintenance and stopping/slowing the deterioration that would be expected with no intervention. Continued maintenance and stabilisation of motor function following any initial improvement is the goal for people with SMA. This is only achieved with disease modifying therapies and is a crucial consideration for the lifetime of anyone living with SMA.

Risdiplam is administered orally and homogenously distributed throughout the entire CNS and body, including the upper spinal cord and brain. This is an important consideration when we look at the potential impacts of SMN deficiency from recent basic research (2, 3).

Roche would struggle to comment on the long-term effectiveness of other disease modifying therapies without access to the relevant data sources. However, the mechanism of action of onasemnogene abeparvovec could, in theory, result in a reduction in effect over the long term. Onasemnagene abeparvovec uses a non-integrating vector, which means that the replacement SMN1 gene is lost when the

affected cell dies and turns over. All of the recipient's cells will be producing SMN after the initial dose of onasemnogene abeparvovec, but those cells that have a faster turnover will stop expressing that protein. In young patients during development, this is the majority of their body's cells. The nerve cells within the CNS would be expected to continue producing SMN for the rest of the recipient's life as they do not turn over, but other high-turnover cells may not. For nusinersen, long-term waning effects are not expected. As with risdiplam, benefit is expected while on treatment. However, shorter-term waning effects between dosing have been reported independent publications for nusinersen where the positive effects on outcomes such as fatigue are noticeably reduced closer to the next planned dose (4). In addition, for nusinersen, there becomes a time when clinicians cannot access the spine adequately for intrathecal administration due to complications such as scoliosis. In this case, patients may well switch treatment, but this does not suggest that the treatment has stopped working while still being administered.

UK clinical expert feedback obtained for the company submission indicated that that the majority of patients receiving active treatment would be expected to remain stable or improve in the long-term. Clinicians also noted that it was clinically plausible for SMA patients treated with BSC to continue losing motor milestones, in line with natural history data. This feedback, and corresponding assumptions, are further supported by the results of the respective open-label extensions for the FIREFISH and SUNFISH symptomatic trials. Treated patients maintained, or continued to improve, important milestones over the 5-year observation periods, see CS Doc B.2.6.1, B.2.6.2 and the additional FIREFISH 5-year addendum for full clinical effectiveness results.

The submitted presymptomatic cost-effectiveness model includes an assumption at 10 years (120 monthly cycles) where transitions are turned off and patients remain in their current motor milestone for the remainder of the time horizon or until death. This is to simulate a developmental plateau, rather than a loss of treatment effect. The 10-year assumption is a conservative assumption based on the fact that, at the time of the original evidence submission, the oldest known efficacy trial of a disease-modifying treatment in SMA (a phase 1 study of nusinersen) began recruitment in late 2011. Particularly in the presymptomatic model, it is important to consider the

fact that these patients will be treated at a very young age so a 6-year “ceiling” for no longer achieving motor milestones is clinically inappropriate as these patients are expected to continue to gain motor abilities and function. On this point in particular, we would advise seeking clinical expert advice.

Type 1 SMA

B6. Is it reasonable to expect a treatment effect duration of 5 years for risdiplam and OA as well as nusinersen? The assumption being that after 5 years, patients cannot improve motor milestones and can only maintain or decrease their milestone improvements.

As explained in our response to B5, there is no rationale for a treatment effectiveness duration for risdiplam. While patients continue to receive treatment, they will continue to derive benefit. Again, it is important to note that, while patients may plateau in motor milestones, the treatment effect is stabilising motor function, and preventing decline, deterioration and loss of previously achieved motor function.

The company Type 1 cost-effectiveness model does include assumptions to limit transitions at various time points in the model. However, we would stress again that this does not relate to a stopping of the risdiplam treatment effect and should potentially be thought of as a developmental plateau. The company would highlight again that, while patients continue to receive treatment, they will continue to derive benefit - even if that benefit is maintenance and not improvement. This is detailed in the company response to clarification question A4 in the July 2024 clarification step. We have provided detail relating to Type 1 SMA from A4b here, for completeness.

> *The separate time periods allow for the granular adjustment of transition probabilities and corresponding assumptions around long-term efficacy in the different treatment arms, with the implementation of this functionality originating from the initial NICE appraisal of risdiplam in SMA (TA755), which were in turn taken from the TA588 appraisal of nusinersen.*
>
> *In the first 24 months of the model:*

- *Patients move between health states in line with the different study (FIREFISH,) or indirect treatment comparison (ITC)-derived transition probabilities.*

After 24 months, it is assumed that:

- *Motor milestones for patients in the active treatment arms (i.e. risdiplam, nusinersen, onasemnogene abeparvovec) can only improve or remain stable, i.e. any backwards transitions to worse health states are deactivated for active treatments from this time point.*

- *Motor milestones for patients in the best supportive care (BSC) arm could no longer experience continued improvement, i.e. any forward transitions to better health states were deactivated from this time point.*

As stated in CS Document B Section B.3.9.2 of the submission, these assumptions were carried forward from TA755, which were in turn aligned with the committee-preferred analysis for the initial NICE appraisal of nusinersen in SMA (TA588); these assumptions were also validated by clinical experts at UK advisory boards and supported by findings from the literature, as described in CS Document B Section B.3.10.

After 66 months in the Type 1 SMA model:

- *A plateauing of treatment effect for all active treatments (i.e. risdiplam, nusinersen, onasemnogene abeparvovec) was assumed. Specifically, any backwards and forwards transitions were deactivated from this time point onward, and it was assumed that patients in the active treatment arms would remain in their current health state until death.*

This assumption and selected time points have been implemented in line with the EAG-preferred analysis in TA755, which itself was aligned with the implementation of a treatment benefit plateau preferred by the committee in TA588.

Please also see the previously submitted FIREFISH five-year addendum. These longer-term efficacy and safety data provide important evidence of the long-term

benefit of risdiplam in patients with infantile-onset (Type 1) SMA. Results show that initial treatment benefits and attained developmental milestones were maintained through Month 60. This shows no sign of the risdiplam treatment effect stopping at 5 years and highlights that, while on treatment, patients still receive treatment benefit.

B7. How likely is the percentage discontinuation in Type 1 for those "walking independently" appropriately reflected by 1%?

As discussed on 26 March 2025, this question does not relate to the Roche analysis.

Health Related Quality of Life

B8. Is there any reason to think that the utility estimate for a specific motor milestone may be higher when receiving risdiplam, nusinersen or OA than when not receiving such treatment for the same motor milestone?

If yes, is there any reason to believe there is a difference between risdiplam, nusinersen or OA?

As stated in CS Doc B.3.13, anecdotal evidence from the clinical and patient community speaks to the opportunity that risdiplam (and likely other disease modifying) treatment has afforded them to be able to attend school, become working taxpayers and play roles within their own community. The change in patients' and families' quality of life with the advent and provision of novel disease modifying therapies is difficult to capture. There is likely to be a health-related quality of life impact associated with 'being on treatment'. This benefit will extend from patients to their caregivers, where provision of treatment is likely associated with a reduction in anxiety and improved mental health, outside of capturing the impact of motor function and disease-related complications. Furthermore, the impact to society that these patients will have is also not accounted for within the economic analysis.

There are also elements of different treatment regimens that would likely drive differences in health-related quality of life. There are key differences in administration between treatments for SMA. Nusinersen is administered via intrathecal injection (lumbar puncture) into the cerebrospinal fluid. After four loading doses within the first 2 months, patients receive a maintenance dose every 4 months. Intrathecal injections can be associated with treatment-related reactions

such as headaches, vomiting and back pain. Risdiplam is given orally each day. Onasemnogene abeparvovec is a gene therapy and is administered once via an intravenous infusion. Clinical and patient opinion to the company highlights the distress and burden associated with continued intrathecal injections and general anaesthetics to allow intrathecal injections in children, especially those with compromised respiratory function. Patients may wake up groggy and confused, and the repeat process can get worse for patients' quality of life over time.

Two studies by Lo et al. 2022 investigated the patient preferences and utilities for treatment attributes in Type 2 and Non-ambulatory Type 3 SMA patients and their carers in the UK and Europe (5, 6). The manuscripts use discrete choice experiments to quantify caregiver and patient preferences for different attributes of SMA treatments. The studies covered a range of treatment attributes, including motor function, breathing function, treatment administration and treatment reactions. Treatment administration had a statistically significant influence on choice. In the UK study, participants were 2.0 times more likely to choose a treatment taken orally on a daily basis than a treatment administered via an intrathecal injection in hospital every 4 months. Caregivers were 2.9 times more likely to choose a treatment taken orally than intrathecal injection. Treatments with no treatment-related reactions were 3.1 times more likely to be chosen than treatments with 3–4 days of fever, headache, vomiting and/or body pain. The European study supported the UK discrete choice experiment, where participants were 1.8 times less likely to choose a treatment administered via an intrathecal injection than orally, all else being equal. When EQ-5D utilities were estimated using UK preference weights, intrathecal injections had a disutility of − 0.071 compared with a daily oral liquid.

When considering efficacy outcomes, Lo et al. showed there was strong preference for both improvement and stability of motor and breathing functions, but avoiding a deterioration in motor and breathing functions was more important to adult patients than an improvement in these functions (5, 6). Treatments with no treatment-related reactions were 3.1 times more likely to be chosen than treatments with 3–4 days of fever, headache, vomiting and/or body pain. Treatment reactions that only lasted for 1–2 days were not significantly different to no risk of treatment-related reactions. Regarding treatment side effects, participants preferred to avoid a 10% risk of liver

injury associated with onasemnogene abeparvovec, compared with a 17% risk of diarrhoea and rash associated with risdiplam. However, participants were no more or less likely to choose a treatment with side effects associated with intrathecal injections (fever, headache, vomiting and/or body pain) associated with nusinersen compared with a treatment with a 17% risk of diarrhoea and rash.

Outside of the motor function health states that are used to capture patient utility in the model, there are other impacts associated with non-motor function outcomes, of which there are likely differences in outcomes between treatments. The homogenous systemic distribution of risdiplam to both the CNS and the peripheral tissues may offer additional benefits over nusinersen. Independent scientific literature has shown that the SMN protein is expressed ubiquitously in the body and suggests that “A suitable therapeutic for SMA should be expressed in all target tissues, including the CNS” (7). Further to this, more recent literature has shown that SMN deficiency can lead to issues outside of the CNS such as vascularisation, protein homeostasis amongst others (2, 8). Again, clinical expert validation on SMA as a multisystemic disorder would be beneficial (9). However, the company submitted models account for these impacts by applying utility decrements to the proportion of patients experiencing worse bulbar, respiratory and scoliosis outcomes.

The company strongly advocates for the appropriate modelling of treatment related impacts to quality of life outside of the motor function outcomes that make up the model health states. It was a criticism of the cost-effectiveness analysis used in the original appraisal that the model did not adequately capture the true impact of SMA, and simplifying utility values would likely move the analysis further away from the truth.

Disease complications

B9. How appropriate is it to include the following disease-related events (rather than treatment-related events) using literature estimates: time to scoliosis? Time to respiratory support (not permanent)? Time to bulbar disfunction?

Is it possible that these disease-related events are already being captured within health-related quality of life and resource use estimates for SMA?

Is there evidence showing a difference in treatment-related risk for any of these disease-related events for risdiplam versus nusinersen or OA?

As detailed in CS Doc B Section B.3.13, due to the simplification of economic modelling, it is not possible to reflect all of the treatment-related benefits. Currently available outcome measures do not capture other important features of life with SMA that are deemed to be important to patients and their families, such as the ability to perform daily activities, respiratory function, swallowing, fatigue and endurance, and that small improvements make a big difference to the ability of an individual to function and thrive.

Section B.3.13 also explains the importance of recognising bulbar function in addition to established motor score measurements. Sitas et al. 2024 conducted a real-world study observing type 2 and 3 SMA patients on risdiplam to collect motor function scores and patient reported outcomes such as quality of life (10). The study found that all patients had reported an increase in their quality of life. 59% of patients who had bulbar symptoms reported improvements in bulbar function, and one-third of patients were seen to have an increase in appetite and subjective improvement in digestion. The challenge of small sample sizes with a rare disease makes it difficult to capture enough data to fulfil modelling requirements, but improvement in non-motor outcome function is important and relevant to patients, families and their clinicians, and the difficulty in capturing it with standardised motor function measures should be taken into consideration. The additional disease related events are very important and evident in the natural history of patients living with SMA, supported by synthesised empirical evidence, and pose substantial disease morbidity (11-14).

The inclusion of costs and utility decrements associated with disease-related events in the economic analysis of risdiplam was a result of committee advice during the original NICE appraisal (TA755). It was stated that likely benefits of risdiplam treatment were not adequately captured in the economic models at that time (also accounting for the already applied motor milestone-specific utility and resource use estimates). This was supported by multiple stakeholder comments received during Technical Engagement highlighting the importance of clinical events such as impaired respiratory or bulbar function with regards to patients' quality of life. Therefore, the company cost-effectiveness models for this evidence submission include resource use costs and utility decrements to capture the impact of disease-related events and attempt to demonstrate the full benefit that DMTs provide to patients living with SMA and their families. Whilst limited data on respiratory support, bulbar dysfunction and scoliosis was available from the respective risdiplam trials, literature sources were considered most appropriate. The company strongly advocate for the appropriate modelling of treatment related impacts outside of the motor function outcomes that primarily make up model health states.

The company argue that disease-related events are not fully captured in quality-of-life estimates by motor milestone. EQ-5D was captured in the Type 2/3 cost-effectiveness analysis and considers health states utility values (not sitting, sitting, standing, walking) and disease related impacts as disutilities (respiratory, bulbar, scoliosis etc). With regards to the disutilities associated with respiratory support and scoliosis in particular, a repeated measures model with fixed and random effects was applied to the EQ-5D-5L data from the ITT population of Part 2 of the SUNFISH study, including analyses by presence of scoliosis and respiratory support at baseline. The results of these analyses identified scoliosis and respiratory support to be drivers of additional disutility, which was consequently calculated for these two morbidities, accordingly. Overall, our 1- ,2- and 5-year SUNFISH utility analyses demonstrate that there is reason to believe there are still significant disease impacts related to disease complications, irrespective of motor function health states (Table 6).

Table 6: SUNFISH Year 1, Year 2 and Year 5 utility estimates

effect	1-year Part 2 estimates - no substates (95% CI)	2-year Part 2 estimates - no substates (95% CI)	5-Year Part 2 estimates - no substates (95% CI)
Not Sitting	[redacted]	[redacted]	[redacted]
Sitting w support	[redacted]	[redacted]	[redacted]
Sitting w/o support	[redacted]	[redacted]	[redacted]
Standing w support	[redacted]	[redacted]	[redacted]
Standing w/o support	[redacted]	[redacted]	
Walking w support	[redacted]	[redacted]	[redacted]
Walking w/o support	[redacted]	[redacted]	
Severe Scoliosis	[redacted]	[redacted]	[redacted]
Respiratory Support	[redacted]	[redacted]	[redacted]
Patient-reported	[redacted]	[redacted]	[redacted]

Sutherland et al., 2022 performs a similar analysis using HUI-2 from the NatHis-SMA natural history data set, a longitudinal prospective study of the natural history of untreated patients with Types 2/3 SMA (15). Baseline HUI-2 scores showed that having non-invasive ventilation, feeding support and scoliosis was associated with a lower patient utility than not having.

With regards to differences in treatment-related risk for these events, anecdotal evidence through conversations with clinical experts leads us to believe that we may see differences between the treatments but, while evidence is being generated, comparative evidence is extremely limited. We suggest speaking to your clinical expert advisors as well as the REACH clinical teams on whether any comparative analyses have been made within the UK RWE data set.

In the cost-effectiveness analysis, with the literature-derived event proportions being specific to different motor milestones, any difference in motor milestone progression between the different disease-modifying treatments would also equally be reflected in the occurrence of respiratory support, bulbar dysfunction and scoliosis over time. Then, the company analysis assigns costs (CS Doc B.3.5.2) and utility decrements (CS Doc B.3.3.5) to account for the impact of these differences.

As detailed in response to B8, the company strongly advocates for the appropriate modelling of disease-related impacts outside of motor function outcomes. It was a criticism of the cost-effectiveness analysis used in the original appraisal that the model did not adequately capture the true impact of SMA, and simplifying the analysis here would likely move further away from the true impact.

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NICE National Institute for Health and Care Excellence

Multiple Technology Appraisal

Nusinersen and risdiplam for treating spinal muscular atrophy (MA review of TA588 and TA755) [ID6195]

Guidance review following a period of managed access - Patient organisation submission

Thank you for agreeing to give us your organisation's views on these treatments following a period of managed access. You can provide a unique perspective on conditions and their treatment that is not typically available from other sources.

PLEASE NOTE: You do not have to answer every question. Your organisations involvement in the managed access agreement for these treatments is likely to determine which questions you can answer.

To help you give your views, please use this questionnaire with **NICE's guide for patient organisations "completing an organisation submission following a period of Managed Access for Technology Appraisals or Highly Specialised Technologies".** Please contact pip@nice.org.uk if you have not received a copy with your invitation to participate.

Information on completing this submission

- Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable
- We are committed to meeting the requirements of copyright legislation. If you intend to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Your response should not be longer than 35 pages.

NICE National Institute for Health and Care Excellence

This form has 8 sections

Section 1 - About you

Section 2 - Living with the condition and current treatment in the NHS

Section 3 - Experience, advantages and disadvantages of these treatments during the Managed Access Agreement [MAA]

Section 4 - Patient views on assessments used during the Managed Access Agreement (MAA)

Section 5 - Patient population (including experience during the Managed Access Agreement (MAA)

Section 6 - Equality

Section 7 - Other issues

Section 8 - Key messages – a brief summary of the 5 most important points from your submission

NICE National Institute for Health and Care Excellence

Section 1. About you

Table 1 Name, job, organisation

1. Your name	**SMA UK**: [redacted] **Treat SMA**: [redacted] **MDUK:** [redacted]
2. Name of organisation	Spinal Muscular Atrophy UK Treat SMA Muscular Dystrophy UK
3. Job title or position	[redacted]
4a. Provide a brief description of the organisation. How many members does it have?	**Spinal Muscular Atrophy UK (SMAUK)** is a national charity, founded in 1985, providing support via our Support Service team, and information about SMA to all those living with the condition and their families. Our e-news is sent to 3,736 recipients and our magazine SMA matters is sent to 3889 households. We also advocate on improving access treatment and issues surround the complexities that living with a rare condition brings. All our health information is accredited by the Patient Information Forum (PIF) and is available via our website in the form of webinars, podcasts and information sheets. We host virtual and in person events that connect the SMA Community together offering a space to share information and offer peer support. **Treat SMA** is a UK charity established back in 2017 made up of volunteers living with spinal muscular atrophy (SMA) and their parents and carers who joined hands to improve the diagnostics, standard of care, social support, and access to treatments in this severe genetic disorder. We support the efforts to speed up diagnostics and introduce treatment as early as possible. TreatSMA aims to ensure hospitals across the country can offer the highest standard of medical care to those with SMA. We promote the Standard of Care document and protocols, to reduce the risk of severe complications of spinal muscular atrophy and improve the quality of life.

<table>
<tr><td></td><td>We believe that everyone with SMA has a right to treatment and work to ensure that people with all types of the SMA get the opportunity to access effective treatments. We co-operate with all other stakeholders in the UK SMA community to bring about broad access to the most appropriate treatment given the individual circumstances and advocate for appropriate levels of social support, including access to physiotherapy, hydrotherapy, occupational therapy, supportive tools and equipment – everything that reduces the burden of SMA and makes life with this severe disease more bearable.

Through our extensive social media and online community reach, we encourage people with SMA, their friends and families to work together and advocate jointly for change.

Muscular Dystrophy UK (MDUK) is the charity bringing individuals, families and professionals together to beat muscle-wasting conditions. Founded in 1959, we have been leading the fight against muscle-wasting conditions ever since. We bring together more than 60 rare and very rare progressive muscle-weakening and wasting conditions, affecting around 110,000 children and adults in the UK. We fund research, provide vital information, advice, resources and support for people with these conditions, their families and the professionals who work with them.

Collaboration lies at the heart of our work and as such this submission has been collated together jointly between our three organisations</td></tr>
<tr><td>4b. Has the organisation received any funding from the company/companies of these treatments and/or comparator products in the last 12 months? [Relevant companies are listed in the appraisal stakeholder list which was provided to you when the appraisal started]
If so, please state the name of company, amount, and purpose of funding.</td><td>SMA UK
<table>
<tr><th>Roche</th><th>£</th></tr>
<tr><td>Community communications and connections</td><td>69,810</td></tr>
<tr><td>Consultancy Fees</td><td>6,477</td></tr>
<tr><td>SMA Care UK Project</td><td>67,354</td></tr>
<tr><td>Biogen</td><td></td></tr>
<tr><td>Children’s book project sponsorship</td><td>15,000</td></tr>
<tr><td>Novartis</td><td></td></tr>
<tr><td>Support Services</td><td>37,500</td></tr>
</table></td></tr>
</table>

<table>
<tr><td></td><td>
Treat SMA
As a voluntary organisation led by people living with SMA, Treat SMA do not receive any funding from industry.

MDUK
<table>
<tr><th>Roche</th><th>£</th></tr>
<tr><td>European Paediatric Neurology Society congress attendance costs</td><td>1,711</td></tr>
<tr><td>Advocacy Panel event participation</td><td>900</td></tr>
<tr><td>Conference fee costs and accommodation expenses to participate in Health and Care Forum fringe event at Conservative Party Conference</td><td>608</td></tr>
<tr><td>Virtual seminar sponsorship</td><td>2,750</td></tr>
<tr><td>Health inequity co-creation exercise participation</td><td>600</td></tr>
<tr><td>Conference fee costs and attendance expenses for the Muscular Dystrophy Association Conference 2023</td><td>TBC</td></tr>
<tr><td>UK SMA Newborn Screening Alliance</td><td>50,000[1]</td></tr>
<tr><td>Novartis</td><td></td></tr>
<tr><td>UK SMA Newborn Screening Alliance</td><td>45,000[2]</td></tr>
</table>
</td></tr>
<tr><td>4c. Do you have any direct or indirect links with, or funding from, the tobacco industry?</td><td>No for all 3 organisations</td></tr>
<tr><td>5. How did you gather information about the experiences of patients and</td><td>SMA UK, Treat SMA and MDUK conducted two surveys of the SMA community to help form this response. The surveys were open between 22nd February and 22nd March. One survey was for carers and one was for people living with SMA. The carer survey received 145 responses (135 informal carers/ 10</td></tr>
</table>

[1] This is funding for the work of the UK SMA Newborn Screening Alliance and is not being retained by MDUK.
[2] This is funding for the work of the UK SMA Newborn Screening Alliance and is not being retained by MDUK.

carers to include in your submission?	professional carers); and the survey for those living with SMA received 114 responses. We are grateful to all those who shared their experiences with us in this way. In addition, 13 detailed case studies provided by members of the SMA community have been used in this response. When we summarise the experience of an individual that has been shared with us in this submission, it has been gathered through this activity. **SMA UK :** • Membership of SMA UK social networks: -Family network- 88 members -Adult network: 23 members -Young adult network: 43 members • Working closely with SMA UK's support team who responded to 207 families through our direct support line in 2023. • SMA UK's Adult advocacy steering group • SMA UK's community podcasts • Personal experience of living with a son with SMA type 1 **Treat SMA:** • Facebook group 2000 members • Treat SMA facebook page 4,400 followers • Adult facebook group 200 members Conclusions were formed from reaching out to the UK Spinal Muscular Atrophy Community in the UK via our social media platforms, specifically facebook.

	Due to the large amount of people in the group we had a fantastic response to our requests which enabled us to cover the wide spectrum which is SMA from all types to ages on both treatments taking into account variables. Visually we had many videos and photos submitted which backed up evidence submitted on how both treatments are working for individuals and how this has not only changes their life but those around them including their siblings, partners, parents, carers and PAs.

Section 2 Living with the condition and current treatments

Table 2 What it's like for patients, carers and families to live with the condition and current NHS treatments

6. What is it like to live with the condition? Consider the experience of living with the condition and the impact on daily life (physical and emotional health, ability to work, adaptations to your home, financial impact, relationships, and social life). For children, consider their ability to go to school, develop emotionally, form friendships and participate in school and social life. Is there any impact on their siblings?	While SMA is categorised under 4 specific types, the range and impact it has on patients in all groups is highly variable and subjective. Two type 1 patients can be impacted in very different ways, even with the same clinical diagnosis in terms of SMN2 copies. The views in this document are heavily summarised and we would urge those reading the document to take time to review the specific patient comments and feedback listed in the appendices to get a far better understanding of how the condition impacts those individuals with and those caring for people with SMA . **Executive Summary** • **Ability to work or gain an education:** Limitations in workplace and educational settings due to physical and care needs, though Access to Work scheme and EHCPs can provide support. • **Emotional health and well-being:** The continuous loss of abilities and chronic sorrow significantly impact mental health, necessitating tailored support strategies. • **Adaptations to the home:** Financial and logistical challenges of home adaptations for accessibility and independence. • **Financial impact:** Significant expenses related to care, equipment, home adaptations, and the need for specialized vehicles, putting a strain on personal finances. • **Relationships:** Strain on family relationships due to care demands and the impact of SMA on siblings' emotional well-being. • **Diet:** Dietary adjustments and assistance required due to difficulties with swallowing and feeding. • **Exercise:** Limitations on physical activity due to mobility and respiratory issues, though specialized physiotherapy can help. • **Travel independently:** Challenges in accessing public transport and the need for specialized vehicles to maintain mobility and independence. 1) Mobility a) Use of Wheelchairs

i) **Manual and Powered Wheelchairs**: The condition necessitates the use of both manual and powered wheelchairs, tailored to the individual's specific mobility limitations and lifestyle requirements.

"In my early 20s, I used to be able to go around the house on my knees, but I can't do that now,". Adult

ii) **Additional Modifications**: To enhance comfort, independence, and quality of life, wheelchairs often require additional modifications not covered by standard healthcare services.,

b) Challenges in Mobility and Independence

i) **Environmental Adaptations**: . home adaptations, widening doorways, installing ramps, and modifying bathrooms are vital for allowing individuals with SMA to navigate their living spaces independently and safely.

ii) **Financial and Logistical Hurdles**: The financial burden of acquiring such specialized equipment and making home adaptations can be immense.

"Financially it is extremely tough, we have spent a lot of money adapting our house and garden for our son's needs." Carer of child

iii) **Specialized Equipment Needs**: Beyond mobility aids, individuals with SMA may require other specialized equipment to facilitate their daily living. This includes adaptive beds, hoists for transfers, and standing frames to support physical health. The process of integrating this equipment into the home requires careful planning and can significantly impact the family's living space and finances.

2) Self-Care

a) Dependency for personal care

i) **Total Reliance on Others**: Individuals with SMA, particularly those with types 1 and 2, exhibit profound muscle weakness, rendering them entirely dependent on others for most aspects of personal care. This includes assistance with transfers from a wheelchair to a bed or other seating, personal hygiene tasks, and even turning in bed to prevent pressure sores.

ii) **Impact of Reduced Arm Strength**: For many, especially those with types 1 and 2 SMA, limited arm strength necessitates total reliance on others even for basic self-care tasks. The

loss of autonomy in these areas significantly impacts individuals' quality of life and mental health, as they navigate the challenges of needing constant care while striving to maintain some degree of independence.

b) Eating and swallowing difficulties

i) **Challenges with Swallowing**: As SMA progresses, it affects bulbar muscles responsible for swallowing and facial expressions. Individuals may experience difficulties with chewing and swallowing, necessitating modifications to their diet to ensure safety and nutritional intake. This often involves careful selection of food textures and assistance with cutting food into small pieces or moistening it to facilitate safer swallowing

"The loss of my son's ability to swallow, smile, and effectively communicate are probably the most difficult aspects of SMA for me to come to terms with…," Carer of child

3) **Dependence on Others for Feeding**: Many individuals with SMA require help with feeding, either due to the physical inability to lift utensils to their mouth or because of the need for mechanical arm supports. The social and emotional implications of these dependencies are significant, affecting individuals' participation in shared meals and social interactions.

, **"The inability to feed myself…has massively impacted my social life. Through extreme anxiety, I am forced to exclude myself from any social events both personal and work due to feeling extremely self-conscious about needing assistance."** Adult

4) Usual Activities

", SMA significantly impacts daily life, affecting individuals' ability to participate fully in the world around them

a) Impact on Education and Employment

i) **Educational Challenges:** Despite cognitive abilities being unaffected by SMA, physical limitations can hinder access to mainstream educational opportunities. Finding a school that is both physically accessible and offers the necessary support for toileting and other personal care needs is a formidable challenge for many.

‘ I looked at 15 nurseries and 28 primary schools and accessibility was very poor at most of them. The attitude of staff is the MOST important thing, though. It doesn't matter if they have previous experience with disabled pupils but they need to have a can-do attitude and not be afraid of them. They need to see the child as a human and not a problem! They need to be able to think outside the box and ensure inclusion.’

Carer of child

ii) **Employment Limitations:** SMA also significantly impacts individuals’ capacity to engage in employment. Workplace adaptations and flexible working arrangements are essential for accommodating the unique needs of those with SMA..

“When my son was diagnosed with SMA Type 1 at 3 months old, I had no choice but to give up my job,”

Carer of child

Social Isolation

iii) **Isolation from Peers:** The need to minimize health risks, especially respiratory infections, often leads families to isolate themselves, significantly limiting social interactions, independence and impacting family dynamics. The quote in section 3 above, about assistance with feeding, highlights how anxieties around needing assistance in public settings hugely impacts social inclusion.

iv) **Limited Access to Social Activities:** The challenges extend to social and leisure activities, where physical and health considerations restrict participation. This limitation not only affects the individuals with SMA but also their family members, altering family dynamics and leisure opportunities.

v) **Challenges in Maintaining Relationships:** The strain on relationships extends beyond the immediate family to affect friendships and romantic relationships. The presence of a carer during personal or intimate moments, for example, can significantly alter the dynamics of these relationships, highlighting the nuanced ways in which SMA impacts personal and social interactions.

vi) **Impact on siblings**

Siblings report feeling that things are all focused on their brother or sister, missing out on attention from parents. They may feel anxious or worried about their sibling’s disability. Options for day trips and family

holidays are significantly limited, giving SMA siblings fewer opportunities than their peers. As an adult sibling the caring role for their brother or sister with SMA may continue alongside formal and/or informal care provision.

'***Having an SMA brother is not completely different to having a brother without SMA, we can still make up games and play, just in different ways. I treat him like a normal brother. But it does make me sad that he cannot eat or walk and run. When he is poorly in hospital, I do feel very sad and worried, and I miss my mum a lot'*** 10 year old sister of child

5) Pain and discomfort in individuals with Spinal Muscular Atrophy (SMA) brings significant challenges that directly affect their quality of life and ability to engage in daily activities. Spinal Curvature and Contractures
    i) **Development of Spinal Curvature (Scoliosis):** Scoliosis is a common issue for individuals with SMA, impacting mobility and overall health. The curvature of the spine can compress internal organs and cause pain
    ii) **Contractures and Joint Issues**: Contractures, where muscles or tendons shorten, leading to stiffness and restricted joint movement, pose daily challenges. The development of contractures contributes to a cycle of pain, reduced mobility, and further physical decline, illustrating the interconnectedness of SMA's physical impacts.

b) Respiratory Issues and Discomfort
    i) **Breathing Difficulties**: Individuals with SMA often experience significant respiratory compromise, leading to discomfort, fatigue, and anxiety. Daily management involves routine respiratory physiotherapy, cough assist devices, and sometimes overnight non-invasive ventilation.
    ii) **Impact on Daily Life**: The challenges of managing respiratory issues significantly affect social interactions and independence. Reduced lung capacity leads to fatigue and decreased voice volume, making even simple conversations exhausting. Many families choose to isolate themselves to minimize health risks, leading to a secluded lifestyle. One individual described how respiratory compromise affected their ability to participate in social activities, stating that even a decrease in voice volume could limit their social interactions, illustrating how respiratory issues compound the challenges of living with SMA.

6) Anxiety and depression

Emotional Toll of SMA

i) **Chronic Sorrow**: The progressive nature of SMA means that individuals are constantly facing the loss of their physical capabilities, a process that engenders a state of ongoing grief or "chronic sorrow." Unlike acute grief, which might diminish over time, chronic sorrow is a persistent mourning over the progressive losses experienced.

ii) **Impact on Mental Health**: The relentless progression of SMA can make traditional depression treatments less effective, as they are not designed to address the ongoing loss of function. The psychological impact extends beyond the individuals with SMA to affect their families and caregivers, who also experience stress, anxiety, and grief.

"Living with a child with SMA is emotionally draining… It is a constant worry about the future and his independence," illustrating the pervasive anxiety about the disease's progression and the future." Carer of child

b) Anxiety Over Health and Future

i) **Fear of Respiratory Illnesses**: The vulnerability to respiratory complications is a constant source of anxiety for those with SMA and their families. A common cold can lead to life-threatening situations, creating a backdrop of fear and uncertainty that permeates daily life. This fear often leads to social isolation in an attempt to protect the individual with SMA from potential infections, further impacting mental health and quality of life.

ii) **Worry About Independence and Care**: As SMA progresses, the increasing dependence on others for basic needs can significantly impact self-esteem and mental health. The worry extends to the availability and quality of care, particularly as caregivers themselves face burnout.

'I currently rely on twenty-four-hour care, which is shared between the carers I employ and my family. Independence is a factor that contributes the most to health and it can be hard in a care crisis to have your needs and wants fulfilled' Adult

"Numbers can't come close to showing how I battled through university – exhausted, bruised, often bleeding – determined to keep up " Adult

	"You never know what is round the corner… There are days when the disease wins," Adult
7. What do carers experience when caring for someone with the condition?	**Appendix 2:1: Quantitative data Appendix 2:2 -2:5: Qualitative data** Caring for someone living with SMA impacts on every part of an individual's life. It is common for one family member to give up a career to take on a full-time caring role. Depending on the severity of the individual living with SMA, the carer role involves supporting with everyday activities as well as learning and delivering more specialist care at home including: - Respiratory physio (cough assist and suction) and ensuring proper use of any ventilatory support. - Physiotherapy and stretches - Personal care and transfers - Planning and risk assessing trips - Ensuring comfort through the night – inc turning and saturation monitoring in some cases. - Managing prescriptions and appointments - Sourcing specialist equipment and adaptations Aspects explored in the survey showed: **Mental health:** 67% of carers occasionally or frequently feel anxious, stressed or down because of their role as a carer. ***'Massively stressful and exhausting always being the sole carer to someone. You don't get a break or time to yourself. Outside services are limited and a lot of the time we feel very alone.'*** Carer of Adult With a lack of capacity in the NHS, patient groups support carers with access to counselling services. **Social Life**: 78% of carers felt their caring role impacted their social life, with 25% reporting that it made it almost impossible to have a social life. ***'I am fortunate enough to have excellent parents and a partner who all support me in being able to maintain some sort of social existence. However, this is still different to that of my friends who have children who don't have sma. Trying to find babysitters or carers outside of your immediate circle is virtually impossible with the higher level of needs required'*** Carer of child **Relationships:** 65% of carers felt their role occasionally of significantly affected their relationships. 5 respondents perceived their caring role to be responsible for their divorce.

	'Relationships in the household can become very strained. My daughter needs can impact everyone in the household with the constant care needed. I would say it has impacted my marriage significantly due to the tiredness and day to day routines. It's certainly not easy but we try our best' Carer of child **Finances:** 89% of carers felt their caring role had an impact on their finances, 51% reporting a significant impact. ***'Electric, fuel for the van, insurance, food, extra hotel room for carer when we go away overnight impact us massively. I can't work apart from 10 hours per week I get paid as part of my son's care team as I'm always on call/ home alone with him.'*** Carer of adult
8. What do patients and carers think of current treatments and care available on the NHS Please state how they help and what the limitations are.	**<u>Current treatments</u>** The only disease modifying treatment routinely available on the NHS to treat SMA is Onasemnogene abeparvovec, branded Zolgensma. ***Limitations*** Only suitable for babies and young children weighing up to 21kg , with up to 3 copies of SMN2, Zolgensma leaves the majority of the current SMA population in the UK without routine access to a disease modifying therapy. When administered early enough, preferably before symptoms appear, Zolgensma can modify the natural path of the disease and we are now seeing children living with the most severe type of SMA following normal developmental patterns, walking, eating and breathing independently. However, Zolgensma is not always suitable for those who fall within the eligibility criteria. There have been children who cannot access it due to initial blood tests revealing antibodies to the AAV9 virus (around 5 in 100 children tested). If the results of the other tests (liver function, full blood count, kidney function, cardiac enzymes) aren't clear, these may indicate it wouldn't be safe to administer Zolgensma. Families are careful not to expose their children to any viruses before the infusion, as any clinical instability would mean the infusion would be postponed. Following Zolgensma infusion, patients with underlying active infection, could be at an increased risk of serious systemic immune response, potentially resulting in more severe clinical courses of the infection, therefore many families choose to shield for all or part of the average 3 month monitoring phase post Zolgensma. This shielding process both pre and post Zolgensma

	puts serious limitations on family's lives, impacting siblings ability to go to school and parents' ability to go to work. In addition to the above, even if administered successfully Zolgensma is not always effective. There are rising number of cases that require additional treatments post Zolgensma infusion. '***The shielding process was pretty long after already spending 5 weeks in hospital, more for my partner being self employed. He had nearly 3 months off work not being paid because of hospital and shielding.'*** Carer of child ***'We are about 8 weeks nearly 9 weeks in from my daughter having Zolgensma, we are still having to shield as best as we can because her liver levels are to high from Zolgensma, she's also had to start a new medicine alongside the steroids because of the liver levels being too high , so lots of extra blood tests. She also had to try the steroids on drip for 3 days, but we knew this could be a side effect from Zolgensma, it can be hard with having other children who still need to go school I feel like it's pretty hard going on them, I'm not able to do anything with them etc.'*** Carer of child Access is also limited by geographical area, with only seven infusion centres across the UK, many families will have to travel long distances and stay away from home to get access. **Current Care** **Management interventions**, particularly for infants with Type 1, focus on **correct positioning** and ameliorating **breathing difficulties**. These include: chest physiotherapy; oral suctioning; medication to reduce secretions; cough assist; non-invasive ventilation. This is very time-consuming for parents and can be distressing for both them and their child. **Spinal scoliosis and kyphosis**, with its physical and emotional impact, is often managed initially with a lycra suit, spinal brace or jacket but surgery may be recommended if it is contributing to breathing difficulties, preventing comfortable sitting or the curvature has progressed beyond a certain point. The majority of adults living with type 2 SMA will have had spinal surgery, usually in their early teens, as will the later treated type ones as they grow up.

	Physiotherapy, Knee-ankle-foot orthosis (KAFOs) and Ankle-foot orthosis (AFOs) as well as standing frames (predominantly paediatric) help manage contractures and pain, chest physiotherapy helps manage breathing difficulties. For those children treated early, regular physiotherapy is now being used to facilitate standing and walking. Interventions, particularly for those with Type 1 and 2, to manage choking, swallowing, fatigue with feeding, digestion, constipation and managing weight, may include **tube feeding, gastrostomy, medication** and **dietary management**. A major management tool, however, is vigilance and time on the part of carers. **Standards of Care in SMA** The standards of care for SMA, published in 2017 are now out of date. The advent of new treatments have brought huge changes to the SMA landscape. Standards of care and management of the condition on the NHS vary across the UK. A real world study in 2022 showed that: *'Access to certain professionals for people with SMA is limited in the UK. Striking differences were noted between paediatric and adult populations. Limited access to care were regularly reported, with half of the study population consistently not accessing full multidisciplinary care. Access to interventions for contracture management were recorded to have significant limitations. Mobility aids and home adaptations are widely available and were also reported as the most valued interventions. Access to nutritional support or speech and language therapy appears only to be available for a small proportion of the participants. Access to respiratory care was good especially in severe forms of SMA. We found pockets of good practice in the UK that align with the SoC. However, access is not equal for adults and children and access to certain professionals is significantly limited.'*[3] The findings of this study reflect what patient groups see in the SMA community. Inconsistencies in provision of therapies, equipment and orthosis across the UK mean many people living with SMA will pay privately for mobility equipment, physiotherapy and physiotherapy equipment, orthotics and other

3 **Real-World Data on Access to Standards of Care for People With Spinal Muscular Atrophy in the UK**

Robert Muni-Lofra et al

	interventions such as neuromuscular electrical stimulation, often on the recommendation from other families via social media and not on specialist clinical advice. Other barriers to optimum care are the lack of clinical evidence in SMA and a lack of communication between tertiary, secondary and primary care providers. People of all ages and all severities of SMA experience a lack of capacity, knowledge and understanding at local level. Capacity for therapies in adult local services is particularly strained.
9. Considering all treatments available to patients are there any unmet needs for patients with this condition? If yes please state what these are	Zolgensma is only available for young children with 3 or less copies of SMA2 and under 21kg who have passed all the clinical assessment. For those living with SMA (which is the majority of prevalent cases) who do not meet Zolgensma's access criteria, there is currently no disease modifying treatment treatment to halt the progression of the disease. Therefore, both children and adults living with SMA across the UK will be living with a progressive decline, losing the ability to walk, sit, breathe and swallow at different rates depending on their severity level. Despite Spinraza having a license to treat all those living with 5Q SMA, those living with type 4 SMA have never had any access to DM treatment. This has caused significant distress. See appendix 1:4 for case study.

Section 3 Experience during the managed access agreements (MAA)

Table 3 Experience, advantages and disadvantages during the MAA period

Please present your responses by treatment under each section.

10. What are patients' and carers' experience of accessing and having these treatments?	**Appendix 3:1 Quantiative data** **Appendix 3:2 Qualiatative data** Ease of access to treatment varies depending on age, location and year of access, with access improving as the MAA rolled out across the UK and awareness of it grew among patients and health professionals.

• Please refer to the MAA re-evaluation patient submission guide	From the qualitative data, we saw some other themes emerge amongst those that struggled to get timely access the treatments on the MAA: • A lack of knowledge of the advances in treatment for SMA amongst local health providers was a barrier for many, with some people having to educate their GPs to get a referral: ***'Had to travel out of area to see a neurologist who was able to prescribe it. It took approximately one year to get this appointment. Once seen by this neurologist I received the prescription quickly.'*** Adult ***'The referral process took extremely long, six months to see a local neurologist and then a further eight months before seeing the specialist clinic'*** Adult • Geographical inequities ***'Living in the South West of England we are always the last to receive new treatments.'*** Adult • Extended timelines due to the MAA exclusion criteria For those falling within the descriptors of the exclusion criteria, access was a longer process involving a multi-disciplinary team of specialist clinicians. We heard form the parents of 3 young babies who were permanently ventilated in PICU when they first accessed treatment. **(See appendix 3:3 for case study).** ***'Being a young parent and having a recent diagnosis of SMA 1 is stressful enough on its own without having the fight we have to go through. Due to my little girl being intubated no treatment was available until we pushed and pushed and eventually got a trial for 3 months of risdiplam (which has worked wonders) now because my daughter is still intubated and the 3 months is nearly up we have to wait for it to go back to a panel meeting to see if treatment can carry on. It is so so disappointing as a parent to have to fight so much for treatment which could prevent so much for***

***children with SMA. And I think it is disgusting that children who are intubated or have tracheostomy's are not eligible for this treatment it is so so cruel*!'** Carer of child

SMA type 1 progresses at an extremely fast pace. Delaying treatment for the most severely affected has caused huge stress for parents and further irreparable damage to the child living with SMA.

'We accessed Spinraza when it was available through the EAP, I am thankful that it was not on the MAA as we would not have been eligible due to the fact he was intubated at the time.'
Carer of child

We also saw some positive comments about the speed of access to treatment, particularly with Risdiplam.

'Very smooth process that was dealt with well by my clinic most of the way but difficult to access sperm banking, which I ultimately didn't pursue as it wasn't important to me'
Adult

'I was amazed that I got a phone call from Polar speed & they keep control of the drug being given. which is nice if I was to ever forget ordering. Polar speed are a friendly team and I felt supported.'
Carer of child

Summary of data appendix 3:1

Benefits of access to Risdiplam	Negatives of access to Risdiplam
Convenient, delivered to your home Non-invasive No hospital admission required Minimal impact on daily life	Taste Liquid is difficult to draw up independently.

Benefits of access to Spinraza	Negatives of access to Spinraza
Only 3 times a year Patients feel safe and well cared for	Specialist hospital can be far from home Takes a day or more out of daily life Invasive procedure

11. What do patients and carers think are the advantages of the treatments? Please refer to the MAA re-evaluation patient submission guide	**Appendix 4:1 Quantiative data** **Appendix 4:2 Qualiatative data** For the youngest and most severely affected, treatment has given a life that would have otherwise lasted less than two years. It has brought physical gains and stability to many. Case studies and social networks show it has also brought hope to the SMA community. Our survey captures the real world impact of Nusinersen and Risdiplam across both physical and mental health. **Strength** The quantitative data from the survey shows majority of people on both treatments perceive their strength to either have stayed the same or to have improved. The free text comments from both treatment options report real world examples of how valuable stability and small gains are to people who, before these treatments were available, were facing a progressive disease and had no hope of maintaining the strength to do everyday tasks. ***'I am now able to lift my hand from my lap to the control of my wheelchair without help'*** Adult ***'I have maintained my strength and improved in some aspects. For example, putting on my headset is very important to me and I no longer strain as much as I did.'*** Teenager **Respiratory Function** Apart from two respondents, everyone living accessing treatments on the MAA feel their respiratory function has either remained the same or improved. Many commented on the obvious gains they have seen in their respiratory function since starting treatment: ***'He was in intubated for every common cold he got when he was little, 10 times in his first 3 years. Now, [aged 7] he manages common colds at home with chest physio and bi-pap.'*** Carer of child ***'I was ventilated 24 hours a day just to stay alive I now only need my ventilator when I'm asleep and can mange all naps off it. I'm so much stronger and haven't had a hospital admission for a common cold in 4 years '*** Adult

	Others commented on the less obvious gains that have had a significant impact on their quality of life: ***'My breathing was always okay, but my cough and strength of breathing have increased greatly. I can now recover from colds quicker and unblock my airways when ill.'*** Adult ***'I can now cough up phlegm a lot easier preventing hospital admissions.'*** Adult The positive impact on social communication was also highlighted by a number or respondents in the free text, all adults living with SMA; ***'I can shout much louder and hold my breath for longer'*** ***'I feel that I can speak longer than any time before without being out of breath. All my friends and relatives noticed that my voice became louder.'*** ***'I no longer run out of breath while talking. This has helped massively with both my energy levels and my ability to interact with people.'*** **Swallow** Only one respondent across both treatments available on the MAA that reported any regression in the ability to swallow. Some have seen gains, but most have noticed that there has been no change. With fear of choking a very real thing in the SMA community, stability in this area is a huge positive for the SMA community. **'There has been no minor or major progression - there has been perhaps less aspiration'** Adult **'My swallow ability is stable and it is very important for me too. Because it is in a rather poor condition and if it progresses, I could lose the ability to eat tough food.'** Adult Some have seen more noticeable gains:

	'I was starting to have difficulty swallowing around foods that were dry but I don't struggle as much now. I always grew up having olive oil to assist with the food so now I just use olive oil so it's back to how it was' Teenager ***'Was told to start thickening powder for fluids as was aspirating. That is no longer needed'***. Carer of child **Fatigue** Levels of fatigue are difficult to capture in clinical data, and the definition of fatigue is a subjective one that varies depending on baseline. Many respondents to this sliding scale question perceived their energy levels to have stayed the same or to have improved since treatment started. Some believed that although their fatigue levels had stayed the same, or increased a little, this could be due to the fact that they felt able to do more without resting during the day. ***I am tired but I do more than before as my left arm has more strength and range. I have increased hours at work so whilst I am tired at the end of a day, I am doing more because I now can.*** Adult '***I no longer need short naps in the day to recover from bursts of activity and feel I can manage a full days school/travel/play without sleeping/resting which wasn't the case before'***, Adult **Mental Health** Living with SMA with or without treatment is a burden on mental health for the individual and the whole family. Treatments on the MAA stop the progression of the disease but they do not reverse the impact up to that point. Maintaining a positive mindset whilst living in a world built for able bodied people will always be a constant mental battle for those living with SMA and their carers but new treatments bring hope. A lack of mental Health services on the NHS impacts the whole SMA community. ***'It's been a real mental soother to know I'm not getting weaker in theory and my results prove it.'*** Type 2 SMA 15-20 yrs ***'It is amazing to know that something is being done to aid sma and it makes me feel a lot less worried about the future'*** Adult living with type 3 SMA

Quality of life

Quality of life can mean different things to different people. The chart below summarises the frequency of 4 identified themes from the free text responders.

Everyday examples of how quality of life has been impacted:

1. Increased independence inc work and social life	**23**
2. Improved health	**10**
3. Stabilisation of condition inc less fear of death	**19**
4. Living not dying	**5**

1. Independence inc work and social life

'Through treatment our daughter is able to walk, a skill that was in decline prior to the commencement of treatment. She currently lives a full, happy, and high quality life including playing with friends' Carer of child

2. Health

'Huge improvement. Able to go to preschool and engage in age appropriate activities alongside peers. Improved respiratory function has also meant that we no longer avoid infection like we used to as a family, so we socialise more and lead a more normal life' Carer of child

3. Stabilisation of condition inc. less fear of death

'I'm not quite sure how to put this. Risdiplam has improved every part of my life. I can now talk to people and they understand every word because my voice box works again. I no longer feel like I'm dying. At all. Let alone soon.' Adult

4. Life itself

'He would not have a life if it was not for treatment' Carer of child

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Carer Quality of Life
The carer survey saw some different themes emerge as to what they perceived had the greatest impact on their quality of life. Alleviation of stress relating to the poor physical health of the people they care for was one of the most common responses in the free text. The frequency of themes found are summarised below, some respondents mentioned more than one of the themes;

<table>
<tr><td>Increased independence of person living with SMA</td><td>20</td></tr>
<tr><td>Increased independence of carer</td><td>7</td></tr>
<tr><td>Improved physical health of person living with SMA</td><td>37</td></tr>
<tr><td>Stabilisation of the condition</td><td>24</td></tr>
<tr><td>Living not dying</td><td>2</td></tr>
<tr><td>Less stress/ worry for carer</td><td>27</td></tr>
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<td>12. What do patients or carers think are the disadvantages of the treatments?
Please refer to the MAA re-evaluation patient submission guide</td>
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The data collected as well as experience supporting people through patient organisations, shows that the treatments do not impact individuals living with SMA in the same way. Two individuals with the same SMN2 copy numbers and presenting similarly clinically will not necessarily have the same treatment outcomes. For a minority of individuals, 2 in our data sample, treatment is not effective, or side effects decrease quality of life.

SMA social media groups and forums have taken a toll on some of the SMA community. People will always compare themselves to those in similar situations and the fact that treatments effect everyone differently has been difficult for many, with unfulfilled high expectations for treatment outcomes.

Treatment has also introduced disruption into some people’s lives, adjusting to the treatment and monitoring schedule has been difficult for some:

‘I think one of the challenges that has come with being on treatment is the patient work/life balance. I think that there is a misconception that clinicians have about people living with SMA. It's almost as if they don't realise we are actually capable of acquiring jobs and contributing to society. So
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	cloying to balance regular hospital checkups that usually take you away from home for either the whole day or multiple days is sometimes challenging. 'Adult Some patients have reported side effects from both treatments that have impacted their quality of life such as headaches from lumbar punctures or gastric problems from Risdiplam. See section 10 for disadvantages of how treatment is accessed. There were not a significant amount of disadvantages reported by the community.
13. What place do you think these treatments have in future NHS treatment and care for the condition? Consider how these treatments have impacted patients and how it fits alongside other treatments and care pathway.	<u>Choice</u> It is important for the SMA community to have a choice of all available treatments on the NHS. There is not one treatment that is effective for all, both clinical and real world evidence has shown that there are non-responders to all of the treatment options, where one treatment is ineffective, another might get better outcomes. Choice and trial and error is currently the only way to optimise treatment outcomes for SMA. When newborn screening for SMA is in place, having the choice of three treatments for up to 4 SMN2 copies will allow a treatment option for all, with the Sprinraza license not limited by SMN2 copies. <u>Access for all</u> Patients have seen benefits from treatment across the severity spectrum. Access for all from those fully ventilated to those living with type 4 is the only way to ensure equity of access for the whole SMA community. <u>Newborn Screening</u> Will health outcomes directly related to speed of access, the future has to be one where people living with SMA are diagnosed through newborn screening, the only way to ensure timely access and optimum outcomes for all living with SMA. <u>Combination therapy</u> Both Risdiplam and Nusinersen impact the function of the SMN2 gene, Zolgensma effectively replaces the faulty or missing SMN1 gene. Clinical trials are currently assessing the efficacy of using dual therapy to maximise the production of the SMN protein.The future could see either of the treatments being used as a combination therapy with Zolgensma.

Section 4 Patients views on assessments used during the MAA

Table 4 Measurements, tests and assessments

Please present your responses by treatment under each section.

14. Results from tests and assessments are used to help reduce uncertainty about the effectiveness of treatment. **How well do you think these tests and assessments worked in measuring the effectiveness of these treatments?**	**Appendix 5:1 Quantiative data** **Appendix 5:2 Qualiatative data** Many agreed the MAA assessments were effective at measuring some physical outcomes of treatment and the official recording of outcomes was appreciated. Perspectives also showed the difficulties of capturing how treatment has impacted daily life. The themes captured by the free text responses are summarised below: 1. No assessment of real-world milestones or daily life activities. ***'Luckily the tests showed a lot of positive impact, however its not the whole picture. Seeing a child every day on treatment, I get to see all the small things she can now accomplish that a test cannot - such as the length of time she can now weight bare or the fact she can now eat her dinner without getting tired.'*** Carer of child ***2.*** A snapshot in time is not a fair assessment, may be assessed when fatigued or having an 'off' day. ***'Time of day the assessment is carried out impacts the results. The later the day the more fatigued' '*** Carer of child **3.** Especially difficult for children in a clinical environment. ***'They look at a snapshot in time on that particular day, at that particular time. Our little boy is often shy when he first meets people/sees people for the first time in a while, so takes a while to warm up. Early on tests may not show real-life results as he'll be more nervous about doing anything, particularly as there are usually other conversations going on in the room at the same time. Additionally at his age he doesn't understand everything that he's asked to do, with some of***

	the tests being things he's never been asked to do before so there's no opportunity to learn/understand what's being asked of him at the time.' Carer of child 4. No measurement of improvements in mental health or confidence. ***'The assessments and tests are good but do not pick up necessarily on how much benefit mentally as well as physically being on the drug gives. It has given my wife and myself hope about the future as even if the drug only slowed down the effects of SMA this would be a massive achievement but as it stands we have actually seen gains with her swallowing and ability to move her arms***.' Carer of adult 5. Some important factors are not included in the assessments. ***'No assessments or tests for bulbar function which has been our biggest improvement. Gone from completely tube fed to mostly oral eating since being on risdiplam.'*** Carer of child
15. Were there any tests or assessments that were difficult or unhelpful from a patient's or carer's perspective?	Whilst the tests were generally considered as effective at measuring gross and fine motor skills, they do not accurately represent outcomes in what is a multi-system condition. Formal assessments of bulbar function and respiratory drive for example would give a more holistic picture of efficacy. The Patient reported outcomes (PROMS) could be an excellent way of collecting real life qualitative data, but will only be successful if embedded into clinical practice with good communication. Many people were not aware of these assessments at all until the end of the MAA period. As the requirement was to complete the PROMs near to the time of your clinic appointment, it would have made sense to complete it whilst in clinic, or whilst waiting for the appointment. Adults living with a slower progression have found the 6 monthly assessments a burden. The appointment, often far from home can take a lot of organising and also a whole day out of work for some. When assessments 6 months apart rarely show any significant differences for adults living with SMA, it would be more helpful and less of a practical and emotional burden to have an annual clinical assessment. ***'[We need] new tests designed specifically for adults with SMA which can measure improvement in much smaller increments. A more joined up and robust approach to the collection of qualitative data which reflect more accurately the positive impact treatment has on the individual.'*** Adult

	There were also several comments made in the survey about a lack of continuity, variations in equipment or clinician from one assessment to the next made people concerned about the validity of the outcomes. ***'I think the test should be videoed, so the assessments are carried out exactly as the previous assessment.'*** Adult The knowledge that any regression in assessment scores could result in removal of treatment causes the SMA community significant distress. If it was made clear to patients that the quantitative data from assessments is looked at holistically with qualitative data collected by a range of methods, there would be less stress on people living with SMA and their carers.
16. Do patients and carers consider that their experiences (clinical, physical, emotional and psychological) were captured adequately in the MAA tests and assessments? If not please explain what was missing.	See section 14
17. What outcomes do you think have not been assessed or captured in the MAA data? Please tell us why	**Respiratory Health** Good respiratory health is often what keeps people living with SMA out of hospital. Lung function tests are carried out by some centres but not all (these tests are not suitable for the more severely affected as creating a seal around the mouthpiece can be very difficult with weak facial muscles). Everyone should experience a multi-disciplinary approach to assessment, with effective collaboration between neuromuscular and respiratory teams.

	Bulbar function Whilst information on bulbar function is collected anecdotally, a more formalised approach is required to provide clinical evidence on the impact of treatments on swallowing, chewing, voice strength and mouth opening. All of these have a significant impact on quality of life for those living with SMA. **Everyday tasks** The main theme running through the research for this submission has been the positive impact of treatment on daily life. Tailoring formal but individualised assessments to capture this would be a step towards more realistic data. For example, speed to fasten buttons or type on a keyboard, whatever measures the individual feel represents improvements in their personal daily life tasks. Improving communication around PROMs would also facilitate this.

Section 5 Patient population

Table 5 Groups who may benefit and those who declined treatment

Please present your responses by treatment under each section.

18. Are there any groups of patients who might benefit more or less than others from these treatments? If so, please describe them and explain why.	Since SMA is a spectrum condition, inevitably some will benefit more than others. Furthermore, some may not even wish to change their on-going lifestyle for personal reasons. However, we must be careful defining benefit as this is a non- quantifiable variable and almost always personal. The truth is – treatment should be available to ALL those who want it and only withdrawn in cases where declines continue to be observed. The lifetime costs of managing the impact of SMA – the healthcare, equipment and home adaptations, and the support at school and work – can be huge. For adults, the value of stabilisation of the condition cannot be underestimated.

19. Were there people who met the MAA eligibility criteria who decided not to start either of these treatments? Please state if known the proportion of eligible patients who did not start the treatment and any reasons for this.	It is estimated that globally, 1/3 of eligible adults have not started treatments. There is currently no knowing how accurate this estimate is, Many adults not accessing treatment are also not engaging with patient organisations or completing surveys. Anecdotally however, we can say that adults living with SMA choose not to access treatment due to concerns about their fertility, or because of a lack of long term evidence. Some, who are experiencing a slow disease progression, are content living with SMA and have adjusted to the lifestyle that it demands. In the paediatric population, now with improved information and communication around treatments there are not currently any families that we know of as patient groups that choose to not access treatment. Historically, there have been a few families who, with clinical support, have chosen not to access treatment due to the progressed nature of the disease and the impact that would have on the quality of life of the child and the family for a lifetime. This could be a decision other families may take in the future which presents ethical issues.

Section 6 Equality

20. Are there any potential equality issues that that should be taken into account when considering this condition and the treatment? See NICE's equality scheme for more details.

We have reported on survey responses from 11 people living with SMA in the home nations (5 Scotland, 3 Northern Ireland, 3 Wales) NICE guidance do not have jurisdiction in these home nations. The Health and Social Care (HSC) in Northern Ireland and Scottish Medicines Consortium (SMC) make decisions on guidance and assessments of these disease modifying treatments.

Nusinersen needs to be administered in treatment centres equipped with the resources for intrathecal administration (injection into the spinal canal). There are no paediatric treatment centres in Wales and no adult treatment centres in any of the Devolved Nations. This means that

patients must either travel very long distances for treatment – potentially hundreds of miles – or have access to a more limited range of treatment options

Section 7 Other issues

21. Are there any other issues that you would like the committee to consider?

Section 8 Key messages

In up to 5 sentences, please summarise the key messages of your statement:

- There is a clear unmet medical need in the case of SMA with fatalities and ongoing deterioration of health in affected individuals that could be immediately addressed through proposed treatments which can stop deterioration and bring about stability, improved respiratory health, preventing the life threatening impact of relatively minor illnesses.
- All patients regardless of type, age, copy number or disease progression must have access to treatments that meets both their clinical and non-clinical circumstances and ability to choose or switch treatments that suit their individual needs in line with licencing agreements.
- The natural history of SMA is progressive. Anything better than deterioration (e.g. stability) should be considered a positive outcome.
- The mental health of people living with SMA and their carers has an immeasurable impact on lives. Receiving treatment (that is not designed to treat psychological issues), has a huge positive influence on the emotional wellbeing of the whole SMA community and their support networks.

- The availability of these two treatments through the MAAs has changed the lives of the SMA community, and combined with the availability of Zolgensma has completely altered the lived experienced of this still devastating condition for individuals and families

Thank you for your time.

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NICE National Institute for Health and Care Excellence

Multiple Technology Appraisal

Nusinersen and risdiplam for treating spinal muscular atrophy (MA review of TA588 and TA755) [ID6195]

Guidance review following a period of managed access - Professional organisation submission

Thank you for agreeing to give us your organisation's views on the technology(ies) and its possible use in the NHS.

You can provide a unique perspective on the technology in the context of current clinical practice that is not typically available from the published literature.

To help you give your views, please use this questionnaire. You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type.

Information on completing this submission

- Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable
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- Your response should not be longer than 13 pages.

About you

1. Your name	[redacted]
2. Name of organisation	Adult SMA REACH, John Walton Muscular Dystrophy Research Centre, Translational and Clinical Research Institute, Newcastle University and Newcastle Hospitals NHS Foundation Trust
3. Job title or position	[redacted]
4. Are you (please select Yes or No):	An employee or representative of a healthcare professional organisation that represents clinicians? Yes A specialist in the treatment of people with this condition? Yes A specialist in the clinical evidence base for this condition or technology? No Other (please specify): Neuromuscular clinician with expertise in managing SMA and other neuromuscular conditions
5a. Brief description of the organisation (including who funds it).	Adult SMA REACH is a project sponsored by Newcastle University and Newcastle Hospitals NHS Foundation Trust. The project has received funding from Biogen and Roche.
5b. Has the organisation received any funding from the manufacturer(s) of the technology(ies) and/or comparator products in the last 12 months? [Relevant manufacturers are listed in the appraisal matrix.] **If so, please state the name of manufacturer, amount, and purpose of funding.**	Chiara Marini Bettolo has received advisory and speaker honorarium via Newcastle University from Biogen and Roche. Adult SMA REACH, Newcastle University has received funding from Biogen and Roche.
5c. Do you have any direct or indirect links with, or funding from, the tobacco industry?	No

The aim of treatment for this condition

6. What is the main aim of treatment? (For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability.)	The main aim of the two disease modifying treatments is to improve life expectancy in the more severe phenotypes, allow motor development, improve motor function, slow down motor function decline, and stabilise the disease. 1. In adults with SMA the aim range from stabilise/slow rate of decline of disease which includes motor, bulbar (swallowing and speech) and respiratory function; improve life expectancy; improve motor, bulbar and respiratory function – the degree will vary depending on subtype and years of disease; improve fatigue, participation in Activities of daily living and quality of life; facilitate access to treatment during transition; reduce burden of care by improving disease outcome; reduce burden of unplanned admissions/rate of hospitalisation by improving disease outcome (e.g. improved respiratory function will result in less hospital admission and reduce ICU bed occupancy)
7. What do you consider a clinically significant treatment response? (For example, a reduction in tumour size by x cm, or a reduction in disease activity by a certain amount.)	In SMA we are dealing with a disease spectrum so defining a clinically significant response to treatment is challenging and has to take into consideration the huge range of variability in between patients depending on subtype, age and years of disease and disease severity/status when treatment was started but also access to Standards of care which is still very variable and inequitable in the UK. However, specifically in adults with SMA, we consider maintaining current function in motor, bulbar and respiratory function as a clinically significant response to treatment. Reduction of chest infection and hospital admission is clinically relevant. Maintaining a level of independency as well as increase stamina or reduced fatigue is clinically relevant. An increase in life expectancy is also expected in the adult cohort. Whilst we use objective measures in clinic to assess this, not all responses to treatment are captured accurately and widely because of restrains of time in clinic and also not all scales to do so being available and yet validated.
8. In your view, is there an unmet need for patients and healthcare professionals in this condition?	The is a huge unmet need for adults with SMA. There is no approved disease modifying treatment for this cohort and in the absence of treatment the disease will inevitably decline across multiple dimensions (mobility, respiratory, bulbar and other systems) relying on increasing care support leading to shorter life expectancy. There is still huge discrepancy in access to care and treatments in the country with some patients needing to travel further distances to access these.

What is the expected place of the technology(ies) in current practice?

9. How is the condition currently treated in the NHS?	Currently adult patients with SMA access care standard in outpatient clinic, and those who wish, have accessed Nusinersen and Risdiplam under the MAA. Standards of care for SMA are however not widely implemented in the UK and there are still huge gaps and some patients don't even have access to these.
9a. Are any clinical guidelines used in the treatment of the condition, and if so, which?	Standards of care for SMA are published and disseminated by Treat-NMD and the REACH networks. Mercuri E, et al SMA Care Group. Diagnosis and management of spinal muscular atrophy: Part 1: Recommendations for diagnosis, rehabilitation, orthopedic and nutritional care. Neuromuscul Disord. 2018 Feb;28(2):103-115. doi: 10.1016/j.nmd.2017.11.005. Epub 2017 Nov 23. PMID: 29290580. However, these have mainly a paediatric focus and there is still huge variability in the UK in terms of implementation and access to care and care management as highlighted in the below paper. Muni-Lofra R, Murphy LB, Adcock K, Farrugia ME, Irwin J, Lilleker JB, McConville J, Merrison A, Parton M, Ryburn L, Scoto M, Marini-Bettolo C, Mayhew A. Real-World Data on Access to Standards of Care for People With Spinal Muscular Atrophy in the UK. Front Neurol. 2022 May 30;13:866243. doi: 10.3389/fneur.2022.866243. PMID: 35707038; PMCID: PMC9190261.
9b. Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please state if your experience is from outside England.)	Since implementation of the MAAs for Nusinersen and Risdiplam, the care pathway for SMA was not well defined and many patients had disengaged with their local services. Through the Adult SMA REACH network, 19 sites have agreed the care pathway for adults with SMA and have also addressed transition aspects. We are however aware of gaps and inequities to access to care in the UK.
9c. What impact would the technology(ies) have on	Neuromuscular clinics have historically been designed and designed well before any standards of care or treatment were available for SMA patients and other neuromuscular patients. The current set up is not suitable

the current pathway of care?	for delivery of these technologies and services have been stretched and have caused delays in implementing technologies and care because of this, raising unreasonable expectations with patients and families. The technologies will require additional resources in clinic which include suitable space, longer clinic slots to do the necessary and required assessment to monitor efficacy and safety and deliver care, suitable equipment, trained multidisciplinary staff. In addition, wider multidisciplinary staff and community will require access to training and education so that patient can access care, treatment and management early on.
10. Will the technology(ies) be used (or is it already used) in the same way as current care in NHS clinical practice?	Patients accessing the technology and care should have access to same level of care. Accessing treatment should not prioritise patients over others who chose not to access it. Both technologies will require regular monitoring of efficacy and safety and the frequency will need to be defined based on efficacy and safety data, however, we are also aware that the frequency of appointment depends on the age, phase of disease, complexities and diluting the frequency of appointments may result in reactive rather than proactive care.
10a. How does healthcare resource use differ between the technology(ies) and current care?	Current care requires knowledge of standards of care and comprehensive knowledge of comorbidities, disease natural history and multidisciplinary requirements of care delivery. A proactive care approach is advisable compared to reactive so that we can provide anticipatory care reducing the number of unnecessary hospital admissions. Not all people with SMA have access to care, this is variable depending for example on postcode and education and other factors. In terms of technologies, Nusinersen is administered intrathecally every 4 months following the initial loading doses. This requires access to suitable space and expertise. There is some variability between Trust on where and how it is administered and typically intrathecal guidance and policy should be followed to ensure patient safety at all times. In most cases the technology is administered in either day unit or theatre under local anaesthetic, sedation or general anaesthetic depending on age and complexity of spine and anxiety related to procedure. Risdiplam is administered orally on a daily basis and is delivered at home via home care delivery. Whilst the administration route implies less burden on clinical services, safety monitoring is still required.
10b. In what clinical setting should the tech technology(ies) nology be	The technologies will need to be will need to be delivered in specialised neuromuscular clinics within neuromuscular centres that have the expertise and approval to deliver and monitor safety and efficacy and have access to an MDT. Clinical sites will be expected to be part of existing clinical networks SMA REACH UK and

used? (For example, primary or secondary care, specialist clinics.)	Adult SMA REACH and engage with stakeholders and implement standards of care. Centres will be expected to discuss different treatment options and seek second opinion if necessary.
10c. What investment is needed to introduce the technology(ies)? (For example, for facilities, equipment, or training.)	Centre will require at least two neuromuscular consultants with access to MDT, two trained neuromuscular physiotherapist, care coordinator, admin support, specialist equipment to deliver outcome measures (RULM kit, spirometers etc), access to interventional radiology, pharmacy support and suitable clinical space for administration, monitoring and also suitable length of clinic consultation time. All centres will require access and infrastructure to be able to monitor safety and have homecare provide agreement in place. The NHS E clinical panel has been an invaluable resource to request expert opinion and a similar setting should be available and possibly facilitated via the already established clinical networks.
11. Do you expect the technology(ies) to provide clinically meaningful benefits compared with current care?	Yes, we anticipate and expected an added benefit compared to just supportive care.
11a. Do you expect the technology(ies) to increase length of life more than current care?	Yes, we anticipate that life expectancy will increase because of improved outcomes on respiratory function, motor function and other domains.
11b. Do you expect the technology(ies) to increase health-related quality of life more than current care?	Yes
12. Are there any groups of people for whom the technology(ies) would be more or less effective (or appropriate) than the general population?	The earlier the technologies are implemented the better the outcome is. So people with a more chronic disease are expected are to have a slower or milder response, however, we anticipate that a benefit is still present in this cohort. In SMA type 4 we have no data , but is reasonable to expect that they would also benefit.

The use of the technology(ies)

13. Will the technology(ies) be easier or more difficult to use for patients or healthcare professionals than current care? Are there any practical implications for its use (for example, any concomitant treatments needed, additional clinical requirements, factors affecting patient acceptability or ease of use or additional tests or monitoring needed.)	Both technologies require good coordination and MDT input for care and treatment and management delivery. Nusinersen is given intrathecally every 4 months which requires a suitable day unit/theatre facilities, expertise and skilled practitioner for intrathcal administration and LP, access to interventional radiology and access to neuromuscular physiotherapist and suitable clinical space. It requires 4 monthly appointment for intrathecal injections and 6 monthly clinic reviews. Risdiplam is administered orally and delivered at home via home delivery and requires 6 monthly monitoring in clinic.
14. Will any rules (informal or formal) be used to start or stop treatment with the technology(ies)? Do these include any additional testing?	Nationally and likely within the SMA REACH networks and together with regulators and PAGs, start and stop rules will need to be agreed to have an equitable and fair approach. Each site should have an MDT approach which involves multiple professionals. A national approach should also be taken to stop treatment and discuss within a format like the national clinical panel or a similar model. Additional clinical assessments will be carried out but additional investigations are anticipated.
15. Do you consider that the use of the technology(ies) will result in any substantial health-related benefits that are unlikely to be included in	Yes, these technologies will result in substantial health-related benefits and these have been difficult to capture. In particular PROMs collection started late during the MAAs. Even if there was just stabilization of function and slower rate of decline this would be invaluable however we need to acknowledge that this change is difficult to capture given the huge disease spectrum.

the quality-adjusted life year (QALY) calculation?	
16. Do you consider the technology(ies) to be innovative in its potential to make a significant and substantial impact on health-related benefits and how might it improve the way that current need is met?	Yes, these technologies are innovative disease modifying treatment for SMA. Prior to these technologies there was no other treatment other than supportive care.
16a. Is the technology(ies) a 'step-change' in the management of the condition?	These technologies are definitely step change in the management of this condition where conservative management was the only other option leading to progressive decline and shorter life expectancy due to the natural history of the disease.
16b. Does the use of the technology(ies) address any particular unmet need of the patient population?	Yes, these are the only two disease modifying treatment option for adults with SMA and therefore address an unmet need in this cohort.
17. How do any side effects or adverse effects of the technology(ies) affect the management of the condition and the patient's quality of life?	Both technologies require regular monitoring blood test monitoring. Nusinersen is delivered intrathecally every 4 months which may result in direct side effects from the LP. Patients generally report little to no side effects and these are generally well managed at home. Risdiplam is oral liquid and is self administered once a day. Patient tend to report GI side effects mainly but these tends to be manageable. The option of two therapies allows to chose and switch in case of side effects and impact on patient burden.

Sources of evidence

18. Do the clinical trials on the technology(ies) reflect current UK clinical practice?	Nusinersen clinical trials were in children and not adults. ENDEAR trial enrolled 122 infants with SMA types I and II and CHERISH trial enrolled 126 children with SMA types II and III). The MAA allows treatment of adults with type 1, 2 and 3 SMA (but not type 4). Risdiplam clinical trials included adults. Four clinical trials have been performed: the FIREFISH trial for patients with SMA type I, the SUNFISH trial for patients with SMA type II/III and included adults up to the age of 25 years, the JEWELFISH trial for patients with SMA who underwent some treatment previously, and the RAINBOWFISH trial for pre-symptomatic patients. The MAA allows treatment of adults with type 1, 2 and 3 SMA without age restriction (but not type 4).
18a. If not, how could the results be extrapolated to the UK setting?	The Adult SMA Reach Datacollection study has provided real world data for adult SMA in the UK. There have been case series of adults treated with nusinersen in Germany Hagenacker T, et al. Nusinersen in adults with 5q spinal muscular atrophy: a non-interventional, multicentre, observational cohort study. Lancet Neurol. 2020 Apr;19(4):317-325. doi: 10.1016/S1474-4422(20)30037-5. Epub 2020 Mar 18. PMID: 32199097. And Italy Coratti G et al Motor function in type 2 and 3 SMA patients treated with Nusinersen: a critical review and meta-analysis. Orphanet J Rare Dis. 2021 Oct 13;16(1):430. doi: 10.1186/s13023-021-02065-z. PMID: 34645478; PMCID: PMC8515709.

	There are been case series of adults treated with risdiplam in Northern Ireland McCluskey G et al. Risdiplam for the treatment of adults with spinal muscular atrophy: Experience of the Northern Ireland neuromuscular service. Muscle Nerve. 2023 Feb;67(2):157-161. doi: 10.1002/mus.27755. Epub 2022 Dec 5. PMID: 36382958 and Germany Bjelica B, Wohnrade C, Cespedes I, Osmanovic A, Schreiber-Katz O, Petri S. Risdiplam therapy in adults with 5q-SMA: observational study on motor function and treatment satisfaction. BMC Neurol. 2024 Feb 17;24(1):67. doi: 10.1186/s12883-024-03562-x. PMID: 38368338; PMCID: PMC10873992.
18b. What, in your view, are the most important outcomes, and were they measured in the trials?	For adults with SMA the most important outcome is stability of disease, maintenance of respiratory function, bulbar fucntion and fatigue management.
18c. If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes?	Multiple outcome measures should be used give the disease spectrum and multiple domains that are to be assessed. These are in continuous development and evolve as we learn from the disease.
18d. Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	No
19. Are you aware of any relevant evidence that might not be found by a	No

systematic review of the trial evidence?	
20. Are you aware of any new evidence for the comparator treatment(s) since the publication of NICE technology appraisal guidance [HST15, HST24]?	No
21. How do data on real-world experience compare with the trial data?	Overall the patient feedback and our clinical experience is positive however, for adults there is a lack of comparator with clinical trials.

Equality

22a. Are there any potential equality issues that should be taken into account when considering this treatment?	The main issue will be about equality of access by geography. REACH networks should continue to engage with centres and disseminate and upskill centres to provide equitable access to treatment and care.
22b. Consider whether these issues are different from issues with current care and why.	I think this issue is for both care and access to treatment.

Key messages

23. In up to 5 bullet points, please summarise the key messages of your submission.	• Bothe technologies are effective in adults with SMA acorss the disease spectrum and stabilise disease, improve fucniton, participation in ADL and quality of life. • Care and these two technologies should be available to all patients with SMA type 1-4 across all ages. • The benefit is variable and outcome measures used in the MAAs may not capture all and consideration should be given to the challenges of the vast disease spectrum. • Adequate clinical support the neuromuscular services delivering these technologies should be given to enable safe, timely, fair and equitable administration of technologies and care. • Services providing these technologies should have access to an MDT and be part of the REACH networks and work aligned with national and international guidane.

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NICE National Institute for Health and Care Excellence

Multiple Technology Appraisal

Nusinersen and risdiplam for treating spinal muscular atrophy (MA review of TA588 and TA755) [ID6195]

Guidance review following a period of managed access - Professional organisation submission

Thank you for agreeing to give us your organisation's views on the technology(ies) and its possible use in the NHS.

You can provide a unique perspective on the technology in the context of current clinical practice that is not typically available from the published literature.

To help you give your views, please use this questionnaire. You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type.

Information on completing this submission

- Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable
- We are committed to meeting the requirements of copyright legislation. If you intend to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Your response should not be longer than 13 pages.

About you

1. Your name	[redacted]
2. Name of organisation	Association of British Neurologists (ABN)
3. Job title or position	
4. Are you (please select Yes or No):	An employee or representative of a healthcare professional organisation that represents clinicians? Yes A specialist in the treatment of people with this condition? Yes A specialist in the clinical evidence base for this condition or technology? No Other (please specify): Neurologist involved in care and treatment of adults with spinal muscular atrophy
5a. Brief description of the organisation (including who funds it).	ABN
5b. Has the organisation received any funding from the manufacturer(s) of the technology(ies) and/or comparator products in the last 12 months? [Relevant manufacturers are listed in the appraisal matrix.] **If so, please state the name of manufacturer, amount, and purpose of funding.**	ABN – no [redacted] – received advisory and speaker fees from Biogen and Roche
5c. Do you have any direct or indirect links with, or funding from, the tobacco industry?	None

The aim of treatment for this condition

6. What is the main aim of treatment? (For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability.)	In children the aim to allow development of motor function, stabilisation of disease and improve life extpectancy: We represent neurologists treating adult patients many of whom have been of affected by spinal muscular atrophy (SMA) since childhood. The aim of treatment in adults with SMA are: 1. Stabilization of motor, bulbar and respiratory function to prevent progression and disability and increase life expectancy 2. Slow the rate of decline of motor, bulbar and respiratory function to prevent progression and disability and increase life expectancy 3. Potentially improve recently lost motor, bulbar and respiratory function 4. Improvement in fatigue, participation in ADLand quality of life 5. Continuation of treatment of people with SMA that has been started in children 6. Facilitate treatment during transition 7. Reduce burden of care 8. Reduce burden of unplanned admissions/rate of hospitalisation

7. What do you consider a clinically significant treatment response? (For example, a reduction in tumour size by x cm, or a reduction in disease activity by a certain amount.)	In adults A clinically significant treatment response in adults is very variable given the spectrum of levels of function and needs to be individualized For all adults with SMA maintaining current function in motor, bulbar and respiratory function has a huge impact on their quality of life and ability to function independently. The natural history is clearly described that without treatment function will decline over years, including loss of ambulation in type 3 SMA and worsening upper limb, bulbar and respiratory function in type 2 SMA. Without treatment type 2 SMA life expectancy was limited to 30-50 years. There is no agreement on which metric to measure. There is a large focus on physical function, but other measures include frequency of chest infections, need for non-invasive ventilation, number of hospital admissions, fatigue, mental health and quality of life. There is no single fit-all outcome measure to apply across the disease spectrum to define a clinically significant response to treatment. For example Clinically significant response for ambulant adult is maintaining independent ambulation Loss of ambulation following e.g. a fracture or other should not be considered a decline and maintaining standing or independent transfer and preserving upper limb function are clinically significant outcomes Clinically significant response in type 2 may be retaining thumb movement to operate power chair or maintaining bulbar function
8. In your view, is there an unmet need for patients and healthcare professionals in this condition?	Yes there is a huge unmet need, as stated above for adults with SMA The natural history is clearly described that without treatment function will decline over years including loss of ambulation in type 3 SMA and worsening upper limb, bulbar and respiratory function in type 2 and type 3 SMA. Without treatment type 2 SMA life expectancy was limited to 30-50 years. There are currently no other disease modifying treatments available for adult with SMA, other than nusinersen and risdiplam

What is the expected place of the technology(ies) in current practice?

9. How is the condition currently treated in the NHS?	For adults with SMA currently best care is Supportive care from MDT with neurology, respiratory, physiotherapy and orthopaedics, dietetics, occupational therapy support as needed For most adults with SMA in England this is not a reality – often they have not seen a neurologist for 10-20 years and do not have access to community physiotherapy, OT etc Currently disease modifying treatment with nusinersen and risidplam is available via managed access agreement (MAA) in designated centre and these patients are seen 6 monthly by neurology and physio.
9a. Are any clinical guidelines used in the treatment of the condition, and if so, which?	International standard of care are available for children but not specifically for adults Mercuri E, et al SMA Care Group. Diagnosis and management of spinal muscular atrophy: Part 1: Recommendations for diagnosis, rehabilitation, orthopedic and nutritional care. Neuromuscul Disord. 2018 Feb;28(2):103-115. doi: 10.1016/j.nmd.2017.11.005. Epub 2017 Nov 23. PMID: 29290580. There is a notable difference in the access of adults to standard of care compared to children. In a recent patient survey, a 59% difference for access to physiotherapy (100% in paediatric, 41% in adults) was observed between adult and paediatric populations. Similar patterns were seen with access to interventions, including a 46% difference for access to supported standing (53% paediatric, 7% adult) and 45% difference for access to splints (59% paediatric, 14% adult). Muni-Lofra R, Murphy LB, Adcock K, Farrugia ME, Irwin J, Lilleker JB, McConville J, Merrison A, Parton M, Ryburn L, Scoto M, Marini-Bettolo C, Mayhew A. Real-World Data on Access to Standards of Care for People With Spinal Muscular Atrophy in the UK. Front Neurol. 2022 May 30;13:866243. doi: 10.3389/fneur.2022.866243. PMID: 35707038; PMCID: PMC9190261.
9b. Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please state if your	Before the MAA there were no defined pathways for adults with SMA. There was significant local variation in care (e.g. frequency of follow up in neurology clinic, respiratory monitoring and access with physio) depending on the local interests of the neurologist and availability of neuromuscular specialist neurologists Our experience is from England and practice may differ in the other devolved nations where the MAA is not implemented.

experience is from outside England.)	The MAA has required for structured care with these patients are seen 6 monthly by neurology, respiratory and physio.
9c. What impact would the technology(ies) have on the current pathway of care?	The availability of nusinersen and risdiplam will require a structured SMA clinics for assessment and monitoring of the drugs with access for all centres to an MDT with at least 2 neurologists, respiratory radiology physiotherapy, and pharmacy resources for decisions about starting and stopping treatment, ensuring pharmacovigilance and equity of access across England. Currently centres prescribing under MAA will have established these structures, however clinic capacity is an issues in terms of space, time and resources allocated. It is important the patients are given the option to access both potential treatment options (nusinersen or risdiplam) because they have different implications arounds side effects and potential impact on fertility and pregnancy.
10. Will the technology(ies) be used (or is it already used) in the same way as current care in NHS clinical practice?	Using treatments in MAA which currently requires 6 monthly physiotherapy outcome monitoring, in the adult population 6 monthly monitoring is not likely to be necessary as adult patients with SMA are generally stable with changes taking place over 5-10 years – therefore the routine clinical use of these drugs is likely to require less frequent clinical review than required in the MAA in adults with SMA where in general the drugs are very well tolerated and appear to be safe (this is likely to be different for children with SMA)
10a. How does healthcare resource use differ between the technology(ies) and current care?	Care without any disease modifying treatment for adults with SMA is often inadequate with many struggling to access a consultant neurologist and very few having access to community physiotherapy and OT. Currently people are receiving treatment via the MAA. For nusinersen this requires visits at 4 month intervals for intrathecal nusinersen usually in the day unit setting with blood monitoring. This needs facilities and expertise to perform lumbar puncture and interventional radiology expertise if needed. Due to the repeated doses most centres will have a maximum capacity for intrathecal injection. For risdiplam this is oral liquid medication prescribed by centres and delivered via home care to people's homes after prescription in the neuromuscular centre. This requires specialist pharmacy knowledge and dispensing. Most centres are performing 6 monthly blood monitoring and ECG monitoring.

	Currently for both treatments the MAA agreement requires people to be reviewed in person every 6 months with physiotherapy outcome measures. In the adult population this could be reduced to annual assessments, as motor function remains stable and no blood abnormalities have been detected.
10b. In what clinical setting should the tech technology(ies) nology be used? (For example, primary or secondary care, specialist clinics.)	Specialised neuromuscular clinics within neurosciences centre will need to prescribe and monitor these drugs. All centres need to have access to MDT with ability discuss the option of all available treatments for the patient and to refer to another centre e.g. those for nusinersen if these are more limited.
10c. What investment is needed to introduce the technology(ies)? (For example, for facilities, equipment, or training.)	All centre currently prescribing under the MAA need at least two neuromuscular neurologists with access to MDT support and physiotherapists able to reliably and accurately performed outcome measures. Centres currently prescribing nusinersen under the MAA have developed expertise in safe administration of intrathecal drugs with IT policies and clinical governance oversight, access to interventional neuroradiology support if require and a system of pharmacovigilance for monitoring blood and prescribing and dispensing intrathecal drugs. Centres currently prescribing risdiplam under the MAA need system of pharmacovigilance for monitoring blood and prescribing and dispensing medication and a service level agreement with homecare provider. All centres introducing these technologies will need access to the above The NHS E clinical panel has been a valuable resource to request expert opinion and a similar setting should be available and possibly facilitated via the already established clinical networks.
11. Do you expect the technology(ies) to provide clinically meaningful benefits compared with current care?	Yes if we assuming current care is supportive care without disease modifying treatment (nusinersen or risdiplam) then the benefits are great, allowing stability of motor function throughout adult life allowing people with SMA to continue to work and not need respiratory support and gastrostomy. The compares to the known natural history of SMA where continued decline in function over time is expected.
11a. Do you expect the technology(ies) to increase	Yes if we assume current care is supportive care without disease modifying treatment (nusinersen or risdiplam) then the stabilization of function (in particular respiratory function) will increase length of life

length of life more than current care?	
11b. Do you expect the technology(ies) to increase health-related quality of life more than current care?	Yes
12. Are there any groups of people for whom the technology(ies) would be more or less effective (or appropriate) than the general population?	From first principles and from data in paediatric population it is likely that these technologies will be more effective in younger adults and those with less loss of neurological function as treating earlier allows stabilization of larger number of motor neurones, but more clinical studies in adult populations are needed to provide evidence based for this statement in clinical reality. Also it is possible that the biological age does not define the motor neurone reserve e.g. ambulant type 3 SMA aged 35 years may find the treatment more effective than a younger patient with type 1 as they would have benefited more earlier in the disease course. This also applies to adults with type 4 SMA who are currently excluded from treatment under MAA and are at a functional level where they may experience considerable benefit.

The use of the technology(ies)

13. Will the technology(ies) be easier or more difficult to use for patients or healthcare professionals than current care? Are there any practical implications for its use (for example, any concomitant treatments needed, additional clinical requirements, factors affecting patient acceptability or ease of use or additional tests or monitoring needed.)	Nusinersen is given intrathecally every 4 months – this requires suitable day unit facilities, practitioner to perform LP and administer the drug and for 50% of patients interventional radiology expertise onsite – at present IT nusinersen is offered at approx 12 sites with approx 5 sites with consistent interventional radiology support Risdiplam needs 6 monthly clinic appointments and blood monitoring and significant pharmacy resource to ensure homecare prescription are available on time. Risdiplam may affect both female and male fertility meaning nusinersen may turn out to be a useful option for those planning a family. There will need to be an established network model across all neurosciences centres to ensure there is equitable access to all available treatments across the country. We need to ensure adequate support in terms of increased clinical resource to adult SMA across the country as these are starting from a much lower historical investment than paedatric clinics and are likely to see a 10 fold increase in adults with SMA over the next 10 years due to the effectiveness of these treatment in extending life. These young adults will need neurology, therapy, nutrition and respiratory support in the adult neuromuscular service.

14. Will any rules (informal or formal) be used to start or stop treatment with the technology(ies)? Do these include any additional testing?	The decision to start, continue, swap or stop disease modifying treatment for all adults with SMA will need to be overseen by an MDT with neuromuscular neurologists, respiratory physicians, physiotherapy, pharmacy and radiology as needed. The members of this MDT will need to view each person with SMA holistically with an individually-focused approach to assess benefits and side effects, mindful that a very small gain or stability of function can be very meaningful to an individual. We also have to be mindful that over 10-20 years of treatment adults with SMA may experience some decline but this is likely to be slower than without treatment. We know this as stable neurological insults e.g. birth injury or traumatic brain injury do decline with aging as do those without neurological disability – this is different to children who have motor development, so improvement is the natural history. This is unlikely to be captured for adults in dropping points in outcome scales developed for children who are undergoing normal motor development. , The natural history of adults over decades in the normal population Is motor decline. The challenge therefore is in correctly identifying patients who are in truth benefiting from treatment despite the fact that they may very gradually have some motor decline. As SMA is a rare condition we would recommend these local MDTs have access to regional/national panels to review difficult decisions. The panels will need funding in terms of HCP time but are unlikely to require additional assessment over normal clinical care.
15. Do you consider that the use of the technology(ies) will result in any substantial health-related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation?	Yes, stabilization of function and slower rate of decline is invaluable. Therefore, given the natural history of decline in SMA no change is an excellent outcome. We need to view each adult with SMA holistically with an individually focused approach to ensure assess to assess benefits and side effects, mindful that a very small gain or stability of function can be very meaningful to an individual. We also have to be mindful that over 10-20 years of treatment adults with SMA may experience some decline, but this is likely to be slower than without treatment. We know this as stable neurological insults e.g. birth injury or traumatic brain injury do decline with aging as do those without neurological disability – this is different to children who have motor development, so improvement is the natural history. This is unlikely to be captured for adults in dropping points in outcome scales developed for children who are undergoing normal motor development. , The natural history of adults over decades in the normal population Is motor decline. The challenge therefore is in correctly identifying patients who are in truth benefiting from treatment despite the fact that they may very gradually have some motor decline.
16. Do you consider the technology(ies) to be innovative in its potential to make a significant and	Yes these SMN2 enhancing therapies (nusinersen and risdiplam) are a huge and completely innovative disease modifying treatment for adults with SMA. Prior to these treatments there was no choice but to support natural decline for adults with SMA and now there is the potential to slow or even stop this decline for adults with SMA.

substantial impact on health-related benefits and how might it improve the way that current need is met?	
16a. Is the technology(ies) a 'step-change' in the management of the condition?	Yes this is the first disease modifying treatment with huge change in motor development in children but also in adults. These SMN2 enhancing therapies are a huge and completely innovative disease modifying treatment for adults with SMA. Prior to these treatments there was no choice but support natural decline for adults with SMA and now there is the potential to slow or even stop this decline for adults with SMA.
16b. Does the use of the technology(ies) address any particular unmet need of the patient population?	Yes these are the only disease modifying treatment option for adults with SMA and therefore fill a huge unmet need
17. How do any side effects or adverse effects of the technology(ies) affect the management of the condition and the patient's quality of life?	The need for nusinersen to be delivered intrathecally every 4 months means a day attendance in hospital and lumbar puncture but reported side effects are limited and very few serious side effects and very few blood monitoring changes are seen. Patients report it is good to have treatment every 4 month and then have no side effects or medication to take . Risdiplam is oral liquid delivered to patients home and self administered once a day. Few changes have been seen on drug monitoring and it appears generally safe with the commonest side effect of diarrhoea which in most cases resolves. The option of two therapies allows personalized choice to accommodate patient-specific issues, for example Risdiplam may affect both female and male fertility meaning nusinersen may turn out to be a useful option for those planning a family. If spinal access become difficult later Risdipam can be used in place of nusinersen.

Sources of evidence

18. Do the clinical trials on the technology(ies) reflect current UK clinical practice?	Clinical trials in nusinersen were in children ENDEAR trial enrolled 122 infants with SMA types I and II and CHERISH trial enrolled 126 children with SMA types II and III. There has been no RCT of nusinersen in adults. The MAA allows treatment of adults with type 1, 2 and 3 SMA (but not type 4).

	Risdiplam Four clinical trials have been performed: the FIREFISH trial for patients with SMA type I, the SUNFISH trial for patients with SMA type II/III and included adults up to the age of 25 years, the JEWELFISH trial for patients with SMA who underwent some treatment previously, and the RAINBOWFISH trial for pre-symptomatic patients. The MAA allows treatment of adults with type 1, 2 and 3 SMA without age restriction (but not type 4).
18a. If not, how could the results be extrapolated to the UK setting?	The Adult SMA Reach Data will give adult data from the UK There have been case series of adults treated with nusinersen in Germany Hagenacker T, et al. Nusinersen in adults with 5q spinal muscular atrophy: a non-interventional, multicentre, observational cohort study. Lancet Neurol. 2020 Apr;19(4):317-325. doi: 10.1016/S1474-4422(20)30037-5. Epub 2020 Mar 18. PMID: 32199097. And Italy Coratti G et al Motor function in type 2 and 3 SMA patients treated with Nusinersen: a critical review and meta-analysis. Orphanet J Rare Dis. 2021 Oct 13;16(1):430. doi: 10.1186/s13023-021-02065-z. PMID: 34645478; PMCID: PMC8515709. There are been case series of adults treated with risdiplam in Northern Ireland McCluskey G et al. Risdiplam for the treatment of adults with spinal muscular atrophy: Experience of the Northern Ireland neuromuscular service. Muscle Nerve. 2023 Feb;67(2):157-161. doi: 10.1002/mus.27755. Epub 2022 Dec 5. PMID: 36382958 and Germany Bjelica B, Wohnrade C, Cespedes I, Osmanovic A, Schreiber-Katz O, Petri S. Risdiplam therapy in adults with 5q-SMA: observational study on motor function and treatment satisfaction. BMC Neurol. 2024 Feb 17;24(1):67. doi: 10.1186/s12883-024-03562-x. PMID: 38368338; PMCID: PMC10873992.
18b. What, in your view, are the most important outcomes, and were they measured in the trials?	For adults with SMA the most important outcome is stability i.e. no change in motor function and prevention of decline over years to decades which was demonstrated in the trial but not over 10-20 years Improvements in motor function reported are often improved head control, better swallowing or movement of one finger to move a power chair and not captured in these scales
18c. If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes?	There is no single measure that can capture all relevant facets of disease a patient is experiencing. It is likely that a suite of measures are required to capture change over time. This includes physical function, but should also have a focus on swallowing function, frequency of chest infections, need for ventilation, number of hospital admissions, fatigue, mental health, quality of life etc.
18d. Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	No

19. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	No
20. Are you aware of any new evidence for the comparator treatment(s) since the publication of NICE technology appraisal guidance [HST15, HST24]?	No
21. How do data on real-world experience compare with the trial data?	As above in the references no additional complications or side effects have been seen in real world experience and in general the experience in adults has been positive with around 50% patients experiencing improvement in function and fatigue that has a positive impact on their quality of life

Equality

22a. Are there any potential equality issues that should be taken into account when considering this treatment?	No
22b. Consider whether these issues are different from issues with current care and why.	This has been a significant issue for adults with SMA during the MAA and will need to be resolved.

Key messages

23. In up to 5 bullet points, please summarise the key messages of your submission.	• Nusinersen and risdiplam are likely to be effective for adults with SMA in stabilizing their motor function over decades and improving function, participation and quality of life, this is very different to children where motor development is expected. In adults motor decline is the norm even without SMA and therefore just because improvement is not seen does not mean there is no benefit. • Adults with type 4 SMA should also have access to these treatments • There are benefits of the flexibility of having both treatment options, with different administration routes,side effects and fertility implications, that are likely to be of use for both populations and individuals over a lifetime • We need to ensure adequate support in terms of increased clinical resource for adult SMA across the country as these are starting from a much lower historical investment than paediatric clinics and are likely to see a 10 fold increase in adults with SMA over the next 10 years due to the effectiveness of these treatments in extending life. These young adults will need neurology, therapy, nutrition and respiratory support in the adult neuromuscular service. • There must be geographical equity of access with all adults with SMA across England having the option of treatment either to be started in adulthood or continued from childhood.

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NICE National Institute for Health and Care Excellence

Multiple Technology Appraisal

Nusinersen and risdiplam for treating spinal muscular atrophy (MA review of TA588 and TA755) [ID6195]

Guidance review following a period of managed access - Professional organisation submission

Thank you for agreeing to give us your organisation's views on the technology(ies) and its possible use in the NHS.

You can provide a unique perspective on the technology in the context of current clinical practice that is not typically available from the published literature.

To help you give your views, please use this questionnaire. You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type.

Information on completing this submission

- Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable
- We are committed to meeting the requirements of copyright legislation. If you intend to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Your response should not be longer than 13 pages.

1. Your name	[redacted]
2. Name of organisation	SMA REACH UK
3. Job title or position	[redacted]
4. Are you (please select Yes or No):	An employee or representative of a healthcare professional organisation that represents clinicians? Yes A specialist in the treatment of people with this condition? Yes A specialist in the clinical evidence base for this condition or technology? Yes Other (please specify): N/A
5a. Brief description of the organisation (including who funds it).	SMA REACH UK is a research project based at Great Ormond Street Hospital for Children, London, working in collaboration with UCL Great Ormond Street Institute of Child Health. Professor Francesco Muntoni is the Chief Investigator. The SMA REACH UK study is made up of sites across the UK – currently 19 active sites are set up under SMA REACH UK all of which currently collect and input both medical and physiotherapy data on the treatment of paediatric SMA patients. This data is inputted into a central database – NND, which is hosted by an external database provider, Certus. The data is from patients treated with all currently available drugs for the treatment of SMA in the UK – Nusinsersen, Risdiplam and Onasemnogene abeparvovec. Data is also collected on untreated patients who have a confirmed SMA diagnosis. All patients must consent for their data to be collected within the database. The SMA REACH UK study is currently funded by Biogen, Roche and Novartis. Historically, SMA charities were the main funders. The data collected is owned by the consortium members, and its access regulated by a steering committee in which advocacy groups are represented.

5b. Has the organisation received any funding from the manufacturer(s) of the technology(ies) and/or comparator products in the last 12 months? [Relevant manufacturers are listed in the appraisal matrix.] **If so, please state the name of manufacturer, amount, and purpose of funding.**	Yes. SMA REACH UK received funding from both Biogen (Nusinersen) and Roche (Risdiplam) in the last 12 months. The purpose of the funding from both companies was to support the SMA REACH UK network through site fee contributions, staff posts including PI's time, as well as training opportunities and other project-related wider meetings. These are aligned with milestones and deliverables to be reached that include data to be shared with the companies. In the last 12 months, Biogen has contributed £231,600.46 to the SMA REACH UK Project. This is due to a no-cost extension until 30th January 2023, a contact amendment in March 2023 to be backdated to 1st February 2023 and then an updated contract for 3 years was signed in November 2023. SMA REACH UK is in contract with Biogen to cover a three-year period. In the last 12 months, Roche have contributed £928,444.45 to the SMA REACH UK Project. The contract with this manufacturer is for a 3-year period. SMA REACH UK also have a contract in place with Novartis Gene Therapies Inc. for the collection of data regarding onasemnogene abeparvovec. This includes contribution to the SMA REACH network to provide site support as well as covering positions within the project team. In the last 12 months, Novartis Gene Therapies Inc. have contributed £165,000 to the SMA REACH UK project.
5c. Do you have any direct or indirect links with, or funding from, the tobacco industry?	No.

6. What is the main aim of treatment? (For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability.)	The aim of the treatment is to improve outcome of patients affected by SMA. Both nusinersen and risdiplam have clearly demonstrated a very statistically robust and clinically meaningful effect on improving clinical outcomes of infants, children and adults affected by SMA. This includes the slowing progression of motor, respiratory and bulbar function shown in both clinical trials and real-world evidence for both treatments. In some cases, dependent on age of treatment initiation, not only was progression stopped but new milestones and improvements have been observed. In some cases, preserving ability to move fingers has meant the difference between operating a powered wheelchair/computer or not. The magnitude of improvement from baseline is largely dependent on the timing of the intervention, with the most favourable results obtained when any of these therapies is initiated shortly after disease onset (or presymptomatically- hence the pressure for UK to align with many other countries to offer SMA newborn screening). Treating affected individuals with chronic disease leads to more measured improvements. However, these have to be taken into the context of a progressive and debilitating disease, so these changes in trajectories are highly significant for patients, carers, and HCP.
7. What do you consider a clinically significant treatment response? (For example, a reduction in tumour size by x cm, or a reduction in disease activity by a certain amount.)	In early symptomatic individuals: slowing/stopping disease progression; achievement of novel motor milestones completely uncharacteristic for the classical disease course (e.g. sitting or standing with support and 4-point increase score on CHOP INTEND); and improved (or prevention of) respiratory and bulbar weakness/ feeding difficulties. For symptomatic patients: slowing/stopping disease progression; changes in the trajectories of loss of motor function; reduced hospitalisation has been clearly documented in our clinical real-world experience, and peer reviewed in publications. For pre-symptomatic patients: a clinically significant response would include acquiring motor milestones as well as maintaining independent respiratory and feeding abilities.

8. In your view, is there an unmet need for patients and healthcare professionals in this condition?	Untreated patients have an immense unmet need Symptomatically treated patients have less unmet needs but still have some unmet needs Presymptomatically treated patients – depending on the SMN2 copy numbers- may have no or modest unmet needs according to publications with any of the 3 DMTs The lack of newborn screening is definitely an unmet need; early diagnosis and early recognition of initial symptoms is still difficult. Orthotics provision is fragmented nationally. Those who are long term ventilated are not eligible through the MAA and this denies this cohort a meaningful quality of life as being long term ventilated does not necessarily mean someone cannot have some independence e.g. ability to speak, operate a powered wheelchair, attend school. The only other treatment available – onasemnogene abeparvovec is only available to those with Type 1 SMA under 21kg, and not all of those who fall in this category can be treated because of contraindications. For as long as SMA is diagnosed through symptoms rather than routine screening, there will be significant unmet need as it is vital to keep all three treatment options given incidence of contraindications exist. Treatment cannot reverse nerve cell death, and we need to continue to explore whether there are additional strategies that can optimise treatment response – both in terms of supportive care and other medications e.g. myostatin inhibition, currently ongoing clinical trials Without treatment, these patients will continue to deteriorate in terms of motor, respiratory and bulbar function. Even when the scales used in clinic to capture response to treatment, are not able to detect any significant changes, patients tend to report perceived benefits and gaining of activities of daily living that are critical for their quality of life.

What is the expected place of the technology(ies) in current practice?

9. How is the condition currently treated in the NHS?	Almost all patients with SMA are diagnoses after symptoms onset; depending on the age of the patient, general health at baseline and SMN2 copy numbers there are three treatments available. Risdiplam and Nusinersen are both available within the framework provided by NICE. The compliance with therapies is excellent. Onasemnogene abeparvovec is also available to Type 1 SMA patients under 21kg (if not contraindicated). Palliative care is also considered and discussed with families.

	All patients will continue to also receive standard of care: BiPAP ventilation when needed, gastrostomy when indicated, physiotherapy rehabilitation (eg use of KAFOs to aid standing), surgical procedures (i.e. scoliosis surgery). Those not eligible through MAA may be on treatment on compassionate grounds/ EAMS scheme.
9a. Are any clinical guidelines used in the treatment of the condition, and if so, which?	There are published SOC guidelines for SMA. However, SOC guidelines were published when not all treatments were available to patients. The SMA REACH network is also involved with regular meetings including all treatment centres- to discuss specific emerging topics (respiratory management of SMA I; hip dysplasia management; scoliosis management for example are topics of current or past discussion). The SMA REACH network is also supporting the effort of the SMA CARE SOC programme, led by Dr Anne-Marie Childs and Dr Chiara Marini-Bettolo, to facilitate the consensus gathering among SMA HCP.
9b. Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please state if your experience is from outside England.)	There is good level of consensus amongst professionals. There is a consensus that treatment should be offered to patients after proper counselling is provided, but there is no consensus on which treatment should be started, as there are no data on superiority of one treatment compared to another. The SMA REACH network provides a forum for discussing individual cases. The National gene therapy MDT has also helped considerably in addressing complex cases, so that equality of access is maintained. Funding needs to be considered for referring centres who take on monitoring and support of patients pre and post disease modifying therapy. Communication is important and needs to be structured. Framework needs to clearly define actions and responsibilities and pathway to escalate concerns. Even if 3 drugs have been approved, we need to continue to collect outcomes, risks and benefits in structured way using REAH framework. NHSE money provided to support Nusinersen treatment has been helpful but there was no central funding despite same requirements for monitoring, nor a tariff was associated with Risdiplam provision under the MAA NHSE should be taking on some responsibility for specialist commissioning of the whole care pathway for those receiving DMTs.
9c. What impact would the technology(ies) have on the current pathway of care?	Both therapies have revolutionised (in a positive way) the clinical outcomes of patients. The volume of work has increased both due to the administration and monitoring of these therapies, and the marked reduction in mortality of SMA type 1 children. In the UK we are already using these technologies for patients under a managed access agreement which implies regular appointments for safety and benefit assessments. All patients receiving either Risdiplam or

	Nusinersen are seen regularly by the neuromuscular team (including a full physiotherapy assessment) for a full assessment at least once/year (paediatric patients are more likely seen twice/year). If approved, the treatments would continue to be used as it has been across the national clinical network. There should be a consideration to including treatments for those who currently receive this only on compassionate grounds. They would become part of Standard of Care for SMA patients.
10. Will the technology(ies) be used (or is it already used) in the same way as current care in NHS clinical practice?	These therapies are now well embedded in the classical care pathway for these patients. I think there will need to be clarity for clinicians regarding treatment choice, and in particular switching from one drug to another and commencing a different treatment in the face of sub optimal outcome.
10a. How does healthcare resource use differ between the technology(ies) and current care?	Nusinersen requires administration via lumbar puncture, and considering a proportion of these patients have complex spines, skilled operators are required. Some centres have interventional radiology services supporting the lumbar punctures, but most of the neuromuscular centres don't. Without continued access to these treatments, many patients will once again have progressive weakness and loss of motor skills, with restricted mobility and increasing dependence together with a higher risk of complications requiring medical intervention, hospital admissions and social care. Untreated individuals will require ongoing supportive care, which as well as limiting their capacity to participate in activities including work/education, will impact their carer's ability to do the same.
10b. In what clinical setting should the tech technology(ies) nology be used? (For example, primary or secondary care, specialist clinics.)	Specialist (neuromuscular) clinics
10c. What investment is needed to introduce the technology(ies)? (For	Mostly the availability of a continuous pathway for the administration of Nusinersen. The growing needs (numerically) of the patients who survive and who will need to access HCP (from physio, to respiratory to orthopedic, to wheelchairs) cannot be underemphasised.

example, for facilities, equipment, or training.)	Clinics capacity is stretched and there should be the understanding that dedicated clinic time and space is needed to review these patients. A comprehensive physiotherapy service should be implemented as well. More training for early recognition/diagnosis should be implemented.
11. Do you expect the technology(ies) to provide clinically meaningful benefits compared with current care?	Not only is our expectation, but it is what is clearly documented by a large number of peer reviewed publications from different countries in the world
11a. Do you expect the technology(ies) to increase length of life more than current care?	There is a dramatic effect of these therapies to reduce mortality especially in SMA1.
11b. Do you expect the technology(ies) to increase health-related quality of life more than current care?	Yes
12. Are there any groups of people for whom the technology(ies) would be more or less effective (or appropriate) than the general population?	SMA type 0, i.e. those with very severe neonatal onset Pre-symptomatic cases diagnosed with newborn screening. Outside NBS, all newly diagnosed patients should be initiated on a treatment as soon as possible.

The use of the technology(ies)

13. Will the technology(ies) be easier or more difficult to use for patients or healthcare professionals than current care? Are there any practical implications	These 2 therapies are now well embedded in most regional centres in the UK Compared with no treatment (natural history): reduced hospital admissions and need for hospital assessments overall but some extra checks such as blood tests monitoring for safety.

for its use (for example, any concomitant treatments needed, additional clinical requirements, factors affecting patient acceptability or ease of use or additional tests or monitoring needed.)	
14. Will any rules (informal or formal) be used to start or stop treatment with the technology(ies)? Do these include any additional testing?	Some guidance about combination therapy, switching and identifying non-response will be helpful so that the same criteria can be used across the UK. Expectations regarding treatment outcomes are still very high in the patient community and this has resulted in pressure to switch/add additional SMN modifying drugs with limited evidence. The NICE Start-Stop rules are helpful but not fully comprehensive and exclude patients (i.e. ventilated) who will benefit from the medications. There are defined rules in the MAA but this could be left to clinician discretion. NHSE could appoint a centralised body to consider this – using the existing clinical panel for example. Stopping treatment should be discussed with families/patients as well as the possibility of switching from one treatment to another. An adverse event/ side effect linked to the technology could be a reason for considering discontinuation/switching treatment. No response and/or no perceived benefits from treatment together with increased burden for the patient/family could also lead to discontinuation/switching treatment
15. Do you consider that the use of the technology(ies) will result in any substantial health-related benefits that are unlikely to be included in	The QALY calculation will maximally benefit when newborn screening will be implemented in England. For patients who are long-term ventilated, the benefits might include enabling continuing use of powered wheelchairs or computer controls. This is unlikely to be captures in existing QALY.

the quality-adjusted life year (QALY) calculation?	
16. Do you consider the technology(ies) to be innovative in its potential to make a significant and substantial impact on health-related benefits and how might it improve the way that current need is met?	These 2 therapies have changed the way SMA progresses to the point that some of the classical descriptions do not apply any more- especially for treatments initiated early. Reducing diagnostic delay will lead to improved outcomes.
16a. Is the technology(ies) a 'step-change' in the management of the condition?	Absolutely yes.
16b. Does the use of the technology(ies) address any particular unmet need of the patient population?	The other DMT, onasemnogene abeparvovec , is only available for patients < 21 Kg, with SMA type 1 and with up to 3 *SMN2* copiesand its administration is precluded in cases with pre-existing AAV9 antibodies or other comorbidities, so nusinersen and risdiplam have a clear role as DMTs in SMA
17. How do any side effects or adverse effects of the technology(ies) affect the management of the condition and the patient's quality of life?	Nusinersen is typically well tolerated with very scarce drug related adverse events.. However, there are adverse events related to the route of administration. Risdiplam is generally well tolerated although in some patients, adverse events require discontinuation. Having both options available for HCP and patients is important. So far both technologies have been well tolerated; only a few patients have stopped treatment in UK. If one is not, then the alternative may be used.

Sources of evidence

18. Do the clinical trials on the technology(ies) reflect current UK clinical practice?	Yes, especially for symptomatic treated patients.
18a. If not, how could the results be extrapolated to the UK setting?	Results of pre-symptomatic patients show the importance of early treatment. In the UK we have a few patients treated pre-symptomatically (siblings of patients with SMA) and treatment effectiveness has been proven as well a very divergent trajectory of these children compared to their older siblings treated after symptom onset
18b. What, in your view, are the most important outcomes, and were they measured in the trials?	Motor milestones Mortality Hospital admissions Impact on bulbar function is not fully studied; Some outcome measures used in trials are not used in the UK clinical practice (i.e. MFM) Patient reported outcomes have not been widely used enough – ultimately the ability to continue to do something such as operating a powered wheelchair, using computers/ tablets or standing is what matters to patients. Fatigue is often reported to have improved but is not captured.

18c. If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes?	Real life improvements were used; there are several cases nationally with improvements in daily actions that matter to patients and re-gained functions.
18d. Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	Not to my knowledge
19. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	No
20. Are you aware of any new evidence for the comparator treatment(s) since the publication of NICE technology appraisal guidance [HST15, HST24]?	
21. How do data on real-world experience compare with the trial data?	They parallel it

Equality

22a. Are there any potential equality issues that should be taken into account when considering this treatment?	Both should be available as some patients cannot tolerate or access one (for example after spinal fusion). Operating on the principle that those who are long term ventilated unnecessarily have a less good quality of life is an equality issue.
22b. Consider whether these issues are different from issues with current care and why.	

Key messages

23. In up to 5 bullet points, please summarise the key messages of your submission.	• SMA DMT have changed the course of the disease in a very fundamental way. Through the availability of the treatments available within the MAA as well as onasemogene abeparvovec the benefit and positive impact this has shown to the population is immense inclusive of physical, social, and mental wellbeing. • Early symptomatic children improve motor outcomes in ways that make textbooks obsolete. • This is improved further in children treated presymptomatically, with many children being phenotypically normal in published series for the 3 DMTs. • In more chronically affected individuals, the stabilisation or modest improvement in the trajectories (motor and respiratory) have been clearly documented in clinical trials and replicated in our real-world evidence, in peer reviewed publications. Whilst modest, given the progressive nature of the condition, this should still be considered a positive outcome. • The implications of these changes in practice for the wider MDT should be considered

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Multiple Technology Appraisal

Nusinersen and risdiplam for treating spinal muscular atrophy (MA review of TA588 and TA755) [ID6195]

Guidance review following a period of managed access - NHS organisation submission

Thank you for agreeing to give us your views on the technologies and the way they should be used in the NHS.

The Department of Health and Social Care and the Welsh Government provide a unique perspective on the technologies, which is not typically available from the published literature. NICE believes it is important to involve NHS organisations that are responsible for commissioning and delivering care in the NHS in the process of making decisions about how technologies should be used in the NHS.

To help you give your views, we have provided a template. The questions are there as prompts to guide you. You do not have to answer every question. Short, focused answers, giving a Department of Health and Social Care perspective on the issues you think the committee needs to consider, are what we need.

About you

Your name	[redacted]
Name of your organisation	NHS England
Please indicate your position in the organisation	Department of Health and Social Care in general? • **Commissioning services for the Department of Health and Social Care specific to the condition for which NICE is considering these technologies?** • Responsible for quality of service delivery in the ICB (e.g. medical director, public health director, director of nursing)? • A specialist in the treatment of people with the condition for which NICE is considering the technologies? • A specialist in the clinical evidence base that is to support the technologies (e.g. participation in clinical trials for the technologies)? • Other (please specify):
Do you have any links with, or funding from, the tobacco industry? Please declare any direct or indirect links to, and receipt of funding from the tobacco industry	No

What is the expected place of the technology in current practice?

How is the condition currently treated in the NHS? **Is there significant geographical variation in current practice?**	The condition is currently treated using nusinersen/risdiplam under the terms of the relevant NICE Managed Access Agreements (MAA). Eligible populations are also treated with the gene-therapy onasemnogene abeparvovec, in line with NICE Highly Specialised Technologies (HST15 and HST24). Patients are treated alongside a range of other multi-disciplinary interventions.

Are there differences in opinion between professionals as to what current practice should be? **What are the current alternatives (if any) to the technologies, and what are their respective advantages and disadvantages?**	Patients are treated in a number of centres across the NorthStar Network which supports access across England for patients with spinal muscular atrophy (SMA). Over the period 2024/5, blueteq forms reported: - Nusinersen: 193 continuation forms for 174 distinct patients with 12 new patient forms for 11 patients. - Risdiplam: 354 continuation forms for 320 patients, and 122 new patient forms for 121 patients. NHS England have operated a Clinical Panel for nusinersen and risdiplam under the terms of the MAA for a number of years. Consensus views from the Clinical Panel regarding some of these questions are set out below. It is noted that a variety of requests received by the Panel e.g. sequential use / combination use which suggests the potential for differing practice. Gene-therapy does exist but only in line with HST. See detail further below re considerations around use of different treatments.

To what extent and in which population(s) are the technologies being used in your local health economy? **Is there variation in how it is being used in your local health economy?** **Is it always used within its licensed indications? If not, under what circumstances does this occur?** **What is the impact of the current use of the technologies on resources?** **What is the outcome of any evaluations or audits of the use of the technologies?** **What is your opinion on the appropriate use of the technologies?**	Reflections from the Nusinersen Clinical Panel on use of therapies: - Access as bridge to gene-therapy - important to support access to therapy as soon as possible after diagnosis so that risdiplam (typically) can be used as a bridge to gene-therapy which cannot necessarily be started straight away. Clinical colleagues feel that the flexibility to do this is important. This could become increasingly important in the future if SMA is introduced to the newborn screening programme. - Dual therapies (noting this doesn't refer to combination treatment) - important to maintain choice between nusinersen and risdiplam as there are benefits in having access to both therapies for patients based on their individual circumstances, at different stages in their life. Circumstances where there may be a need for such flexibility include pregnancy and breastfeeding (coming off risdiplam); degree of disability; adverse effects; spinal factors which can make intrathecal administration difficult; levels of ambulation; considerations around route of administration. The natural history of both treatments is that they will continue to improve but, in this context, clinicians deemed it beneficial to have access to both with clinical experience being vital in determining suitability. The Panel suggested data on switching may be helpful to analyse. - Safeguarding access - route of administration for nusinersen provides assurance that patient has had the prescribed treatment whereas administration of risdiplam cannot be monitored in the same way; this is particularly important in patient populations where there are factors within the environment which mean risdiplam may not be reliably administered by carers (i.e. where clinicians do not have confidence that this will be administered by a parent/carer because of their particular circumstances). - Starting/Stopping criteria: o Under terms of the current MAA, clinicians noted there can be challenges in defining respiratory deterioration. Clinical colleagues suggest that evidence of motor response may be considered sufficient measure of success/failure. o Desirability of stopping criteria – baring severe respiratory failure, clinicians considered that assessment of benefit could be better assessed on a case-by-case basis whist noting the need for an overarching evidence-based framework. From a commissioning standpoint, it would be important to ensure that there is a framework that is used to ensure VfM. o Context: ▪ There are challenges in monitoring benefit in a patient who is growing (children and young adults) as there will inevitably be changes due to their growth which, in and of itself, can

	lead to loss of power due to increases in weight and height. This doesn't necessarily constitute failure of treatment. ▪ Assessment of benefit is best considered through tailored assessments as milestones cannot always be standardised. The natural history of SMA must also be taken into account, where evidence shows that decline is often most significant in early years. This is also the case for consideration of other responses which can be nuanced including quality of life benefits from treatment. Clinicians note that benefits can sometimes be reflected as stability (in context that SMA is a progressive disorder) or factors like stamina (not currently measured in a systematic way). Clinicians acknowledge it can be hard to assess benefit in those who are vey weak; in this population albeit things like fine motor skills (which aren't currently measured) can be important and of valuable benefit. The Panel noted that there is a need for caution against inadvertent discrimination by not recognising benefit in this population. ▪ For adult populations which may range from 17-70+, benefits of the drugs would most commonly be reflected in stability. o As noted above, it is important that there remains a degree of objectivity with regards starting/stopping criteria (particularly from a commissioning standpoint). However, within the bounds of an evidence-based framework there should be scope for advice to be sought e.g. from a panel of experts to allow scope for more complex/nuanced cases to be considered by experts. - Clinicians noted that not all adult populations with SMA are in scope, for instance, adult-onset SMA Type 4 – there are approximately 10 patients in the country who would benefit but aren't able to currently. From a commissioning standpoint, demonstration of cost-effectiveness would be important in this cohort. *Off-label use:* The Clinical Panel have received applications from clinicians seeking access to the drug for pre-natal use in circumstances where the fetus has been diagnosed with SMA. Requests have been declined under terms of the MAA and on basis that these drugs are not licensed for use in this scenario. The Panel most frequently receive requests from referring centres for sequential use (gene-therapy plus one of risdiplam/nusinersen). In these cases, improvements in motor response may have been seen but not necessarily to the level expected by parents, or in some cases, clinicians. Referrals may also seek to make a case for possible respiratory decline.

Potential impact on the NHS if NICE recommends the technology(ies)

What impact would the guidance have on the delivery of care for patients with this condition?	Guidance would support continued access to these treatments (if both nusinersen and risdiplam were recommended) for children with SMA alongside use of the gene-therapy, as clinically appropriate. Care is already being provided to patients under the terms of the MAA. If only one of the therapies were recommended this would have implications for current and future cohorts, including switching. As described above, there are examples where either one of the drugs is more suitable depending on the patient profile. There are also considerations around continued access to the drugs under terms of MAA which mean that one of these is not assured for ongoing access to existing patient cohorts. Note – An In Service Evaluation of screening for SMA is in development. The outcome of the NICE process could have a bearing on the ongoing viability of this. Latest information available here UK NSC publishes SMA screening evidence documents – UK National Screening Committee
In what setting should/could the technologies be used – for example, primary or secondary care, specialist clinics? Would there be any requirements for additional resources (for example, staff, support services, facilities or equipment)?	Care is already being provided to patients within secondary/tertiary care (and therefore resourced) under the terms of the MAA through the Northstar network of providers (list available on request). NHSE currently pay a year of care tariff to providers for every patient treated with nusinersen. This reflects costs associated with patients needing maintenance doses three infusions/year (post loading dose). Risdiplam is currently delivered to patients via a company sponsored homecare scheme.
Can you estimate the likely budget impact? If this is not possible, please comment on what factors	NHSE have already contributed to NICE evaluation. If further information needed, please let us know.

should be considered (for example, costs, and epidemiological and clinical assumptions).	
Would implementing the technologies have resource implications for other services (for example, the trade-off between using funds to buy more diabetes nurses versus more insulin pumps, or the loss of funds to other programmes)?	Implementation of technologies has the potential to improve outcomes for patients with SMA avoiding costs to society for care for patients who do not have treatment and subsequently deteriorate more quickly than they would with treatment.
Would there be any need for education and training of NHS staff?	As both drugs are already in use and teams are familiar with them we do not envisage a material impact.

Equality

Please let us know if you think that this appraisal: **Could exclude from full consideration any people protected by the equality legislation who fall within the patient population for which [the treatment(s)] is/are/will be licenced** **Could lead to recommendations that have a different impact on people protected by the equality legislation than on the wider population, e.g. by making it more difficult in practice for a specific group to access the technologies** **Could lead to recommendations that have any adverse impact on people with a particular disability or disabilities.**	It will be important to recognise benefits of nusinersen/risdiplam treatment for severely disabled patients where evidence of benefit may not also be as apparent as for other populations.
Please tell us what evidence should be obtained to enable the committee to identify and consider such impacts.	

NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others.

Other issues

Please include here any other issues you would like the appraisal committee to consider when appraising this technologies	N/a

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Spinal muscular atrophy: nusinersen (MAA review of TA588) and risdiplam (MAA review of TA755) [ID6195]

Produced by Newcastle University

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Ryan PW Kenny was involved with the development of statistical analysis plans for the analysis of managed access agreement data for the paediatric and adult SMA registries, for both nusinersen and risdiplam.

Nicole O'Connor was employed by Newcastle University prior to 2020 on an unrestricted education grant funded by Biogen to work with the international SMA community in managing the dissemination of updated standards of care for SMA and also received unrestricted educational grants from Roche to support delivery of related masterclasses.

None of the other authors have any competing interests to declare.

Contributions of authors:

Ryan PW Kenny contributed to the critique of the company clinical effectiveness sections, undertook the analysis of the MAA data, contributed to the writing of the clinical effectiveness, background, discussion and conclusion sections of the EAG report.

Giovany Orozco-Leal contributed to the critique of the company cost-effectiveness submissions, developed the EAG economic model, contributed to the writing of the cost-effectiveness sections of the EAG report.

Nawaraj Bhattarai contributed to the critique of the company cost-effectiveness submission, developed the EAG economic model, contributed to the writing of the cost-effectiveness sections of the EAG report and performance of the economic analysis.

Eugenie Evelynne Johnson led the qualitative analysis for the report, contributed to the writing of the qualitative analysis sections, contributed to data extraction for the clinical effectiveness evidence, and contributed to study selection for the SLR of economic evaluations.

Louise Tanner contributed to the EAG SLR of clinical effectiveness update, contributed to the writing of the clinical effectiveness sections of the report.

Nicole O'Connor contributed to the qualitative analysis for the report, contributed to the writing of the qualitative analysis sections of the report.

Lakshmi Jayachandran contributed to the EAG SLR of economic evaluations update, contributed to the writing of the economic sections of the report.

Julia Whitehall contributed to the EAG SLR of economic evaluations update, contributed to the writing of the economic sections of the report.

Hannah O'Keefe produced search strategies and performed the search and contributed to the writing of the report.

Claire Eastaugh contributed to production of search strategies, performed the search, and formatting of the references/report.

Opeyemi Agbeleye contributed to screening of systematic review update results, data extraction for the clinical effectiveness evidence and to the writing of the report.

Negar Yousefzadeh contributed to the screening of systematic review update results, data extraction for the clinical effectiveness evidence and systematic literature review update, and to the writing of the report.

Fiona Beyer led the clinical effectiveness section of the report, contributed to screening of systematic review update results, critical appraisals and synthesis of the evidence. She contributed to the writing of the background, clinical effectiveness, and discussion sections.

Stephen Rice provided advice on the critiques of the company submissions and the development of the economic models.

Gill Norman advised on the clinical effectiveness assessment, edited the report and acted as co-project lead.

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Report key:

[redacted]

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1 Abstract

Background

Spinal muscular atrophy (SMA) is a rare genetic condition that causes muscle weakness and loss of function over time. In the most severe form untreated SMA results in death in infancy or early childhood.

Aim

The Newcastle Evidence Assessment Group (EAG) were asked by the National Institute of Health and Care Excellence (NICE) to assess the clinical and cost-effectiveness of two treatments for SMA: nusinersen and risdiplam.

Methods

The EAG consulted with the companies (Biogen, Roche), professional organisations, clinicians and patient organisations throughout. A qualitative framework analysis was undertaken using information provided to NICE, discussions between the EAG and patient and professional organisations, and free-text data provided by SMA registries.

The EAG updated the original systematic literature reviews (SLR) of clinical and economic evidence to March 2025. Conference abstracts, excluded from the original review, were included. Controlled studies and economic evaluations were critically appraised using standard tools. Data were narratively synthesised according to the drug, SMA type and outcome measure assessed. Reports from the Managed Access Agreements (MAA) for nusinersen and risdiplam from adult and paediatric registries, were critically assessed.

The EAG reviewed and critiqued company submissions including clinical and economic evidence and the economic models and the evidence used to parameterise these for each population group, including additional information submitted following points for clarification.

The EAG conducted its own economic analyses, drawing on evidence and models submitted by both companies. Because of the differences in population characteristics for nusinersen and risdiplam treatments, the treatments were evaluated using separate models. However, efforts were made to align the analyses for consistency and to address the key uncertainties surrounding the cost-effectiveness of each therapy within the context of the decision problem.

Results

The qualitative analysis suggested that treatment may maintain or improve motor, bulbar and respiratory function in those with SMA. However, it was not always possible to determine which treatment people had received. The insensitivity of tools to identify improvements in fine motor skills between motor milestones and the importance of these smaller improvements in motor function, and the importance of maintenance of function were also emphasised.

The updated SLR included 147 studies. For nusinersen 130 studies (22 new) were included, (three RCTs, eight controlled studies, 119 single arm studies). Thirteen studies (three new) assessed risdiplam, (one RCT, 12 single arm studies). Four studies (three new) included patients on both treatments, (one non-randomised controlled study, three single arm studies). Twenty were ongoing. The SLR results suggested both nusinersen and risdiplam, separately, improved or maintained motor function for people with presymptomatic and types 1 to 3 SMA. There is less evidence, and no controlled studies, that include presymptomatic patients. For

nusinersen, some studies reported differences in effectiveness between population subgroups in relation to age and SMA type. Evidence also suggested that nusinersen provided stability for respiratory function, while the evidence on risdiplam suggested mixed effects on ventilation. Separately, both showed mixed results regarding impact on bulbar function and quality of life measures in carers and patients. Importantly, there were higher survival rates amongst type 1 patients treated with nusinersen, and for both treatments survival was substantially higher than is the case for untreated type 1 patients. However, for risdiplam, there was a lack of controlled studies providing evidence on mortality. Adverse events were generally not serious for either nusinersen or risdiplam. A single study directly comparing nusinersen and risdiplam suggested no statistically significant differences between treatments in people with types 2 and 3 SMA at the 6-month follow up, but baseline imbalances in prognostic factors limit data comparability.

The MAA data suggested maintenance or improvement in motor function outcomes was common for both nusinersen and risdiplam separately across types 1, 2, and 3 SMA. Data for patient-reported outcomes measures (PROMs) was limited and showed mixed results for both treatments. However, maintenance or improvement was reported for some patient-reported scales for both nusinersen and risdiplam. Similarly, for both treatments separately, data for QoL was limited but suggested some improvement. Importantly, mortality rates in the MAA were low for both treatments and deaths appeared unrelated to treatments. Risdiplam data was more limited, reflecting its later availability through MAA.

The updated SLR for cost-effectiveness included 21 studies. The economic evaluations included comparisons between some or all the following SMA treatments: nusinersen; risdiplam; onasemnogene abeparvovec (OA); and standard of care/BSC. All studies adopted a Markov model with health states defined by functional motor milestones underpinning disease progression. Most quantified health benefits in quality-adjusted life years (QALYs) and life years gained (LYGs) and included cost-effectiveness evaluations with ICER as the outcome. Sources for health state utilities and costs, time horizon, modelling methods, outcomes, and involvement of patients and professionals all differed.

The EAG's base case cost-effectiveness analysis using the Biogen model showed that nusinersen [redacted] when compared with BSC. The scenario analysis indicated that nusinersen is likely [redacted] OA in treating presymptomatic and type 1 patients. The EAG's analysis using the Roche model showed that risdiplam was [redacted] when compared with BSC. However, risdiplam was [redacted]. In the scenario analysis, when equivalence in effectiveness was assumed between risdiplam and OA, risdiplam was [redacted] when treating the presymptomatic population, whereas it was [redacted] type 1 population.

Conclusions

The EAG's results mainly align with work from by the drug companies and by other international health agencies. There was some evidence that both nusinersen and risdiplam improved or stabilised motor function but there was mixed evidence for other outcomes. There was insufficient evidence to estimate the relative net health benefits of either treatment. Due to the limitations in the data for both nusinersen and risdiplam, the results should be viewed

cautiously. Further research is required to strengthen the evidence base, particularly for outcomes considered important by professionals and patients.

2 Executive Summary

Background

Spinal muscular atrophy (SMA) is a rare, progressive neuromuscular disease most commonly caused by a genetic mutation in the survival motor neuron (SMN) gene on chromosome 5q. This genetic mutation causes gradual breakdown of motor neurons in the spinal cord and brainstem, leading to progressive muscle weakness, atrophy and, eventually, paralysis in late-stage disease. The condition affects muscles that involve crawling, walking, arm movement, head and neck movement, swallowing, and breathing. SMA is diagnosed through genetic testing and clinical examinations and has historically been categorised into types 0, 1, 2, 3, and 4 according to age of onset. The onset of neuromuscular weakness can range from birth to adulthood.

Currently, SMA is managed through multidisciplinary supportive care, which aims to minimise the impact of disability by addressing complications and improving quality of life. Care pathways have been developed for both paediatric and adult patients and the guidance informed by the international standard of care. The only treatment option currently recommended by the National Institute for Health and Care Excellence (NICE) is onasemnogene abeparvovec (OA; Zolgensma), a gene therapy. However, OA is only available for treating 5q SMA with a biallelic mutation in the SMN1 gene, either a) for presymptomatic babies aged 12 months and under with up to three copies of the SMN2 gene, or b) for type 1 babies who are not permanently ventilated or need tracheostomy and who are aged six months and under, or 7 to 12 months with agreement of the national multidisciplinary team.

There are two disease-modifying therapies that have been previously reviewed as NICE Single Technology Appraisals (STAs) and recommended for use under a Managed Access Agreement (MAA): nusinersen (Spinraza, Biogen) and risdiplam (Evrysdi, Roche). Nusinersen is a 2'-O-methoxyethyl antisense oligonucleotide administered by intrathecal injection. It stimulates the survival motor neuron-2 SMN2 gene to increase SMN protein levels. The intrathecal injection (12 mg/5 mL) requires an initial loading phase of four doses on days 0, 14, 28 and 63. Maintenance doses are subsequently provided every four months. Risdiplam (Evrysdi, Roche) is a small-molecule survival motor neuron-2 (SMN2) gene splicing modifier which increases SMN protein levels in the central nervous system. It is administered orally through an oral syringe once per day.

Nusinersen and risdiplam were reviewed separately in TA588 and TA755 in 2019 and 2021, respectively, and both were recommended under an MAA with the instruction to collect further longer-term data. In this latest stage of a Multiple Technology Assessment (MTA), the Newcastle Evidence Assessment Group (EAG) were asked by NICE to assess the clinical and cost-effectiveness of both treatments for SMA.

Aims

This report describes the MTA investigating the clinical and cost effectiveness of nusinersen and risdiplam as treatments for SMA.

Structure of the report and justification of approach

This MTA was undertaken following two previous appraisals of the individual technologies (TA588 and TA755) and subsequent MAAs in each case. This is a condition in which the available data from clinical trials is acknowledged to not be fully reflective of the lived experience of patients and carers and where considerable uncertainties were identified in the original appraisals. To reflect this, the EAG have undertaken work to analyse quantitative and qualitative data available from the MAA. In addition, the EAG have undertaken qualitative analysis of data from patient submissions and from meetings with representatives of professional organisations and patient groups, as well as free-text data provided by both adult and paediatric registries. These analyses are presented in addition to the critiques of the submissions from Biogen and Roche, updated systematic literature reviews of clinical and cost effectiveness evidence, and economic modelling. The qualitative analyses should be considered both individually and as providing essential context to the systematic reviews and models.

Methods

Throughout the MTA process, the EAG consulted with both Biogen and Roche, professional organisations, clinicians, and representatives of patient organisations. Three meetings each were held with Biogen, Roche, professional and patient organisations to discuss the EAG's approach to the qualitative analysis, clinical SLR, and economic modelling, as well as to discuss preliminary results. These meetings included representation from NICE. Individual clinicians were also consulted to provide further, condition-specific context and validation for the methods used by the EAG. The discussions from all meetings helped to shape the approach of the EAG to the MTA, including report structure, inclusion of additional outcomes and the approach to the economic modelling.

Critique of the company submissions

The EAG reviewed and critically appraised the clinical evidence and economic models submitted by the companies, as well as additional information in response to points for clarification requested by the EAG. The EAG critiqued the submitted clinical effectiveness evidence, economic model structures and the economic evidence used to parameterise the economic models for each of the population groups, which was then summarised within the report.

Qualitative analysis

The EAG conducted qualitative framework analyses to identify areas of key concern surrounding living with SMA, as well as surrounding the potential benefits of nusinersen and risdiplam from the perspective of those with a lived experience of SMA. Several sources were used to inform the qualitative analysis, including: transcripts of meetings between the EAG and both professional and patient organisations; patient and professional organisation submissions to NICE; professional and patient expert submissions to NICE; case studies and quotations included as part of an appendix to the submission to NICE provided by SMA UK, Muscular Dystrophy UK and SMA Reach UK; and free-text data provided to the EAG about both paediatric and adult populations from SMA REACH UK.

A framework analysis was undertaken, focusing on identifying the issues of most importance to people with a lived experience of SMA, as well as the impacts of treatment with nusinersen and risdiplam. The EAG developed the coding framework based on the decision problem and

discussions with patient and professional organisations. Two members of the EAG iteratively developed the final framework, which was transferred to the software Nvivo for coding. Two members of the EAG undertook two pilot coding phases to establish concordance between coders and identify areas where the coding framework could be modified. Following this, most of the sources were coded by a single EAG researcher and checked by a second. Any potentially missing or erroneous codes identified by the second researcher were discussed and agreed prior to analysis.

The coded data were interrogated to identify key subthemes from the framework inductively. Following initial discussion of the methods and coding with professional and patient organisations, both researchers wrote narratives surrounding the major themes and sub-themes identified from the coding phase, including illustrative quotations where appropriate. The narratives were written from a pragmatic perspective to present the findings of the qualitative data without additional theory generation or interpretation. This step was repeated when free-text data from the registry was received. Once written, researchers read the narratives alongside the original coding to ensure there were no potentially missing sub-themes, that they were written from the pragmatic standpoint, and that the narratives and direct quotations used were adequately contextualised insofar as possible.

SLR of clinical effectiveness

Searches from the original review[1] were updated in March 2025 to incorporate newly published records meeting the eligibility criteria. The search results were screened in duplicate, along with the list of excluded studies from the original review, to identify new evidence, including from conference abstracts which were excluded from the earlier review. Data were extracted into a data extraction form created in Excel, which had been piloted and refined to capture all the data required for the synthesis. For the review update the EAG extracted data where possible on some additional outcomes identified as important by the patient and professional groups. Randomised controlled trials (RCTs) and non-randomised controlled studies were critically appraised using the Risk of Bias v2 (RoB v2) and Risk Of Bias In Non-randomised Studies - of Interventions (ROBINS-I) tools, respectively. The results were narratively synthesised according to the following hierarchy: drug (nusinersen or risdiplam); outcome type (e.g. motor outcomes); outcome measure (e.g. CHOP INTEND); and SMA type. Newly included data is identified within the review.

Managed Access Agreement (MAA)

The EAG critically assessed the MAA reports for both nusinersen and risdiplam; in some instances, data were updated for outcomes in both the paediatric and adult registries for both treatments. The analyses for nusinersen and risdiplam were sometimes limited due to small sample sizes, especially at later time points. However, the registries noted these limitations and the EAG agreed with the way in which data was analysed. Motor outcomes with enough data were analysed using mixed models for repeated measures (MMRM), while other outcomes (e.g. patient-reported outcomes) were presented using descriptive statistics.

SLR of economic evidence

Searches from the original review were updated in March 2025 to incorporate newly published records meeting the eligibility criteria. Data were extracted into a data extraction form created in Excel, which had been piloted and refined to capture all the data required for the synthesis.

In line with the original review, the critical appraisal strategy involved assessing all included economic evaluations using the Consolidated Health Economic Evaluation Reporting Standard (CHEERS) 2022 checklist, as well as appraising records against the Philips' checklist. Each record was assessed by one reviewer and checked by a second reviewer, with any disagreements being resolved by discussion or consultation with a third reviewer. The evidence identified on modelling techniques, structures and inputs (including clinical, survival analysis methods, resource use and costs, utility estimates) that were required to generate the models, assumptions and key outcomes were summarised. Any key issues that should be considered in model-based economic analyses conducted in the future were also summarised.

Economic modelling

The EAG conducted its own economic analyses, drawing on the evidence and models submitted by both companies. Because of the differences in population characteristics for nusinersen and risdiplam treatments, the treatments were evaluated using separate models (adapted versions of Biogen and Roche models separately for each SMA type). However, efforts were made to align the analyses for consistency and to address the key uncertainties surrounding the cost-effectiveness of the relevant disease-modifying therapies within the context of the decision problem.

In the base-case analyses, the EAG used adapted Biogen and Roche models to compare nusinersen versus BSC, and risdiplam versus BSC, respectively, across presymptomatic, type 1, and type 2/3 SMA populations.

For the Biogen (nusinersen) model, the EAG's base-case did not include carer utility, which had been incorporated in the company model. Instead the EAG explored the impact of carer utility through scenario analysis. Several additional scenarios were conducted to explore the impact of uncertainty in the parameters, including a comparison between nusinersen and OA, with and without assuming equivalence between the treatments.

For the Roche (risdiplam) model, the EAG's base-case also excluded carer utility and aligned key parameters such as time horizons, health state utility values, and healthcare resource use with those used in the Biogen (nusinersen) model. Additional scenario analyses were conducted comparing risdiplam vs nusinersen, and risdiplam vs OA, with and without assuming equivalence, alongside various other scenarios exploring the impact of uncertainty in the cost and utility parameters.

Results: key findings

Critique of company submissions

A critique of the indirect treatment comparisons (ITCs) was conducted for both company submissions (nusinersen – Biogen; risdiplam – Roche). Biogen used matching-adjusted indirect comparisons (MAICs) to compare nusinersen to either OA or risdiplam. If a MAIC was still deemed unfeasible, a simulated treatment comparison (STC) was implemented. Biogen noted that the amount of bias (systematic error) in these estimates is unknown, likely to be substantial, and could even exceed the magnitude of treatment effects being estimated. Fourteen analyses were conducted by Biogen (seven comparing to OA and seven comparing to risdiplam). For both comparisons there was a common issue of the effective sample size (ESS) being below 30, with some less than 10. These small ESS suggest a potential for high

variability between the populations being compared, meaning the estimate may be unstable. When a MAIC was deemed unfeasible, an STC was used with non-linear data (i.e. for the Hammersmith Functional Motor Scale Expanded (HFMSE) and Revised Upper Limb Module (RULM) motor outcomes when comparing to risdiplam). This is commonly the case in SMA, where it is possible to show improvements, maintenance or deterioration over time, so results can be open to bias. Specifically, as the results are generated via a linear regression model using individual patient data (IPD) from one trial compared to aggregate data from the comparator trial, the non-linearity assumption may be violated. If there is non-linearity substituting the mean covariate values from the comparator trial into the regression, this can lead to biased estimates due to issues between the relationship of the mean of the outcome and the mean of the covariates.

Roche also used MAICs or STCs depending on feasibility. Eighteen analyses were conducted by Roche (12 comparing risdiplam to nusinersen and six comparing to OA). The same issue of non-linearity for STCs is present in these analyses as in the aforementioned nusinersen (Biogen) analyses. For example, risdiplam vs OA in type 1 patients utilises an STC. When comparing risdiplam to nusinersen in unanchored MAICs, the ESS was above 35, meaning there was a potential for less bias and uncertainty in the results. In type 2/3 patients, Roche conducted an anchored MAIC, which was not conducted by Biogen. Doing this required the assumption that the placebo and sham arms were comparable, which may not be the case. The lack of comparability between the placebo and sham arms is supported by a reduced ESS of less than 10 in the comparator arm. Additionally, the ESS in the intervention arm was less than 30. The company highlighted this as a limitation and mentioned the increased uncertainty of the relative effects. There are inherent differences between the populations who are eligible for each treatment, with the reduced ESS mainly driven by age. Additionally, the severity of deterioration in those receiving risdiplam at baseline was usually higher than that of patients receiving nusinersen. Therefore, such anchored comparisons should be interpreted with caution.

Overall, both companies attempted to make the analyses possible and plausible with the data available. Concerns about sample sizes and naïve analysis are warranted. However, this is mainly driven by availability of data in a rare disease.

The economic model structures used by the companies were appropriate conceptualisations of the decision problem and disease progression. However, important differences in patient characteristics and the clinical definitions of motor milestones made it difficult to compare the effectiveness of therapies across models. This limitation also affected the interpretation of results from the MAA, further reducing their applicability to the cost-effectiveness models. Beyond the limitations arising from differences in clinical outcome measures, the quality of relative effectiveness data available for ITCs further restricted the EAG's ability to assess the relative effectiveness of disease-modifying therapies in the company's base-case models. As a result, these comparisons had to be explored through scenario analyses. Patient health-related quality of life (HRQoL) was a major source of uncertainty in both submissions, largely due to the challenges of measuring HRQoL in children and the rarity and severity of the disease. The greatest uncertainty stemmed from QoL estimates associated with severe health states, such as permanent ventilation, non-sitting and sitting-related states. The EAG acknowledges that the perspective of informal carers is an important consideration in this disease area, and that NICE guidelines permit the inclusion of carer health-related quality of life (HRQoL) in appraisals. However, the two company submissions adopted markedly

different approaches to incorporating informal carer HRQoL, relying on data elicited outside the clinical trials.

Another major source of uncertainty in the cost-effectiveness analysis across both company submissions was the estimation of disease-related costs for the most severe health states, including permanent ventilation, non-sitting and sitting-related states. At these levels of severity, the cost of care can be close to the maximum willingness-to-pay threshold of the healthcare system. As a result, any treatment that increases costs, regardless of its effectiveness, risks exceeding this willingness to pay threshold. The EAG identified substantial variation in cost estimates for the model health states, driven by a lack of robust data.

Overall, in presymptomatic patients, both risdiplam and nusinersen had the potential to improve motor milestones to the least severe levels of the disease and reduce the risk of permanent ventilation. However, the evidence was insufficient to draw strong conclusions compared to BSC. For type 1 patients, both treatments appeared to reduce the risk of permanent ventilation and maintain motor function around sitting-related health states, although significant evidence gaps remained for risdiplam. In patients with type 2 and 3 SMA, there was stronger evidence that both treatments helped maintain motor milestones related to sitting when compared to BSC. These findings have important implications for the economic analysis, as the costs of care in sitting-related health states are substantial and must be weighed against gains in patient quality of life. However, this also constrains the analysis to motor milestones measured by instruments that may lack sensitivity to fully capture the disease's complexity. For this reason the context provided by qualitative data should be considered alongside the results of the modelling.

Qualitative analysis

The EAG's qualitative analysis highlighted the experiences of those living with SMA and their carers, including their experiences of treatment. The analysis covered themes related to NICE's decision problem, as well as themes that were raised as important by patient and professional organisations in discussion with the EAG and within the wider literature. These included: ability to socialise; activities of daily living; impact on ability to socialise; impact on education; impact on families and carers; independence; patient choice; psychological impact; and the "spectrum" of SMA (whereby two people with the same SMA type may have very different functional abilities and life experiences).

The qualitative analysis emphasised the great impacts of SMA on people's motor, bulbar and respiratory functions, as well as the impact SMA had on their overall quality of life. With regards to respiratory function, people also often highlighted a link between respiratory infections and hospitalisation. The analysis also emphasised that SMA impacts people's ability to do daily activities (such as eating, washing and putting on clothes), their ability to socialise with other people, and that SMA had a psychological impact on people with SMA, those who care for them and their wider personal networks. People also discussed the economic implications of SMA, including the personal financial burden of needing to buy new equipment (e.g. wheelchairs) or travelling to medical appointments.

People's experiences of nusinersen and risdiplam were also explored. Although there were occasional reports to the contrary, the qualitative analysis suggested that both treatments have a positive impact on people with SMA, particularly with regards to maintaining or improving the condition. However, it was often not clear what treatments the people in the

analyses were taking, making it challenging to find out more about what effect each of the treatments separately had on the lives of people with SMA and their carers.

Crucially, when the EAG spoke to clinicians and representatives of patient organisations, they stated that the current ways in which some outcomes are measured, such as motor function, were not currently sensitive enough to be able to capture what people with SMA and their families consider to be meaningful changes in their own abilities. Furthermore, the importance of maintaining function was emphasised as being just as meaningful and important to patients as improvements in their overall condition. Additionally, they highlighted that outcomes such as bulbar function and fatigue were particularly important functional outcomes to patients and their families and carers but that these were not well captured within the current evidence base.

It should be noted that the qualitative analysis had several limitations, including the use of framework analysis, which was appropriate for the timescale of the project but meant that a deeper exploration of the data through thematic analysis was not undertaken. Some of the data provided across the submissions often had few details about the demographics of those who contributed (e.g. SMA type) or what treatment they had been administered. This made it challenging in some cases to be able to connect peoples' experiences, particularly of treatment effects, with either nusinersen or risdiplam. Furthermore, there were caveats surrounding the registry data provided to the EAG. The data from the adult registry lacked detailed demographic information, meaning it was not possible to include details such as adults' SMA type, functional status or age at diagnosis. The registries also noted in discussion with the EAG that those providing free-text data for the paediatric registry were not always the primary caregiver for the child. As it was not possible to note when this was the case, the EAG were unable to provide this context in the report. Finally, the EAG originally aimed to weave the results of the qualitative analysis throughout the report but, due to these constraints relating to structure and the nature of the data, this was not possible.

Clinical effectiveness SLR

The total number of records included in the SLR was 147. Of these, 130 assessed nusinersen (of which 22 were new in the update), comprising three RCTs, eight controlled studies and 119 single arm studies; 13 assessed risdiplam (of which three were new), including one RCT and 12 were single arm studies); four administered both nusinersen and risdiplam (of which three were new), including one non-randomised controlled study and three single arm studies; 20 were ongoing trials. Risk of bias was assessed using the RoB v2 for RCTs and the ROBINS-I v2 for non-randomised controlled studies. Potential sources of bias were identified in all studies assessed, with no studies rated as having low risk of bias overall. For nusinersen, the three RCTs were rated as 'some concerns' overall. Nine non-randomised, controlled studies were rated as 'moderate' risk of bias and 15 were rated as 'serious' risk of bias. For risdiplam, one RCT was rated as 'some concerns' on its overall risk of bias assessment. For the comparison between nusinersen and risdiplam, one non-randomised controlled study was rated as 'serious' risk of bias overall. The quality of single-arm studies was not assessed due to the timelines and volume of included evidence, which is consistent with the approach taken in the earlier review. No evidence was identified assessing the effectiveness of nusinersen or risdiplam in patients with types 0 and 4 SMA. As highlighted by some submissions within the qualitative analysis, this may present an equality issue for these patients.

For the effects of nusinersen on motor outcomes, the evidence suggests improved or maintained motor function on average across the spectrum of SMA types included for each of the outcomes assessed, relative to a control group of before-after observations, for follow-up timepoints of up to five years. Some studies reported differences in effectiveness between population subgroups in relation to age and SMA type. Favourable results were also reported in relation to mortality, with higher survival rates amongst nusinersen-treated patients overall. The long-term safety profile of nusinersen was found to be favourable. Stability or maintenance in respiratory function was generally suggested. Mixed results were reported regarding the effects on bulbar function and quality of life of carers and SMA patients.

For risdiplam, patients continued to improve or maintain their motor function in all measures for all SMA types included. There was mixed evidence for the effects of risdiplam on bulbar function and ventilation. Evidence suggested maintenance or small increases or decreases in respiratory function, although the evidence was sparse. Due to the lack of controlled studies, the evidence on mortality was limited by the inability to compare longevity between people who were and were not treated with risdiplam but survival for type 1 patients was higher than in untreated populations. Adverse effects were generally not serious.

From the limited evidence available, nusinersen and risdiplam appeared to have comparable efficacy, although study limitations (e.g. baseline imbalances in prognostic factors) undermine the comparability of the data.

Managed Access Agreement (MAA)

The results of both the nusinersen and risdiplam MAAs separately suggested maintenance or improvement, mostly for motor outcomes, across all types assessed. From the paediatric registry, nusinersen had longer follow-up data available than risdiplam for motor outcomes (~4+ years vs ~1.5+ years, respectively). While the adult registry for risdiplam extended to ~4 years, the patient numbers were smaller at this point for risdiplam than those in the nusinersen MAA. This is to be expected given the timeline of when each drug was made available, with nusinersen being made available first. Data for patient-reported outcome measures was lacking for both treatments and suggested some varying results. However, maintenance or improvement was reported for some scales for both nusinersen and risdiplam. Similarly, for both treatments separately, data surrounding QoL were also lacking but did suggest some improvement. Importantly, mortality rates in the MAA were generally low for both treatments and deaths that did occur appeared to be unrelated to the treatments.

SLR of economic evidence

The updated SLR of economic evidence included 21 studies. All the included studies from the SLR undertook economic evaluation of SMA treatments. The studies varied based on the patient population, interventions and comparators, outcome measures, modelling methods adopted, resource use and costs, health-state utility estimates, time horizons, analyses, assumptions and limitations, and patient and professional engagements. SMA types 1, 2 and/or 3 were considered in most of the studies, with some using subgroup analysis based on age and disease characteristics.

There was a consensus in the type of model adopted for cost-effectiveness evaluation, with the studies using Markov models for estimating the SMA treatment effectiveness. There was a need for generating robust and reliable data on long-term follow-up and real-world evidence

on treatment efficacy that could enhance the accuracy of evaluation and improve the decision-making on SMA treatments. There were significant variations in sources and methods used for utility estimates among different studies, due to a lack of consensus around the best source and methods that could be used to elicit the utility estimates. The resource use quantification and subsequent cost estimation was influenced by variations in data sources, age-adjusted cost estimates, assumptions in treatment modelling, definitions of BSC or standard of care, and other complexities and heterogeneity around SMA treatment modelling assumptions, resulting in the cost-effectiveness results across the studies being unsuitable for comparison. It would be difficult to draw conclusions to inform SMA treatment modelling choices from the results of the SLR. But these studies could be used to analyse the impact of different data sources, methods and assumptions in modelling SMA treatments. The assessment of cost-effectiveness SLR results indicates a need for robust and reliable data on treatment effectiveness, real-world evidence generation of utility estimates and consensus in adopting resource use and estimating costs for SMA treatment evaluation.

Economic modelling

The EAG's cost-effectiveness analysis, using the Biogen model, indicated that [redacted] for the treatment of presymptomatic SMA population when compared with the BSC. For type 1 and type 2/3 SMA populations, [redacted] at NICE's willingness pay threshold of £30,000 per QALY. Given the limitations in the available evidence, nusinersen is also [redacted] than OA in the treatment of both presymptomatic and type 1 populations.

The EAG's cost-effectiveness analysis, using the Roche model, indicated that risdiplam [redacted] for the treatment of presymptomatic, type 1 or type 2/3 SMA populations when compared with BSC. [redacted] When effectiveness equivalence was assumed between risdiplam and OA, [redacted].

Our conclusions on cost-effectiveness of nusinersen and risdiplam are broadly consistent with those reported in the company submissions and by other international HTA bodies. However, these results are largely based on limited evidence and should be interpreted with caution. In the absence of robust comparative data, there remains insufficient evidence to reliably estimate the relative net health benefits of risdiplam, nusinersen or OA in patients with SMA. Therefore, there is a clear and continued need for further evidence to minimise the uncertainty in the cost-effectiveness analysis of these treatments for SMA.

Key issues identified by the EAG

The EAG identified several issues during the MTA report process that may introduce uncertainties into the clinical and cost-effectiveness results. These are summarised in the table below.

Issue	Summary
Comparability of the patients receiving nusinersen or risdiplam	**What is the issue:** There are notable differences in the eligibility criteria between nusinersen and risdiplam. For example, nusinersen is an intrathecal injection which requires spinal access, and spine deformities can lead to difficulties implementing the treatment. These differences in eligibility lead to some patients not being able to receive one treatment who may be eligible for another. Additionally, patients receiving risdiplam were generally more severe than those who were treated with nusinersen. **Why this is considered important:** The issues of comparability of the two treatment patient groups leads to uncertainty in the ITC analyses from the company submissions. These patient differences led to the EAG considering the two treatments separately. Therefore, both treatments are reviewed separately to each other and then some discussion about general themes between the two treatments are discussed. There is also very little clinical evidence directly comparing the two treatments. As a consequence, the economic modelling was undertaken for the two treatments separately in presymptomatic, type 1, and type 2/3 for both nusinersen (Biogen model) and risdiplam (Roche model).
Insensitivity of tools to assess motor function to capture improvements considered important by patients, families and their carers	**What is the issue:** The tools used to measure motor function generally lack the granularity to capture improvements in motor function that patients, carers, and clinicians may deem important. This issue was emphasised by both professionals and representatives of patient organisations in discussion with the EAG throughout the MTA process. There is also a focus on gross motor skills within the evidence base (e.g. crawling, sitting), whereas fine motor skills such as being able to move the hand towards an object (e.g. wheelchair control) are not captured and these are considered crucial skills to be maintained. **Why this is considered important:** The utility scores used for each model's health states may inadequately capture nuanced motor improvements from treatments that are meaningful to SMA patients, as well as their families and carers (e.g. lifting the head, being able to hold something, or even being able to sit independently for a few seconds). A utility increment of 0.1 has been assumed and incorporated into the economic model to account for these nuanced improvements from treatments not adequately being captured. However, the EAG caution that this utility increment may not correctly reflect these improvements but would give indicative results from the consideration of additional utility gains.
Lack of data for bulbar function, non-ventilatory respiratory support and scoliosis, which impacts clinical conclusions and leads to in ability to	**What is the issue:** The clinical effectiveness evidence of the treatments on outcomes such as bulbar function was lacking. Patients, carers, and professionals highlighted these as key outcomes for improving quality of life when meeting with the EAG. However, it is difficult to make meaningful conclusions due to lack of data for these outcomes.

Issue	Summary
incorporate utility and cost impacts of in the economic models	**Why this is considered important:** The EAG's base-case models did not explicitly incorporate the utility and cost impacts of bulbar function, non-ventilatory respiratory support and scoliosis separately. These impacts were assumed to be captured within the HSUVs and associated resource utilisation costs. The EAG was concerned that including these elements separately could result in double counting and therefore over-estimating their impact on cost-effectiveness. However, based on input from the clinical experts and patient organisations, the EAG recognises the particular importance of maintaining or improving bulbar function for people with SMA. In response, the EAG conducted a scenario analysis within the type 2/3 models, incorporating both utility decrement and additional healthcare costs associated with bulbar function. Due to a lack of relevant data, it was not possible to model the impact of bulbar function for presymptomatic or type 1 populations. Even within the type 2/3 model, the data used to inform the bulbar dysfunction were limited and several assumptions were required. Therefore, the results of this scenario analysis should be interpreted with caution.
Lack of data for outcomes considered most important by patients	**What is the issue:** In discussion with the EAG and from the qualitative analyses, bulbar function, and stamina and fatigue were outcomes within the NICE decision problem that were considered important by professionals, patients, and carers. Furthermore, several outcomes not included within the decision problem were also considered to be important, including activities of daily living; ability to socialise; independence; impact on carers and families; and the impact on education and work. The EAG added the outcomes considered important by stakeholders into the data extraction form for the update to the clinical SLR, as well as those included within the decision problem. However, for most of these outcomes, data were lacking for both nusinersen and risdiplam. **Why this is considered important:** Although the EAG attempted to identify evidence surrounding outcomes that patients and professionals stated are important, there is currently a lack of evidence surrounding bulbar function, and stamina and fatigue, meaning the EAG's ability to draw any conclusions surrounding these outcomes is limited. The impact of the lack of data surrounding bulbar function on the economic models has already been identified as a key issue.
No data for type 0 or 4 SMA	**What is the issue:** The EAG did not identify any evidence surrounding the effectiveness or cost-effectiveness of nusinersen or risdiplam in patients with SMA types 0 and 4. **Why this is considered important:** Patients with either type 0 or type 4 SMA are not represented within the clinical and cost-effectiveness sections of this report due to the lack of data. Representatives of patient organisations highlighted to the EAG that the lack of access to the MAA for adults with type 4 SMA is a potential equality issue.

Issue	Summary
Patient heterogeneity	**What is the issue:** Even within individual functional states (e.g. sitters), there is a large range of heterogeneity in terms of capabilities and care requirements. The qualitative analysis and discussion between professional and patient organisations with the EAG highlighted this heterogeneity within SMA, emphasising differences in the trajectory of the condition, even between individuals with the same SMA type and SMN2 copy numbers. **Why this is considered important:** The modelling the EAG were able to undertake is based on the functional states and was not able to capture the granularity of changes within those states which may be more important to individual patients than transitions between states. There is therefore uncertainty about the extent to which the maintenance or improvement of function is adequately captured.
Lack of controlled trials for presymptomatic patients	**What is the issue:** There are no controlled studies that include any therapy for presymptomatic patients. Risdiplam also lacked controlled studies for type 1 patients. **Why this is considered important:** The lack of data means that the evidence for this population is more uncertain.
Effectiveness data from single-arm trials used to inform the economic models	**What is the issue:** The effectiveness data (e.g. transitions, relative effect, decline in health states) used in the cost-effectiveness models largely come from single arm trials in the absence of RCTs. **Why this is considered important:** Whilst it may not always be feasible or ethical to conduct a RCT for treatments in rare diseases like 5q SMA, it therefore becomes necessary to use the effectiveness data coming from single arm trials. However, using evidence from single arm trials where principles of randomisation and blinding cannot be applied, may introduce bias into the results, often in favour of the treatments under evaluation. It should also be noted that the pivotal studies (ENDEAR; CHERISH) for the symptomatic SMA types (2/3) for nusinersen were sham-controlled studies.
Heterogeneity in the motor milestones used to define disease progression in the model	**What is the issue:** The motor milestone scores used in defining disease progression in terms of model health states are derived from different tools which vary in their scoring system. **Why this is considered important:** The EAG note that assuming equivalence of health states defined by tools varying in their scoring system may add further uncertainty in motor functions, patient health states, and ultimately in the cost-effectiveness outcomes due to the sensitivity in how well the tools capture the true impact of the disease as valued by patients and carers.
Lack of data to be able to incorporate carer utility increments into the base-case economic models	**What is the issue:** The impact on families and carers for those living with SMA was highlighted as being important both in discussions between the EAG and patient organisations and the qualitative analyses. However, carer utility increments have not been incorporated in the EAG base-case models due to concerns around the methodological approach, the number

Issue	Summary
	of assumptions required to incorporate carer utilities, and the robustness of the available evidence to allow this. **Why this is considered important:** Exclusion of carer utility gains/losses from the EAG base-case models may undermine the full value of treatments. However, the impact of incorporating carer utility in the cost-effectiveness results was explored in the scenario analyses to determine the potential impact on cost-effectiveness and can be incorporated into decision making.
Data surrounding discontinuation of treatment only available for nusinersen	**What is the issue:** Discontinuation from treatments were informed by the MAA data but were only incorporated into the Biogen model for nusinersen. Roche did not account for treatment discontinuation in their economic model, reasoning that discontinuation from risdiplam was unlikely in clinical practice - a justification based on the trial data, REACH data, and clinical expert feedback. **Why this is considered important:** Not incorporating treatment discontinuation in the Roche models may favour risdiplam as the EAG's discussions with clinical experts suggested that people may discontinue or switch from risdiplam due to known adverse events, such as potential effects on fertility. The EAG also notes that the discontinuation data used in the models were based on short-term MAA follow-up, which may overestimate the sustained benefits from treatment over the patient's lifetime. In addition, discontinuation from nusinersen incorporated into the Biogen (nusinersen) model assume that patients discontinuing treatments would go on to receive BSC, accruing the costs and outcomes of BSC after discontinuation. However, in clinical practice, those discontinuing may switch to alternative DMTs rather than BSC alone. Due to the lack of robust evidence, the potential impact of treatment switching could not be modelled. Therefore, the EAG caution that assumptions surrounding treatment discontinuations may introduce additional uncertainty into the cost-effectiveness results.
Uncertainty in patient utilities for severe health states	**What is the issue:** The EAG found large variation in the utility values used to calculate health-related quality of life for patients across the previous technology appraisals for nusinersen, risdiplam and OA (TA588, TA755, HST24). **Why is this considered important:** DMTs have a larger impact on patients at the more severe stages of the disease or when patients are unable to stand with or without support. Therefore, the size of the benefit in the economic assessment is directly linked with these estimates. Furthermore, as this relates to the most severe stages of the disease, with some values considered close to equivalence or worse than being in the "dead" health state, it is important that they reflect patient preferences appropriately.
Uncertainty in patient costs for severe health states	**What is the issue**: The EAG found large variation in the disease-related cost values for the more severe health states,

Issue	Summary
	particularly for patients who are unable to stand with or without support. **Why is this considered important**: The level of health care costs becomes considerably higher at the highest levels of severity of the disease or the lower levels of motor function (not yet standing with or without support). These estimates were crucial in defining whether the introduction of a new DMT into the disease pathway was cost-effective, yet evidence in this area was scarce.
Abbreviations: BSC = best supportive care; DMTs = disease modifying therapy; EAG = Evidence Assessment Group; HSUV = health state utility value; MAA = Managed Access Agreement; MAIC = matching-adjusted indirect comparison; OA = onasemnogene abeparvovec; RCT = randomised controlled trial; SLR = systematic literature review; SMA = spinal muscular atrophy; SMN2 = survival motor neuron 2.	

Conclusions and recommendations for further research

For both nusinersen and risdiplam, there was evidence of maintenance or improvement in motor functions. Maintenance was considered an important outcome by professionals and patient organisations. Data on other outcomes, such as quality of life, showed mixed results for both treatments. The cost-effectiveness studies included in the updated SLR were heterogenous. The SLRs indicate a need for robust and reliable data on treatment effectiveness, real-world evidence generation of utility estimates and consensus in adopting resource use and estimating costs for SMA treatment evaluation. The findings of the EAG's cost-effectiveness analysis were comparable to those reported in the original technology appraisals of nusinersen (TA588) and risdiplam (TA755).

The previous technology assessments highlighted a lack of longitudinal and comparative data for both nusinersen and risdiplam. This has been partially addressed by longer follow-up periods of the clinical trials (~8 years for nusinersen and 5 years for risdiplam), and use of an MAA for some outcomes, mainly motor function. However, the lack of a comparative clinical trial comparing type 1 patients receiving risdiplam to treatment-naïve patients, noted in the original technology assessment for risdiplam has not been addressed. Direct comparative evidence between the two treatments and OA is also lacking. However, differences in populations eligible for the treatments make direct comparisons challenging. Furthermore, the qualitative analysis highlighted that treatments may have an impact on fine motor skills that are not well captured by the current tools used to measure motor function across SMA types.

The cost-effectiveness results are based on limited evidence and should be interpreted as such. In the absence of comparative data, the EAG concludes that there is insufficient evidence to estimate the relative net health benefits of risdiplam or nusinersen in patients with SMA. Therefore, there is a clear and continued need for further evidence to minimise the uncertainty in the cost-effectiveness analysis of these treatments for SMA. Future research should also aim to collect data highlighted as important by patient groups (e.g. activities of daily living, stamina and fatigue).

3 Plain English Summary

Background

Spinal muscular atrophy (SMA) is a rare genetic condition that causes muscle weakness and wasting away over time. There are five types of SMA: Type 0, where the condition begins before birth; type 1, which starts in babies less than six months old; type 2, which starts in babies and toddlers aged 6 to 17 months; type 3, which starts in children and teenagers from 18 months to 17 years old; and type 4, which starts in adulthood. SMA can affect people very differently but common symptoms people with SMA may experience include muscle weakness, movement problems and problems with breathing and swallowing. Without treatment children with type 1 SMA are likely to die in infancy. SMA has a considerable effect on the quality of life of people with the condition, caregivers and their families. People with SMA often require continual support from others, which can involve full-time care and attention. This kind of support is physically demanding but can also greatly impact on the mental health and wellbeing of people with SMA, their families and carers.

Currently, there is only one treatment for SMA recommended for use within the National Health Service (NHS), a gene therapy called onasemnogene abeparvovec (OA). OA is available for treating 5q SMA with a biallelic mutation in the SMN1 gene, either a) for presymptomatic babies aged 12 months and under with up to three copies of the SMN2 gene, or b) for type 1 babies who are not permanently ventilated or need tracheostomy and who are aged six months and under, or 7 to 12 months with agreement of the national multidisciplinary team. However, there are two other treatments, nusinersen and risdiplam, that are available to people with SMA under strict criteria as part of a Managed Access Agreement (MAA). Nusinersen is delivered by a spinal injection (a lumbar puncture) every four months. Risdiplam is a medication that is taken orally every day. Both nusinersen and risdiplam have each been previously assessed separately in a process known as a Single Technology Appraisal (STA). Both these STAs found uncertainties about the data available at the time they were produced.

The Evidence Assessment Group (EAG) at Newcastle University were asked by NICE to consider the evidence for nusinersen and risdiplam in an assessment called a Multiple Technology Appraisal (MTA). The EAG does not decide whether nusinersen and risdiplam will be recommended; NICE will decide if these treatments are recommended for wider use within the NHS. The aim of the EAG's report is to help the NICE Committee in their decision-making process on whether these treatments should be approved for use within the NHS.

How the EAG assessed the technologies

The EAG had three discussions each with clinicians and representatives of patient groups to shape the methods and talk about some of the results. The EAG also consulted with other clinical advisors in online meetings and had meetings with the two companies who make the treatments throughout the process of developing the report.

The EAG did not compare nusinersen and risdiplam directly within the report. This is because the EAG believed that the people in the trials who receive nusinersen and risdiplam are too different to be able to compare how well each of the treatments works.

The EAG were provided with reports about nusinersen and risdiplam from the companies who make the treatments. These reports contained information about how well both nusinersen and risdiplam might work for treating SMA, as well as if they may be considered good value

for money for the NHS. The EAG read the submissions from both companies to see how robust the evidence they provided was before highlighting any uncertainties in this MTA report.

The EAG included qualitative information about peoples' experiences of SMA and treatments for SMA, as well as the perspectives of professional and patient organisations. The outcome measures considered important by representatives of professional and patient organisations, as well as those requested by NICE in their overall scope for the work, became the themes for the qualitative analysis. The findings from the qualitative analysis were included in this MTA report to help contextualise the findings with lived experiences of SMA and having treatment.

The EAG also brought all the relevant clinical evidence about nusinersen and risdiplam together in a process called an evidence synthesis to find out more about how well the treatments work for different SMA types. This was done by building on work a previous report from another EAG and adding in new information. The EAG also received data from the MAA about both nusinersen and risdiplam. These data were also analysed by the EAG to find out more about how well both nusinersen and risdiplam work in real life.

The EAG studied all the relevant evidence related to cost-effectiveness analyses in studies about SMA treatments. New evidence was added to the initial evidence from the previous report. The information from this evidence was collected and studied to understand more about the health benefits, costs, and other factors which were considered in the economic modelling of treatments for SMA.

Finally, the EAG adapted existing separate economic models to find out how cost-effective nusinersen and risdiplam are. The two main economic models assessed how cost-effective nusinersen and risdiplam each were when compared with best supportive care (BSC). The EAG also created exploratory economic models to assess the cost-effectiveness of the following comparisons: nusinersen compared with risdiplam; nusinersen compared with OA; and risdiplam compared with OA. A separate economic model was created for each type of SMA, as long as there were enough data available for individual SMA types.

Main results of the MTA

The EAG's qualitative analysis highlighted the experiences of those living with SMA and their carers, including their experiences of treatment. The analysis further emphasised the major impacts of SMA on people's ability to move, swallow, and breathe, and on their overall quality of life. They also stated that SMA impacted their ability to do daily activities (such as eating, washing and putting on clothes), their ability to socialise with other people, and that SMA had a psychological impact on people with SMA, those who care for them and their wider personal networks. Their experiences of having nusinersen and risdiplam were also explored, but it was often not clear what treatments the people in the analyses were taking, making it challenging to find out more about what effect each of the treatments had on the lives of people with SMA and their carers.

Additionally, when the EAG spoke to clinicians, including specialist physiotherapists, and representatives of patient organisations, they said that the current ways in which some outcomes are measured, such as someone's ability to move, were not sensitive enough to be able to capture what people with SMA and their families consider to be meaningful changes in their own abilities and lives. They also said that there were outcome measures important to

patients and their families, such as bulbar function (which affects someone's ability to swallow and breathe) and fatigue, that are not well reported in the evidence we currently have.

When looking at the clinical evidence that both companies submitted to NICE, the EAG found that there were concerns around how many people were included in the statistical analyses but that both companies tried to make the analyses possible with the data they had available. When looking at the evidence on nusinersen and risdiplam separately in their evidence synthesis, the EAG added new information to what had already been done previously as well as adding information from sources such as conference abstracts. There was more data about nusinersen than risdiplam, but this is expected because nusinersen has been available for a longer time. The EAG found that, generally, nusinersen and risdiplam both either maintained or improved motor functions for people with SMA types 1, 2 and 3. There were more mixed results from the data about how much nusinersen and risdiplam impact on bulbar function and people's quality of life. More people who received nusinersen survived for longer, but there was less information about survival for people taking risdiplam, though there was longer-term data available for nusinersen. However, for both treatments survival was substantially higher for people taking them than is the case for untreated type 1 patients. When side-effects were reported for either drug, they were generally not serious. The EAG did not find any evidence about people with type 0 or type 4 SMA, which people in the qualitative analysis suggested may lead to an equality issue.

The EAG also looked at data that has been collected for various outcomes during the MAA period for both nusinersen and risdiplam. The results from the MAA suggest that both nusinersen and risdiplam separately could maintain or improve motor function across all SMA types. There was generally more data for nusinersen compared to risdiplam. This is because the MAA for risdiplam started after the one for nusinersen. For outcomes that were reported by patients, which generally assessed quality of life, there was a lack of data for both nusinersen and risdiplam. What data was available suggested that people maintained or improved their score for some measurements but for others there were mixed results. Importantly, the number of people who died was small and these deaths were not linked to either of the treatments.

When the EAG looked at published evidence about the economic impacts of the treatments, it was found that there was a lack of real-world evidence and the studies were all very varied in how they analysed the data. This meant that a lot of assumptions were made around the costs, survival rates, disease progression, and treatment effects.

Finally, the EAG looked at how cost-effective nusinersen and risdiplam are for treating people with presymptomatic, type 1, and type 2/3 SMA. By "cost-effective", we mean that the price per quality-adjusted life year (a measure of the burden of a condition that includes both the quality and the quantity of life lived) is below the threshold NICE would be willing to pay. The results from the analysis indicated that nusinersen [redacted]

For risdiplam, the results from the EAG's analysis indicated that it was [redacted]

What the EAG's results mean

What the EAG found in their report is aligned with what has been reported by the companies who make the treatments, and by other international health agencies. However, because there is limited evidence about nusinersen and risdiplam, the results should be viewed cautiously. Without strong data, it is difficult to confidently say which treatments provide the most benefit. Therefore, more research about nusinersen and risdiplam is needed. This should include research surrounding outcome measures that patient groups and professionals highlighted as being important to the community, such as bulbar function, stamina and fatigue, activities of daily living, the impact on carers and families, and independence.

Abbreviations

6MWT	6 minute walk test
ADL	Activities of Daily Living
AE	Adverse events
AIC	Akaike's Information Criterion
ATEND	Adapted Test of Neuromuscular Disorders
BiPAP	Bilevel positive airway pressure
BSID-III	Bayley Scales of Infant and Toddler Development, Third Edition
BI	Budget impact
BIC	Bayesian information criterion
BSC	Best supportive care
CE	Cost-effectiveness
CEA	Cost-effectiveness analysis
CEAC	Cost-effectiveness acceptability curve
CEM	Cost-effectiveness model
CGIC	Clinical global impression of change
CGI-S	Clinical global impressions - severity
CHMP	Committee for Medicinal Products for Human Use
CHOP-INTEND	Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders
CI	Confidence interval
CrI	Credible interval
CLIP-Q	Conducting collaborative and intensive pragmatic qualitative research
CPAP	Continuous positive airway pressure
CS	Company's submission
CSR	Clinical study report
DMD	Duchenne muscular dystrophy
DMT	Disease-modifying therapy
DSU	Decision Support Unit
EAG	Evidence Assessment Group
EAP	Expanded Access Programme
EK2	Egen Klassifikation 2
ESS	Effective sample size
FAD	Final appraisal document
FDA	Food and Drug Administration
FEV1	Forced expiratory volume in 1 second
FVC	Forced vital capacity
HFMSE	Hammersmith Functional Motor Scale (expanded)
HINE-2	Hammersmith Infant Neurological Examination - Part 2
HR	Hazard ratio
HRQoL	Health-related quality of life
HSUV	Health state utility value
HST	Highly Specialised Technology
HTA	Health technology assessment
IC	Indirect comparison
ICER	Incremental cost-effectiveness ratio
IPD	Individual patient data
ITC	Indirect treatment comparison
ITT	Intention-to-treat
LY	Life year
MAIC	Matching-adjusted indirect comparison
MeSH	Medical subject headings
MFM32	Motor Function Measure
MEP	Maximal expiratory pressure

MIP	Maximal inspiratory pressure
MMRM	Mixed model repeated measures
MTA	Multiple Technology Appraisal
MTC	Mixed treatment comparison
NA	Not applicable
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
NIHR	National Institute for Health Research
NIV	Non-invasive ventilation
NMA	Network meta-analysis
NR	Not reported
OA	Onasemnogene abeparvovec
OS	Overall survival
PAS	Patient access scheme
PCF	Peak cough flow
PFS	Progression-free survival
PFVC	Predicted forced vital capacity
PGI-I	Patient global impression of improvement score
PGI-S	Patient global impression of severity score
PROMIS	Patient-reported outcomes measurement information system
PROMS	Patient-reported outcome measures
PSA	Probabilistic sensitivity analysis
PSS	Personal Social Services
PSSRU	Personal Social Services Research Unit
QALY	Quality adjusted life year
QoL	Quality of life
RCT	Randomised controlled trial
RHS	Revised Hammersmith Scale
RR	Risk ratio
RP	Respiratory plethysmography
RULM	Revised Upper Limb Module
SAE	Serious adverse events
SD	Standard deviation
SE	Standard error
SLR	Systematic literature review
SMN	Survival of motor neuron protein
SNIP	Sniff nasal inspiratory pressure
SoC	Standard of care
SMA	Spinal muscular atrophy
SMAIS-ULM	SMA Independence Scale – Upper Limb Module
STA	Single Technology Appraisal
STC	Simulated treatment comparison
TA	Technology Assessment
TEAE	Treatment emergent adverse events
TTO	Time trade-off
TSD	Technical support document
TTOT	Time-to-off treatment
UK	United Kingdom
USA	United States of America
WHO	World Health Organization
WTP	Willingness-to-pay

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4 Background

4.1 Introduction

This report describes the latest stage in the Multiple Technology Assessment (MTA) investigating the clinical and cost effectiveness of nusinersen and risdiplam for Spinal Muscular Atrophy (SMA). Nusinersen and risdiplam were reviewed separately in TA588 and TA755 respectively in 2019 and 2021, and both were recommended under a managed access agreement (MAA) with the instruction to collect further longer term data.[2,3] Following the MAA periods, an MTA was initiated in 2023 which comprised critical appraisal of the companies' submitted evidence, systematic reviews of the clinical and cost effectiveness evidence, and an independent economic evaluation.[1] This report by the Newcastle External Assessment Group (EAG) describes an update to the systematic literature reviews of clinical and cost effectiveness, further critique of the company submissions, and a separate independent economic evaluation. It also includes analysis of the data (both quantitative and qualitative) from the MAA and a qualitative analysis of data submitted from patient groups which provide important context to the data from other sources.

4.2 Description of SMA

SMA is a rare, progressive neuromuscular disease most commonly caused by a genetic mutation in the survival motor neuron (SMN1) gene situated on chromosome 5q. Healthy people have both the SMN1 gene, which produces the functional full-length SMN protein, and the SMN2 gene, which produces mostly degraded and only a small amount of functional SMN protein. People with SMA have a faulty SMN1 gene and a varying number of SMN2 gene copies so their ability to produce SMN protein is reduced. This causes the gradual breakdown of motor neurons in the spinal cord and brainstem, leading to progressive muscle weakness, atrophy and eventually paralysis in late-stage disease. It affects muscles that involve crawling, walking, arm movement, head and neck movement, swallowing and breathing.[4;5;6]

SMA is diagnosed through genetic testing and clinical examinations. It has historically been categorised into types 0, 1, 2, 3, and 4 according to age of onset (see Table 4.1), and the onset of neuromuscular weakness can range from birth to adulthood. Presymptomatic SMA is defined as SMA detected through genetic testing before the appearance of clinical symptoms. Although this classification system does not always accurately capture the patient experience and is being impacted by the change in prognosis resulting from the availability of treatments, it has been used in the marketing authorisation and some of the clinical evidence and continues to be used in this report.

Table 4.1: SMA types (taken from Mercuri's SMA primer)[4]

SMA type	Typical age at presentation (range)	Maximal motor function achieved with supportive care	Feeding and communication	Pulmonary function	Survival[a] with supportive care
0	Foetal	Nil	Nil	Very poor	Days–weeks
1	3 months (0–6 months)	No sitting or rolling	Poor, requires support	Poor, requires support	Months (median ~10 months)
2	12 months (7–18 months)	Sits, no walking	Variably affected	Reduced, often needs support	Years (median >20 years)
3	3 years (1.5–10 years)	Walks (limited)	Normal	No symptoms, mild reduction possible	Normal
4	>18 years	Walks (normal)	Normal	Normal	Normal

[a]Survival is according to natural history and includes 'event-free survival' (ventilation support for <16 h/day for ≥14 days)
Abbreviations: SMA = spinal muscular atrophy

Note that the difference between types 0 to 4 are considered by some to be somewhat arbitrary, and the age cut-offs not exact. An alternative picture can be found in Schorling 2020 figure 1[7]

Type 1 SMA is the most common type of diagnosed disease, occurring in 60% of cases. It is often referred to as early-onset or infantile-onset SMA as it manifests during the first six months of life. It involves rapid degeneration of motor neurons and subsequent reduction in motor function within months. Early treatment leads to better prognosis, but treatment initiation can lead to significantly improved motor function up to and beyond one year of age.

Types 2 and 3 SMA are often referred to as later-onset SMA, as they manifest between six and 18 months, and above 18 months to 18 years respectively. Progression does not tend to be linear and different children will improve, stabilise and deteriorate at different times, so it is difficult to predict the response to treatment. It should be noted that there can be overlap in functional status between type 1 patients and type 2/3 patients in terms of whether they are able to sit supported or stand.

Type 4 SMA presents in adulthood (adult-onset) and although it is milder than other types and does not affect lifespan, it leads to muscle weakness.

Type 0 SMA, also known as congenital SMA, is already evident in utero and babies tend to be born with severe weakness and respiratory distress, with a lifespan of days or weeks.[8]

Presymptomatic SMA is defined as genetically confirmed 5q SMA but lacking any clinical signs or symptoms. It can be identified by newborn screening and is usually identified in the UK through genetic testing prompted by a family member with the disease. Trials have

demonstrated that a significant proportion of treated presymptomatic patients achieve motor milestones at a similar time to their healthy peers.[5]

One of the prognostic factors for SMA is the number of copies of a gene called SMN2. SMN2 can partially compensate for deficiencies in SMN1; on average a lower number of copies of SMN2 correlates with poorer prognosis although this is not the case for all individuals. Most patients with type 1 SMA have two SMN2 copies, most with type 2 have three SMN2 copies and patients with type 3 tend to have either three or four SMN2 copies.[4]

Other prognostic factors include the amount of time that passes and the severity of functional impairment before treatment initiation; more time and more severe impairment tends to lead to a poorer prognosis and poorer response to treatment. The EAG learned from a clinical expert that the amount of physiotherapist input can influence the development of contractures which restricts function. Differences in physiotherapist input can arise from the level of core health services in different geographical areas, the availability of regular physiotherapy during the school day, and the amount by which families have the resources to top this up.

SMA has a substantial effect on the quality of life of patients, caregivers and their families.[9,10] People with SMA experience considerable impairment in mobility, dexterity, pain and emotional wellbeing.[9] They often experience challenges with independence, which can lead to feelings of isolation and hinder initiation or maintenance of close relationships and opportunities to socialise.[10] Limitations in mobility influence accessibility to school, work and social activities.[11] Fatigue affects people of all ages and types of SMA, affecting the ability to perform daily activities and participate in daily life.[11,12] Individuals with SMA often require continuous support, which may involve full-time care and attention. This support demands significant physical effort, such as lifting and carrying, and can lead to sleep deprivation for both patients and caregivers. Additionally, it can cause stress and anxiety related to the potential loss of abilities in the future. The impact on mental health including anxiety, depression and social isolation can be severe for both adolescents and adults with SMA and their carers.[11,12] Complications of SMA such as scoliosis (curvature of the spine) can add to a person's difficulties with movement and cause pain due to the compression of internal organs.

4.3 Care pathway and guidelines

SMA is managed through multidisciplinary support care, which aims to minimise the impact of disability by addressing complications and improving quality of life. The care pathway has been developed for both paediatrics[13] and adult[14] patients. The guidance was informed by the international standard of care.[15,16] The treatment expectations are noted to be subjective and based on the individual patient needs. It is imperative to make sure the right treatment is provided to individuals; therefore the following must be considered: treatment access, access to supportive care, education level, geography, social isolation, information, peer-to-peer exchange and access to technology.[13,14]

In paediatrics, babies showing the following signs may be suspected of SMA.[13]

- Floppiness
- Reduced movements in early weeks
- Recurrent chest infections
- Difficulty feeding
- Failure to gain weight

- Motor delay or loss/regression of skills
- Acute respiratory distress
- Acute respiratory distress requiring respiratory support

The child may be forwarded to a neuromuscular service within 1-14 days, depending on severity. Diagnosis is completed via an SMN1 genetic test (using a method called multiplex ligation-dependent probe amplification). If confirmed, a multidisciplinary team should be deployed to meet the child's needs. This usually entails a co-ordinator who is responsible for all aspects of care, including:[15]

- Pulmonary care
- Acute care
- Other organ involvement
- Medication
- Nutritional, gastrointestinal and bone health
- Orthopaedic care
- Neuromuscular/rehabilitation

The condition should be continually managed using such specialist management, as above, and assess eligibility for treatment. Both nusinersen and risdiplam are currently provided by the MAA; onasemnogene abeparvovec (OA) is a gene therapy, see Table 4.2 for eligibility criteria of treatments. Treatment is agreed by the national multidisciplinary team.[17] If treatment is not indicated, palliative care is undertaken.

Those with an established diagnosis will transition from paediatric care to adult care. Such transitions for those with chronic disabilities, such as SMA, is often difficult. Where adults are suspected as having SMA a referral can be made for diagnosis at this stage.[14] Assessments for treatment and/or ongoing management occur within 18 weeks. Specialist management is carried out with a similar approach as for paediatrics, i.e. a multidisciplinary team. Currently, the MAA is the only way for treatments be accessed, if eligible, for the adult patients. Regular assessments should be made and reviewed. Non-sitters, sitters, and walkers likely have different orthopaedic and spine, motor, and nutrition, gastrointestinal and bone health requirements. For example, for non-sitters and sitters the orthopaedic and spine care should look to reduce impact on tight joints, prevent scoliosis, provide customised upright seating/standing frames, among other things. For patients who are ambulant, function and mobility, exercise (e.g. swimming), and stretching (for contractures) should be promoted, among other things.[14]

Table 4.2: Eligibility criteria for each available treatment: nusinersen, risdiplam and onasemnogene abeparvovec

Nusinersen eligibility criteria (MAA)[18,19]	Risdiplam eligibility criteria (MAA)[20]	Onasemnogene abeparvovec eligibility criteria[17]
People with early- (type 1) or later-onset (types 2 and 3) SMA People with presymptomatic SMA with homozygous gene deletion or homozygous mutation or compound heterozygous mutation of the SMN1 gene (chromosome 5) found via presymptomatic genetic testing No type 0 or type 4	Clinically confirmed type 1, 2 or 3 or with presymptomatic SMA and one to four SMN2 copies	Only if presymptomatic 5q SMA with a biallelic mutation in the SMN1 gene and up to 3 copies of the SMN2 gene in babies aged 12 months and under Patients with type 1 SMA, if: • they are 6 months or younger, or • they are aged 7 to 12 months, and their treatment is agreed by the national multidisciplinary team
No permanent ventilation (≥16 hours/day for 21 consecutive days in the absence of acute reversible infection) or tracheostomy requirement at baseline	No permanent ventilation (≥16 hours/day for 21 consecutive days in the absence of acute reversible infection)/ tracheostomy requirement at baseline. Patients who do not meet this criterion but otherwise meet the eligibility criteria should be discussed with the NHS England Clinical Panel	
Nusinersen is used as a monotherapy	Risdiplam is used as a monotherapy	
Must not have had successful treatment with onasemnogene abeparvovec	Must not have had successful treatment with onasemnogene abeparvovec[a]	
Intrathecal injection must be technically feasible in the opinion of the treating clinician and not contraindicated	Mandated data items have been collected prior to starting treatment within this MAA. Patients who have started treatment for SMA prior to this MAA are not required to	

	repeat an assessment if a previous assessment has captured all mandated data items within the last 6 months[b]	
Must not have received spinal fusion surgery following a diagnosis of scoliosis which, in the opinion of the treating clinician, prohibits safe administration	Patient/carer has signed the 'Managed Access Patient Agreement' and agreed to the associated monitoring, clinical assessments and sharing of data for the purpose of the MAA	
Must not have severe contractures that, in the opinion of the treating clinician, prohibit measurement of motor milestones	Clinician confirms they will submit data to SMA reach; have made patient/carer aware that there are other treatments for SMA, which may be more suitable for that patient; and confirm annually, via Blueteq form, that the patient continues to receive benefit from treatment	
Patient scope: Clinical diagnosis of SMA type 1, 2, or 3; presymptomatic SMA confirmed to have SMA via genetic testing and has one to four SMN2 copies [a] Non-successful treatment with OA defined as a reduction in motor ability: total worsening of scale score corroborated by two consecutive measurements from any two scales (>2 points on horizontal kick or 1 point on other HINE scores [excluding voluntary grasp], >4 points on CHOP-INTEND, or >3 point on RHS); AND/OR a deterioration in respiratory function: an increasing requirement for respiratory support overnight and/or, for that patient, an uncharacteristic increase in respiratory infections requiring hospital treatment that cannot be accounted for by aspiration or intrinsic lung disease [b] Mandatory data items listed in Table 2 (section 7) of risdiplam MAA[20]		

4.4 Measurement of disease outcomes

Various challenges exist in measuring response to treatment in people with SMA. Because the disease affects people from newborns into adulthood, different scales are used to measure motor function accounting for comparative 'normal' development history. When different scales are used in trials it makes it difficult to be sure that the results are comparable and measuring the same thing. The EAG was informed by a clinical expert that when children get to the point that they need to switch scales, it can be concerning for patients and carers that they see a change from a high score on the previously used scale to a low score on the new scale, so they use both initially for reassurance. SMA also affects people with very different levels of severity ranging from permanent ventilation, a feeding tube and very little voluntary movement, through to a relatively small amount of muscle weakness. Access to 'best supportive care' is variable and inequitable in the UK. Patients and carers have reported that commonly used outcome measures do not successfully reflect their lived experience, and can have a negative impact if they receive a low score despite feeling improvement and satisfaction in their lives.[12] It can also be the case that a 'small' change in terms of outcome measure can reflect a huge impact in terms of daily life for both patient and carer, such as the ability to operate one's own wheelchair. Because fatigue is such a common symptom of SMA, the time of day at which measurements are made can influence the scores – the same person may score lower later in the day when they are feeling more fatigued. All of this makes defining a clinically significant response to treatment challenging.

4.4.1 Motor function

Because SMA has such a variety of severity and can begin from very early life through to adulthood, different outcome measures are used to measure motor function as appropriate to age and severity (see Table 4.3). It should be noted that, particularly for children, outcome scores can vary for reasons other than motor function decline; for example if there is spinal fusion or spinal surgery their scores will dip before returning, and if they experience a growth spurt their motor function may appear to decline as their muscles are dealing with more weight. It is important to capture both age-appropriate gross motor milestones and fine motor skills. This can all make it difficult to compare across studies. Patients have reported that motor outcome measures do not always capture important improvements – for example, even very small improvements in fine motor skills and upper limb function were identified as very important because they allow patients to maintain independence.[3]

Table 4.3: Outcome measures for motor function

Outcome measure	Outcome measure name in full (where appropriate)	Description
WHO Motor Development Milestones		Tracks gross motor development milestones in infants and young children.
CHOP INTEND	Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders	Assesses motor skills (such as spontaneous movement of upper and lower extremity, hand grasping, rolling, and head control) in infants with SMA. Change of ≥ 4 in CHOP-INTEND represents an estimate of a meaningful improvement in motor function. CHOP-INTEND was described to the EAG by a clinical expert as the most useful outcome measure for infants.
HINE-2	Hammersmith Infant Neurological Examination - Part 2	Evaluates motor milestones (head control, sitting, voluntary grasp, ability to kick, rolling, crawling, standing, and walking) in infants and young children with SMA. Achievement of important motor milestones and higher scores on the HINE-2 scale (≥ 2-point increase in the ability to kick [or maximal score] or a 1-point increase in head control, rolling, sitting, crawling, standing, or walking) are therefore considered to be a clinically relevant improvement for an infant with type 1 SMA.
BSID-III	Bayley Scales of Infant and Toddler Development, Third Edition	Assesses developmental functioning in infants and toddlers, including motor skills such as head control, sitting, crawling, kicking. The ability to achieve a sitting position unsupported at 12 months, as measured by the BSID-III, is considered a clinically meaningful and important milestone in type 1 SMA.
RHS	Revised Hammersmith Scale	Evaluate a broad spectrum of motor functions in SMA (including 10m run test, 6m walk test, rise from floor for ambulant type 2/3 SMA patients).
HFMS/E	Hammersmith Functional Motor Scale (expanded)	Assesses motor function (sitting, rolling, transitions relating to crawling and kneeling, and standing/stepping, but no items to assess the fine motor function of the hand, wrist, or elbow) in non-ambulant individuals with type 2 or 3 SMA. A change of ≥ 0 in HFMSE total score representing stabilisation or improvement of motor function is clinically meaningful and a change of ≥3 in

Outcome measure	Outcome measure name in full (where appropriate)	Description
		HFMSE represents an estimate of a meaningful improvement in motor function.
RULM	Revised Upper Limb Module	Assessment of upper limb motor performance, including shoulder, elbow, wrist and hand function, in people with SMA. A change of ≥0 in RULM total score representing stabilisation or improvement of motor function is clinically meaningful, and a change of ≥ 2 represents an estimate of a meaningful improvement in motor function.
MFM32	Motor Function Measure	Assesses motor function abilities in individuals with neuromuscular diseases, including SMA. It assesses three domains of motor function: D1 (standing and transfers), D2 (axial and proximal motor function), and D3 (distal motor function).
ATEND	Adapted Test of Neuromuscular Disorders	Clinical rated outcome in development for children and adults with SMA who are no longer able to sit or who have never been able to sit. A change of ≥ 0 in MFM32 total score representing stabilisation or improvement of motor is clinically meaningful in this patient population, and threshold of improvement on the MFM32 scale, such as ≥3 points, should be considered as a marked improvement for patients as it may represent either the acquisition of a new function or the improvement in performance of several functions.
CMAP	Compound Muscle Action Potential amplitude	Measures the electrical response of muscles to nerve stimulation, indicating motor neuron health.
MUNIX	Motor unit index	A biomarker used to assess loss of motor units in later-onset SMA patients.
ALSFRS-R	Revised Amyotrophic Lateral Sclerosis Functional Rating Scale	Considers bulbar, fine and gross motor (upper and lower limbs), and respiratory outcomes original used for those with amyotrophic lateral sclerosis but is used in SMA assessment (validation is lacking).

Outcome measure	Outcome measure name in full (where appropriate)	Description
MRC-SS	Medical Research Council Sum Score	Assessment of muscular strength.
MMT	Motor Muscle Testing	Assessment of muscular strength.
MUNE	Motor Unit Number Estimation	An electrophysiological method of estimating the number of motor neurons innervating a muscle group.
GFFS	Grip and Finger Flexion Strength	Measurement of grip strength.
6MWT	6-Minute Walk Test	Sub-maximal functional exercise test to assess aerobic capacity and endurance, maximum distance covered in 6 minutes.
TUG	Timed Up and Go	Timed test where patients are required to stand up from a chair, walk to a line at normal pace (3 metres away), walk back to the chair and sit down again.

4.4.2 Bulbar function

Bulbar function impacts a person's ability to swallow and communicate verbally. This can be measured by nutritional support (including nasogastric feeding and gastrostomy), swallowing function, and speech therapy support.

4.4.3 Frequency and duration of hospitalisation

The most frequent reason for hospitalisation is respiratory events. Hospitalisations are measured in terms of admission rates, number of admissions, proportion of time hospitalised, patient years, or days in hospital. Sometimes they are reported as AEs.

4.4.4 Respiratory function

Because SMA influences the respiratory muscles, it is important to measure respiratory function. Several outcome measures are used (Table 4.4).

Table 4.4: Outcome measures for respiratory function

Outcome measure	Outcome measure name in full (where appropriate)	Description
FEV1	Forced expiratory volume in one second	Measures the amount of air a person can forcibly exhale from the lungs in the first second of a forced breath.
FVC	Forced vital capacity	Measures the total amount of air a person can forcibly exhale from the lungs.
MEP	Maximal expiratory pressure	Assesses the strength of expiratory muscles.
MIP	Maximal inspiratory pressure	Assesses the strength of inspiratory muscles.
NIV	Non-invasive ventilation usage	Tracks the use of ventilatory support in individuals with SMA.
PCF	Peak cough flow	Assesses the strength of cough, indicating respiratory muscle function.
PEFR	Peak expiratory flow rate	Measures how fast a person can exhale air from their lungs.
PFVC	Predicted forced vital capacity	Estimates the expected FVC based on demographic factors.
RP	Respiratory plethysmography	Measures thoraco-abdominal movements to assess respiratory patterns.
SNIP	Sniff nasal inspiratory pressure	Measures inspiratory muscle strength via nasal pressure.

Tracheostomy		A surgical procedure to create an opening in the neck to place a tube into a person's windpipe, aiding in breathing.
VC	Vital capacity	Maximum amount of air a person can exhale after taking the deepest breath possible.

4.4.5 Complications

The most common complications of SMA are scoliosis or curvature of the spine, and muscle contractures which reduce the person's range of motion, both of which cause pain. Other complications include the need for support with feeding and the risk of aspiration pneumonia.

4.4.6 Non-invasive or invasive ventilation

People with type 1 SMA may require non-invasive ventilation or cough-assist as much as daily. Non-invasive ventilation methods include Bilevel Positive Airway Pressure (BiPAP) or Continuous Positive Airway Pressure (CPAP), whilst invasive ventilation uses an endotracheal tube (through the mouth) or tracheostomy (inserted through the neck). Permanent ventilation is defined as tracheostomy or ≥ 16 hours ventilation per day continuously for at least 21 consecutive days. The EAG learned from a clinical expert that although it is unusual for a person not to remain on permanent ventilation once they get there, it does not necessarily preclude a participative and relatively good quality of life.

4.4.7 Stamina and fatigue

SMA very commonly affects stamina and fatigue levels, which have an important impact on day-to-day life.

4.4.8 Mortality

According to natural history studies, the mean age at death of patients with type 1 SMA is 19.2 months (SD 10.1 months).[21] Patients with type 2 SMA would be expected to survive into adulthood and those with type 3 tend to have a normal lifespan. Therefore, the impact on mortality for type 1 patients is key.

4.4.9 Adverse effects of treatment

The most common adverse effects associated with nusinersen are headache, back pain and vomiting, which are usually associated with administration via lumbar puncture rather than the drug itself. Other potential adverse effects of nusinersen include renal toxicity, thrombocytopenia and coagulation abnormalities, and hydrocephalus.

The most common adverse effects associated with risdiplam are fever, rash, diarrhoea, and headache.

4.4.10 Health-related quality of life and PROMs

Table 4.5: Outcome measures for health-related quality of life

Outcome measure	Outcome measure name in full (where appropriate)	Description
ACEND	Assessment of Caregiver Experience with Neuromuscular Disease	Quantifies caregiver impact experienced by parents of children affected with severe neuromuscular diseases, including children with SMA
Caregiver Burden Scale		Assesses the impact of caregiving on the caregiver's quality of life.
EQ-5D-5L	EQ-5D-5L (5 level version)	Self-report survey that measures quality of life across 5 domains: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression
EQ-5D-Y	EQ-5D-Y (youth version)	Child-friendly version of EQ-5D-5L allowing patient reporting by young people from eight years of age
INQoL	Individualised Neuromuscular Quality of Life Questionnaire	Individualised neuromuscular quality of life tool; a patient-reported tool specific to patients with neuromuscular diseases
ITQoL-SF47	Infant Toddler Quality of Life Questionnaire 47-ithem Short-Form	Infant toddler quality of life questionnaire; for children between two months and five years of age.
PedsQL	Pediatric Quality of Life Inventory	Paediatric quality of life inventory; a brief measure of patient reported health-related quality of life in children and young people
QoL-NMD	Quality of Life in Neuromuscular Disease Questionnaire	Quality of life in neuromuscular disease; a patient reported outcome measure designed for patients with a slowly progressive neuromuscular disease with motor deficiency
SF-36	36-item Short-Form Survey	Short-form health survey; a patient-reported measure of general health status
PGI-S	Patient Global Impression of Severity	A single question asking the patient to rate how their condition is now on a scale

Outcome measure	Outcome measure name in full (where appropriate)	Description
PGI-I	Patient Global Impression of Improvement	A single question asking the patient to rate their perception of improvement on a scale
EK-2	Egen Klassifikation 2	Aims to focus on meaningful changes that benefit from intervention, including eating, chewing, use of hands and fatigue
SMAIS-ULM	SMA Independence Scale-Upper Limb Module	To assess the degree of assistance required to perform typical daily activities in individuals with Type 2 and 3 (non-ambulatory) SMA
CGI-I	Clinical Global Impression Improvement	A single question asking the clinician to assess improvement or worsening of a patient's condition

4.5 Description of technologies under assessment

Because nusinersen and risdiplam have very different administration routes and schedules, they give patients a choice between a daily oral dose at home (convenient but constant) or a quarterly spinal injection in hospital (less convenient but patients can forget about treatment between injections). Patients may choose to switch from nusinersen to risdiplam, for example if scoliosis starts to influence the success of injections, or from risdiplam to nusinersen, for example if they are considering starting a family.

4.5.1 Nusinersen

Nusinersen (Spinraza, Biogen) is a 2'-O-methoxyethyl antisense oligonucleotide which stimulates the survival motor neuron SMN2 gene to increase SMN protein levels.[6] It is administered by intrathecal injection, and where patients are very young or have difficult spines (e.g. deformities or fusions) doctors can use ultrasound or other imaging techniques to aid administration. The intrathecal injection (12mg/5mL) requires an initial loading phase of four doses on days 0, 14, 28 and 63. Maintenance doses are then provided every four months.

Nusinersen was originally assessed under TA588, which showed the treatment improved a range of outcomes that are important to people with type 1, 2 and 3. However, there was a lack of long-term evidence, leading to uncertainty of the efficacy of the treatment. The committee recommended further data collection would help address such uncertainty. Additionally, the cost-effectiveness estimates presented were higher than what NICE usually considers to be a cost-effective use of NHS resources. Again, interpretation of the potential cost implications was difficult due to limited long term evidence. Additionally, it was unable to distinguish between the SMA subtypes and what differences could be achieved in various SMA patients. The committee therefore recommended the treatment was made available through an MAA for patients with 5q SMA if they have presymptomatic, type 1, 2 or 3 disease. No evidence was presented by the company for types 0 or 4.

For type 1, 2, and 3 SMA, the committee noted that nusinersen improves motor function but other health benefits were less certain. Survival outcomes were improved for type 1 but other health outcomes were uncertain. Little data was available for the presymptomatic population. Due to this uncertainty the managed access agreement provided for further data to be collected. The committee noted that there may be a delayed response to nusinersen for some people (for at least 2 years).

4.5.2 Risdiplam

Risdiplam (Evrysdi, Roche) is a small-molecule survival motor neuron-2 (SMN2) gene splicing modifier which increases SMN protein levels in the central nervous system. It is administered orally through an oral syringe once per day.

Risdiplam was originally assessed under TA755, which showed the treatment improved motor function in SMA type 1, 2 and 3. Additionally, there was evidence that those with type 1 may live longer when being treated with risdiplam. Some evidence also suggested risdiplam may be effective for people with presymptomatic SMA. However, there was a lack of evidence comparing risdiplam with usual care in type 1 patients. Furthermore, there was a lack of long-term evidence, making judgements uncertain. The cost-effectiveness estimates were higher than what NICE usually considers to be a cost-effective use of NHS resources. The committee therefore recommended the treat was made available through an MAA for patients with 5q SMA if they have type 1, 2, or 3 disease, or presymptomatic SMA with 1 to 4 SMN2 copies.

The committee concluded that risdiplam improves motor function in SMA types 1 to 3, and interim trial data showed some evidence of improvement in motor function for presymptomatic SMA. There was some evidence that risdiplam improves survival in people with type 1 SMA.

The committee decided that the evidence would be reviewed when the final results of the key trials in SMA type 1 and type 2/3 (FIREFISH and SUNFISH) are published, and this report incorporates these results.

4.5.3 Identification of important subgroups

The important subgroups are defined in the NICE decision problem, which can be seen in Section 5.

4.6 Layout of report

This report provides the EAG critique of each company's submission. It then describes the methods of each element of the EAG's work, beginning with the qualitative analysis of submissions and meeting content, then the update of the previous clinical effectiveness SLR, the update of the cost-effectiveness SLR, and finally the EAG's cost-effectiveness analysis. The results of the clinical effectiveness and cost-effectiveness SLRs are presented, followed by the EAG's cost-effectiveness analysis. The MAA data is provided for outcomes where appropriate. Qualitative results are presented in a separate section after the quantitative results. Finally, we present the EAG's conclusions.

5 Definition of the decision problem

The final scope as defined by NICE is reproduced in Table 5.1.

Table 5.1: NICE decision problem

Domain	Eligibility
Interventions	• Nusinersen • Risdiplam Interventions are monotherapies in addition to existing clinical services and established clinical management.
Population	People with types 0, 1, 2, 3 or 4 5q SMA, or presymptomatic 5q SMA confirmed with genetic testing, with 1 to 4 SMN2 copies
Subgroups	If the evidence allows the following subgroups will be considered: 1. Number of SMN2 gene copies in people with presymptomatic SMA 2. Functional status (non-sitter, sitter, walker) 3. People who have had prior active treatment for SMA
Comparators	• Established clinical management • Best supportive care The interventions will be compared to each other In addition, for children aged 12 months and under with a biallelic mutation in the SMN1 gene and present with a clinical diagnosis of type 1 5q SMA or presymptomatically with up to 3 copies of the SMN2 gene • Onasemnogene abeparvovec
Outcomes	The outcome measures to be considered include: • motor function (including, where applicable, both age-appropriate gross motor milestones and fine motor skills) • bulbar function (including, for example, swallowing and ability to communicate) • frequency and duration of hospitalisation • respiratory function • complications of spinal muscular atrophy (including, for example, scoliosis and muscle contractures) • need for non-invasive or invasive ventilation • stamina and fatigue • mortality • adverse effects of treatment • health-related quality of life (for patients and carers)
Economic analysis	The reference case stipulates that the cost effectiveness of treatments should be expressed in terms of incremental cost per quality-adjusted life year. The reference case stipulates that the time horizon for estimating clinical and cost effectiveness should be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared. Costs will be considered from an NHS and Personal Social Services perspective.

	The availability of any commercial arrangements for the intervention, comparator and subsequent treatment technologies will be taken into account. The availability of any managed access arrangement for the intervention will be taken into account.
Abbreviations: SMA = spinal muscular atrophy; SMN2 = survival motor neuron 2	

After considering the consultation responses and meeting with patient and professional groups, the EAG added further outcomes to consider (in consultation with NICE), where data were available:

- Ability to socialise
- Activities of daily living
- Psychological impact
- Independence
- Impact on education
- Impact on family and carers
- Impact on the ability to work
- Looking to the future
- Maintenance or stabilisation of condition
- Patient choice
- Spectrum of SMA

6 Critique of Biogen submission

6.1 Biogen decision problem

The Biogen decision problem is reproduced in Table 6.1, followed by a critique of the submitted systematic review.

Table 6.1: Biogen decision problem, reproduced from Biogen document B, Table 1

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
Population	People with types 0, 1, 2, 3, or 4 5q SMA, or presymptomatic 5q SMA confirmed with genetic testing with 1 to 4 *SMN2* copies	Presymptomatic SMA and SMA types 1, 2 and 3	The evidence base on nusinersen is limited to people with presymptomatic SMA, and symptomatic infantile-onset (type 1) and later-onset SMA (types 2 and 3). Type 0 SMA was excluded from the submission due to futility of treatment for these patients. The evidence base on nusinersen in type 4 SMA is insufficient for HTA purposes, hence this population is also excluded from cost-effectiveness modelling.
Intervention	• Nusinersen • Risdiplam Interventions are monotherapies in addition to existing clinical services and established clinical management.	Nusinersen	Not applicable; Biogen are the manufacturer of nusinersen only.
Comparator(s)	• Established clinical management • Best supportive care • The interventions will be compared to each other	Direct evidence is presented comparing nusinersen with established clinical management/best supportive care.	The sham control used in phase III ENDEAR and CHERISH trials can be considered to represent established clinical management/ best supportive care.

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
	In addition, onasemnogene abeparvovec will be considered as a comparator for children aged ≤12 months with a biallelic mutation in the *SMN1* gene and present with a clinical diagnosis of type 1 5q SMA or presymptomatically with up to 3 copies of the *SMN2* gene	Indirect evidence only is available against risdiplam and onasemnogene abeparvovec. This is subject to substantial uncertainty due to differences in trial populations and outcome assessments.	No direct evidence is currently available against risdiplam or onasemnogene abeparvovec; consequently, ITCs were performed with the aim to inform relative efficacy. However, limitations of the ITCs render them unsuitable to inform cost-effectiveness modelling. Therefore, this submission focuses on the comparison between nusinersen and BSC.
Outcomes	• Motor function (including, where applicable, both age-appropriate gross motor milestones and fine motor skills) • Bulbar function (including, for example, swallowing and ability to communicate) • Frequency and duration of hospitalization • Respiratory function • Complications of spinal muscular atrophy (including, for example, scoliosis and muscle contractures) • Need for non-invasive or invasive ventilation • Stamina and fatigue • Mortality • Adverse effects of treatment	As specified in the NICE scope.	Maintenance of respiratory function, which is most critical in type 1 SMA was included in the primary endpoint of the ENDEAR trial, i.e., time to death or permanent ventilation, with long-term assessment continued in the SHINE open-label extension. Information on stamina and fatigue, as measured using the 6-Minute Walk Test, is limited to ambulant patients.

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
	• Health-related quality of life (for patients and carers)		
Economic analysis	• The reference case stipulates that the cost effectiveness of treatments should be expressed in terms of incremental cost per quality-adjusted life year. • The reference case stipulates that the time horizon for estimating clinical and cost effectiveness should be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared. • Costs will be considered from an NHS and Personal Social Services perspective. • The availability of any commercial arrangements for the intervention, comparator, and subsequent treatment technologies will be taken into account. The availability of any managed access arrangement for the intervention will be taken into account.	As per the reference case	Not applicable
Subgroups to be considered	If the evidence allows the following subgroups will be considered: • Number of *SMN2* gene copies in people with presymptomatic SMA	• Subgroup analyses stratified by *SMN2* copy number are available for the presymptomatic population treated in NURTURE	Subgroup analyses stratified by functional status and prior therapy are at present only available from the real-world data collection as part of the Managed Access Agreement

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
	• Functional status (non-sitter, sitter, walker) • People who have had prior active treatment for SMA	• Subgroup analyses stratified by functional status and prior therapy are available from the Managed Access Agreement established by TA588	established by TA588; no data is stratified by functional status from the clinical development programme. The efficacy of nusinersen in patients who received prior therapy is currently being assessed in the ongoing studies ASCEND and RESPOND, which include patients previously treated with risdiplam and onasemnogene abeparvovec.
Special considerations including issues related to equity or equality	None stated	Although nusinersen will be appraised through a multiple technology appraisal, its assessment is anticipated to have several features that are commonly seen in the highly specialised technologies programme. Therefore, decision modifiers and flexibility in NICE's decision making should be taken into account.	Not applicable
Abbreviations: BSC = best supportive care; ITC = indirect treatment comparison; NICE = National Institute for Health and Care Excellence; SMA = spinal muscular atrophy; SMN2 = Survival Motor Neuron 2; TA = Technology Appraisal			

6.2 Critique of Biogen SLR

6.2.1 Search strategies

The company conducted the original search in January 2023 and updated this search in November 2023. A range of electronic bibliographic databases were searched, and the company did not report the use of search filters. Conference abstracts were sought on multiple databases year by year, from 2020 to 2023 inclusive. The company state that date limitations of 2020 onwards, removal of animal studies and case reports were imposed on the searches.

The search strategy encompassed concepts from the SMA population, combined with the nusinersen, onasemnogene abeparvovec (OA) or risdiplam concepts of the decision problem.

The EAG appraised the searches using the PRESS checklist and the latest NICE methods manual.[22,23] The number of records retrieved per search line was shown and the methods and terms used to search the conference abstracts were presented as might be expected when using the PRISMA-S reporting guidance.[24]

6.2.2 Inclusion and exclusion criteria

6.2.2.1 Population

The Biogen SLR included patients with presymptomatic SMA and SMA types 0, 1, 2, 3, 4, and they planned to extract data about all these populations (Table 6.2). However, in the submission they stated that patients with type 0 or type 4 SMA were excluded. They cited clinical expert advice that treatment for type 0 patients is futile and that there was insufficient evidence to inform evaluation for type 4 patients.

6.2.2.2 Intervention

Interventions included nusinersen and risdiplam as monotherapies in addition to established clinical management.

6.2.2.3 Comparators

Comparators comprised established clinical management, BSC, or OA in patients eligible for that treatment. Biogen noted that direct evidence is only available comparing nusinersen and best supportive care. They conducted indirect comparisons (ITCs), which are discussed in Section 6.2.4.

6.2.2.4 Outcomes

Biogen included all the outcomes listed within the decision problem, as well as specifying outcomes relating to speech and communication, growth, and use or discontinuation of concomitant medications. They noted that pulmonary function is only available from real world evidence.

6.2.3 SLR methods

The EAG have few concerns about the eligibility criteria of the Biogen SLR and the methods of the review. The restriction to studies that included at least 100 participants meant that a number of eligible smaller studies were omitted, but no controlled studies. See Table 6.2 for explanation of the methods for each step of the SLR. The EAG's assessments (detailed in bold) are on a three-point Likert scale (key concern, some concerns or appropriate).

Table 6.2: EAG evaluation of Biogen SLR

Systematic review stage	Section in CS where methods are reported	EAG's assessment of the robustness of methods
Data sources	Appendix D section 2.1	**Appropriate** Multidisciplinary electronic databases were searched and described in full. Relevant conferences for SMA have been searched and justification has been given where access was limited or prevented. The company searched for ongoing/unpublished studies via trial registries.
Search strategies	Appendix D section 2.1	**Appropriate** Relevant search terms were used and combined appropriately. The searches did not use exclude by using Boolean "NOT" terms. No limitations have been applied without justification.
Search filters	Appendix D section 2.1	**Appropriate** Study design filters were not used, except the removal of news, editorials and case studies, which were reported and justified appropriately.
Eligibility criteria	Appendix D section 1	**Some concerns** Eligibility criteria matched the NICE decision problem in terms of population, intervention, comparators and outcomes. They included RCTs, non-randomised controlled trials, single-arm interventional trials (with or without a historical control group), prospective or retrospective comparative observational studies, and non-comparative observational studies that include at least 100 participants. The latter condition omitted a sizable number of smaller studies which may affect the comprehensiveness of the results.
Screening	Appendix D section 2.2	**Appropriate** Both title and abstract and full text screening were each conducted by two reviewers independently, with disagreements adjudicated by a third reviewer.
Data extraction	Appendix D section 2.3	**Appropriate** One reviewer conducted data extraction using a piloted data extraction sheet in Excel. A second reviewer checked the data points, with a third reviewer adjudicating disagreements.
Quality appraisal	Appendix D section 2.4	**Appropriate** One reviewer conducted critical appraisal using Cochrane and JBI tools for specific study designs, and a second reviewer checked with a third reviewer adjudicating disagreements.
Data synthesis	Appendix D sections 3 and 6	**Appropriate** Since no trials were found comparing nusinersen to risdiplam or OA, the company conducted a feasibility assessment for an indirect comparison between the drugs. They conducted a series of MAICs for type 1 SMA but did not include the data in the models. They judged that heterogeneity was too great to conduct a network meta-analysis for type 2/3 SMA. The EAG agrees with the company's judgement.

Systematic review stage	Section in CS where methods are reported	EAG's assessment of the robustness of methods
Abbreviations: CS = company submission; EAG = Evidence Assessment Group; JBI = Joanna Briggs Institute; MAIC = matching-adjusted indirect comparison; NICE = National Institute for Health and Care Excellence; OA = onasemnogene abeparvovec; SLR = systematic literature review; SMA = spinal muscular atrophy; RCT = randomised controlled trial; ROBINS-I = Risk Of Bias In Non-randomised Studies - of Interventions		

6.2.4 Critique of Biogen ITC

Biogen utilised unanchored matching-adjusted indirect comparisons (MAICs) for the comparison of nusinersen to either OA or risdiplam. They stated that available data did not allow for an anchored MAIC to be conducted. In the unanchored MAICs, all available covariates were included, where possible. If it was not possible, due to poor overlap of covariates or MAIC implementation not providing satisfactory matching (reweighting) between individual patient data (IPD) and aggregate data, a LASSO regression technique was applied to reduce the number of covariates. However, if a MAIC was still deemed unfeasible, a simulated treatment comparison (STC) was implemented. Additionally, all analyses took place using complete cases only. The company highlighted that such ITCs are in line with NICE Technical Support Document (TSD) 18,[25] and went on to state that specific care must be taken regarding the possible biases of such analyses. Specifically, that the amount of bias (systematic error) in these estimates is unknown, is likely to be substantial, and could even exceed the magnitude of treatment effects which are being estimated.

Fourteen analyses were conducted by Biogen (seven comparing nusinersen to OA and seven to risdiplam). When comparing to OA, most analyses suggest [redacted] at age 14 months in presymptomatic or type 1 SMA. However, for type 1, 'stands and walks alone at 18 months of age' (BSD-III) assessment was not formally possible via the MAIC due to no events (i.e. no patients achieved this milestone in nusinersen study; CS3-A or CS3-B). There was a [redacted] in type 1 SMA patients. However, these results should be interpreted with caution as the MAICs effective sample sizes (ESS) were mostly <30 (n = 5), two of which were <10. The remaining two were <35. These small ESS suggest a potential for high variability between the populations being compared, meaning the estimate may be unstable, in line with NICE TSD 18.[25]

When comparing nusinersen to risdiplam, the same issues of ESS were apparent. Five of the available analyses were <30, which compared HINE-2 in type 1 subgroups (e.g. sitting without support). All analyses suggest [redacted] in type 1 SMA patients. The same can be said for overall survival 12 months into the study, which showed [redacted]. It is worth noting for this analysis that CHOP-INTEND at baseline was much higher in the nusinersen group compared to the risdiplam group (27.2 vs 22.0), and there was also a higher proportion of individuals with baseline feeding issues (48% vs 15%). For the outcomes of HFMSE and RULM (compared between baseline and 12 months) there were [redacted] between the two drugs. However, these analyses were derived using STCs due to a MAIC being deemed unfeasible because of failing to match covariates. The company suggest this was due to a lack of overlap at age of screening and symptom onset, leading to the MAIC failing to match the covariates. The company states that these are crucial covariates and therefore decided not to run LASSO to reduce the covariates in the MAIC, rather opting for the STC. The EAG

agrees with this assessment, however, as the results are derived from an STC, there may be inherent biases. For example, when data is non-linear, which can commonly be the case in SMA where it is possible to show improvements, maintenance or deterioration over time, results can be open to bias.[26] Specifically, as the results are generated via a linear regression model using IPD from one trial (in this case, nusinersen) compared to aggregate data from the comparator trial (risdiplam) the non-linearity assumption may be violated. If there is non-linearity substituting the mean covariate values from the comparator trial into the regression can lead to biased estimates, due to issues between the relationship of the mean of the outcome and the mean of the covariates.[27] Therefore, it is important to consider the results with caution.

The EAG note that additional consideration was needed for time frames when comparing between the studies. For example, HINE-2 assessments, IPD and aggregate data did not align. They therefore implemented the rule that a subject was included in the IPD if they had a HINE-2 or WHO motor milestone assessment at ≤ 24 months into the study, and if there was more than one publication for a study, the company used the publication with the latest time point. However, this may have biased the estimate against nusinersen, so to mitigate this they implemented the additional rule that if the assessment fitting the above condition was < 21 months into the study for a given subject, that subject was dropped from the comparison.

Overall, clear attempts were made to make the analyses possible and plausible with the data available to the company for statistical assessments. Some concerns arise with the comparability of the different cohorts, where the ESS is low after matching. Additionally, for type 2/3 the analysis is based on STC. However, given the inherent differences between the populations, not running an anchored MAIC may make sense clinically. Table 6.3 provides an overview of the results from the Biogen company submission.

Table 6.3: Overview of the results from the Biogen company submission

Outcome	Population	Analysis Type	Comparator	Covariates	Sample size/ ESS	Conclusion
WHO MM stands with support before 18 months	Presymptomatic	Unanchored MAIC	OA (STR1VE-EU and STR1VE-US)	Sex, age at first dose, weight, SMN2 copy number, baseline CHOP-INTEND score	NURTURE: 25/8.78	[redacted]
WHO MM walks alone before 18 months	Presymptomatic	Unanchored MAIC	OA (STR1VE-EU and STR1VE-US)	Sex, age at first dose, weight, SMN2 copy number, baseline CHOP-INTEND score	NURTURE: 25/8.78	[redacted]
BSID-III sitting without support at 18 months	Type 1	Unanchored MAIC	OA (STR1VE-EU and STR1VE-US)	Sex, age at screening, age at symptom onset, weight, SMN2 copy number, baseline ventilation support (yes/no), baseline feeding issues (yes/no), baseline CHOP-INTEND score.	CS3A and CS3B: 46/12.61	[redacted]
BSID-III stands with support at 18 months	Type 1	Unanchored MAIC	OA (STR1VE-EU and STR1VE-US)	Sex, age at screening, age at symptom onset, weight, SMN2 copy number, baseline ventilation support (yes/no), baseline feeding issues (yes/no), baseline CHOP-INTEND score.	CS3A and CS3B:46/12.61	[redacted]
BSID-III walks alone at 18 months	Type 1	Unanchored MAIC	OA (STR1VE-EU and	Sex, age at screening, age at symptom onset, weight, SMN2 copy number,	CS3A and CS3B:46/12.61	[redacted]

Outcome	Population	Analysis Type	Comparator	Covariates	Sample size/ ESS	Conclusion
			STR1VE-US)	baseline ventilation support (yes/no), baseline feeding issues (yes/no), baseline CHOP-INTEND score.		
No permanent ventilation at age 14 months	Type 1	Unanchored MAIC	OA (STR1VE-EU and STR1VE-US)	Sex, age at screening, age at symptom onset, weight, SMN2 copy number, baseline ventilation support (yes/no), baseline feeding issues (yes/no), baseline CHOP-INTEND score.	CS3A and CS3B:79/31.89	[redacted]
Overall survival at age 18 months	Type 1	Unanchored MAIC	OA (STR1VE-EU and STR1VE-US)	Sex, age at screening, age at symptom onset, weight, SMN2 copy number, baseline ventilation support (yes/no), baseline feeding issues (yes/no), baseline CHOP-INTEND score.	CS3A and CS3B:92/34.13	[redacted]
HINE-2 sitting without support at 24 months into study	Type 1	Unanchored MAIC	Risdiplam (FIREFISH)	Sex, age at screening, age at symptom onset, baseline disease duration, SMN2 copy number, baseline CHOP-INTEND score.	CS3A and CS3B:52/23.88 Note: with baseline feeding issues as a covariate ESS = 3.5	[redacted]
HINE-2 stands with support	Type 1	Unanchored MAIC	Risdiplam (FIREFISH)	Sex, age at screening, age at symptom onset, baseline	CS3A and CS3B: 52/23.88	[redacted]

Outcome	Population	Analysis Type	Comparator	Covariates	Sample size/ ESS	Conclusion
at 24 months into study				disease duration, SMN2 copy number, baseline CHOP-INTEND score.	Note: with baseline feeding issues as a covariate ESS = 3.5	
HINE-2 walks alone at 24 months into study	Type 1	Unanchored MAIC	Risdiplam (FIREFISH)	Sex, age at screening, age at symptom onset, baseline disease duration, SMN2 copy number, baseline CHOP-INTEND score.	CS3A and CS3B: 52/23.88 Note: with baseline feeding issues as a covariate ESS = 3.5	[redacted]
Overall survival 12 months into study	Type 1	Unanchored MAIC	Risdiplam (FIREFISH)	Sex, age at screening, age at symptom onset, baseline disease duration, SMN2 copy number, baseline feeding issues, baseline CHOP-INTEND score.	CS3A and CS3B: 92/28.11	[redacted]
HFMSE baseline to 12 months	Type 2/3	STC	Risdiplam (SUNFISH Part II)	Sex, age at screening, age at symptom onset, SMN2 copy number, baseline RULM score, baseline HFMSE score.	STC performed as MAIC was not feasible because it failed to match covariates	[redacted]

Outcome	Population	Analysis Type	Comparator	Covariates	Sample size/ ESS	Conclusion
RULM baseline to 12 months	Type 2/3	STC	Risdiplam (SUNFISH Part II)	Sex, age at screening, age at symptom onset, SMN2 copy number, baseline RULM score, baseline HFMSE score.	STC performed as MAIC was not feasible because it failed to match covariates	[redacted]

Abbreviations: BSID-III = Bayley Scales of Infant and Toddler Development, Third Edition; CHOP-INTEND = Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders; ESS = Effective Sample Size; HFMSE = Hammersmith Functional Motor Scale (expanded); HINE-2 = Hammersmith Infant Neurological Examination - Part 2; MAIC = matching-adjusted indirect comparison; OA = onasemnogene abeparvovec; RULM = Revised Upper Limb Module; SMN2 = Survival Motor Neuron 2; STC = simulated treatment comparison; WHO MM = World Health Organization Motor Milestones

6.2.5 Critique of Biogen MAA

6.2.5.1 Paediatric registry

The paediatric registry updated the following items in April 2025:

- WHO MM information
- Mixed model for repeated measure (MMRM) analysis for HINE-2 in SMA type 1,
- Responders analysis (defined as an increase in 1 point on HINE and 9 points on CHOP-INTEND)
- Number of patients with permanent ventilation
- Number of patients requiring tracheostomy
- Overall survival
- EK-2 overview

Data for WHO MM was provided over time, with number of patients per SMA type who improved or maintained motor function reported. Additional analyses were conducted using linear interpolation, when patients had missing data, based on the patients' observed data at flanking visits.

In the original report, MMRMs were conducted for the following outcomes and SMA types:

- CHOP-INTEND: type 1, including an analysis splitting patients by those were expanded access programme (EAP) and non-EAP
- RHS: type 2/3
- RULM: type 2/3
- RHS/CHOP-INTEND: type 1, analysis for those initially measured on CHOP-INTEND but baseline was redefined to RHS after ceiling effect reached on CHOP-INTEND, or patient achieved skills not measured by CHOP-INTEND (i.e. rolling and sitting)
- RULM/CHOP-INTEND: type 1, analysis for those initially measured on CHOP-INTEND but baseline was redefined to RULM for children age ≥2.5 years old, who can sit (supported/unsupported) and have functional use of their upper limbs

MMRM models include the following covariates:

- Baseline score
- SMA type 2/3 – where appropriate
- Baseline function (non-sitters, sitters, walkers) – although this is confounded with baseline score
- Weight at baseline visit
- Age at symptom onset (month)
- Age at treatment initiation (years)
- Duration of disease at baseline visit: age of diagnosis to age at treatment initiation (years)
- Time between treatment initiation and baseline visit (days)

Age of diagnosis was preferred to age of symptom onset, as this does not rely as often on patient recall.

Descriptive data was also provided for RHS timed tests (10 metre run test and rise from floor test). MMRM was not feasible for these outcomes.

Over the original and updated reports, MMRM were conducted when feasible (i.e. there was enough data). In cases of insufficient data, results are generally reported narratively and tabulated (e.g. means and SDs). Not all outcome provided are mandated (e.g. EK-2) but are still provided, with the caveat that data cleaning was not as thorough for MAA mandated items.

Overall, the analyses of the data are conducted when plausible and the limitations of the data are clearly highlighted within the report.

The following PROMs outcomes were also reported (December 2023 report):

- Patient global impression of severity score (PGI-S); higher value is worse
- Patient global impression of improvement score (PGI-I); higher value is worse
- SMA independence scale (SMAIS); higher values equate to higher independence
- EQ-5D-5L/EQ-5D-Y; higher values indicate more problems; visual analogue scale (VAS, 0-100); higher value indicates better health

As patient numbers were low and data lacked maturity, only descriptive statistics are presented. The EAG consider this appropriate.

6.2.5.2 Adult registry

The adult registry updated all analyses from the original report (April 2024) therefore, the new (April 2025) report is to be considered here. Data was presented for the following:

- WHO MM information
- MMRM for ATEND (left and right)
- MMRM for EK2
- MMRM for RULM
- MMRM for RHS
- MMRM for 6 Minute Walk Test (6MWT)

MMRMs were adjusted for the following baseline covariates:

- Patient (random effect)
- Age at symptom onset (fixed effect)
- Age at treatment initiation (fixed effect)
- SMA type (fixed effect)
- Treatment duration at time of visit (fixed effect)
- Disease duration (age at treatment state minus age at symptom onset; fixed effect)

To increase data availability, the registry removed the requirement for at least one follow-up score and weight as a covariate. Removal of the criterion of at least one follow-up score increased both the number of patients and value of data (i.e. scores) contributing to the models. Weight was not used due to a large amount of missing data. The previous report (April 2024) included baseline score, baseline-visit interaction, and baseline motor function; reasons for not including these in the updated report are not explicitly stated. The previous report also included a sensitivity analysis for patients naïve to treatment and pre-treated patients. Additionally, the updated report (April 2025) split by status (i.e. non-sitters, sitters, and walkers), whereas the previous report (April 2024) assessed type 2/3 patients as a whole. The new report therefore offers more granularity in terms of subgroups of SMA type 2/3 patients but does suffer from smaller patient sample sizes. When patient numbers are below five, no results are calculated for that follow-up period.

Overall, the analyses are conducted using appropriate methods and attempts have been made to provide context to the results and consider type 2/3 patients as separately as possible.

6.2.6 Results of Biogen SLR

Two phase III, randomised controlled trials of nusinersen versus sham procedure have been conducted for patients with type 1 SMA (ENDEAR),[28] and type 2/3 SMA (CHERISH) respectively.[29] For patients who were not eligible for these trials, a phase II randomised trial was available (EMBRACE).[30] The part 1 randomised element of EMBRACE finished early and patients were offered the opportunity to transition to the open-label extension. There is no randomised evidence for presymptomatic patients, only a single arm study that treated genetically diagnosed infants in the first six weeks of life (NURTURE).[31] These studies, plus relevant dose-finding studies and the open-label extension study that enrolled types 1, 2 and 3 patients from the other studies (SHINE), are shown in Table 6.4.

Table 6.4: Overview of clinical effectiveness evidence for nusinersen (reproduced from Biogen submission Table 5)

Study	NURTURE	CS3A	ENDEAR	CS2/CS12	CHERISH	EMBRACE	SHINE
Study design	Phase II, open-label, multicentre, single-arm study	Phase II, open-label, multiple dose, single-arm, multi-centre study	Randomised, double blind, multicentre (including UK), phase III, sham-procedure controlled	CS2: Phase I/IIa, open-label, multicentre, multiple-dose, dose escalation study CS12: Phase I, multicentre, open-label, multiple-dose extension study	Randomised, double-blind, multicentre, phase III, sham-procedure controlled	Phase II, randomised, double-blind, sham-procedure controlled study	Open-label extension study
Population	Presymptomatic infants genetically diagnosed with SMA (likely to develop early or later onset SMA)	Symptomatic infantile-onset (type 1) SMA	Symptomatic infantile-onset (type 1) SMA	Symptomatic later-onset (type 2/3) SMA	Symptomatic later-onset (type 2/3) SMA	Patients with SMA who are not eligible to participate in ENDEAR and CHERISH	Patients who participated in the initial studies (ENDEAR, CHERISH, EMBRACE, CS3a, and CS12)
Intervention(s)	Nusinersen (N=25)	Nusinersen (N=21)	Nusinersen (N=80)	Nusinersen (N=34 in CS2 and N=47 in CS12)	Nusinersen (N=84)	Nusinersen (N=14)	Nusinersen (N=327)
Comparator(s)	None	None	Sham procedure (N=41)	None	Sham procedure control (N=42)	Sham procedure (N=7)	None

Study	NURTURE	CS3A	ENDEAR	CS2/CS12	CHERISH	EMBRACE	SHINE
Indicate if study used in the economic model	Yes	No, phase III data is available from ENDEAR	Yes	No, phase III data is available from CHERISH	Yes	No	Yes

Participation in ENDEAR was limited to those with two SMN2 copies, with SMA symptom onset within the first six months but not the first week of life. For CHERISH, participants had to be between 2-12 years and able to sit but not walk independently; they were excluded from the trial if they had a gastric feeding tube, severe contractures or scoliosis, or needed ventilation for more than six hours during a 24-hour period. Participants in CHERISH only received three loading doses of nusinersen with a maintenance dose after six months, whereas ENDEAR participants received the recommended four loading doses plus maintenance doses after four months. It should also be noted that the enrolled population was more homogeneous than the population encountered in clinical practice due to restrictions in the eligibility criteria (i.e., no severe contractures or scoliosis, respiratory insufficiency, or reliance on a gastric tube). Furthermore, the age profile of enrolled children was younger than would be seen in clinical practice.[32]

The company reported that none of the presymptomatic patients had died or required permanent ventilation by a median age of 4.9 years (range 3.8 to 5.5 years), compared to an estimated average age of mortality from natural history of 19.2 months (SD 10.1 months).[21] Children with three SMN2 copies were walking independently within normal developmental timeframes; 13 of the 15 children with two SMN2 copies achieved the WHO motor milestone of standing alone and walking alone, whilst 14 achieved hands and knees crawling and walking with assistance, and all achieved sitting without support and standing with assistance. A total of 88% of children achieved the maximum CHOP-INTEND score, and mean HFMSE scores showed continuous improvement.

For type 1 patients, the nusinersen group showed a 62.8% reduction in the risk of death and a 47% reduction in risk of death or permanent ventilation compared to the sham group. They showed progressive mean increases in motor function according to WHO motor milestones, HINE-2 and CHOP-INTEND. Fewer patients discontinued treatment in the treatment group than the sham group, for reasons not attributed to the treatment.

For type 2/3 patients, most on nusinersen experience clinically meaningful and statistically significant increase in motor scores (WHO motor milestones, HFMSE and RULM) at 15 months.

Results of the extension studies suggest that longer term treatment is beneficial; [redacted].[32]

The company reported a favourable safety profile. The most reported AEs were headache, vomiting, and back pain, and were attributed mostly to the administration of the drug via lumbar puncture.

An evaluation of the risk of bias in these studies can be found in section 13.2.

6.3 Critique of Biogen economic models

The EAG reviewed and critically appraised the economic models and the additional information in response to the points for clarification submitted by Biogen.[33];[34] In this section, we assess the company submission against the NICE reference case checklist[35] and then we present a critique of the submitted economic model structures and the economic evidence

used to parameterise these economic models according to the population groups defined in the decision problem (presymptomatic, type 1 and type 2/3 SMA).[6]

6.3.1 NICE decision problem

The company submission was evaluated against the NICE reference case checklist[35] and the findings are summarised in Table 6.5.

Table 6.5: Comparison of company's and NICE decision problem

Element of health technology assessment	Reference case (based on NICE scope/methods)	EAG comment on company's submission
Defining the decision problem	People with types 0, 1, 2, 3 or 4 5q SMA, or presymptomatic 5q SMA confirmed with genetic testing with 1 to 4 SMN2 copies	The company submission did not report on type 0 and 5q SMA type 4 because of paucity of evidence to conduct an economic evaluation. The company reported the economic evaluation results separately for presymptomatic SMA, along with subgroup analysis for 2 SMN2 gene copies SMA and 3 SMN2 gene copies SMA subpopulations; type1 SMA and type 2/3 SMA populations.
Intervention	Interventions are monotherapies in addition to existing clinical services and established clinical management.	The company assessed the cost-effectiveness of nusinersen.
Comparators	Established clinical management in the NHS, including the Best supportive care (BSC) The interventions will be compared to each other In addition, Onasemnogene Abeparvovec (OA) will be used as comparator treatment for children aged 12 months and under with a bi-allelic mutation in the SMN1 gene and present with a clinical diagnosis of type 1 5q SMA or presymptomatically	Because of lack of evidence, the company did not consider risdiplam and OA appropriate comparators against nusinersen for economic analysis. OA was not an appropriate comparator for type 2/3 SMA population and not considered.

Element of health technology assessment	Reference case (based on NICE scope/methods)	EAG comment on company's submission
	with up to 3 copies of the SMN2 gene.	
Perspective on outcomes	The outcome measures to be considered include: • Motor function (including, where applicable, both age-appropriate gross motor milestones and fine motor skills) • Bulbar function (including, for example, swallowing and ability to communicate) • Frequency and duration of hospitalisation • Respiratory function • Complications of spinal muscular atrophy (including, for example, scoliosis and muscle contractures) • Need for non-invasive or invasive ventilation • Stamina and fatigue • Mortality • Adverse effects of treatment • Health-related quality of life (for patients and carers)	Presymptomatic model: Nusinersen: WHO motor milestone achievement from NURTURE[31,36]. BSC: weighted average of relative efficacy from ENDEAR[28] and CHERISH[29] Type 1 SMA model: Nusinersen: a combination of HINE-2 (aged two or less) and WHO motor milestone (above age 2) achievement data from ENDEAR[28] and SHINE BSC: HINE-2 motor milestones from sham control arm of ENDEAR[28] Mortality data also informed by ENDEAR[28] and SHINE[37]. Type 2/3 SMA model: Nusinersen: WHO motor milestones data from CHERISH[29] and SHINE[37] BSC: WHO motor milestones from CHERISH[29] Mortality data informed by Wijngaarde et al. 2020[38] and general population mortality Bulbar dysfunction, non-permanent respiratory support, scoliosis, stamina and fatigue impact not considered separately because of data limitations.

Element of health technology assessment	Reference case (based on NICE scope/methods)	EAG comment on company's submission
Perspective on costs	Costs will be considered from an NHS and Personal Social Services perspective.	Appropriate
Type of economic evaluation	Cost utility analysis	Cost utility analysis was conducted comparing nusinersen against BSC.
Time horizon	The reference case stipulates that the time horizon for estimating clinical and cost effectiveness should be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared.	100-year time horizon covering the lifetime of the patient.
Synthesis of evidence on health effects	Based on systematic review	Presymptomatic model: Weighted average of relative risk of no treatment response from CHERISH[29] and ENDEAR[28] Type 1 SMA model: Health effects measure taken from ENDEAR[28] and SHINE[37] Type 2/3 SMA model: Health effects measure taken from CHERISH[29] and SHINE[37]
Measuring and valuing health effects	Express health effects in QALYs for cost-effectiveness analyses.	Appropriate
Source of data for measurement of health-related quality of life	For the reference case, report the measurement of changes in health-related quality of life directly from patients.	HST24[17] and carer HSUVs from TA588[2]
Source of preference data for valuation of changes in health-related quality of life	The utility of these changes should be based on public preferences using a choice-based method.	Appropriate

Element of health technology assessment	Reference case (based on NICE scope/methods)	EAG comment on company's submission
Equity considerations	No additional equity considerations in the NICE scope.	Appropriate
Evidence on resource use and costs	Resource use and cost data should have been identified systematically	Resource use and cost data informed by the HST24[17] were inflated to price year 2021/22.
Discounting	Annual discount rate of 3.5% for costs and outcomes.	Appropriate

Source:[33];[35]

Abbreviations: BSC, best supportive care; EAG = Evidence Assessment Group; HSP = highly specialised technologies; OA = Onasemnogene Abeparvovec; SMA = spinal muscular atrophy, SMN= survival motor neuron; QALY = quality-adjusted life year

6.3.2 Presymptomatic SMA population

6.3.2.1 Model structure

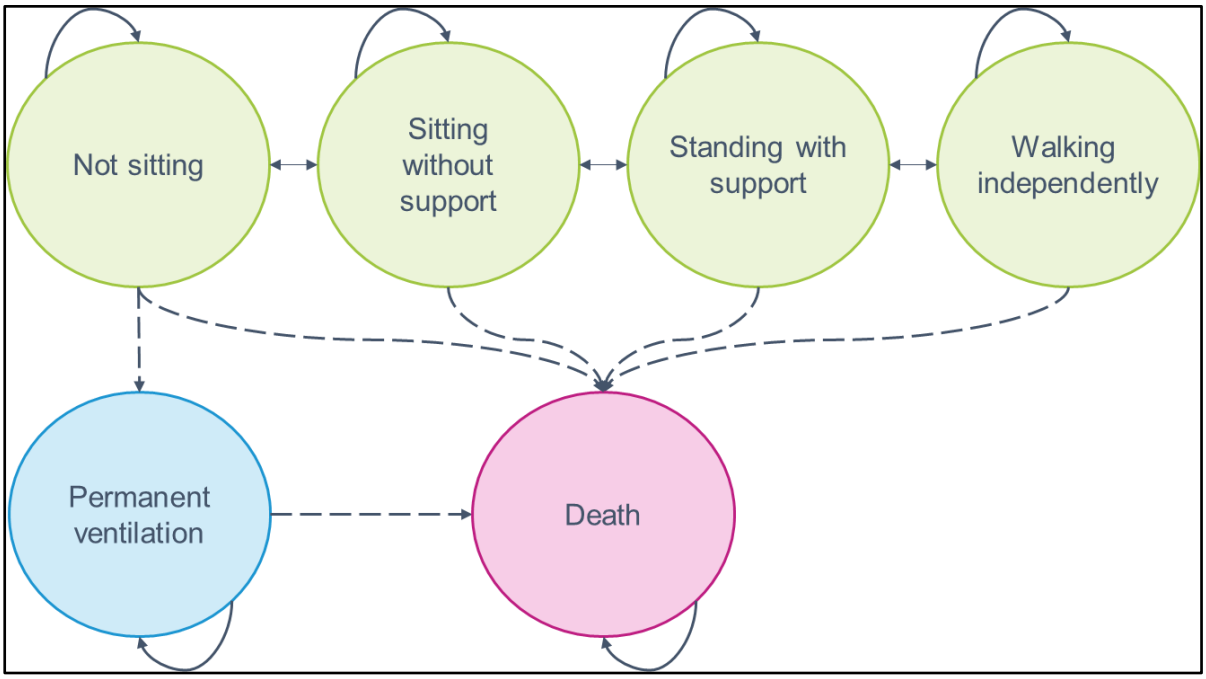
6.3.2.1.1 Type of model

Biogen used a Markov model to represent the natural history of presymptomatic 5q SMA which was primarily informed by the previous NICE TA588[2] for nusinersen (Figure 1). Both the models for presymptomatic and type 1 population had the same structure.

6.3.2.1.2 Health states and transitions

The Markov model was built in Microsoft Excel with 6 health states: 'not sitting', 'sitting without support', 'standing with support', 'walking independently' based on the highest mobility milestone attained, 'permanent ventilation' and 'death'.[33] All states were based on gross motor milestones clinically defined using WHO motor milestones (WHO MM),[39] except for 'permanent ventilation' and 'death'. All patients started in the 'not sitting' state, in part due to the baseline age of the presymptomatic patient cohort (mean [redacted]) in the NURTURE trial, and could transition to another health state or remain in the same health state after each model cycle (4 months).[33] It was assumed that only patients in the 'not sitting' health state could transition to the 'permanent ventilation' health state defined in line with the NURTURE trial as: requiring a tracheostomy or having at least 16 hours of ventilatory support per day for more than 21 days.[33] Once patients reached this latter health state it was assumed they could not improve and therefore remained in that state until they die (absorbing state).[33]

Figure 1. Model structure for presymptomatic and type 1 SMA populations used by Biogen



Source: Biogen CS Section B 3.2.2, Figure 35[33]
Abbreviations: SMA = spinal muscular atrophy

The health state occupancy for patients receiving nusinersen were informed by the ongoing NURTURE trial[31] with an expected follow-up of 72 months (6 years) (see Table 6.6 below). In the points for clarification letter[34] the company confirmed that the outcome measures using HINE-2 from NURTURE[31] informed model state occupancy over the first 24 months. The WHO MM[39] data from NURTURE was used to inform state occupancy after 24 months. The company assumed equivalence between motor milestones as defined by HINE-2, and the health states in the economic model defined by WHO MM.[39] [39]The definitions for motor milestones are reported in Table 6.7.

Table 6.6: HINE-2 and WHO motor milestones that informed model state occupancy for nusinersen

Time point	Not Sitting	Sitting without support	Standing with support	Walking independently
Total population				
Baseline	[redacted]	[redacted]	[redacted]	[redacted]
Month 6	[redacted]	[redacted]	[redacted]	[redacted]
Month 9	[redacted]	[redacted]	[redacted]	[redacted]
Month 12	[redacted]	[redacted]	[redacted]	[redacted]
Month 15	[redacted]	[redacted]	[redacted]	[redacted]
Month 18	[redacted]	[redacted]	[redacted]	[redacted]
Month 24	[redacted]	[redacted]	[redacted]	[redacted]

Time point	Not Sitting	Sitting without support	Standing with support	Walking independently
Month 36	[redacted]	[redacted]	[redacted]	[redacted]
Month 48	[redacted]	[redacted]	[redacted]	[redacted]
Month 60	[redacted]	[redacted]	[redacted]	[redacted]
Month 72	[redacted]	[redacted]	[redacted]	[redacted]

Source: Biogen CS Section B 3.3.1, Table 39[33]
Abbreviations: HINE-2 = Hammersmith Infant Neurological Examination – Part 2

Table 6.7: Comparison of motor milestone definitions for HINE-2 and WHO motor milestone measures

Model health states	HINE-2 definitions	WHO motor milestones
Not sitting	<3 in the HINE-2 sitting dimension	-
Sitting without support	Score 3-4 in sitting ability (stable sitting or pivot achievement) and a score of less than 2 in standing ability.	Sits up straight with head erect for 10 seconds without support from hands.
Standing with support	Score of 2 in standing ability. Any score in other items except walking ability.	Stands in an upright position on both feet holding onto a stable object with support from hands only for 10 seconds. The body does not touch the stable object.
Walking independently	Score of 3 in walking ability. Any score in other items.	5 steps independently. One leg moves while the other supports weight.

Source: Biogen CS Section B 3.2.2, Table 34[33]
Abbreviations: HINE-2 = Hammersmith Infant Neurological Examination – Part 2; WHO = World Health Organization

At 6 years of age (corresponding to the last assessment time point in NURTURE),[31,36] patients receiving nusinersen treatment were assumed to either retain or decline their motor milestone for the remainder of their lives. Patients could only lose one motor milestone per model cycle, and the risk of decline for patients receiving nusinersen was relative to the risk of decline from BSC. Patients receiving nusinersen were assumed to have no risk of progression to 'permanent ventilation' based on results from NURTURE.[31]

State occupancy for BSC (Table 6.8) was based on a weighted average of data from the BSC arms of the ENDEAR[28] and CHERISH[29] trials with a follow-up of 15 months, a pragmatic choice following the fact that NURTURE[31] is a single-arm trial. SMA types were weighted based on a disease distribution from Calucho et al.[40] After the points for clarification[34], the company further detailed that the primary outcome in ENDEAR[28] used HINE-2, hence the

model assumed equivalence between HINE-2 scores and model milestones (see Table 6.7 to see how model states are defined according HINE-2 scores and WHO motor milestones).[39]

Table 6.8: Model state occupancy for BSC

Time point	Not Sitting	Sitting without support	Standing with support	Walking independently
Total population				
Baseline	[redacted]	[redacted]	[redacted]	[redacted]
Month 6	[redacted]	[redacted]	[redacted]	[redacted]
Month 9	[redacted]	[redacted]	[redacted]	[redacted]
Month 12	[redacted]	[redacted]	[redacted]	[redacted]
Month 15	[redacted]	[redacted]	[redacted]	[redacted]

Source: Biogen CS Section B 3.3.1 Table 42[33]
Abbreviations: BSC = best supportive care

Since participants in the CHERISH[29] trial were older than those in ENDEAR[28], they reached mobility milestones earlier. Thus, applying these state occupancy data directly to the patients receiving BSC in the presymptomatic model would have led to implausible levels of motor milestone attainment. The company therefore adjusted the level of motor milestone attainment by type 2 and 3 patients in CHERISH[29] trial by up to two health states, thereby increasing the time to achieve motor milestones. For example: in patients with SMA type 3 attaining 'walking independently' at 6 months post baseline (baseline age of 5.29 months), the adjustments would mean that the patients attain this milestone at 15 months post baseline (assumed age of [redacted] at baseline for presymptomatic population).

After 15 months (1.25 years) of receiving BSC, patients were assumed to retain or decline their motor milestone by a maximum of one milestone per cycle. The risk of decline was constant over time, based on Wadman et al.[41] and varied by health state and type SMN2 gene subgroup. It was assumed that only the patients in the 'not sitting' state had the probability to transition to 'permanent ventilation'. The risk of BSC patients moving to permanent ventilation was constant over time and was based on estimates by Wijngaarde et al.[38] and in line with the approach taken in HST24.[17]

EAG comment: The EAG is satisfied that the model structure used by the company to assess the cost-effectiveness of nusinersen versus BSC captures the costs and benefits appropriately. However, the EAG highlights some potential issues in the following sections. The HINE-2 outcome measure was collected in the NURTURE[31] trial informing clinical effectiveness of nusinersen treatment. Whilst the WHO MM is based on typical age-related norms for motor development, HINE-2 is based on clinically assessed scores.. These differences between the measures could have impacted the state occupancy and ultimately the number of patients at risk of 'permanent ventilation'. Therefore, assuming equivalence between the HINE-2 and WHO MM during the early stages of treatment could have potentially introduced structural uncertainties in the presymptomatic model.

The EAG understands there is a lack of data on patients with presymptomatic SMA receiving BSC however, cautions that adjustments to the state occupancy for patients receiving BSC in

the presymptomatic model, which are derived from the level of motor milestones within two health states attained patients with type 2 and 3 in the CHERISH[29] trial, could have potentially favoured nusinersen.

6.3.2.2 Population

The population considered in the presymptomatic model reflected that of the NURTURE[31] baseline characteristics (Table 6.9).

Table 6.9: Baseline population characteristics in the presymptomatic model

Characteristics	Total presymptomatic population [redacted]	Two copies of SMN2 [redacted]	Three copies of SMN2 [redacted]
Baseline age in years (mean (SE))	[redacted]	[redacted]	[redacted]
Sex (female %)	[redacted]	[redacted]	[redacted]
Baseline weight in kg (mean (SE))	[redacted]	[redacted]	[redacted]

Source: Biogen CS Section B 3.3.1 Table 36[33]

Abbreviations: SE= standard error; SMN = survival of motor neuron

EAG comment: The EAG considers the company's consideration of the population (total presymptomatic, two SMN2 copies, three SMN2 copies) in their model appropriate.

6.3.2.3 Interventions and comparators

The presymptomatic model compared nusinersen against BSC in a population with the characteristics reported in Table 6.9.

Intervention: The company modelled nusinersen as the first-line therapy according to its marketing authorisation as SMA treatment. In the economic model, in line with the marketing authorisation, the patient cohort receiving nusinersen were administered four loading doses of 12 mg nusinersen in the first four-month cycle, and then in the subsequent cycles, the cohort received one maintenance dose of 12 mg nusinersen per cycle.[33] All ages received the same dose which was administered intrathecally.

Comparator: The company modelled BSC as the comparator across all populations and reflected the mix of gastrointestinal, respiratory, nutritional and orthopaedic interventions delivered by a multidisciplinary team. The company did not compare nusinersen against risdiplam or OA because of poor availability of data; and the results from the ITC had major limitations and were not considered appropriate.

EAG comment: Biogen's decision problem assumes that patients diagnosed with presymptomatic SMA receive nusinersen, while those with a missed presymptomatic diagnosis receive BSC without access to a disease-modifying therapy. However, following consultation with the company, the EAG found little evidence to support the idea that a presymptomatic diagnosed patient would be excluded from receiving any available disease-modifying therapy. Based on both the clinical context and the evidence available, the EAG cautions against the use of BSC as an appropriate comparator in the presymptomatic SMA

population. In addition, all studies involving presymptomatic population were single-arm, and the EAG notes that the company model relied on strong assumptions of outcomes (reflecting SMA patients not treated) under BSC. Nevertheless, the current NICE scope does not specify whether BSC is an appropriate comparator for all the SMA types[6], and the EAG also recognises the broader data limitations for BSC and other treatment comparators such as OA and risdiplam.

6.3.2.4 Perspective, time horizon and discounting

The analysis was conducted from the perspective of the NHS and Personal Social Services and with a time horizon of 100 years in the base case. The costs and benefits were discounted at annual rate of 3.5%.

EAG comment: The EAG considers the approach taken in the company model appropriate and in line with the NICE guidelines[42]. The 100-year time horizon is long enough to capture the costs and benefits of treatment received over the average lifetime of the patients.

6.3.2.5 Treatment effectiveness and extrapolation

The evidence of treatment effectiveness for nusinersen used in the presymptomatic model was informed by the NURTURE trial.[31,36] The model used the WHO MM outcomes over the first 72 months directly from NURTURE (see section 6.3.2.1.2). Relative estimates of efficacy for nusinersen versus BSC were not available from single-arm trials including NURTURE.[31,36] Therefore, in the absence of long-term data, the relative efficacy estimates from the ENDEAR[28] (for type 1 SMA) and CHERISH[29] (for type 2/3 SMA) trials were used in the presymptomatic population to estimate the risk of decline in the nusinersen cohort.

The company presented an unanchored MAIC between nusinersen and OA for the presymptomatic population using endpoints for WHO MM 'standing with support' and 'walking independently'.[33] The results of this analysis were not used in the economic model. The reasons that the company provided included assessment timelines that did not align for the clinical outcomes and small sample sizes from the study population of each treatment.

EAG comment: On the relative risk of decline calculation, the EAG is concerned that this approach pools estimates of relative risk with different clinical definitions without adequately acknowledging the limitations of this approach. It is also worth noting that there was no evidence of difference (not statistically significant) in the risk difference between nusinersen and BSC treatment response in CHERISH.[29] Additionally, the analysis conflates the clinical definitions, treating lack of milestone improvement equivalent to motor milestone decline, which may introduce uncertainty. However, the EAG acknowledges the limited availability of data. In addition, the EAG finds the company's justification for not using unanchored MAIC results to compare nusinersen vs OA appropriate. Nevertheless, the EAG explored a comparison between nusinersen vs OA using the unanchored MAIC results despite being poor in terms of data.[33].

6.3.2.6 Health related quality of life

Utilities were based on the most recent NICE appraisal for treating presymptomatic SMA, HST24.[17] Age and gender adjustments to utilities have been made using a multiplicative approach following NICE guidelines. Utility values depended on model health-state. An on-treatment utility increment of 0.1 (based on clinical expert opinion) was also included for all patients while they received nusinersen, which allowed accommodation of any additional

gains in health-related quality of life (such as additional upper limb function) that were not captured in the health state utility values. The same set of health-state related utility values were used across all models regardless of the SMA types and regardless of treatment (Table 6.10). In a scenario analysis, the company considered the health-state utility values used as an exploratory analysis by a previous EAG in TA755 for treatment of SMA with risdiplam.[3]

Table 6.10: Health state utility values used in the company base-case models

Health state	Utility
Permanent ventilation	0
Not sitting	0.19
Sitting	0.6
Standing	0.77
Walking	Equivalent to general population
Additional utilities	
Treatment benefit	0.1
Source: Biogen CS Section B 3.4.5 Table 62[33]	

6.3.2.7 Approach to care-giver health-related quality of life

The company adopted a utility increment approach for care givers based on model health states. The model further assumes that carer utility values depend on the model health state and not on the SMA type or the treatment received (i.e. carer utilities only increase with the attainment and maintenance of motor milestones regardless of treatment or SMA type). Therefore, the company used the same carer utility values across the models. The approach was based on EAG feedback from TA755.[3] The company did not conduct any scenario analyses using alternative carer utility values. It was assumed that there would be 1 carer for each SMA patient across health states (initial 2 carers corrected by the company in the addendum; see Table 6.11).

Table 6.11: Health state utility values for carers and the number of carers used in company base-case models

Health state	Number of carers	Utilities
Permanent ventilation	1	0.484
Not sitting	1	0.484
Sitting without support	1	0.628
Standing with assistance	1	0.771
Walking independently	1	Population norm
Source: Biogen CS Section B 3.4.5 Table 62[33]		

EAG comment: The EAG considers the health state utility values used in the company models appropriate. The EAG acknowledges that patients can get improvements in quality of life within each motor milestone (e.g. holding objects, lifting toys, or simply being able to sit for few secs etc) and these nuanced benefits may not be adequately captured by the generic preference-based measure (EQ-5D-3L). The importance of these subtle improvements in

quality of life have been raised in the EAG's engagement with patients and professionals. (see Section 13.5)

The EAG acknowledges the importance of including the experience of informal carers in this appraisal; however, there are no standardised methodologies to quantify the impact on health-related quality of life from informal carers, and the data specific to SMA is scarce. Therefore, in the EAG base-case, models focussed primarily on the quality of life of patients. The data for informal carers were used and presented as an additional scenario for the purposes of transparency, allowing an explicit assessment of the disease burden for patients alone, and for patients and their carers together.

6.3.2.8 Resource use and costs

The company used a list price of £75,000 per 12mg/5ml vial of nusinersen plus an administration cost of the drug (£836 per dose, assumed as a proxy for diagnostic spinal puncture). However, after applying a PAS of [redacted] the acquisition cost of nusinersen were reduced to [redacted] per dose. No concomitant medication costs were applied into the economic model.

The company did not apply additional drug acquisition cost, administration or concomitant costs for BSC.

The company used the healthcare resource utilisation costs that were previously used in the NICE appraisal of OA (HST24[17]) (Table 6.12). In the absence of costs for the "standing" health state, the company assumed them to be equivalent to the "walking" health state. In addition, the company used alternative health state costs from the previous NICE risdiplam appraisal (TA755)[3] in the scenario analyses (Table 6.13).

Table 6.12: Health care resource utilisation costs applied to the health states in the company models

Resource category	Permanent ventilation	Non-sitter	Sitting	Standing and Walking
Drugs	£619	£810	£781	£1,012
Medical tests	£880	£1,152	£917	£675
Medical visits	£3,669	£4,801	£2,805	£2,461
Hospitalisations	£218,987	£70,829	£40,577	£276
Accident and Emergency	£375	£490	£201	£80
Health material	£3,590	£4,400	£2,274	£652
Social services	£55,590	£30,019	£20,013	£3,177
Total	**£283,710**	**£112,500**	**£67,567**	**£8,333**
Source: Biogen CS Section B 3.5.2 Table 65[33]				

Table 6.13: Alternative health care utilisation costs applied to health states in the company models

Health state	Annual cost reported in TA588[2]	Inflated annual cost (applied in CEM) ¥	Inflated cost per 4-month cycle
Permanent ventilation*	£136,444	£150,989	£50,330
Not sitting	£77,968	£86,280	£28,760
Sitting	£55,185	£61,068	£20,356
Standing	£20,229	£22,385	£7,462
Walking	£20,229	£22,385	£7,462

* The annual cost for 'permanent ventilation' is assumed to be equivalent to the cost of 'not sitting' as per TA588[2] with a 175% increase in costs as applied in TA755[3]
¥ Costs are inflated from cost year 2016/17 to 2021/22 using an inflation index of 1.11 using indices derived from PSSRU 2022, NHSCII pay and prices., PSSRU: Personal Social Services Research Unit, NHSCII: NHS cost inflation index
Abbreviations: CEM, cost-effectiveness model

EAG comment: The EAG considers the company's estimate of resource utilisation and health states costs appropriate.

6.3.2.9 Adverse events

There were no reported adverse events attributed to nusinersen for presymptomatic patients in the NURTURE[31] trial. The company did not apply adverse events and associated costs/utility decrements into their economic models. There were no other additional costs applied into the models. As a justification for not including the treatment related adverse events, the company referred to TA588,[2] TA755[3] and HST15,[43] where the impact of any adverse events was not explicitly incorporated into the economic model as they were considered to be accounted already by the health state utility values given the nature of SMA.

EAG comment: The EAG considers the company's approach not to incorporate any additional costs and utility impacts of treatment related adverse events into the model due to low incidence (< 5% of severe treatment-related events) aligns with previous appraisals and is appropriate. In any case, there were no adverse events attributed to nusinersen for presymptomatic patients in the trial.[31] However, had there been adverse events, it could be argued that incorporating them into the model would have led to the double counting of associated impact.

6.3.2.10 Survival

The company did not use the survival data from NURTURE to inform the nusinersen cohort in the presymptomatic model because all patients were alive with a mean age of 4.9 years and had no permanent ventilation at the data cut-off. Therefore, the company utilised the digitised version of the appropriate parametric curves from HST24[17] for 'permanent ventilation', 'not sitting' and 'sitting' cohorts in the model states. The mortality estimates from 'standing without support' and 'walking independently' health states were informed by UK general population mortality data. The company used the national life tables from 2017-19 for the UK general

population mortality data to minimise the impact of COVID-19 in the then available life tables from 2020-22.[44] In the absence of comparative data, the company used the same survival data for nusinersen (across all subgroups) and BSC.

EAG comment: The EAG acknowledges the limited availability of data and considers the company's approach of incorporating the health-state dependent mortality appropriate. The EAG is satisfied with the company's choice of parametric curves from HST24.[17]

6.3.2.11 Discontinuation

The company assumed that any patient who transitions to 'permanent ventilation' would discontinue nusinersen treatment because of inability to undergo the intrathecal administration needed. The company utilised the Managed Access Agreement (MAA)[19] data to inform discontinuation of treatment for reasons other than permanent ventilation. There were insufficient data to estimate the discontinuation rates using the MAA data for presymptomatic population. However, due to the similar prognosis between presymptomatic SMA and type 2/3 SMA, the company used MAA discontinuation results for nusinersen in the SMA 5q type 2 and 3 populations. In the absence of data from MAA, discontinuation data from the 'walking independently' health state was applied to the 'standing with support' health state. Discontinuation rates were applied over time and differed by model health state but not by sub-population. The company assumed that after discontinuation, the cohort moved on to receive BSC and incurred costs and outcomes specific to BSC.

EAG comment: The EAG acknowledges the limitations in the available data and considers the company's approach in incorporating discontinuation appropriate. However, it is likely that those discontinuing nusinersen may not transition to receive BSC alone, but instead may receive alternative disease modifying treatments. This would have implications for both the costs and outcomes, which are not fully captured in the current models.

6.3.2.12 Decision modifier: Severity

The company included carer utilities in the base-case analysis, and in line with the TSD23[45] recommendation, did not include a severity modifier when carer utility increments were applied. However, severity modifiers were included in the scenario analyses where carer utility increments were removed. A highest QALY shortfall of 1.7 was applied to the type 1 model, and 1.2 was applied to the presymptomatic model, whereas no QALY shortfall was applicable to the type 2/3 model.

EAG comment: The EAG considers the company's approach of incorporation of severity modifier in QALYs gains in treatment of SMA to be appropriate, given the severity of the condition. However, the EAG cautions that applying a severity modifier may risk double counting if the health state utility values used to calculate the QALYs already reflect disease severity. Therefore, for transparency and explicit assessments the EAG assessed the impact of incorporating the severity modifier only as an additional analysis presented alongside the base-case.

6.3.2.13 Company's cost-effectiveness results (presymptomatic SMA population)

The company reported both the deterministic and probabilistic results, and the deterministic sensitivity analysis and scenario analyses results. The base-case results are based on the analysis which included carer utilities and considered the PAS discounted price for nusinersen.

Based on the updated results presented in the company response to the points for clarification (March 2025),[34] in the base-case analysis, nusinersen [redacted] over BSC with an ICER of [redacted] Table 6.14). The probabilistic results were generally stable. Nusinersen had a [redacted] probability of being cost-effective compared to BSC at a £30,000/QALY willingness to pay threshold.

Table 6.14: Deterministic and probabilistic results for presymptomatic population reported by the company (using nusinersen PAS price)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER versus baseline (£/QALY)	NHB at £30,000/ QALY
Deterministic								
Nusinersen	[redacted]	20.88	[redacted]	-	-	-	-	-
BSC	[redacted]	19.91	[redacted]	[redacted]	0.97	[redacted]	[redacted]	[redacted]
Probabilistic								
Nusinersen	[redacted]	20.93	[redacted]	-	-	-	-	-
BSC	[redacted]	19.92	[redacted]	[redacted]	1.01	[redacted]	[redacted]	[redacted]
Probability cost-effective								[redacted]

Abbreviations: BSC = best supportive care; ICER = incremental cost-effectiveness ratio; LYG = life years gained; NHB = net health benefit; QALYs = quality-adjusted life years
Source: originally reported in Biogen CS Section B 3.9.1 Table 72 and Table 73[33], results updated by the company in points for clarification[34]

6.3.2.13.1 Deterministic sensitivity analysis (presymptomatic population)

One-way sensitivity analysis conducted by the company by varying key input parameters, was reported to show that health-state costs had the highest impact on ICER, followed by relative risk of decline in the nusinersen treatment arm (Figure 2).

Figure 2: Tornado diagram showing the one-way sensitivity analyses for nusinersen on presymptomatic population reported by the company



Abbreviations: BSC = best supportive care; ICER = incremental cost-effectiveness ratio; QALYs = quality-adjusted life years

Source: originally reported in Biogen CS Section B 3.10.2 Figure 56[33], results updated by the company in points for clarification[34]

6.3.2.13.2 Company's scenario analysis (presymptomatic population)

The company conducted a range of scenario analyses which assessed the impact caused by a change in a parameter on the base-case results (Table 6.15). Assuming the health state costs from TA588[2] increased the deterministic ICER above the £30,000/QALY threshold, while assuming no long-term decline in motor milestones for nusinersen led to it being more effective and less costly than BSC. Deterministic sub-group analyses showed that, for the subgroup with 2 copies of SMN2, nusinersen [redacted] than BSC in the probabilistic analysis. For the subgroup with 3 copies of SMN2 nusinersen had a deterministic ICER of [redacted].

Table 6.15: Company's scenario analyses for the presymptomatic population (Deterministic analysis)

Scenario	Scenario analysis	ICER
0	Reference	[redacted]
1	Assumption that nusinersen cohort does not decline	[redacted]
2	The rate of decline for BSC is halved	[redacted]
3	Remove carer utility increments	[redacted]
4	Remove active treatment increments	[redacted]
5	Remove all increments	[redacted]
6	Alternate utility source: TA588	[redacted]
7	Costs from TA588	[redacted]

Abbreviations: BSC = best supportive care; ICER = incremental cost effectiveness ratio
Source**:** originally reported in Biogen CS Section B 3.10.3 Table 97[33], results updated by the company after the points for clarification[34]

EAG comment: The EAG considers the company's presentation of cost-effectiveness results appropriate. The scenario analyses undertaken also are reasonable. However, there was a quite large increase in ICER when costs from TA588[2] were used, this highlights that there would be a huge impact in the cost-effectiveness driven by any uncertainties in the health state costs.

6.3.3 Type 1 SMA

6.3.3.1 Model structure

6.3.3.1.1 Type of model

Same as the presymptomatic model. See section 6.3.3.1.1.

6.3.3.1.2 Health states/events and transitions:

Biogen generated a Markov state transition model based on motor milestones for the type I SMA population. The model structure was same as the one for presymptomatic population (see Section 6.3.2.1). The motor milestones included were the same as in the presymptomatic model, that is: 'non-sitting', 'sitting without support', 'standing with support' and 'walking independently'. The model for type 1 SMA also included a 'permanent ventilation' health state. The model had all patients start in the 'not sitting' health state due to mean age at baseline

being less than 6 months. The transition to the 'permanent ventilation' state was only possible from the 'not sitting' health state.

Health state definitions were combined based on both the WHO MM[39] and the HINE-2 scoring measures. Patients with a minimum score of 3 in the sitting dimension of HINE-2 were assumed to be at 'sitting without support', a minimum score of 2 in the standing dimension of HINE-2 were assumed as 'standing with support', a minimum score of 3 in the walking ability of HINE-2 were assumed as 'walking independently'. This assumption was based on the evidence from the ENDEAR[28] trial which had a 13-month duration and focused on HINE-2 scores as a primary outcome measure. While the SHINE[37] study, which informed long-term effectiveness, assessed motor function using WHO MM instead of HINE-2.

After the points for clarification letter[34], the company detailed their approach for defining state occupancy for the nusinersen arm, which was based on data from both ENDEAR[28] and SHINE[37] Motor function as measured by HINE-2 from ENDEAR informed state occupancy in the first 12 months from baseline, and SHINE informed the occupancy after 12 months by assuming equivalence between HINE-2 and WHO MM outcome measures. The state occupancy data used in the nusinersen arm of the type 1 model submitted by the company are reported in Table 6.16.

The state occupancy for the patients receiving BSC in the company model was informed by ENDEAR[28] (follow-up of 13 months), where the patients never achieved the ability to sit without support (see Table 6.17).

Table 6.16: Motor milestone (health) state occupancy for nusinersen defined in HINE-2 and WHO motor milestones from the combined ENDEAR-SHINE population

Time point	Not Sitting	Sitting without support	Standing with support	Walking independently
Baseline	[redacted]	[redacted]	[redacted]	[redacted]
Month 3	[redacted]	[redacted]	[redacted]	[redacted]
Month 6	[redacted]	[redacted]	[redacted]	[redacted]
Month 9	[redacted]	[redacted]	[redacted]	[redacted]
Month 12	[redacted]	[redacted]	[redacted]	[redacted]
Month 15	[redacted]	[redacted]	[redacted]	[redacted]
Month 18	[redacted]	[redacted]	[redacted]	[redacted]
Month 24	[redacted]	[redacted]	[redacted]	[redacted]
Month 36	[redacted]	[redacted]	[redacted]	[redacted]
Month 48	[redacted]	[redacted]	[redacted]	[redacted]
Month 60	[redacted]	[redacted]	[redacted]	[redacted]
Source: Biogen CS Section B 3.3.2 Table 48[33]				

Table 6.17: Motor milestone (health) state occupancy for BSC from ENDEAR

Time point	Not Sitting	Sitting without support	Standing with support	Walking independently
Baseline	[redacted]	[redacted]	[redacted]	[redacted]
Month 6	[redacted]	[redacted]	[redacted]	[redacted]
Month 9	[redacted]	[redacted]	[redacted]	[redacted]
Month 12	[redacted]	[redacted]	[redacted]	[redacted]

Source: Biogen CS Section B 3.3.2 Table 50[33]
Abbreviations: BSC = best supportive care

ENDEAR[28] and SHINE[37] together had a follow-up of 60 months; after this period patients receiving nusinersen were assumed to either maintain the motor milestones gained, or risk losing one motor milestone following each model cycle. The relative risk of no treatment response between nusinersen and BSC observed in ENDEAR[28] was used as the relative risk of losing one motor milestone over the time horizon beyond 60 months.

State occupancy for patients receiving BSC was informed by ENDEAR[28] (follow-up of 13 months), after 12 months patients were assumed to either maintain the motor milestones gained, or risk losing one motor milestone following each model cycle. The baseline risk of losing motor milestones was taken from Wadman et al[41]. and was assumed constant over time to vary by health state. [redacted].

EAG comment: The EAG discussed the patient transition, and the likelihood of motor milestone decline with the clinicians and physiotherapists**.** Though the decline may not be constant over time and may vary with the case, the EAG acknowledges the current data limitations and difficulties in modelling them. Therefore, the EAG finds the company's approach of estimating data for state occupancy and motor milestone decline appropriate.

6.3.3.2 Population

The baseline characteristics of the patient cohort used in the type 1 SMA model reflected those of the participants in the ENDEAR[28] trial (see Table 6.18).

Table 6.18: Baseline population characteristics in the type 1 SMA nusinersen model

Characteristics	Total population [redacted]
Baseline age in years (mean)	[redacted]
Sex (female %)	[redacted]
Baseline weight in kg (mean)	[redacted]

Source: Biogen CS Section B 3.3.2 Table 47[33]

EAG comment: The EAG considers the population characteristics used in the type 1 SMA model appropriate and representative of type-1 SMA population.

6.3.3.3 Interventions and comparators

Same as the presymptomatic model (see Section 6.3.4.3)

6.3.3.4 Perspective, time horizon and discounting

Same as the presymptomatic model (see Section 6.3.2.4)

6.3.3.5 Treatment effectiveness and extrapolation

The efficacy results used in the type 1 SMA model were informed by the ENDEAR[28] and SHINE[37] trials. ENDEAR[28] had a follow-up of 13 months, therefore the company used data from SHINE[37] to overcome the limitations of short follow-up; ENDEAR[28] and SHINE[37] combined had a total follow-up of 60 months. Participants in SHINE[37] included all participants from ENDEAR[28], irrespective of whether they received nusinersen or sham procedure in ENDEAR.

EAG comment: The EAG acknowledges short follow-up data limitations from ENDEAR[28] and considers the company's approach of overcoming it by using data from SHINE[37] appropriate. However, it should be noted that SHINE[37] was a single-arm study and therefore in the absence of an appropriate comparator, the efficacy data for nusinersen could have been overestimated.

6.3.3.6 Health related quality of life

Same as the presymptomatic model (see Section 6.3.2.7)

6.3.3.7 Resource use and costs

Same as the presymptomatic model (see Section 6.3.2.8)

6.3.3.8 Adverse events

Same as the presymptomatic model (see Section 6.3.2.9)

6.3.3.9 Survival

The patient cohort in the type 1 SMA model could transition to 'death' from all the health states in the model. Individual patient level data from ENDEAR[28] and SHINE[37] was utilised to inform all-cause mortality for the nusinersen treatment cohort in 'permanent ventilation', 'no sitting' and 'sitting without support' health states. Rank preserving structural failure time models (RPSFTM) were used to adjust for treatment switching from ENDEAR[28] to SHINE.[37] Overall survival for the BSC cohort came from the control arm of ENDEAR.[28] Kaplan Meier curves for overall survival were generated and since the proportional hazards assumption was met for all covariables, a joint parametric model was used to extrapolate both arms over the model time horizon. The Weibull parametric curve was selected as it best represented long-term clinical practice (Figure 4). The risk rate was modelled over time and assumed relative hazard rates were constant over time for disease-related mortality, while net hazard rates decreased and then plateaued for both treatments (Figure 5).

The company assumed that there is no increased risk of mortality for the type 1 SMA patient cohort in the 'standing with support' and 'walking independently' health states when compared to the general population. Therefore, the company utilised general population mortality data to inform survival in these two states.

Figure 3: Overall survival in nusinersen and BSC patient cohorts (type 1)



Source: EAG produced from company submitted models

Abbreviations: BSC = best supportive care; OS = overall survival

Figure 4: Comparison of mortality risk between nusinersen and BSC patient cohorts (type 1)



Source: EAG produced from company submitted models
Abbreviations: BSC = best supportive care; OS = overall survival

The company's type 1 SMA model assumed that patients could only transition to 'permanent ventilation' from the 'not sitting' health state. The proportion of patients in the nusinersen treatment cohort moving to 'permanent ventilation' was informed by pooled data from ENDEAR[28] and SHINE.[37] However, the proportion of the BSC cohort moving to 'permanent ventilation' was informed by data from ENDEAR[28] alone. Since the proportional hazards assumption was not met, different parametric models were fitted into each Kaplan Meier curve, with a log-normal function for nusinersen and a log-logistic function for BSC considered most plausible by clinical experts. Figure 5 showed an increase in the permanent ventilation hazard for BSC over the first year before decreasing over the subsequent years. Figure 6 showed that the relative risk for nusinersen versus BSC lowered over the first year and became marginally closer over the long term.

Figure 5: Time to permanent ventilation in nusinersen and BSC patient cohorts (type 1)



Source: EAG produced from company submitted models
Abbreviations: BSC = best supportive care; PV: permanent ventilation

Figure 6: Hazard ratio for permanent ventilation (BSC vs nusinersen, type 1)



Source: EAG produced from company submitted models
Abbreviations: BSC = best supportive care; Nus: Nusinersen

EAG comment: The EAG considers the approach taken by the company to estimate the survival data appropriate. Consideration of RPSFTM is expected to improve the internal validity of survival data when treatment switching occurs. The EAG appreciates the use of clinical opinion and goodness-of-fit measures while finding the most plausible parametric curve.

6.3.3.10 Discontinuation

In line with the presymptomatic model (see section 6.3.2.11), the company assumed that any patient who transitions to permanent ventilation would discontinue nusinersen treatment because of their inability to receive the intrathecal administration needed. The company utilised the MAA)[19] data to inform discontinuation in 'not sitting' and 'sitting without support' health states. The MAA)[19] data reported by the company showed that 32 out of 44 patients who discontinued over the 3.5 years switched to OA, where the company reasoned that these patients would have remained in the nusinersen treatment if OA had not become available during the MAA)[19] study and they were not included in the discontinuation data. No patients during the MAA)[19] achieved the ability to stand or walk, and any ability to walk or stand would be considered the result of highly effective treatment. Therefore, the company assumed that when the treatment is considered highly effective, the discontinuation would be low for the health states, 'walking independently' and 'standing with support'. The company assumed a discontinuation rate from nusinersen to BSC of 1.5% per 4-month model cycle for patients 'not sitting' and 'sitting without support' and 1% per-cycle or 'standing with support' and 'walking independently'. After discontinuation, the cohort moved on to receive BSC and incurred costs and outcomes specific to BSC.

EAG comment: The EAG acknowledges the data limitations and considers the company's approach in incorporating discontinuation appropriate. However, it is likely that those discontinuing may not necessarily go on to receive BSC, and instead may go on to receive

other disease modifying treatments, when there would be impact on costs and outcomes. Furthermore, the MAA[19] data have short follow-ups which may not be sufficiently long-enough to correctly capture the discontinuations from nusinersen.

6.3.3.11 Disease modifier: severity

Same as presymptomatic model (see Section 6.3.2.12).

6.3.3.12 Company's cost-effectiveness results (type 1)

The company reported both the deterministic and probabilistic results, and the deterministic sensitivity analysis and scenario analyses results. The base-case results are based on the analysis which included carer utilities and considered the PAS discounted price for nusinersen. In the base-case analysis, nusinersen was [redacted] over BSC, with an ICER of [redacted] (Table 6.19), which is higher than the NICE's £20,000 willingness to pay threshold. The probabilistic results were generally stable. Nusinersen had a [redacted] probability of being cost-effective compared to BSC at a NICE's £30,000/QALY willingness to pay threshold.

Table 6.19: Deterministic and probabilistic results for the type 1 SMA population reported by the company (using nusinersen PAS price)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER versus baseline (£/QALY)	NHB at £30,000 / QALY
Deterministic								
Nusinersen	[redacted]	8.38	[redacted]	-	-	-	-	-
BSC	[redacted]	2.91	[redacted]	[redacted]	5.47	[redacted]	[redacted]	[redacted]
Probabilistic								
Nusinersen	[redacted]	8.37	[redacted]	-	-	-	-	-
BSC	[redacted]	3.05	[redacted]	[redacted]	5.32	[redacted]	[redacted]	[redacted]
Probability cost-effective at £30k willingness to pay								[redacted]

Source: originally reported in Biogen CS Section B 3.9.2 Table 79 and Table 80,[33] results updated by the company after the points for clarification[34]

Abbreviations: BSC = best supportive care; ICER = incremental cost-effectiveness ratio; LYG = life years gained; NHB = net health benefit; QALYs= quality-adjusted life years

6.3.3.12.1 Deterministic sensitivity analysis (type 1)

One-way sensitivity analysis conducted by the company by varying key input parameters was reported to show that health state utilities had the highest impact on ICER, followed by cost of permanent ventilation and health state costs (Figure 7).

Figure 7: Tornado diagram showing the one-way sensitivity analyses on the type 1 SMA population reported by the company



Abbreviations: BSC = best supportive care; ICER = incremental cost effectiveness ratio; QALY = quality adjusted life year
Source: originally reported in Biogen CS Section B 3.10.2 Figure 57,[33] results updated after the points for clarification[34]

6.3.3.12.2 Company's scenario analysis (type 1 SMA)

Assuming utilities from TA588[2] increased the ICER [redacted] to maximum, while removing the background care costs for extended years survived decreased the ICER [redacted] below the £20,000/QALY threshold (Table 6.20).

Table 6.20: Company's scenario analyses for type 1 SMA population

Scenario	Scenario analysis	ICER
0	**Reference**	[redacted]
1	Alternate utility source: TA588	[redacted]
2	Exclude caregiver utility increments	[redacted]
3	Exclude active treatment utility increments	[redacted]
4	Costs from TA588 (Wickenstones)	[redacted]
5	Health state costs for active treatments set to 0 GBP (£) at total discounted BSC LYs	[redacted]
6	Assumption that nusinersen cohort does not decline	[redacted]
7	The rate of decline for BSC is halved	[redacted]

Source: originally reported in Biogen CS Section B 3.10.3 Table 98,[33] results updated after the points for clarification[34]
Abbreviations: BSC = best supportive care; ICER = incremental cost effectiveness ratio; LY = life years

EAG comment: The EAG considers the company's presentation of cost-effectiveness results appropriate. The scenario analyses undertaken also are reasonable.

6.3.4 Type 2/3 SMA

6.3.4.1 Model structure

6.3.4.1.1 Type of model:

The company developed a de novo Markov model (

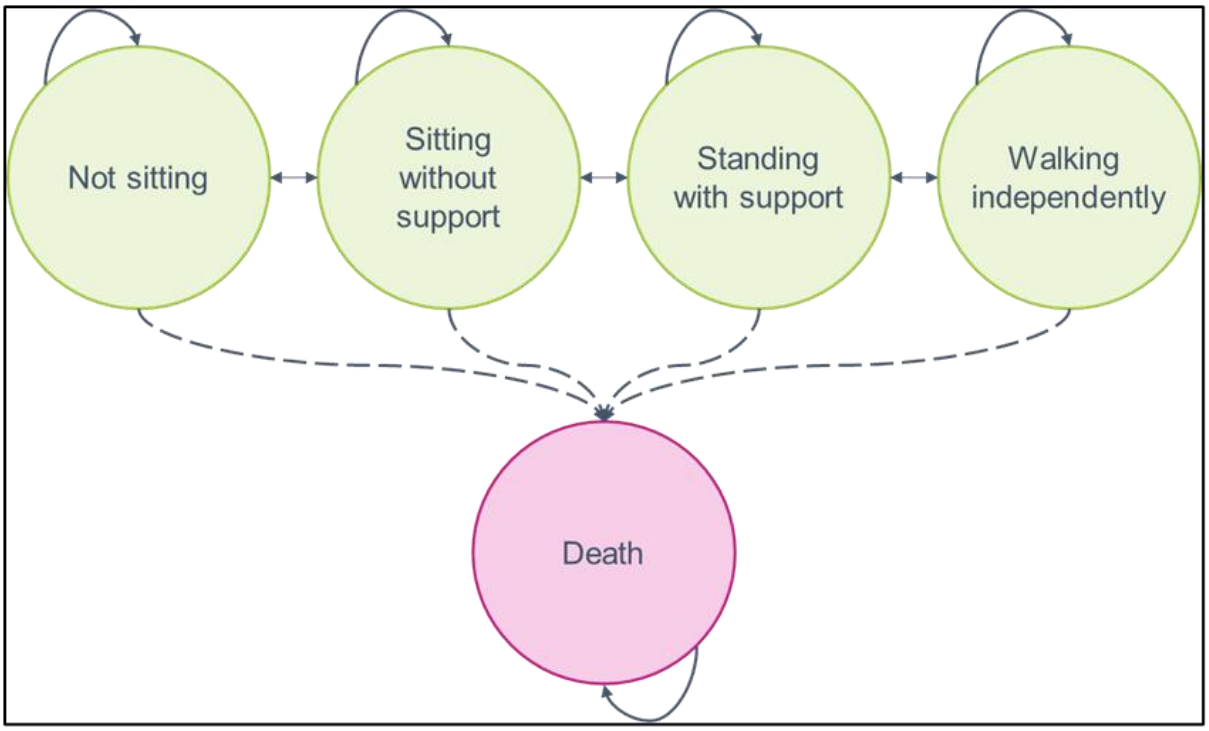
Figure **8**) in Microsoft Excel program to assess the cost-effectiveness of nusinersen in type 2/3 SMA population (later onset) primarily informed by TA588.[2]

6.3.4.1.2 Health states/ events and transitions

The economic evaluation model used to assess the cost-effectiveness of nusinersen in the type 2/3 SMA population had 5 states that captured the gross motor milestones: ‘not sitting’, ‘sitting without support’, ‘standing with support’, ‘walking independently’, and ‘death’ as an absorbing state (

Figure **8**). The motor milestones were defined using the WHO instrument.[39] Unlike the economic models for presymptomatic and type 1 SMA, the economic model for type 2/3 SMA did not include the 'permanent ventilation' state, for which the company provided a justification. The company reported that the decision not to include permanent ventilation aligned with the evidence that permanent ventilation is quite rare in type 2/3 SMA population, and this decision was validated by clinical experts at the advisory board.

Figure 8: Model structure for the later-onset SMA population used by the company (type 2/3)



Source: Biogen CS Section B 3.2.2 Figure 36[33]

EAG comment: The EAG considers the type 2/3 SMA model used by the company appropriate and aligned with the SMA clinical pathway and motor milestones.

6.3.4.2 Population

The model cohort used reflected the baseline characteristics of the ITT population in CHERISH[29] and SHINE[37] clinical trials for nusinersen. However, both trials consisted of participants predominantly with type 2 SMA, and therefore did not adequately reflect a type 3 SMA population. Therefore, the company utilised information from Wadman et al[41] to account for the characteristics of a sub population with type 3 SMA. The company assumed that 100% of the cohort with type 3 SMA were walking at the baseline to reflect the clinical definition of type 3 SMA that all patients with type 3 SMA 'acquire autonomous ambulation' or are walkers. An overall population mean, generated by combining these two populations (type 2 and type 3), informed the economic model. The company reported the type 2, type 3 and combined type 2/3 population characteristics in Table 6.21.

Table 6.21: Type 2/3 SMA population characteristics reported by the company

Characteristics	Total later-onset SMA [redacted]	Type 2 SMA* [redacted]	Type 3 SMA** ([redacted]
Baseline age (years, mean [SE])	[redacted]	[redacted]	[redacted]
Sex (female, %)	[redacted]	[redacted]	[redacted]
Baseline weight (kg, mean [SE])	[redacted]	[redacted]	[redacted]

Characteristics	Total later-onset SMA [redacted]	Type 2 SMA* [redacted]	Type 3 SMA** ([redacted]
Source: Biogen CS Section B 3.3.3 Table 55[33] *Based on the baseline characteristics of all nusinersen and control patients in the CHERISH study[29] **Informed by baseline data from the natural history study reported by Wadman et al[41] Abbreviations: SMA = spinal muscular atrophy; SE = standard error			

EAG comment: The EAG considers the population characteristics used in the type 2/3 SMA model appropriate and representative of type 2/3 SMA population.

6.3.4.3 Interventions and comparators

Same as presymptomatic model (see Section 6.3.2.3)

6.3.4.4 Perspective, time horizon and discounting

Same as presymptomatic model (see Section 6.3.2.4)

6.3.4.5 Treatment effectiveness and extrapolation

The nusinersen effectiveness data used in the type 2/3 SMA economic model primarily came from the CHERISH[29] and SHINE[37] trials. CHERISH[29] was a 15-month multinational trial comparing treatment with nusinersen compared to a sham procedure as a control. To overcome limitations due to the short duration of CHERISH[29], the participants from CHERISH[29] were enrolled in the SHINE[37] trial and were categorised (as previous nusinersen or sham) according to the treatment they received in CHERISH[29]. The WHO MM data, informed by patient level data from CHERISH[29] and SHINE[37] over the first 96 months, were directly used in the economic model as a proportion of the cohort occupying each health state in the model (Table 6.22).

Table 6.22: Company-reported WHO motor milestone data from CHERISH and SHINE for nusinersen patients used in the type 2/3 SMA model

Time point	Not Sitting	Sitting without support	Standing with support	Walking independently
Baseline	[redacted]	[redacted]	[redacted]	[redacted]
Month 6	[redacted]	[redacted]	[redacted]	[redacted]
Month 9	[redacted]	[redacted]	[redacted]	[redacted]
Month 12	[redacted]	[redacted]	[redacted]	[redacted]
Month 15	[redacted]	[redacted]	[redacted]	[redacted]
Month 18	[redacted]	[redacted]	[redacted]	[redacted]
Month 24	[redacted]	[redacted]	[redacted]	[redacted]
Month 36	[redacted]	[redacted]	[redacted]	[redacted]
Month 48	[redacted]	[redacted]	[redacted]	[redacted]
Month 60	[redacted]	[redacted]	[redacted]	[redacted]
Month 72	[redacted]	[redacted]	[redacted]	[redacted]
Month 84	[redacted]	[redacted]	[redacted]	[redacted]

Time point	Not Sitting	Sitting without support	Standing with support	Walking independently
Month 96	[redacted]	[redacted]	[redacted]	[redacted]

Source: Biogen CS Section B 3.3.3 Table 56[33]
*Includes patients who were reported as walking independently but were reallocated to meet the definition for type 2 SMA.

The company assumed all type 2 sub-populations 'walking independently' by the end of the trial follow-up in CHERISH[29] and SHINE[37] trials to be 'standing with support' and they were allocated in the economic model accordingly for both nusinersen and BSC arms. It was reported that this assumption is based on the standard definition of SMA where patients following natural history should not be able to walk. The reason behind making the similar assumption for both the model arms was to avoid biasing the model in favour of nusinersen. The company assumed that all type 3 sub-populations "walking independently" at baseline maintained the ability to walk over the first 96 months of the economic model time horizon. This assumption was supported by Wadman et al[41], where the ability to walk was sustained until the mean age of 11 years and 34 years for type 3A and 3B populations respectively. As stated earlier, the economic model for type 2/3 SMA used data from combined type 2 and 3 populations.

The company did not have long-term data beyond the 96 months follow-up for nusinersen on the ability of type 2/3 patients to walk, therefore assumption was made for the model cohort to decline by a maximum of one milestone per cycle or by multiple milestones over their lifetime. It was reported that the assumption adhered to what clinical experts observe in clinical practice. The probability of decline for each state was estimated relative to the BSC data reported by Wadman et al[41] (Table 6.23). The inverse of relative risk of improvement ([redacted]; corrected estimate after points for clarifications from the EAG), derived using the 15-month follow-up data from CHERISH[29] trial on proportions who gained at least one WHO motor milestones each trial arm, were applied to the long-term probabilities of decline in the BSC to derive the probability of decline for nusinersen. These probabilities were assumed equal across all populations and applied for all model cycles 8 years onwards (to reflect the time point at which the trial data ends).

Table 6.23: Per-cycle probability of decline for nusinersen applied in the company type 2/3 SMA model cycles 8 years onwards

Health state	Per cycle probability of decline (%)		
	Total later-onset SMA	Type 2 SMA	Type 3 SMA
Sitting without support to not sitting	[redacted]	[redacted]	[redacted]
Standing with support to sitting without support	[redacted]	[redacted]	[redacted]
Walking independently to standing with support	[redacted]	[redacted]	[redacted]

Source: originally reported in Biogen CS Section B 3.3.3 Table 57,[33] corrected after points for clarification[34]
Abbreviations: SMA = spinal muscular atrophy

The company assumed equivalence of outcomes from the sham control arm of CHERISH[29] trial and BSC. Therefore, the patient data from the sham arm informed the proportion of patients in each of the model health states over 15 months of the model time horizon (reflective of CHERISH follow-up duration). The long-term probability of decline was derived from Wadman et al. 2018[41] (Table 6.24) and was applied in each model cycle beyond 15 months. Similar to the nusinersen arm, the assumption was made for the model cohort to decline by a maximum of one milestone per cycle or by multiple milestones over their lifetime.

Table 6.24: WHO motor milestones used in the BSC arm of the company type 2/3 SMA model

Time point	Not Sitting	Sitting without support	Standing with support	Walking independently
Baseline	[redacted]	[redacted]	[redacted]	[redacted]
Month 6	[redacted]	[redacted]	[redacted]	[redacted]
Month 9	[redacted]	[redacted]	[redacted]	[redacted]
Month 12	[redacted]	[redacted]	[redacted]	[redacted]
Month 15	[redacted]	[redacted]	[redacted]	[redacted]

*Includes patients who were reported as walking independently but were reallocated to meet the definition for type 2 SMA.
Source: Biogen CS Section B 3.3.3 Table 58[33]
Abbreviations: SMA = spinal muscular atrophy

Table 6.25: Per-cycle probability of decline for BSC cohort used in the company type 2/3 SMA model cycles 8 years onwards

Health state	Per cycle probability of decline (%)		
	Total later-onset SMA	Type 2 SMA	Type 3 SMA
Sitting without support to not sitting	[redacted]	[redacted]	[redacted]
Standing with support to sitting without support	[redacted]	[redacted]	[redacted]
Walking independently to standing with support	[redacted]	[redacted]	[redacted]

Source: originally reported in Biogen CS Section B 3.3.3 Table 59[33] corrected after points for clarification[34]
Abbreviations: BSC = best supportive care; SMA = spinal muscular atrophy

EAG comment: The EAG acknowledges data limitations and considers the company's approach appropriate.

6.3.4.6 Health related quality of life

Same as presymptomatic model (see Section 6.3.2.6).

6.3.4.7 Resource use and costs

Same as presymptomatic model (see Section 6.3.2.8).

6.3.4.8 Adverse events

Same as presymptomatic model (see Section 6.3.2.9).

6.3.4.9 Survival

The health state specific survival data from the SHINE[37] extension study were considered immature ([redacted]), therefore for "not sitting" and "sitting without support" the company used data estimated using survival curves from a Dutch natural history conducted by Wijngaarde et al. 2020.[38] A gamma distribution was fitted to survival data from type1c SMA patients for "not sitting" and exponential distribution was fitted to survival data from type 2a and type2b SMA patients for "sitting without support" following the approach in HST24.[17] Although HST24[17] focuses on presymptomatic patients, Biogen argued these set of survival estimates reflected the severity of the disease at the "not sitting" and "sitting without support" states. A hazard ratio was applied to these survival data to reflect those with England and Wales setting. Like the presymptomatic and type1 SMA population, the survival data for health states "standing with support" and "walking independently" were assumed to be equivalent to the general population survival. The company reported that long-term survival data were considered appropriate for both the type 2 and type 3 SMA population.

EAG comment: The EAG acknowledges the limitations in the evidence available and considers the approach taken by the company to estimate the survival data appropriate. However, the company used the survival curves directly from HST24 which does not report the hazard ratio that was applied to derive the survival data reflecting the England and Wales setting. Therefore, the EAG could not comment on the appropriateness of the hazard ratio applied.

6.3.4.10 Discontinuation

Discontinuation probability data for the type 2/3 SMA were informed by the MAA data over a 3.5 period and were converted to a 4-month probability aligning with the model cycle length (Table 6.26). As no discontinuation data was available for patients who could stand, the company applied the discontinuation rate for "walking independently" to "standing with support". The company assumed that these probabilities remained constant over the model time horizon and were considered equivalent for both the type 2 and type 3 sub-populations. After discontinuation, the cohort moved on to receive BSC and incurred costs and outcomes specific to BSC.

Table 6.26: Per-cycle probability of discontinuation used in company model for type 2/3 SMA

Treatment discontinuation / loss of response	Total population
Per-cycle discontinuation in not sitting (%)	3.2%
Per-cycle discontinuation in sitting without support (%)	3.1%
Per-cycle discontinuation in standing with support (%)	1.0%
Per-cycle discontinuation in walking independently (%)	1.0%
Source: Biogen CS Section B 3.3.3 Table 60[33]	

EAG comment: The EAG considers the company's approach to treatment discontinuation to be appropriate. However, it is likely that patients who discontinue may not necessarily transition to BSC alone, but instead some may receive alternative disease modifying treatments, which could have implications for both costs and health outcomes.

6.3.4.11 Decision modifier: Severity

Same as presymptomatic model (see Section 6.3.2.12)

6.3.4.12 Companies' cost-effectiveness results (type 2 and 3 SMA)

The company reported both the deterministic and probabilistic results, and the deterministic sensitivity analysis and scenario analyses results. The base-case results are based on the analysis which included carer utilities and considered the PAS discounted price for nusinersen. In the base-case analysis (based on the executable model received after corrections to relative risk in the points for clarification[34]), nusinersen was [redacted] over BSC with an ICER of [redacted](Table 6.27) which was higher than the NICE £20,000 willingness to pay threshold. The probabilistic results were generally stable. Nusinersen had a [redacted] probability of being cost-effective compared to BSC at NICE's £30,000/QALY willingness to pay threshold.

Table 6.27: Deterministic and probabilistic results for type 2/3 SMA population reported by the company (using nusinersen PAS price)

Technology	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER versus baseline (£/QALY)	NHB at £30,000 / QALY
Deterministic								
Nusinersen	[redacted]	23.17	[redacted]	-	-	-	-	-
BSC	[redacted]	22.86	[redacted]	[redacted]	0.31	[redacted]	[redacted]	[redacted]
Probabilistic								
Nusinersen	[redacted]	23.19	[redacted]	-	-	-	-	-
BSC	[redacted]	22.86	[redacted]	[redacted]	0.33	[redacted]	[redacted]	[redacted]
Probability cost-effective at £30k willingness to pay								[redacted]

Source: originally reported in Biogen CS Section B 3.9.3 Table 86 and Table 87,[33] corrected after points for clarification[34]

Abbreviations: BSC = best supportive care; ICER – incremental cost effectiveness ratio; NHB = Net Health Benefits; LYG = life-years gained; QALYs = quality adjusted life year

6.3.4.12.1 Deterministic sensitivity analysis (Type 2 and 3 SMA)

The parameters with the biggest impact on ICERs were variation in health-state utilities, health-state costs per cycle, treatment-related increases in utility, and discontinuation rates (Figure 9).

Figure 9: Tornado diagram showing the one-way sensitivity analyses on type 2/3 SMA population reported by the company



Source: originally reported in Biogen CS Section B 3.10.2 Figure 58,[33] results updated after the points for clarification[34]
Abbreviations: BSC = best supportive care; ICER = incremental cost effectiveness ratio; QALY = quality adjusted life year

6.3.4.12.2 Companies' scenario analysis (type 2 and 3 SMA)

Scenarios with the largest impact on cost-effectiveness were assuming no long-term decline with nusinersen and assuming no treatment-related utility increments (Table 6.28). However, the drop in ICER should be noted when alternative source of utility was used.

Table 6.28: Company's scenario analyses for type 2/3 SMA population

Scenario	Scenario analysis	ICER
0	Reference	[redacted]
1	The rate of decline for BSC is halved	[redacted]
2	Remove carer utility increments	[redacted]
3	Remove active treatment increments	[redacted]
4	Assumption that nusinersen cohort does not decline	[redacted]
5	Alternate utility source: TA588	[redacted]
6	Costs from TA588	[redacted]
7	Type 2 sub-population standing with support and walking independently as per CHERISH / SHINE	[redacted]

Source: originally reported in Biogen CS Section B 3.10.3 Table 99[33], results updated after the points for clarification[34]
Abbreviations: BSC = best supportive care; ICER = incremental cost effectiveness ratio;

EAG comment: The EAG considers the company's presentation of cost-effectiveness results to be appropriate and the scenario analyses undertaken are also reasonable. However, it should be noted that uncertainty in the utility data could significantly impact the ICER, with any changes in these data potentially leading to substantial variations in the results.

6.3.5 Model validation and face validity check

The company reported that a technical validity check was conducted for all the three models where the checks primarily ensured the formulae used in the models were correct and appropriately applied. A quality assurance checklist was utilised and covered a range of tests including sense checks such as changing certain inputs to zero and confirming the effect was as expected. The technical validity check was conducted by a health economist not directly involved in the model development.

In addition, face validity of the models was examined during UK advisory board by describing the model structure and inputs to UK clinical experts and health economists to ensure the model approach appropriately captured the costs and outcomes in UK clinical practice. The company reported that there were some specific changes after the advice from the advisory board.

EAG comment: The EAG identified some errors in the calculations of relative risks used in the models, which was subsequently corrected by the company following the EAG's points for clarifications.[34] In addition, there were some minor errors (e.g. omission of the total additional utility gains from treatment in the total undiscounted QALYs). However, these issues did not change the conclusions. The VBA codes used in the model appeared appropriate.

7 Critique of Roche submission

7.1 Critique of Roche decision problem

Roche stated that their decision problem was “as per NICE final scope and in line with NICE reference case” in relation to all elements (population, intervention, comparator and outcomes). However, there were some differences between eligibility criteria of the Roche SLR from the NICE decision problem.

7.1.1 Population

The eligible population included people with type 1 or type 2/3 SMA and did not include people with type 0 or type 4 SMA, who were included in the NICE decision problem. These exclusions mean that there is no cost-effectiveness evidence surrounding risdiplam for these populations and conclusions about cost-effectiveness therefore cannot be drawn for these subgroups.

7.1.2 Intervention

In addition to risdiplam and nusinersen, the company included reldesemtiv, apitegromab, RO7204239 and branaplam as interventions, although they noted that this was outside of scope for this submission. Although a discrepancy compared with the NICE decision problem, this would not have led to missing data and is not considered an area of concern by the EAG.

7.1.3 Comparators

The company specified comparators as comparing the interventions of interest to each other, or to placebo or standard of care.

7.1.4 Outcomes

The company included all outcomes from the NICE decision problem, except for stamina and fatigue. It should be noted that that stamina and fatigue are outcomes considered important by professional and patient organisations in discussion with the EAG.

Table 7.1: Roche decision problem, reproduced from document B table 1

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
Population	People with 5q spinal muscular atrophy	As per NICE final scope and in line with NICE reference case	N/A
Intervention	Risdiplam	As per NICE final scope and in line with NICE reference case	N/A
Comparator(s)	• Established clinical management • The interventions will be compared to each other In addition, for children aged 12 months and under with a bi-allelic mutation in the *SMN1* gene and present with a clinical diagnosis of type 1 SMA or presymptomatically with up to 3 copies of the *SMN2* gene • Onasemnogene abeparvovec • Nusinersen • Best Supportive Care (BSC)	As per NICE final scope and in line with NICE reference case	N/A
Outcomes	The outcome measures to be considered include: • Motor function (including, where applicable, both age-appropriate gross motor milestones and fine motor skills) • Bulbar function (including, for example, swallowing and ability to communicate) • Frequency and duration of hospitalisation	As per NICE final scope and in line with NICE reference case	N/A

	• Respiratory function • Complications of spinal muscular atrophy (including, for example, scoliosis and muscle contractures) • Need for non-invasive or invasive ventilation • Stamina and fatigue • Mortality • Adverse effects of treatment • Health-related quality of life		
Economic analysis	The reference case stipulates that the cost effectiveness of treatments should be expressed in terms of incremental cost per quality-adjusted life year. The reference case stipulates that the time horizon for estimating clinical and cost effectiveness should be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared. Costs will be considered from an NHS and Personal Social Services perspective. The availability of any commercial arrangements for the intervention, comparator and subsequent treatment technologies will be taken into account. The availability of any managed access arrangement for the intervention will be taken into account.	In the presymptomatic population, a cost-comparison has been used to compare risdiplam to nusinersen and onasemnogene abeparvovec	Given insufficient comparative efficacy data, equal efficacy had to be assumed

Subgroups to be considered	If the evidence allows the following subgroups will be considered: • SMA type • Number of *SMN2* gene copies • Functional status (non-sitter, sitter, walker) • People who have had prior active treatment for SMA	As per NICE final scope and in line with NICE reference case	N/A
Special considerations including issues related to equity or equality	In the current funding situation, the MAA for risdiplam excludes patients who are permanently ventilated or have a tracheostomy. The situation has developed significantly in the past few years, and clinicians now report an improvement in quality of life or a slowing of the expected deterioration in motor / respiratory function.	Permanently ventilated patients have been presented as a subgroup to consider (B.2.7.5)	In the current situation, the decision to treat permanently ventilated patients must be taken to an NHSE panel, delaying treatment and potentially worsening prognosis
Abbreviations: MAA = managed access agreement; NICE = National Institute for Health and Care Excellence; SMN1 = survival motor neuron 1 ; SMN2 = survival motor neuron 2;			

7.2 Critique of Roche SLR

7.2.1 Search strategies

The company conducted the original search in January 2018, and updated this search in January 2020, and again in June 2021, and finally in February 2023. A range of electronic bibliographic databases were searched, and the company report study design limitations but did not report the use of design filters. Conference abstracts were sought on multiple databases covering year to year inclusive. The company stated that English language limitations were imposed on the searches.

The search strategy has not been provided by the company and, whilst the PICO is provided, there is no reporting of the concepts used in the search.

7.2.2 The EAG were unable to appraise the searches using the PRESS checklist and the latest NICE methods manual.[22,23] The number of records retrieved per search line was not shown and the methods and terms used to search the conference abstracts were not presented as might be expected when using the PRISMA-S reporting guidance.[24] It was therefore impossible to judge whether the evidence presented in the company's SLR was complete. Inclusion and exclusion criteria

Table 7.2 presents the inclusion and exclusion criteria for the Roche SLR.

Table 7.2: Inclusion and exclusion criteria for Roche SLR, reproduced from Appendix D table 3

Domain	Details
Population	• Indication: SMA (Presymptomatic: Type 1, Type 2, and Type 3) • Age groups: Paediatric and adult • Ethnicity: no restrictions
Intervention	Studies assessing the following pharmacological interventions in SMA were included: • Risdiplam (Evrysdi) • Nusinersen (Spinraza) • Onasemnogene abeparvovec (Zolgensma) • Reldesemtiv (CK-107) • Apitegromab (SRK-015) • RO7204239 • Branaplam (LMI070)
Comparator	• Studies comparing interventions of interest (as monotherapy or combination therapy) either to each other or to placebo or standard of care were included • Studies assessing interventions of interest without any comparator group (single-arm studies) were also included

Domain	Details
Outcomes*	• Efficacy: Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders (CHOP-INTEND); Bayley Scales of Infant and Toddler Development-Third Edition (Bayley-III); Hammersmith Infant Neurological Examination-Section 2 (HINE-2); Hammersmith Functional Motor Scale (HFMS); Hammersmith Functional Motor Scale-Expanded (HFMSE); Motor Function Measure-32 (MFM-32); achievement of motor milestones; WHO motor milestones; survival rates; event-free survival (time to death/ use of permanent ventilation); ventilator use; Upper Limb Module (ULM); Revised Upper Limb Module (RULM); 6-Minute Walk Test (6-MWT); compound muscle action potential (CMAP) amplitude; respiratory outcomes; scoliosis; hospitalisation; bulbar function • HRQoL: Paediatric Quality of Life Inventory (PedsQL) • Safety: Adverse events (AEs), discontinuations
Study design	Inclusion criteria • RCTs • Non-RCTs • Single-arm trials • Real-world observational studies (prospective and retrospective) Exclusion criteria • Cross-sectional studies • Case series / case reports Previously published systematic reviews and meta-analyses were included for bibliographic searches to identify relevant primary studies.
Language	English language only
Country	No restriction
Search timeframe	• Original SLR (2018): Database inception- 31st January 2018 • First update (2020): 1st February 2018- 22nd January 2020 • Second update (2021): 1st January 2020- 8th June 2021 • Third update (2023): 1st June 2021- 16th February 2023
Abbreviations: RCT = randomised controlled trial; SLR = systematic literature review	

The eligible population included people with type 1 or type 2/3 SMA and did not include people with type 0 or type 4 SMA. In addition to risdiplam and nusinersen, the company included reldesemtiv, apitegromab, RO7204239 and Branaplam as interventions. Although they noted that this was outside of scope for this submission, this would not have led to missing data. The company specified comparators as comparing the interventions of interest to each other or to placebo or standard of care. Eligible outcomes included motor function, paediatric quality of life, adverse events and discontinuations (see Table 7.2 for details).

7.2.3 SLR methods

Table 7.3: EAG evaluation of Roche SLR

Systematic review stage	Section in CS where methods are reported	EAG's assessment of the robustness of methods
Data sources	Appendix D Section D1	**Appropriate** Multidisciplinary electronic databases searched and described in full. The company have searched relevant SMA conferences. The company have searched for ongoing/unpublished studies in a range of databases.
Search strategies	Not reported	**Key concern** Due to non-reporting of the search strategy, it is impossible to know if relevant search terms used and combined appropriately. Furthermore, it is impossible to know if the searches excluded (NOT) terms. English language limitations have been applied without justification.
Search filters	Not reported	**Key concern** Due to non-reporting of the search strategy it is impossible to know if design were filters used, and if so whether this was done appropriately.
Eligibility criteria	Appendix D, D.1 table 3	**Some concerns** The population included people with presymptomatic SMA and SMA types 1, 2, and 3 but did not include people with types 0 and 4. Interventions included drugs not mentioned in the NICE decision problem as well as risdiplam, nusinersen and OA (although they were noted by the company as out of scope for this appraisal and would not lead to missing relevant evidence in the SLR). The company did not include stamina or fatigue in their pre-specified outcomes. They included RCTs, non-RCTs and single-arm studies. They excluded case studies and case reports and did not report any specific limitations on number of patients in a study.
Screening	Appendix D, D.1	**Appropriate** Both titles and abstract and full text screening were each conducted by two people independently, with disagreements adjudicated by a reviewer.
Data extraction	NR	**Some concerns** No information is given about the data extraction process for the SLR, although there is a note in the legend of table 3 indicating 'a comprehensive list of ~40 outcomes from the data extraction sheet'. It could be assumed that the data extraction process was similar to that described for the economic SLR where

		one reviewer extracted data and a second reviewer independently checked it.
Quality appraisal	NR	**Some concerns** No information is given about the methods for appraising the quality of the included studies, although from Table 4 in Appendix D it appears that they used the Cochrane Risk of Bias tool for RCTs. There appears to be no quality appraisal presented for other study designs.
Data synthesis	Document B sections B.2.9.2	**Some concerns/key issue** Since no trials were found comparing risdiplam to nusinersen or OA, the company conducted a feasibility assessment for an indirect comparison between the drugs. They conducted a naïve comparison for the presymptomatic population, MAICs for type 1 patients, and an anchored MAIC for type 2/3 patients (Section 7.2.4).
Abbreviations: CS = company submission; EAG = Evidence Assessment Group; MAIC = matching-adjusted indirect comparison; OA = Onasemnogene abeparvovec; SLR = systematic literature review		

7.2.4 Critique of Roche ITC

Roche utilised naïve treatment comparisons for presymptomatic patients, unanchored MAICs and STCs for type 1 patients, unanchored and anchored MAICs in type 2/3 patients. For the selection of covariates, Roche utilised information from multiple sources, including a prognostic review, other published literature and clinical opinion. Explanations of what covariates were included per comparison for each group of SMA patients are tabulated (tables 54-56 in Roche document B) with justification for include or exclude designation.[46]

Eighteen analyses were conducted by Roche (12 comparing to nusinersen and six comparing to OA). A MAIC or STC assessment of presymptomatic patients was deemed not feasible. This was due to the low numbers and differences between key variables (e.g. number of SMN2 copies). To allow for this comparison, Roche synchronised the timing of outcomes, using a schedule matching method.[47] The naïve comparisons in this group were conducted using t-test analyses. The company state that these analyses were purely exploratory and only conducted on the absolute mean value at each time point. The analyses therefore do not take into account any differences between the studies. No statistically significant differences were found between nusinersen or OA and risdiplam for CHOP-INTEND, HINE-2, or BSID-III motor milestones (inclusive of sitting without support, standing alone, standing with assistance, and walking unaided).

In type 1 patients, when comparing risdiplam to OA, an STC was the preferred analysis, although the company submission does report the results for both the STC and unanchored MAICs. STC was preferred due to the reduction in ESS, which was <5 compared to STR1VE-US and <20 compared to STR1VE-EU (see Table 7.4). The EAG agree with this preference, however, as the results are derived from an STC, there may be inherent biases. For example, when data is non-linear, which can commonly be the case in SMA where it is possible to show improvements, maintenance or deterioration over time, results can be open to bias.[26]

Specifically, as the results are generated via a linear regression model using IPD from one trial (in this case, risdiplam) compared to aggregate data from the comparator trial (in this case, OA) the non-linearity assumption may be violated. If there is non-linearity, substituting the mean covariate values from the comparator trial into the regression can lead to biased estimates, due to issues between the relationship of the mean of the outcome and the mean of the covariates.[27] Therefore, it is important to consider the results with caution. For risdiplam compared to nusinersen, unanchored MAICs suggested a statistically significant difference between the treatments for CHOP-INTEND, HINE-2, adverse events and survival (see Table 7.4). The ESS for these analyses is >35, which suggest the potential for less bias and uncertainty in these results.[48] Additionally, it is worth noting that the trials included in this analysis (FIREFISH; risdiplam and ENDEA-SHINE; nusinersen) had different eligibility criteria and only considered matching on age at first dose, disease duration at baseline, and mean baseline total CHOP-INTEND score. Therefore, differences in the populations are likely not fully accounted for.

In type 2/3 patients, when comparing risdiplam to nusinersen, an anchored MAIC was utilised when assessing up to 12 months. An unanchored MAIC was utilised for assessing beyond 12 months, as the placebo and sham groups from the studies began treatment and therefore there was no comparator. To conduct the anchored MAICs, the company assumed the placebo and sham arms of the trials were the same. However, the placebo (oral, as the intervention) and sham (small needle prick to simulate the intervention) may not be comparable due to the difference in modality. Furthermore, the ESS for the placebo arm in risdiplam for this comparison was <10 and the intervention arm was <30 (see Table 7.4). The company highlights this as a limitation and mentions the increase in uncertainty of the relative effects. This is in line with NICE TSD 18,[25] which states that a small ESS suggests a potential for high variability between the populations being compared, meaning the estimate may be unstable. It is therefore recommended to treat the results of the anchored MAIC with caution. Additionally, the company highlight that when using the comparator arms for matching, these arms become the assumed target population (rather than the intended intervention arms). This presents an issue for type 2/3 patient comparisons due to the differences in eligibility criteria, as most SUNFISH (risdiplam) patients would not have been enrolled in CHERISH (nusinersen). The company also mentioned attempts to increase ESS for the anchored MAIC, via stepwise exclusion of covariates (i.e. SMN2 copies and baseline score). However, the reduction in ESS was mainly driven by age, and removal of other factors had minimal impact on ESS. The anchored MAICs suggested no statistically significant differences between risdiplam and nusinersen. The one unanchored MAIC for RULM (baseline change to 12, 24 and 36 months) also suggested no statistically significant differences between the two treatments.

Overall, clear attempts were made to make the analyses possible and plausible with the data available to the company for statistical assessments. Concerns about sample sizes and naïve analysis are warranted. However, this is mainly driven by availability of data in a rare disease. The anchored MAIC in type 2/3 was conducted using the data available. However, it does raise concerns in terms of the comparability of the placebo and sham arms of the trials. Additionally, the reduced ESS in both the intervention and control arms suggest a lack of comparability between the two cohorts. Table 7.4 provides an overview of the results from the Roche company submission.

Table 7.4: Overview of the results from the Roche company submission

Outcome	Population	Analysis Type	Comparator	Covariates	Sample size/ ESS	Conclusion
CHOP-INTEND	Presymptomatic	Naïve comparison	Nusinersen (NURTURE)	SMN2 copy number, mean age at first dose, mean baseline total CHOP INTEND score	RAINBOWFISH: 13 NURTURE: 15 Note: ESS not applicable	RAINBOWFISH vs NURTURE suggests no statistically significant differences.
HINE-2	Presymptomatic	Naïve comparison	Nusinersen (NURTURE)	SMN2 copy number, mean age at first dose, mean baseline total CHOP INTEND score	RAINBOWFISH: 13 NURTURE: 15 Note: ESS not applicable	RAINBOWFISH vs NURTURE suggests no statistically significant differences.
BSID-III motor milestones	Presymptomatic	Naïve comparison	Nusinersen (NURTURE)	SMN2 copy number, mean age at first dose, mean baseline total CHOP INTEND score	RAINBOWFISH: 13 NURTURE: 15 Note: ESS not applicable	RAINBOWFISH vs NURTURE demonstrated no statistically significant differences for sitting without support, standing alone, standing with assistance, and walking unaided.
BSID-III motor milestones	Presymptomatic	Naïve comparison	OA (SPR1NT)	SMN2 copy number, mean age at first dose,	RAINBOWFISH: 13	RAINBOWFISH vs SPR1NT suggest no

Outcome	Population	Analysis Type	Comparator	Covariates	Sample size/ ESS	Conclusion
				mean baseline total CHOP INTEND score	SPR1NT: 10 Note: ESS not applicable	statistically significant differences.
CHOP-INTEND	Type 1	Unanchored MAIC	Nusinersen (ENDEAR-SHINE)	Mean age at first dose, mean baseline total CHOP INTEND score, mean disease duration at baseline	FIREFISH: 58/40.6	FIREFISH vs ENDEAR-SHINE suggested statistically significant difference in obtaining improvement (≥4 points) in favour of risdiplam.
HINE-2	Type 1	Unanchored MAIC	Nusinersen (ENDEAR-SHINE)	Mean age at first dose, mean baseline total CHOP INTEND score, mean disease duration at baseline	FIREFISH: 58/40.6	FIREFISH vs ENDEAR suggested statistically significant difference in motor milestone response in favour of risdiplam.
Adverse events	Type 1	Unanchored MAIC	Nusinersen (ENDEAR-SHINE)	Mean age at first dose, mean baseline total CHOP INTEND score, mean disease duration at baseline	FIREFISH: 58/40.6	FIREFISH vs ENDEAR-SHINE suggested statistically less adverse events in favour of risdiplam.
Event free survival	Type 1	Unanchored MAIC	Nusinersen (ENDEAR-SHINE)	Mean age at first dose, mean baseline total CHOP INTEND score, mean disease duration at baseline	FIREFISH: 58/40.6	FIREFISH vs ENDEAR-SHINE suggested statistically significant increase in event free survival in favour of risdiplam.

Outcome	Population	Analysis Type	Comparator	Covariates	Sample size/ ESS	Conclusion
Overall survival	Type 1	Unanchored MAIC	Nusinersen (ENDEAR-SHINE)	Mean age at first dose, mean baseline total CHOP INTEND score, mean disease duration at baseline	FIREFISH: 58/40.6	FIREFISH vs ENDEAR-SHINE suggested statistically significant increase in survival in favour of risdiplam.
CHOP-INTEND	Type 1	STC (preferred) Unanchored MAIC	OA (STR1VE)	Mean age at first dose, mean baseline total CHOP INTEND score	FIREFISH vs STR1VE-US: 58/2.1 FIREFISH vs STR1VE-EU: 62/15.32	FIREFISH vs STR1VE suggested no statistically significant differences, with wide 95% confidence intervals for odds ratios.
Adverse events	Type 1	STC (preferred) Unanchored MAIC	OA (STR1VE)	Mean age at first dose, mean baseline total CHOP INTEND score	FIREFISH vs STR1VE-US: 58/2.1 FIREFISH vs STR1VE-EU: 62/15.32	FIREFISH vs STR1VE suggested no statistically significant differences.
BSID-III motor milestones	Type 1	STC (preferred) Unanchored MAIC	OA (STR1VE)	Mean age at first dose, mean baseline total CHOP INTEND score	FIREFISH vs STR1VE-US: 58/2.1	FIREFISH vs STR1VE suggested no statistically significant differences.

Outcome	Population	Analysis Type	Comparator	Covariates	Sample size/ ESS	Conclusion
					FIREFISH vs STR1VE-EU: 62/15.32	
Event free survival	Type 1	STC (preferred) Unanchored MAIC	OA (STR1VE)	Mean age at first dose, mean baseline total CHOP INTEND score	FIREFISH vs STR1VE-US: 58/2.1 FIREFISH vs STR1VE-EU: 62/15.32	FIREFISH vs STR1VE suggested no statistically significant differences.
Ventilation free survival	Type 1	STC (preferred) Unanchored MAIC	OA (STR1VE)	Mean age at first dose, mean baseline total CHOP INTEND score	FIREFISH vs STR1VE-US: 58/2.1 FIREFISH vs STR1VE-EU: 62/15.32	FIREFISH vs STR1VE suggested no statistically significant differences.
RULM change from baseline to 12 months	Type 2/3	Anchored MAIC	Nusinersen (CHERISH)	Mean age at screening, mean RULM baseline score, and mean SMN2 copy number	SUNFISH risdiplam: 43/28.3 SUNFISH placebo: 25/8.8	SUNFISH vs CHERISH suggested no statistically significant differences and wide 95% confidence intervals.

Outcome	Population	Analysis Type	Comparator	Covariates	Sample size/ ESS	Conclusion
RULM change from baseline to 12, 24, and 36 months	Type 2/3	Unanchored MAIC	Nusinersen (CHERISH)	Mean age at screening, mean RULM baseline score, and mean SMN2 copy number	SUNFISH: 43/29.8	SUNFISH vs CHERISH suggested no statistically significant differences at each timepoint.
HFMSE	Type 2/3	Anchored MAIC	Nusinersen (CHERISH)	Mean age at screening, mean RULM baseline score, and mean SMN2 copy number (note: analyses not presented but assumed to be same as previous)	SUNFISH risdiplam: 43/28.3 SUNFISH placebo: 25/8.8	SUNFISH vs CHERISH analysis observed differences in response for placebo of SUNFISH to natural history and sham of CHERISH. MAIC results not reported.
Adverse events	Type 2/3	Anchored MAIC	Nusinersen (CHERISH)	Mean age at screening, mean RULM baseline score, and mean SMN2 copy number	SUNFISH risdiplam: 43/28.3 SUNFISH placebo: 25/8.8	SUNFISH vs CHERISH suggested no statistically significant differences and wide 95% confidence intervals.

Abbreviations: BSID-III = Bayley Scales of Infant and Toddler Development, Third Edition; CHOP-INTEND = Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders; ESS = Effective sample size; HFMSE = Hammersmith Functional Motor Scale (expanded); HINE-2 = Hammersmith Infant Neurological Examination - Part 2; MAIC = matching-adjusted indirect comparison; OA = onasemnogene abeparvovec; RULM = Revised Upper Limb Module; STC = Simulated Treatment Comparison

7.2.5 Critique of Roche MAA

7.2.5.1 Paediatric registry

The paediatric registry updated the following items in April 2025.

- WHO MM information
- Updated descriptive data for HINE-2 in SMA type 1,
- Mortality
- Number of patients with permanent ventilation
- EK-2 overview

Data for WHO MM was provided over time, with number of patients per SMA type, who WAS in each classification (e.g. non-sitters, sitting without support, crawling).

In the original report, MMRMs were conducted for the following outcomes and SMA types.

- RHS: type 2/3
- RULM: type 2/3

MMRM models include the following covariates.

- Age at symptom onset
- Age at treatment initiation
- Time between diagnosis and treatment initiation
- Baseline motor function milestone categorised by walkers/sitters or non-sitters (for SMA Type 2/3 model only)
- Weight

No statistical analysis was undertaken for the following motor outcomes:

- CHOP-INTEND: type 1
- RHS: type 1
- RULM: type 1
- HINE: type 1

Modelling was deemed infeasible due to low patient numbers, instead descriptive data is reported.

Over the original and updated reports, MMRM were conducted when feasible (i.e. there was enough data). In cases of insufficient data, results are generally reported narratively and tabulated (e.g. means and SDs). Not all outcomes provided are mandated (e.g. EK-2) but are still provided, with the caveat that data cleaning was not as thorough for MAA mandated items.

Overall, the EAG considers that analyses of the data are conducted when plausible and the limitations of the data are clearly highlighted within the report.

7.2.5.2 Adult registry

The adult registry updated all analyses from the original report (December 2023) therefore the new (April 2025) report is to be considered here. Data was presented for the following:

- WHO MM information
- MMRM for ATEND (left and right)

- MMRM for EK2
- MMRM for RULM
- MMRM for RHS
- MMRM for 6 Minute Walk Test (6MWT)

MMRMs were adjusted for the following baseline covariates.

- Patient (random effect)
- Age at symptom onset (fixed effect)
- Age at treatment initiation (fixed effect)
- SMA type (fixed effect)
- Treatment duration at time of visit (fixed effect)
- Disease duration (age at treatment state minus age at symptom onset; fixed effect)

To increase data availability, the registry removed requirement for at least one follow-up score and weight as a covariate. Removal of the criteria of at least one follow-up score increased both the number of patients and value of data (i.e. scores) contributing to the models. Weight was not used due to a large amount of missing data. The previous report (December 2023) included a sensitivity analysis for patients naïve to treatment and pre-treated patients. Additionally, the updated report (April 2025) split by status (i.e. non-sitters, sitters, and walkers), whereas the previous report (December 2023) assessed type 2/3 patients as a whole. The new report therefore offers more granularity in terms of subgroups of SMA 2/3 patients but does suffer from smaller patient sample sizes. When patient numbers are below five, no results are calculated for that follow-up period.

Overall, the EAG considers that analyses are conducted using appropriate methods and attempts have been made to provide context to the results and consider type 2/3 patients as separately as possible.

7.2.6 Results of Roche SLR

One phase II randomised controlled trial has been conducted for children and young people with type 2 and non-ambulant type 3 SMA, comparing risdiplam with placebo in part 1, and then shifting to an open-label phase in part 2 (SUNFISH) with five year follow-up.[49-55] This is the only controlled trial of risdiplam.

A phase II/III single arm trial has been conducted for infants between 1 and 7 months with type 1 SMA (FIREFISH),[56-58] with a primary analysis at month 12 and open-label extension phase of three years. An ongoing phase II single arm trial for presymptomatic genetically diagnosed infants under 6 weeks of age (RAINBOWFISH)[59-62] is due to complete in 2027. A phase II single arm trial (JEWELFISH) has recently completed for adult and paediatric patients who have previously received nusinersen, OA or olesoxime (a drug previously in development but terminated).[63,64]

Finally, the company incorporated real-world data from the adult and paediatric REACH registries into their economic model.

Further characteristics of these studies are shown in Table 7.5.

Table 7.5: Overview of clinical effectiveness evidence for risdiplam (reproduced from Roche submission table 5)

Study	**BP39056 (FIREFISH)**
Study design	Open-label, two-part seamless, multicentre, single-arm study. Part 1 objectives: safety, tolerability, PK and PD, dose selection for Part 2 Part 2 objectives: efficacy, safety and tolerability, PK and PD
Population	Infants with type 1 SMA aged ≥1 month and ≤7 months at the time of enrolment
Intervention(s)	Risdiplam
Comparator(s)	None (single arm)
Indicate if study supports application for marketing authorisation	Yes
Indicate if study used in the economic model	Yes
Rationale for use/non-use in the model	FIREFISH is a Phase II/III trial providing efficacy and safety evidence for risdiplam in people with type 1 SMA. Data from Part 2 of the study were used to inform the efficacy and safety of risdiplam in the economic model
Reported outcomes specified in the decision problem	Motor function (BSID III, HINE-2, CHOP-INTEND); bulbar function; survival and ventilation-free survival; healthcare utilisation; adverse events, HRQoL
Study	**BP39055 (SUNFISH)**
Study design	Two-part seamless, randomised, multicentre, placebo-controlled, double-blind study. Part 1 objectives: safety, tolerability, PK and PD, dose selection for Part 2 Part 2 objectives: efficacy, safety and tolerability, PK and PD
Population	People aged 2–25 years with type 2 and non-ambulant type 3 SMA
Intervention(s)	Risdiplam
Comparator(s)	Placebo for the first 12 months Single arm OLE for the remaining 4 years
Indicate if study supports application for marketing authorisation	Yes
Indicate if study used in the economic model	Yes
Rationale for use/non-use in the model	SUNFISH is a Phase II/III trial providing efficacy and safety evidence for risdiplam in people with type 2 or 3 SMA. Data from Part 2 of the study were used to inform the efficacy and safety of risdiplam in the economic model
Reported outcomes specified in the decision problem	Motor function (MFM32, RULM, HFMSE); adverse events; HRQoL
Study	**RAINBOWFISH**

Study design	Open-label, single-arm, multicentre study
Population	People aged from birth to 6 weeks (at first dose) who have been genetically diagnosed with SMA (*SMN1* deletion and any *SMN2* copies) but not yet presenting with SMA symptoms
Intervention(s)	Risdiplam
Comparator(s)	None (single arm)
Indicate if study supports application for marketing authorisation	Yes
Indicate if study used in the economic model	Yes
Rationale for use/non-use in the model	RAINBOWFISH provides efficacy and safety evidence for risdiplam for presymptomatic patients with a genetic diagnosis of SMA. Data from this study were used to inform the efficacy and safety of risdiplam in the economic model
Reported outcomes specified in the decision problem	Motor function (BSID-III, HINE-2, CHOP-INTEND, survival and ventilation-free survival, nutritional status (ability to swallow and feed orally)
All other reported outcomes	Development of clinically manifested SMA, growth measures (weight, length, height, head circumference, chest circumference), degree of innervation (CMAP amplitude)
Study	**BP39054 (JEWELFISH)**
Study design	Multicentre, open label, non-comparative, single-arm, exploratory study in SMA patients previously enrolled in BP29420 (MOONFISH) or previously treated with nusinersen, onasemnogene abeparvovec or olesoxime. 24 month treatment period plus extension phase
Population	People aged 6 months to 60 years with type 1, 2 and 3 SMA
Intervention(s)	Risdiplam
Comparator(s)	None (single arm)
Indicate if study supports application for marketing authorisation	Yes
Indicate if study used in the economic model	No
Rationale for use/non-use in the model	The primary objective was safety, all efficacy outcomes were exploratory
Reported outcomes specified in the decision problem	Adverse events, motor function (MFM-32, HFMSE, RULM, 6MWT, BSID-III, HINE-2), HRQoL, survival and ventilation-free survival
Study	**REACH registries**
Study design	Adult and paediatric SMA registry datasets, collecting observational data on the use of risdiplam within the real world setting.
Population	Patients treated with risdiplam under the MAA
Intervention(s)	Risdiplam
Comparator(s)	None (observational study)

Indicate if study supports application for marketing authorisation	No
Indicate if study used in the economic model	The baseline characteristics are included as a scenario analysis.
Rationale if study not used in model	The REACH registries provide real-world efficacy evidence for risdiplam paediatric and adult SMA patients. The observational baseline data from this study were used to inform a scenarios analysis in the economic model. However, the efficacy and safety data was insufficient to be modelled.
Reported outcomes specified in the decision problem	Motor function (CHOP-INTEND, RHS, RULM, HINE, Adult registry; ATEND, EK2), survival and ventilation-free survival
Abbreviations: ATEND = Adapted Test of Neuromuscular Disorders; BSID-III = Bayley Scales of Infant and Toddler Development, Third Edition; CHOP-INTEND = Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders; ESS = Effective sample size; HFMSE = Hammersmith Functional Motor Scale (expanded); HINE-2 = Hammersmith Infant Neurological Examination - Part 2; HRQoL = health-related quality of life; MAIC = matching-adjusted indirect comparison; OA = onasemnogene abeparvovec; RULM = Revised Upper Limb Module; SMN = survival of motor neuron protein; STC = Simulated Treatment Comparison	

The company concluded that presymptomatic patients receiving risdiplam achieved motor milestones and high levels of motor function after 12 months of treatment, all patients were alive without the need for permanent ventilation, and all could feed orally and swallow.

Risdiplam was reported to be associated with prolonged survival and clinically meaningful improvements in motor function for type 1 patients at the primary endpoints and in longer term analyses up to four years.

For type 2/3 patients, clinically meaningful and statistically significant improvement was reported for MFM32 and RULM scores after 12 months, [redacted]. A numerical (but not statistically significant) improvement was reported for HFMSE scores at 12 months.

The registry data, although limited and potentially skewed by poorer baseline characteristics (due to patients being severe enough to be ineligible for nusinersen), suggested that paediatric type 1 patients improved motor function and type 2/3 patients showed an initial improvement followed by stabilisation. For adult patients there were signs of improving or stabilising their upper limb function.

Risdiplam was reported to be well-tolerated up to five years. [redacted]

The EAG notes uncertainty in the evidence due to a lack of controlled trials of risdiplam in presymptomatic and type 1 patients. In particular, without a comparator group it is difficult to be clear how much the treatment is maintaining function or preventing decline compared to natural history, especially for children where growth and consequent increase in weight

influences their function and confounds the effect of treatment. However, it appears that risdiplam has increased survival and achieved positive motor outcomes for people with presymptomatic, type 1, and type 2/3 SMA with no serious safety concerns up to five years.

7.3 Critique of Roche economic models

The EAG reviewed and critically appraised the economic models and the additional information in response to the points for clarification submitted by Roche.[46,65] In this section, the EAG assesses the company submission against the NICE reference case checklist[35] and then present a critique of the submitted economic model structures and economic evidence used to parameterise these economic models, according to the population groups defined in the decision problem (presymptomatic, type 1 and type 2/3 SMA).[6,46]

7.3.1 NICE decision problem

The company submission[46] was evaluated against the NICE reference case checklist[35] and the findings are summarised in Table 7.6.

Table 7.6. Comparison of company's and NICE decision problem

Element of health technology assessment	Reference case	EAG comment on company's submission
Defining the decision problem	People with types 0, 1, 2, 3 or 4 5q SMA, or presymptomatic 5q SMA confirmed with genetic testing with 1 to 4 SMN2 copies.	The company submission did not report on type 0 and 5q SMA type 4 because of paucity of evidence to conduct an economic evaluation. The company reported the economic evaluation results separately for presymptomatic SMA, type 1 SMA and type 2/3 SMA populations.
Intervention	Interventions are monotherapies in addition to existing clinical services and established clinical management.	The company assessed cost-effectiveness of risdiplam.
Comparators	Established clinical management in the NHS, including the Best supportive care (BSC) The interventions will be compared to each other In addition, Onasemnogene Abeparvovec (OA) will be used as comparator treatment for children aged 12 months and under with a bi-allelic mutation in the SMN1 gene and present	The company considered nusinersen, OA and BSC as comparators. However, BSC was not considered appropriate comparator for presymptomatic population. In addition, OA was not considered an appropriate comparator for type 2/3 SMA population.

Element of health technology assessment	Reference case	EAG comment on company's submission
	with a clinical diagnosis of type 1 5q SMA or presymptomatically with up to 3 copies of the SMN2 gene.	
Perspective on outcomes	The outcome measures to be considered include: • Motor function (including, where applicable, both age-appropriate gross motor milestones and fine motor skills) • Bulbar function (including, for example, swallowing and ability to communicate) • Frequency and duration of hospitalisation • Respiratory function • Complications of spinal muscular atrophy (including, for example, scoliosis and muscle contractures) • Need for non-invasive or invasive ventilation • Stamina and fatigue • Mortality • Adverse effects of treatment • Health-related quality of life (for patients and carers)	Presymptomatic: risdiplam/nusinersen/OA: naïve comparison led to the assumption of equivalent efficacy. Motor milestones defined by HINE-2 scores with a continuous time Markov multi-state model fitted to the data of RAINBOWFISH.[62] Mortality from general population QALYs considered (though any difference nullified). Type 1: Risdiplam vs BSC/nusinersen: motor milestones informed by unanchored MAIC between ENDEAR and FIREFISH[66] Risdiplam vs OA: motor milestones informed by unanchored MAIC using results from FIREFISH[58] and STR1VE-EU[67] Mortality data from FIREFISH[58] Type 2/3: Risdiplam vs BSC: motor milestones informed by SUNFISH[55] Risdiplam vs nusinersen: motor milestones informed by unanchored MAIC from CHERISH[29]/SUNFISH[55] Mortality data: pooled pseudo IPD data from literature for type 2, and general population data for type 3.

Element of health technology assessment	Reference case	EAG comment on company's submission
		Bulbar dysfunction, non-permanent respiratory support, scoliosis, considered across populations.
Perspective on costs	Costs will be considered from an NHS and Personal Social Services perspective.	Appropriate
Type of economic evaluation	Cost utility analysis using QALYs. Cost comparison.	Presymptomatic: Cost-comparison for risdiplam vs nusinersen, risdiplam vs OA Type 1 and type 2/3: Cost utility analysis for risdiplam vs nusinersen, risdiplam vs BSC, risdiplam vs OA (only for type 1)
Time horizon	The reference case stipulates that the time horizon for estimating clinical and cost effectiveness should be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared.	Presymptomatic and type 1: 30 years Type 2/3: 80 years
Synthesis of evidence on health effects	Based on systematic review.	Cost-comparison based on naïve comparison results.
Measuring and valuing health effects	Express health effects in QALYs for cost-effectiveness analyses.	Presymptomatic: Assumed equivalent efficacy, QALYs difference assumed to cancel out type 1 and type 2/3: QALYs
Source of data for measurement of health-related quality of life	For the reference case, report the measurement of changes in health-related quality of life directly from patients.	Presymptomatic and type 1: patient HSUVs from TA588[2] and carer HSUVs from Bastida et al. 2017.[68] Type 2/3: patient HSUVs from Lloyd et al. 2019[69] and carer HSUVs from Bastida et al. 2017[68] and UK general population utility.
Source of preference data for valuation of changes in	The utility of these changes should be based on public preferences using a choice-based method.	Appropriate

Element of health technology assessment	Reference case	EAG comment on company's submission
health-related quality of life		
Equity considerations	No additional equity considerations in the NICE scope.	Appropriate
Evidence on resource use and costs	Resource use and cost data should have been identified systematically.	de novo Roche study/ TA588for scenario analysis[2]
Discounting	Annual discount rate of 3.5% for costs and outcomes.	Appropriate

Source: Company submission[46] and NICE reference case[35]
Abbreviations: BSC = best supportive care; EAG = Evidence Assessment Group; HSUV = health state utility values; MAIC = matching-adjusted indirect comparison; OA = Onasemnogene Abeparvovec; QALY = quality-adjusted life years; SMA = spinal muscular atrophy; SMN= survival motor neuron

7.3.2 Presymptomatic population

7.3.2.1 Model structure

7.3.2.1.1 Type of model

Roche used a Markov model to represent the natural history of presymptomatic 5q SMA which was primarily informed by the previous NICE TA755 for risdiplam (see Figure 10).[3]

7.3.2.1.2 Health states and transitions

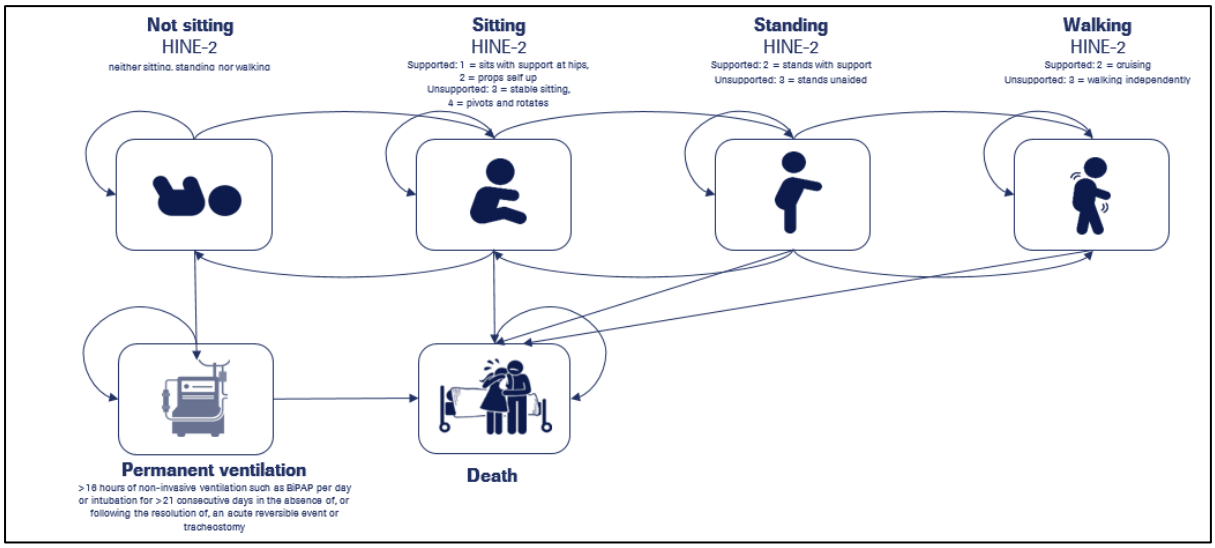
The Markov model was built in Microsoft Excel with four mutually exclusive health states: 'not sitting', 'sitting' (with or without support), 'standing' (with or without support), and 'walking' (with or without support), informed by the items of the HINE-2 scale representing motor milestones.[46] Patients in the 'sitting' state corresponded to a HINE-2 sitting score of at least 1; the 'standing' state to a minimum HINE-2 standing score of 2; and the 'walking' to a minimum HINE-2 walking score of 2.[46] The model states and their respective HINE-2 score equivalent used are presented in Table 7.7. An additional state for 'permanent ventilation' was explicitly included to represent SMA's impact on prognosis and to reflect current clinical practice. The definition of permanent ventilation was informed by the FIREFISH trial as: > 16 hours of non-invasive ventilation per day or intubation for > 21 consecutive days.[46,56].

Table 7.7: Model health state definitions based on HINE-2 scores

Model states	HINE-2 score equivalent
Not sitting	< 1 in the HINE-2 sitting dimension
Sitting (with or without support)	≥ 1 in the HINE-2 sitting dimension to <2 standing dimension
Standing (with or without support)	≥ 2 in the HINE-2 standing dimension to <2 walking dimension
Walking (with or without support)	≥ 2 in the HINE-2 walking dimension
Permanent ventilation	> 16 hours of non-invasive ventilation per day or intubation for > 21 consecutive days

Source: prepared by the EAG based on HINE-2 scale
Abbreviations: HINE-2 = Hammersmith Infant Neurological Examination — Part 2

Figure 10: Model structure for presymptomatic and type 1 SMA populations used by Roche



Source: company submission, Document B, Figure 28[46]
Abbreviations: HINE-2 = Hammersmith Infant Neurological Examination — Part 2

Patient data from the single-arm RAINBOWFISH trial with a follow-up of one year were used to inform the transition probabilities in the risdiplam arm.[59] This independent patient data was fitted using a continuous time Markov multi-state model to generate monthly probabilities of improving, deteriorating, or maintaining motor milestones corresponding to the model health-states.[46] It was assumed that patients could only improve, maintain, or deteriorate by one motor milestone each month (equivalent to 1 model cycle). Probabilities were estimated for the 2 SMN copies group and the > 2 SMN2 group, and used a weighted average based on 2 SMN group proportions from RAINBOWFISH.[59]

Table 7.8 reports the base-case transition probabilities for risdiplam used in the presymptomatic model. The company assumed equal efficacy and utilised the same transition probabilities for nusinersen and OA.

Table 7.8: Base-case transition probabilities for risdiplam, nusinersen and OA

From\To	Non-sitting	Sitting	Standing	Walking
Non-sitting	[redacted]	[redacted]	[redacted]	[redacted]
Sitting	[redacted]	[redacted]	[redacted]	[redacted]
Standing	[redacted]	[redacted]	[redacted]	[redacted]
Walking	[redacted]	[redacted]	[redacted]	[redacted]

Source: company submission, Document B, Table 106[46]
Abbreviations: HINE-2 = Hammersmith Infant Neurological Examination — Part 2; OA = onasemnogene abeparvovec

After the points for clarification, the company detailed that multiple models were tested adjusting for covariates and were assessed for goodness of fit to the study data using the Akaike Information Criteria (AIC), as well as visual plots.[65] Figure 11 shows the visual plots presented by Roche comparing risdiplam trial data with their modelled prediction.

Figure 11: Observed versus multi-state Markov model predicted prevalence for RAINBOWFISH motor milestones (Overall SMN2 copy number, all forward transitions constrained to be equal)



Source: company submission after points for clarification[65]
Abbreviations: SMN = survival motor neuron

The model assumed that, after 10 years, patients receiving either risdiplam, nusinersen or OA maintain the motor milestones achieved. BSC was not considered a suitable comparator, therefore it does not feature in the analysis.[46] Since no events of permanent ventilation were observed during RAINBOWFISH,[59] it was assumed that patients receiving any disease-modifying therapy were not at risk of moving to permanent ventilation.

EAG comment: The EAG considers the model structure, and company's approach to derive transitions across motor milestones for risdiplam, to be largely appropriate. However, the EAG raises concern about the long-term assumptions of sustained motor milestones during treatment, as clinical feedback indicated that a risk of motor milestone decline may still be present, even with continued treatment.

The EAG chose to align the long-term effectiveness assumptions in the Roche model with those used in the Biogen model to ensure consistency in disease progression over the long-term. This approach assumed that the benefit of disease modifying therapies (DMTs) was not lifelong, instead DMTs enable patients to achieve motor milestone improvements for a period consistent with the available clinical trial evidence. After this period, patients were assumed to either maintain their motor milestones or at risk of gradually losing them over the long-term. For risdiplam treatment effectiveness was assumed to last 72 months by the EAG, similar to the available follow-up data for nusinersen,[31]- which is a favourable assumption to risdiplam, given that the follow-up from RAINBOWFISH was only 12 months.[59]

Patients receiving BSC were assumed to gain improvements in motor milestones over the first 12 months, based on Roche's internal natural history data.[46] Beyond 12 months the rate of motor milestone decline corresponded to the natural history of SMA disease reported by Wadman et al. 2019[41] using a disease distribution across SMA types 1, 2, and 3 from Calucho et al. 2018[40]. For risdiplam, the relative rate of motor milestone decline was assumed to be an average of the rates of decline used in the type 1 and the type 2 and 3 population models.

Table 7.9 Long-term risk of decline for BSC based on natural history of disease

Long-term decline estimates for BSC	Type 1	Type 2 and 3	Presymptomatic
BSC sitting to not sitting	0.003	0.002	0.002
BSC standing to sitting	0.035	0.025	0.021
BSC walking to standing	0.071	0.051	0.043

Source: produced by the EAG from Wadman et al[41]
Abbreviations: BSC = best supporting care

7.3.2.2 Population

The population modelled reflected the baseline characteristics of RAINBOWFISH trial (see Table 7.10).[59]

Table 7.10: Baseline characteristics of the presymptomatic population in the Roche model

Characteristics	Overall (N=18)	SMN2 2 copies (N=7)	SMN2 > 2 copies (N=11)
Age at first dose in days (median (range))	27.33 (7.28)	22.86 (5.37)	30.18 (7.07)
Female (n (%))	10 (55.56%)	3 (42.86%)	7 (63.4%)
Weight (kg(SD))	3.98 (0.7250)	3.76 (0.427)	4.12 (0.853)
SMN2 copies (n(%))			
2 copies	7 (38.89%)	7 (100%)	0 (0%)
3 copies	7 (38.89%)	0 (0%)	7 (63.4%)
≥ 4 copies	4 (22.22%)	0 (0%)	4 (36.36%)

Source: company submission, document B, Table 105[65]
Abbreviations: SD = standard deviation; SMN = survival motor neuron

7.3.2.3 Interventions and comparators

The presymptomatic model compared risdiplam against nusinersen and OA in a population with the characteristics like those reported above in Section 7.3.2.27.3.2.2.[65]

Intervention**:** The company modelled risdiplam as the first-line therapy according to its marketing authorisation as a treatment.[46,70] In the company's submitted economic model, in line with the marketing authorisation, the patient cohort receiving risdiplam were orally administered a daily dose determined by the patient's age and body weight (see Table 7.11).

Table 7.11: Risdiplam dosing regimen

Age	Dose administered
16 days to 2 months of age	0.15 mg/kg
2 months to <2 years of age	0.20 mg/kg
≥ 2 years of age (<20 kg)	0.25 mg/kg
≥ 2 years of age (≥ 20 kg)	5mg
Source: company submission, document B, Table 104[65] Abbreviations: kg = kilograms; mg = milligrams	

Comparator: The company modelled nusinersen and OA as the comparators for presymptomatic populations. The decision model submitted by Roche included BSC as a comparator based on data from an internal natural history study.[46] However, the company did not consider BSC a relevant comparator for the presymptomatic population, reasoning that patients are likely to receive a disease modifying therapy upon diagnosis of SMA, therefore overlooking the results comparing risdiplam with BSC.[46]

EAG comment: The base-case submitted by Roche for the presymptomatic population did not include BSC as an appropriate comparator, arguing that in current clinical practice patients diagnosed with SMA are expected to receive a DMT. However, the EAG is concerned about the gaps in clinical evidence that make comparisons between risdiplam and other DMTs highly unreliable.[71]

Considering the limitations in relative effectiveness evidence between DMTs, the EAG decided to focus the economic decision problem in the presymptomatic population on comparing risdiplam against BSC for analytical purposes, while acknowledging that current clinical practice is constantly evolving. Comparisons between risdiplam and other DMTs will be presented as scenario analyses using the evidence available, highlighting the caveats around the potential for bias. As RAINBOWFISH[59] was a single-arm trial, the EAG relied on internal natural history of disease data from Roche to model BSC.[46]

7.3.2.4 Perspective, time horizon and discounting

The analysis was conducted from the perspective of the NHS and Personal Social Services (taking account of costs directly related to the medical treatment of patients with SMA, and the quality of life of patients with SMA and their carers) and with a time horizon of [redacted] (considered to cover the lifetime) in the base case.[65] The costs and benefits were discounted at annual rate of 3.5% in accordance with the NICE methods guidelines.[42]

EAG comment: To fully capture the impact of the disease and the interventions across time, the EAG considers a lifetime horizon covering 100 years to be appropriate. In contrast, the

[redacted] approach used in the company's model risks putting an excessive focus exclusively on the BSC arm and may underestimate the survival gains from treatment.

7.3.2.5 Treatment effectiveness and extrapolation

As detailed above, monthly transition probabilities for risdiplam between motor milestone-based health states were derived from the first year of follow-up of the ITT population in RAINBOWFISH[59]. However, as this was a single-arm trial, in order to model the BSC arm Roche presented data from its own natural history of disease study.[46] Monthly transition probabilities were derived from this data but it was unclear to the EAG how well patient characteristics matched this population with the RAINBOWFISH[59] study, and what methodology was used to derive these monthly probabilities. Table 7.12 reported the monthly transition probabilities used for BSC.

Table 7.12: Monthly transition probabilities for the BSC arm for the presymptomatic population in the Roche model

From\To	Non-sitting	Sitting	Standing	Walking
Non-sitting	[redacted]	[redacted]	[redacted]	[redacted]
Sitting	[redacted]	[redacted]	[redacted]	[redacted]
Standing	[redacted]	[redacted]	[redacted]	[redacted]
Walking	[redacted]	[redacted]	[redacted]	[redacted]
Source: EAG extracted data from company submitted models				

The company presented the results of a series of naïve comparisons between risdiplam and nusinersen using results from RAINBOWFISH[59] and NURTURE[31] across HINE-2 and BSID-III.[65] As these comparisons were not controlled by confounders and results were not statistically different, the model assumed there was evidence of equivalent effectiveness with nusinersen.[65] Similarly, a naïve comparison between risdiplam and OA using BSID-III results from RAINBOWFISH[59] and SPR1NT was conducted, where no statistically significant difference was found.[65] Therefore, equivalent effectiveness was also assumed between risdiplam and OA.[65]

EAG comment: The EAG questions the conclusion that an absence of statistically significant differences in mobility scores from a naïve comparison alone, is evidence of equivalence in effectiveness across DMTs. While the EAG acknowledges the gaps in comparative data for this population, it remains unclear whether a cost-comparison approach was appropriate to assess the impact of uncertainty in clinical effectiveness across treatments.[72]

Although the EAG's base-case analysis compared risdiplam with BSC, the EAG conducted a scenario analysis using CUA to compare the DMTs. While the EAG was unable to use the naïve comparison data for OA, the approach assumed a degree of uncertainty around the assumption of equivalent effectiveness. The EAG also explored scenario analysis using the naïve comparison estimates between risdiplam and nusinersen.

7.3.2.6 Health related quality of life

Patient Health-Related-Quality of Life (HRQoL) data was collected neither from RAINBOWFISH[59] nor FIREFISH.[58]To model HRQoL in presymptomatic and Type 1 SMA patients, the company relied on the health state utility values from TA755,[3] which themselves were based on Lloyd et al 2019[69] and TA588[17].[46] Additional scenario analyses were presented

using alternative utilities from TA588[2] and Lloyd et al. 2019.[69] See Table 7.13 for the base-case utility values in the model.

Table 7.13: Utility values used in the Roche economic model for presymptomatic and Type 1 SMA

Roche model base-case			Scenario 1		Scenario 2	
Model health state	**Mean utility**	**Source**	**Mean utility**	**Source**	**Mean utility**	**Source**
Permanent ventilation	-0.02	TA755 and UK clinical experts[3]	-0.330	Lloyd et al. 2019[69]	-0.240	TA588[2]
Not sitting	0.10		-0.120		-0.120	
Sitting	0.20		-0.040		-0.105	
Standing	0.70		0.375		0.375	
Walking	0.85		0.615		0.615	
Source: Company submission, document B, Table 121, Table 122 and Table 123[46] Abbreviations: TA = Technology appraisal						

The base-case analysis submitted by the company combined both patient and carer quality of life for informal carers in the same analysis.[46] Carer utilities in the base-case analysis depended on the patient health state in the model (Table 7.14); carer utilities at the not sitting state were taken from TA588[2], sourced from Bastida et al 2017,[2,68] while carer utilities at the walking state were assumed to be equivalent to general utilities in the UK population, with values validated by clinical experts. Roche also conducted a burden of illness study, but the results were deemed to lack clinical validity, these estimates were used as a scenario analysis instead.[46] The analysis also assumed an average of 2.2 informal carers needed per patient based on internal data.[46] Finally, the model presented assumed direct increase in utility from therapy at the 'not sitting' and 'sitting' health-states of 0.2 for patients and 0.05 for carers.

Table 7.14: Carer utilities used in the company model

Patient health-state	Base-case carer utility	Source	Alternative values	Source
PV	0.484	TA588 based on Bastida et al. 2017[68]	0.633	Roche UK burden of illness study[46]
Not sitting	0.484		0.751	
Sitting	0.628		0.737	
Standing	0.771		0.72	
Walking	0.915		0.754	
Source: Company submission, document B[46] Abbreviations: PV = permanent ventilation; TA = technology appraisal				

EAG comment: The EAG recognises that finding utility values for young people is especially challenging. In this scenario our concerns surrounded the critiques that have been made in TA588[2] regarding the face validity of patient utility estimates used for this appraisal. Therefore, the EAG has adopted the approach used in a more recent appraisal for OA in presymptomatic patients (HST24[17]).

The EAG was also concerned about the negative utility value for permanent ventilation, which could be interpreted as worse than being dead, as utility values generally anchor dead at 0; after our consultation with a clinical expert, it was considered that it could send a problematic message to both clinicians and patients. Using an approach from HST24 assumes that utility at permanent ventilation is equal to 0, which the EAG recognises is still not an ideal situation as patients are still alive despite being at a severe health-state.[17]

In the presence of negative health-state utilities for the scenario analysis, the EAG has assumed that negative utility values are equivalent to 0 (i.e. equivalent but not worse than death). Regarding the direct impact of disease-modifying therapies, the EAG has assumed these provide an increment of 10% above the mean utility across all health-states where treatment is delivered, to make our analysis consistent across both company submissions.

The EAG was concerned about the approach for combining both patient and informal carer quality of life in the base-case analysis. The data on informal carer utility was not the result of data collection in the clinical trials, and it was difficult to ratify its validity beyond clinical expert opinion. Moreover, as the critique from the Biogen submission showed, there is a lack of a standardised methodology to include carer quality of life (see Section 6.3.2.6).

The EAG understands the importance of the perspective of informal carers in SMA and the value of including the impact on informal carers in this appraisal. For transparency and clarity in our analyses the EAG focused its base-case analysis exclusively on patient quality of life. An additional scenario analysis was presented including treatment impacts on patient and informal carer quality of life with the aim of exploring the potential impact of treatment on both patients and informal carers. This scenario assumed 1 carer on average for consistency with the Biogen analysis, where carer utilities and average carer characteristics were extracted from a recently published study by Lo et al, 2022.[73]

The EAG has also updated the approach used to adjust utility values based on age and gender based on the general UK population using the latest advice from the NICE methods guidelines and the latest DSU guidance.[74]

7.3.2.7 Resource use and costs

The list price used for one 60 mg/80 ml vial of risdiplam was £7,900.[46] A simple PAS discount of [redacted] was applied to the price of risdiplam for a total of [redacted].[46] While a majority of patients receive risdiplam via homecare which is covered by Roche, it was assumed that a small proportion of patients ([redacted]) receive risdiplam during hospital care through a pharmacist.[46]

In line with the SmPC, the economic model for presymptomatic and type 1 SMA patients also assumed that patients <2 years old require an average monthly dose of 0.2 mg/kg (of bodyweight) until they reach the age of 2 years, followed by a monthly dose of 0.25 mg/kg of bodyweight until they reach a bodyweight of 20 kg (approximately [redacted] of age predicted in the model). Above a bodyweight of 20 kg patients receive a monthly dose of risdiplam of 5 mg. Trial data and natural history of disease studies were pooled to generate patient weight estimates. Relative dose intensity was assumed to be equal to the FIREFISH part 2 trial at [redacted].[46]

Comparator interventions resource use**:** List prices were used for nusinersen at £75,000 per one 12 mg/5 ml vial. Hospital administration costs were derived from an NHSE annual tariff of £10,815.[46] Nusinersen is administered via 4 loading doses during the first 2 months, and a

maintenance dose every 4 months. For OA, a single cost including both administration and drug cost of £1,600,081 was applied.

Health-state related resource use**:** Roche reported the results of its own Delphi panel study collecting expert opinion on quantitative estimates for health-care resource use (HCRU) related to the management of SMA Type 1 and Type 2/3.[46] Results showed that resource use was high in SMA patients, particularly regarding disease-related healthcare visits, surgeries, and procedures. Costs from NHS reference values were used to derive monthly costs for each motor milestone-related health state. Resource use values from TA588 were used as a scenario analysis.[2] The health state related costs used in the models were same for presymptomatic and type 1 populations (Table 7.15).

Table 7.15: Monthly health-state related costs applied to the presymptomatic and Type 1 Roche models

Costs per cycle: base-case				Costs per cycle from TA588[2]
Health state	**Paediatric patient**	**Adult patient**	**One-off costs**	**Paediatric and adult**
Permanent ventilation	£1,557	£761	£15,834	£23,247
Unable to sit	£1,966	£697	£15,547	£13,284
Sitting	£1,504	£521	£12,964	£9,704
Standing	£989	£189	£7,359	£1,951
Walking	£414	£121	£3,702	£1,951
Source: company submission, document B, Table 134[46]				

EAG comment: The EAG acknowledges the Roche's effort to use HES data to derive health-state costs for the model, recognising the challenges of generating motor milestone-related resource use estimates for SMA outside of trial data and adapting them to the UK context. However, the EAG is concerned about the substantial differences in monthly costs between TA588[2] and those used for the base-case analysis derived from the Delphi panel; and the EAG considers this to reflect the uncertainties around the cost of disease in SMA that were highlighted in TA588.[2]

To maintain consistency with the current company submission and previous SMA appraisals, the EAG used health state costs from the latest NICE submission in this area (HST24).[17] The EAG also explored the costs from the Roche study as a scenario analysis, and acknowledges this as a key area of uncertainty, given the treatment has a direct impact in total patient costs particularly between the 'not sitting' and 'sitting' health states.

7.3.2.8 Adverse events

The company did not include the costs associated with adverse events in the model.[46] This was informed by RAINBOWFISH[59], FIREFISH[58], and SUNFISH[55] which had less than 5% of severe treatment-related adverse events.[46] The economic model did include the impact of non-permanent respiratory support and bulbar dysfunction as disease-related events for the BSC arm only, using data from an SMA natural history study conducted by Roche.[46]

EAG comment: The EAG was concerned about potential double counting of disease-related events in patient HRQoL, particularly for BSC, since the health-state utility values are expected to already reflect the impact of the disease on the general SMA patient population. Additionally, the data used to model these impacts on patient HRQoL was neither derived from clinical trial data nor was validated by clinicians, and therefore raises the risks of underestimating the patient HRQoL values. To ensure consistency across economic models, the EAG assumed that the utility values for each motor milestone fully captures the impact of the disease and related events.

7.3.2.9 Survival

During the first-year follow-up of RAINBOWFISH[59], no events related to permanent ventilation, or death were observed. The base-case assumed that DMTs did not carry a risk of permanent ventilation, while survival was assumed to correspond with the UK general population. Therefore, all DMTs had the same survival rates.

EAG comment: Since the EAG has opted for a decision problem comparing risdiplam with BSC, patients in the BSC arm were assumed to be at risk of progressing to permanent ventilation or experiencing an increased mortality risk related to the severity of SMA. Furthermore, the EAG also considered that the Roche approach to modelling overall survival did not adequately capture the increased mortality risks associated with high disease severity.

To address these concerns, and improve consistency in the economic evidence for SMA, the EAG adopted a similar approach to that used in the Biogen submission. This approach assumed an increased mortality risk for patients in the 'permanent ventilation', 'not sitting', and 'sitting' health states. These assumptions were informed by digitised survival curves from the latest NICE submission looking at presymptomatic patients treated with OA (HST24[17]).

7.3.2.10 Discontinuation

As no discontinuation events were observed during the RAINBOWFISH trial, treatment discontinuation was not included explicitly in the economic model.[46,59] This assumption was extended to nusinersen. OA only requires a single delivery; therefore, discontinuation assumptions did not apply to it.

EAG comment: Although the EAG disagrees with the notion that discontinuation from risdiplam is clinically implausible, particularly given known concerns such as potential impacts on fertility, it acknowledges that there is an evidence gap on long-term discontinuation rates. In the absence of long-term discontinuation data, the EAG's economic model maintained the assumption of no discontinuation for either risdiplam or nusinersen, recognising this is a favourable assumption to both therapies.

7.3.2.11 Decision modifier: Severity

The base-case analysis presented comparing risdiplam with BSC met the criteria for a severity multiplier of 1.7 on the incremental QALYs; however, the BSC was not considered a relevant comparator in the presymptomatic population as almost all patients do get treated.[46]

EAG comment: Since BSC was not considered a relevant comparator and risdiplam's independent comparisons with nusinersen and OA were a cost-comparison only, a severity modifier for incremental QALYs would not have impacted the results in the presymptomatic model. In its submission, the company applied the severity modifier to its base-case risdiplam

versus BSC analysis, which also included carer utilities.[46] The EAG considered the application of severity modifier while also including care utilities inappropriate, as the severity modifier should be applied solely on patient utility values. Therefore, the EAG has reported the company results, while also reporting separate results for informal carers and with the use of the severity modifier on patients' utilities only.

7.3.2.12 Company's cost-effectiveness results (presymptomatic population)

Deterministic results from the Roche base-case analysis (based on risdiplam PAS prices) showed that risdiplam was [redacted] compared to nusinersen, and risdiplam was [redacted] compared to OA (Table 7.16). The comparison with BSC was deemed to be not applicable for this population, but model results suggested risdiplam was [redacted] compared to BSC with an ICER of [redacted] Removing the severity modifier from the patient and carers scenario led to an ICER of [redacted] (Table 7.17). Applying the severity modifier to patient utilities only led to an ICER of [redacted] (Table 7.18). The probability of risdiplam being cost-effective at a WTP of £30,000/QALY was [redacted].

Table 7.16: Deterministic and probabilistic results for the presymptomatic population reported in the Roche submission (using risdiplam PAS price)

Technologies	Total costs (£)	Total LYs	Total QALYs	Inc. costs (£)	Inc. LYs	Inc. QALYs	ICER (£/ QALY)
Deterministic							
Risdiplam	[redacted]	18.64	[redacted]	-	-	-	-
Nusinersen	[redacted]	18.64	[redacted]	[redacted]	0	0	[redacted]
OA	[redacted]	18.64	[redacted]	[redacted]	0	0	[redacted]
BSC*	[redacted]	13.95	[redacted]	[redacted]	4.7	[redacted]	[redacted]
Probabilistic							
Risdiplam	[redacted]	-	[redacted]		-	-	-
Nusinersen	[redacted]	-	[redacted]	[redacted]	-	[redacted]	[redacted]
OA	[redacted]	-	[redacted]	[redacted]	-	[redacted]	[redacted]
BSC*	[redacted]	-	[redacted]	[redacted]	-	[redacted]	[redacted]

*BSC not deemed relevant for Roche's Base-case decision problem
Source: Company submission[46]
Abbreviations: BSC = best supportive care; LY = life years; OA = onasemnogene abeparvovec; QALY = quality-adjusted life year

Table 7.17: Deterministic results using carer utilities without the severity modifier (with risdiplam PAS price)

Technologies	Total costs (£)	Total LYs	Total QALYs	Inc. costs (£)	Inc. LYs	Inc. QALYs	ICER (£/QALY)
Deterministic							
Risdiplam	[redacted]	18.64	[redacted]	-	-	-	-
Nusinersen	[redacted]	18.64	[redacted]	[redacted]	0.00	0.00	[redacted]

OA	[redacted]	18.64	[redacted]	[redacted]	0.00	0.00	[redacted]
BSC	[redacted]	13.95	[redacted]	[redacted]	4.70	[redacted]	[redacted]

Source: Company submission[46]
Abbreviations: BSC = best supportive care; LY = life years; OA = onasemnogene abeparvovec; QALY = quality-adjusted life year

Table 7.18: Deterministic results using patient utilities with the severity modifier (with risdiplam PAS price)

Technologies	Total costs (£)	Total LYs	Total QALYs	Inc. costs (£)	Inc. LYs	Inc. QALYs	ICER (£/QALY)
Deterministic							
Risdiplam	[redacted]	18.64	[redacted]	-	-	-	-
Nusinersen	[redacted]	18.64	[redacted]	[redacted]	0.00	0.00	[redacted]
OA	[redacted]	18.64	[redacted]	[redacted]	0.00	0.00	[redacted]
BSC	[redacted]	13.95	[redacted]	[redacted]	4.70	[redacted]	[redacted]

Source: Company submission[46]
Abbreviations: BSC = best supportive care; LY = life years; OA = Onasemnogene Abeparvovec; QALY = quality-adjusted life year

7.3.2.12.1 Deterministic sensitivity analysis (presymptomatic population)

Risdiplam versus nusinersen

For the comparison between risdiplam and nusinersen parameters with the biggest impacts on cost were drug related costs for nusinersen and risdiplam. Parameters that can have an impact on quality of life between risdiplam and nusinersen were differences in patient utility at 'sitting' and 'not sitting' followed by carer utility at 'sitting' and 'not sitting'.

Figure 12: Deterministic sensitivity analysis on incremental costs: risdiplam versus nusinersen (presymptomatic)



Abbreviations: p.a = per annum; RDI = relative dose intensity

Figure 13: Deterministic sensitivity analysis on incremental QALYs: risdiplam versus nusinersen (presymptomatic)



Abbreviations: p.a = per annum; QALY = quality-adjusted life year

Risdiplam versus OA

For the comparison between risdiplam and OA parameters with the biggest impacts on cost were drug related costs for risdiplam and OA. Parameters that had an impact on quality of life between risdiplam and OA were differences in patient utility at “sitting” and “not sitting” followed by carer utility at “sitting” and “not sitting”.

Figure 14: Deterministic sensitivity analysis on incremental costs: risdiplam versus OA (presymptomatic)



Abbreviations: kg = kilograms; p.a = per annum; RDI = relative dose intensity; OA = onasemnogene abeparvovec

Figure 15: Deterministic sensitivity analysis on incremental QALYs: risdiplam versus OA (presymptomatic)



Abbreviations: p.a = per annum; QALY = quality-adjusted life year; OA = onasemnogene abeparvovec

Risdiplam versus BSC

For the comparison between risdiplam and BSC parameters with the biggest impacts on cost were drug related costs for risdiplam, and disease-related costs for children at ‘sitting’ and ‘not sitting’ health states. Parameters that had an impact on quality of life between risdiplam and BSC were differences in patient and carer utilities at ‘walking’ and the number of carers.

Figure 16: Deterministic sensitivity analysis on incremental costs: risdiplam versus BSC (presymptomatic)



Abbreviations: BSC = best supportive care; RDI = relative dose intensity

Figure 17: Deterministic sensitivity analysis on incremental QALYs: risdiplam versus BSC (presymptomatic)



Abbreviations: BSC = best supportive care; HSUV = health state utility value; QALY = quality-adjusted life year

7.3.2.12.2 Company's scenario analysis (presymptomatic population)

The scenario analysis showed that for the cost comparisons between risdiplam and nusinersen and risdiplam and OA the largest impact on costs were changes to the discount rates, and including VAT savings from risdiplam home care. For the comparison with BSC the largest impacts were from changing the source data for BSC, changing resource use to values from TA588, and changing caregiver utilities.

Table 7.19: Results of Roche's scenario analysis (presymptomatic population)

Scenario	ICER vs BSC	% ICER change	Incremental costs vs nusinersen	% change	Incremental costs vs OA	% change
Base case	[redacted]	-	[redacted]	[redacted]	[redacted]	[redacted]
Efficacy scenarios						
Comparative efficacy vs. BSC: Source for BSC set to PNCR data with SMN2 copies matched to RF	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Source for % scoliosis: change to Wijngaarde et al 2019[38]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Source for % bulbar dysfunction: change to Wadman et al 2017[41]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Source for % respiratory support: change to van der Heul et al 2019[75]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
HCRU scenarios						
Alignment with TA588 source for HCRU[2]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Alignment with TA588 source for HCRU and PV health state costs: 175% increase from the "Not Sitting" health state[2]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Utility values scenarios						
Source for patient utility values: EQ-5D-3L (NICE ERG TA588)[2]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Source for patient utility values: EQ-5D-Y (Lloyd et al., 2019)[69]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Source for caregiver utility values: Roche utility survey	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Source for caregiver utility values: UK Burden of Illness Study	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Other Scenarios						
Inclusion of VAT saving from risdiplam homecare	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Number of carers lowered to 2	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Number of carers increased to 3	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Scenario	ICER vs BSC	% ICER change	Incremental costs vs nusinersen	% change	Incremental costs vs OA	% change
Discount rate for both costs and benefits is lowered to 1.5%	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Discount rate for benefits is lowered to 1.5%, discount rate for costs remains 3.5%	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Source: Company submission[46]
Abbreviations: BSC = best supportive care; HCRU = health care resource use; ICER = incremental cost-effectiveness ratio; NICE = National Institute for Health and Care Excellence; OA = onasemnogene abeparvovec; TA = technology appraisal; UK = United Kingdom; VAT = value added tax

7.3.3 Type 1 SMA population

7.3.3.1 Model structure

7.3.3.1.1 Type of model

Same as the presymptomatic model (see section 7.3.2.1)

7.3.3.1.2 Health states and transitions

Model health states and motor milestones definition same as presymptomatic model (see Section 7.3.2.1.2)

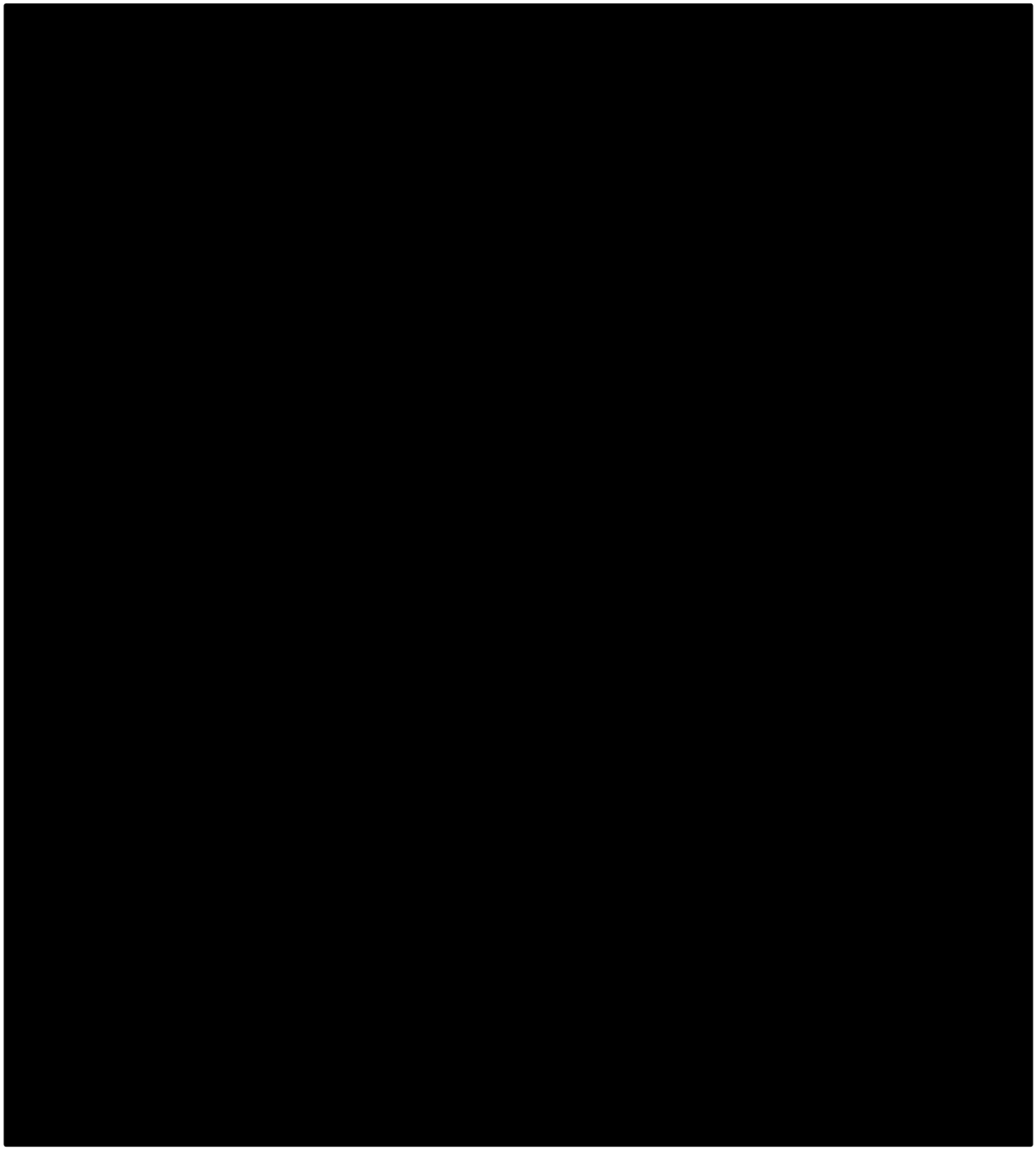
In addition, transition probabilities for the risdiplam arm were based on the 48-month follow-up data from the FIREFISH trial.[56] Data were fit into a continuous time Markov multi-state model, using baseline HINE-2 score as a covariate for transitions between 'not sitting' and 'sitting'. Transition probabilities were adjusted to only allow an improvement or loss of a single motor milestone (as captured in the model states) per 1 month model-cycle. After the points for clarification letter, the company detailed that multiple models were tested adjusting for covariates and were assessed for goodness of fit to the study data using AIC scores, as well as visual plots.[65]

Table 7.20: Monthly transitions probabilities for risdiplam based on the selected continuous time Markov multi-state model using HINE-2 defined motor milestones from the FIREFISH population

From\To	Non-sitting	Sitting	Standing	Walking
Non-sitting	[redacted]	[redacted]	[redacted]	[redacted]
Sitting	[redacted]	[redacted]	[redacted]	[redacted]
Standing	[redacted]	[redacted]	[redacted]	[redacted]
Walking	[redacted]	[redacted]	[redacted]	[redacted]

Source: company submission, document B[46]
Abbreviations: HINE-2 = Hammersmith Infant Neurological Examination — Part 2

Figure 18: Observed versus multi-state Markov model predicted prevalence for FIREFISH motor milestones (HINE-2)



Source: company submission[46]

After 24 months (2 years), the model assumes patients do not lose the motor milestones gained from a DMT, and after 66 months (5.5 years) risdiplam and nusinersen patients were assumed to only maintain the motor milestones captured by the model states. OA patients were assumed to have continued treatment effectiveness, while patients not receiving disease-modifying treatments and BSC were at risk of losing motor milestones. Since FIREFISH was a single-arm trial, transition probabilities for BSC, nusinersen, and OA were based on the unanchored MAIC analysis.[56,66]

EAG comment: The EAG considers the model structure, and the approach used by the company to derive transitions across motor milestones for risdiplam to be appropriate for the decision. Long-term assumptions of maintenance of motor milestones under treatment were of concern to the EAG, as clinical feedback suggested that long-term risks of motor decline may be present even during treatment.

The EAG decided to align the approach to long-term effectiveness in the Roche model with that of the Biogen model to ensure consistency in the assumptions of disease progression over the long-term. This meant that the effect of disease modifying therapies was not lifelong, instead DMTs allow patients to reach motor milestone improvements for a duration of time that matches the available clinical trial evidence. After this period, patients either maintain their motor milestones or are at risk of losing them over the long-term. For risdiplam this was 60 months of motor milestone improvement based on FIREFISH trial data.[56]

Patients receiving BSC were assumed to gain improvements in motor milestones over the first 12 months based on FIREFISH trial data and the unanchored MAIC estimates with ENDEAR.[56,66] After 12 months the rate of motor milestone decline corresponds to the natural history of SMA disease reported by Wadman et al. 2019.[41] The relative rate of motor milestone decline for risdiplam was extracted from Ribero et al. 2022 which reports that 80% of risdiplam patients are treatment responders compared to BSC.[66]

7.3.3.2 Population

FIREFISH baseline characteristics: mean age at baseline was 0.48 years, mean bodyweight at baseline was 5kg and 57% were females.[56]

7.3.3.3 Interventions and comparators

The type 1 SMA model compared risdiplam against nusinersen, BSC and OA in a population with characteristics like those reported above in section 7.3.3.2.

Intervention: Same as the presymptomatic model (see Section 7.3.2.3)

Comparators**:** Same as the presymptomatic model (see Section 7.3.2.3), however, unlike the presymptomatic model, the type 1 model also used BSC as a comparator in addition to nusinersen and OA.

EAG comment: In line with the critique of the clinical evidence and the limitations of the comparative effectiveness analysis, the EAG's base-case economic analysis focused on comparing risdiplam with BSC. As FIREFISH was a single-arm trial, the comparative analysis relied on estimates derived from the unanchored MAIC between FIREFISH and ENDEAR to inform the BSC arm;[56,66] the EAG recognises the limitations of this approach, given the small sample size and presence of confounding variables that could not be adequately adjusted for in the indirect comparison.[71]

7.3.3.4 Perspective, time horizon and discounting

Same as the presymptomatic model (see Section 7.3.2.4)

EAG comment: In order to fully capture the impact of the disease and the interventions across time, the EAG considers a lifetime horizon covering 100 years to be appropriate, as the [redacted] approach selected by the company risks putting an excessive focus exclusively on the BSC arm and not accounting for survival gains from treatment.

7.3.3.5 Treatment effectiveness and extrapolation

It was not clear from the report how the BSC arm was modelled. The company submission reported that ITC estimates used in TA755 for BSC were used in their current model[3] however, the EAG was not able to corroborate this as the information is marked as confidential in the public documentation. The committee discussion from TA755 noted concerns around the methods used to estimate the effectiveness of BSC, the same concerns are likely to apply here.[3] The EAG understands model estimates for BSC come from the unanchored MAIC between ENDEAR and FIREFISH.[66] The model includes relative effectiveness estimates in the BSC arm for OS, EFS (not on permanent ventilation or dead), and motor milestone improvements. Table 7.21 reports the relative effectiveness estimates used in the economic model to derive transition probabilities for BSC. The EAG considers that the difference between the 'sitting to standing' odds ratio (OR) and the 'standing to walking' OR may be a typo as this assumption was not reported in the company submission.

Table 7.21: Relative effectiveness estimates used in the Roche economic model to derive monthly transition probabilities for BSC

BSC	uMAIC	95% CI	95% CI
Event Free Survival (EFS, HR)*	[redacted]	[redacted]	[redacted]
Overall Survival (OS, HR)	[redacted]	[redacted]	[redacted]
Not Sitting to Sitting (OR)	[redacted]	[redacted]	[redacted]
Sitting to Standing (OR)	[redacted]	[redacted]	[redacted]
Standing to Walking (OR)	[redacted]	[redacted]	[redacted]

*EFS = alive and not on permanent ventilation
Abbreviations: BSC = best supportive care; uMAIC = unanchored multiple adjusted indirect comparison; CI = confidence interval; HR = hazards ratio; OR = odds ratio

To compare nusinersen versus risdiplam the company used estimates from the unanchored MAIC using results from ENDEAR and FIREFISH.[66] Hazard ratios were derived for OS and EFS, whereas effectiveness estimates for motor milestone improvements were presented as odds ratios for HINE-2 endpoints and were transformed to monthly probabilities. Table 7.22 reports the relative effectiveness estimates used in the economic model to derive transition probabilities for nusinersen.

Table 7.22: Relative effectiveness estimates used in the Roche economic model to derive monthly transition probabilities for nusinersen

Nusinersen	uMAIC	95% CI	95% CI
Event Free Survival (EFS, HR)	[redacted]	[redacted]	[redacted]
Overall Survival (OS, HR)	[redacted]	[redacted]	[redacted]
Not Sitting to Sitting (OR)	[redacted]	[redacted]	[redacted]
Sitting to Standing (OR)	[redacted]	[redacted]	[redacted]
Standing to Walking (OR)	[redacted]	[redacted]	[redacted]

*EFS = alive and not on permanent ventilation
Abbreviations: BSC = best supportive care; EFS = event-free survival; uMAIC = unanchored multiple adjusted indirect comparison; CI = confidence interval; HR = hazards ratio; OR = odds ratio

For modelling the relative effectiveness of risdiplam versus OA the company used estimates from the unanchored MAIC using results from FIREFISH [58] and STR1VE-EU[46,67] The economic model used the hazard ratio of the comparison for EFS, and a MAIC using HINE-2 and BSID-III as clinical endpoints for risdiplam and OA, respectively, to estimate odds ratios for motor milestone improvements and transform them into monthly probabilities. The uncertainty around motor milestone improvements was not explicitly included in the economic model. Table 7.23 reports the relative effectiveness estimates used in the economic model to derive transition probabilities for OA.

Table 7.23: Relative effectiveness estimates used in the Roche economic model to derive monthly transition probabilities for OA

OA	uMAIC	95% CI	95% CI
Event Free Survival (EFS, HR)	[redacted]	[redacted]	[redacted]
Overall Survival (OS, HR)	[redacted]	[redacted]	[redacted]
Not Sitting to Sitting (OR)	[redacted]	[redacted]	[redacted]
Sitting to Standing (OR)	[redacted]	[redacted]	[redacted]
Standing to Walking (OR)	[redacted]	[redacted]	[redacted]

*EFS = alive and not on permanent ventilation
Abbreviations: BSC = best supportive care; CI = confidence interval; uMAIC = unanchored multiple adjusted indirect comparison; HR = hazards ratio; OR = odds ratio; OA= onasemnogene abeparvovec

EAG comment: As detailed in Section 7.2, the EAG's decision problem focused on the comparison between risdiplam and BSC. Due to the lack of evidence comparing these to modes of treatment, the analysis relied on the unanchored MAIC estimates between FIREFISH[58] and ENDEAR.[28]

Beyond the changes to the decision problem, the EAG noted several issues with the estimates used for the comparison of risdiplam against other modes of treatment. The OR estimates comparing risdiplam with BSC did not match the OR estimates reported in Ribero et al 2022[66]. As the EAG was not able to corroborate the estimates in the company's base-case analysis, our analysis focused on using the published estimates from Ribero et al 2022 when it was deemed appropriate.[66]

Outside the base-case analysis comparing risdiplam with BSC, the EAG explored scenarios where patients eligible for risdiplam were also eligible for nusinersen, and where patients eligible for risdiplam were also eligible for OA. The estimates of relative effectiveness in the EAG scenario analyses were extracted from Ribero et al 2022[66] where available.

Where estimates of relative effectiveness were unavailable, the EAG assumed treatment equivalence. This was consistent with the approach taken by the company, however unlike the company the EAG explicitly incorporated uncertainty around the assumption of equivalence. The EAG was also concerned about how uncertainty in the relative effectiveness estimates was handled in the economic model and therefore revised the input methodology to better reflect this uncertainty.

7.3.3.6 Health related quality of life

Same as the presymptomatic model (see section 7.3.2.6)

7.3.3.7 Resource use and costs

Same assumptions as the presymptomatic model (see section 7.3.2.7).

In line with SMPC, the economic model for type 1 SMA patients also assumed that patients < 2 years old require an average monthly dose of 0.2 mg/kg (of bodyweight) until they reach the age of 2, followed by a monthly dose of 0.25 mg/kg of bodyweight until they reach a bodyweight of 20 kg (approximately [redacted] of age predicted in the model). Above a bodyweight of 20 kg patients receive a monthly dose of risdiplam of 5 mg. Trial data and natural history of disease studies were pooled to generate patient weight estimates. Relative dose intensity was assumed to be equal to the FIREFISH part 2 trial at [redacted].[46]

EAG comment: The critique to the presymptomatic methods also applies here (see Section 7.3.2.7).

7.3.3.8 Adverse events

The company did not include the costs associated with adverse events in the model. This was informed by RAINBOWFISH, FIREFISH, and SUNFISH where the incidence was less than 5% of severe treatment-related adverse events.[46] The economic model did include the impact of non-permanent respiratory support from Wadman et al. 2017,[41] severe scoliosis from Winjgaarde et al. 2019,[38] and bulbar dysfunction from van der Heul et al. 2019[75] as disease-related events across all treatments. Their occurrence depends on motor milestone health-states in the model (i.e. by improving motor milestones disease modifying therapies decrease the occurrences of these events).

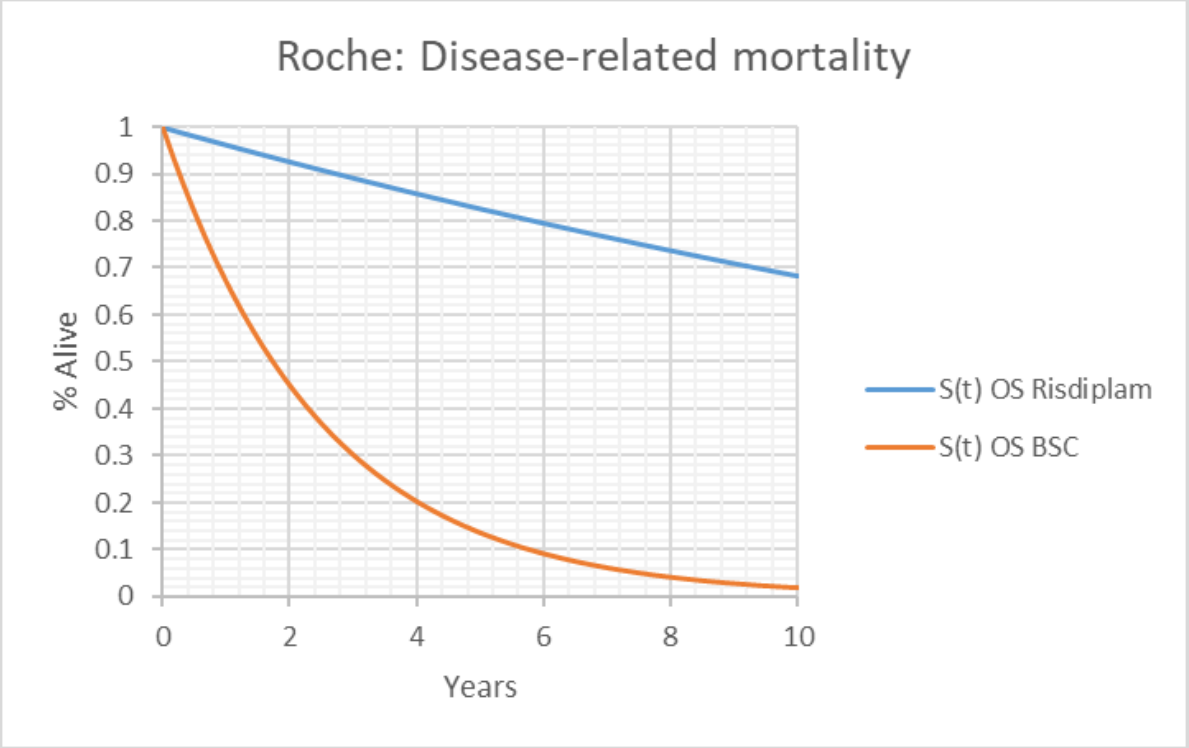
EAG comment: The EAG was concerned about double counting disease-related events in patient HRQoL, as the health-state utility values are expected to include the impact of the disease on the general SMA patient population. Moreover, the data used to model their impact on patient HRQoL is not derived from clinical trial data and has not been validated by clinicians; it therefore risks further underestimating the HRQoL values of the patient population. To maintain consistency across economic models, the EAG assumed that the utility values for each motor milestone capture the impact of the disease and disease-related events.

7.3.3.9 Survival

Patient data on time to event for permanent ventilation or death informed EFS in FIREFISH part 1 and 2 over 48 months and was used to inform the risdiplam arm.[56] The company's approach to calculating time to permanent ventilation involved subtracting the predicted survival curve of mortality from the predicted EFS curve (free from permanent ventilation or death). Survival analysis was performed on time to permanent ventilation or death to fit a parametric survival model. The exponential survival model was chosen based on clinical expert opinion to model the risk of permanent ventilation or death despite being ranked as the lowest statistical fit. The Generalised Gamma curve was reported as having the best statistical fit, yet this curve was also reported as not converging, therefore it was unclear how statistical fit was assessed in the first place.

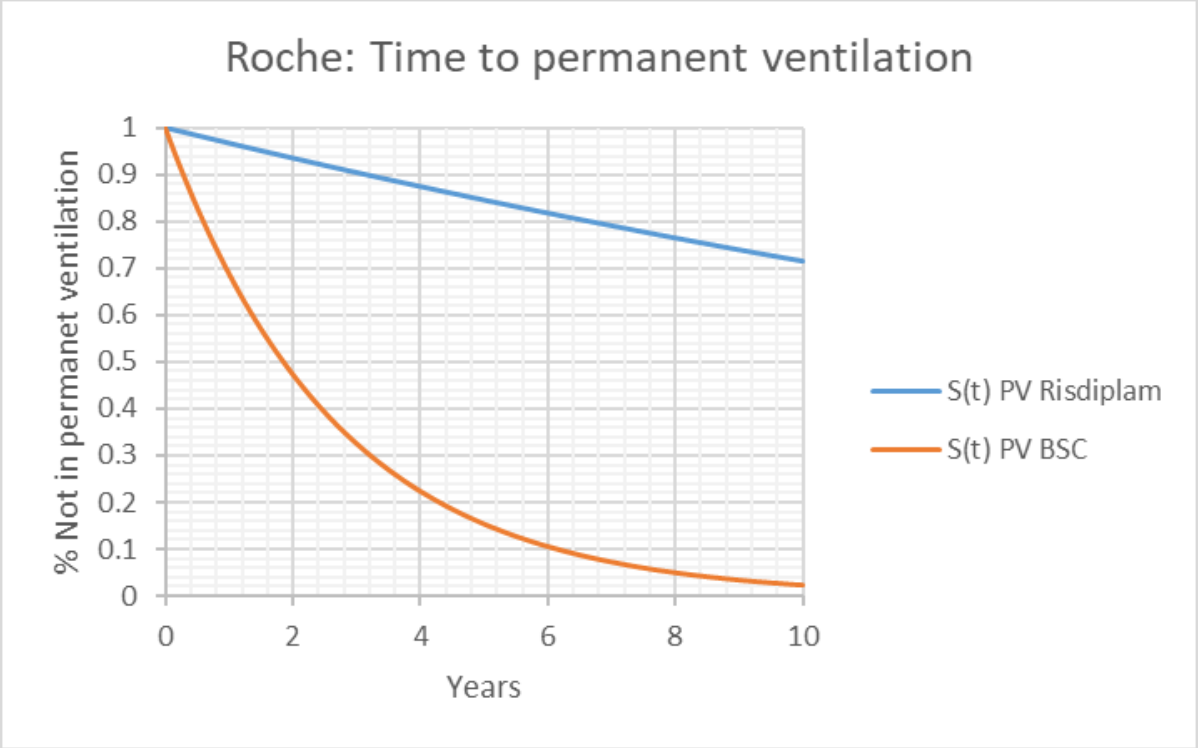
Overall survival data from FIREFISH part 1 and 2 over 48 months was used to inform the risk of mortality in risdiplam.[56] The company fitted a parametric survival model to predict survival over the long term. The exponential curve was chosen based on expert opinion despite having a lower statistical fit compared to other parametric models.

Figure 19: Disease-related overall survival for type 1 patients: risdiplam and BSC



Abbreviations: BSC = best supportive care; OS = overall survival

Figure 20: "Free from permanent ventilation" survival for type 1 patients: risdiplam and BSC



Abbreviations: BSC = best supportive care; PV = permanent ventilation

EAG comment: Long-term predictions of overall survival and EFS (free from death or permanent ventilation) for the BSC treatment arm largely reflected the severity of the condition. The EAG had concerns about the potential that longer-term changes in the relative risks of BSC beyond the trial follow-up may not have been captured due to the nature of the data, as FIREFISH was a single-arm trial that relied on an unanchored MAIC to predict the risks of BSC.[56]

The long-term predictions of permanent ventilation derived from the difference in the probability of OS and EFS (free from death or permanent ventilation) meant that if the risk of death was high enough relative to the risk of not being event free, the risk of permanent ventilation would be zero. Acknowledging these limitations stemming from the data available from the clinical trials, the EAG considers the methodological analysis of the evidence to be adequate.

7.3.3.10 Discontinuation

No assumption of treatment-related discontinuation applied for risdiplam and nusinersen, see Section 7.3.2.10 for details and EAG comment.

7.3.3.11 Decision modifier: severity

The company analysed the proportional and absolute shortfall of BSC, and the comparators nusinersen and OA, and applied a severity multiplier of 1.7 to the incremental QALY results across all pairwise comparisons.

EAG comment: In the submission, the company compared risdiplam versus nusinersen, OA, and BSC applying the severity modifier, respectively, to their base-case scenario which also included carer utilities. The EAG considered this an erroneous approach, as the severity modifier should only be based on and applied to patient utilities. The EAG has reported the company results, as well as separate results for informal carers and the severity modifier on patient utilities only.

7.3.3.12 Company's cost-effectiveness results (type 1 SMA)

In the company's base-case scenario analysis including the patient and informal carer quality of life estimates, severity modifiers, and using PAS discount prices for risdiplam against the comparator's list price, [redacted] against nusinersen and OA, and it was more effective and more costly compared to BSC. The increase in costs per QALY gained for risdiplam compared to BSC was [redacted], higher than NICE's £30,000/QALY threshold. Removing the severity modifier applied to both patient and carer utilities resulted in an ICER of [redacted]. Re-applying the severity modifier to patient utilities only resulted in an ICER of [redacted].

The probability of risdiplam being cost-effective at a WTP of £30,000/QALY was [redacted].

Table 7.24: Deterministic and probabilistic results for the type 1 population reported in the Roche submission (using risdiplam PAS price)

Technologies	Total costs (£)	Total LYs	Total QALYs	Inc. costs (£)	Inc. LYs	Inc. QALYs	ICER (£/QALY)
Deterministic							
Risdiplam	[redacted]	13.48	[redacted]	-	-	-	-

Technologies	Total costs (£)	Total LYs	Total QALYs	Inc. costs (£)	Inc. LYs	Inc. QALYs	ICER (£/QALY)
Nusinersen	[redacted]	11.26	[redacted]	[redacted]	2.22	[redacted]	[redacted]
OA	[redacted]	12.92	[redacted]	[redacted]	0.56	[redacted]	[redacted]
BSC	[redacted]	6.79	[redacted]	[redacted]	6.69	[redacted]	[redacted]
Probabilistic							
Risdiplam	[redacted]		[redacted]				
Nusinersen	[redacted]		[redacted]	[redacted]		[redacted]	[redacted]
OA	[redacted]		[redacted]	[redacted]		[redacted]	[redacted]
BSC	[redacted]		[redacted]	[redacted]		[redacted]	[redacted]

Source: company submission[46]
Abbreviations: BSC = best supportive care; LY = life year; OA = onasemnogene abeparvovec; QALY = quality-adjusted life year;

Table 7.25: Deterministic results using carer utilities without the severity modifier (using risdiplam PAS price)

Technologies	Total costs (£)	Total LYs	Total QALYs	Inc. costs (£)	Inc. LYs	Inc. QALYs	ICER (£/QALY)
Deterministic							
Risdiplam	[redacted]	13.48	[redacted]				
Nusinersen	[redacted]	11.26	[redacted]	[redacted]	2.22	[redacted]	[redacted]
OA	[redacted]	12.92	[redacted]	[redacted]	0.56	[redacted]	[redacted]
BSC	[redacted]	6.79	[redacted]	[redacted]	6.69	[redacted]	[redacted]

Source: company submission[46]
Abbreviations: BSC = best supportive care; LY = life year; OA = onasemnogene abeparvovec; QALY = quality-adjusted life year

Table 7.26: Deterministic results using patient utilities only with the severity modifier (using risdiplam PAS price)

Technologies	Total costs (£)	Total LYs	Total QALYs	Inc. costs (£)	Inc. LYs	Inc. QALYs	ICER (£/QALY)
Deterministic							
Risdiplam	[redacted]	13.48	[redacted]	-	-	-	-
Nusinersen	[redacted]	11.26	[redacted]	[redacted]	2.22	[redacted]	[redacted]
OA	[redacted]	12.92	[redacted]	[redacted]	0.56	[redacted]	[redacted]
BSC	[redacted]	6.79	[redacted]	[redacted]	6.69	[redacted]	[redacted]

Source: company submission[46]

Abbreviations: BSC = best supportive care; LY = life year; OA = onasemnogene abeparvovec; QALY = quality-adjusted life year

7.3.3.12.1 Deterministic sensitivity analysis (type 1)

Risdiplam compared to BSC

The parameters with the most impact on the ICER between risdiplam and BSC were the HR of OS, the HR of EFS, the cost of risdiplam, and the caregiver utility at sitting. The biggest impact on costs came from the cost of risdiplam, and relative effectiveness on OS and EFS. Similarly, the biggest impact on quality of life came from the relative effectiveness on OS and EFS, and carer utility at the “sitting” health-state.

Figure 21: Deterministic sensitivity analysis on incremental QALYs: risdiplam versus BSC (type 1)



Abbreviations: ICER = incremental cost-effectiveness ratio; HR = hazard ratio; HSUV = health state utility value; OS = overall survival; QALY = quality-adjusted life year; RDI = relative dose intensity

Risdiplam versus nusinersen

Parameters with the biggest impacts on costs were the drug costs of nusinersen and the cost of risdiplam, as well as the relative effectiveness on OS and EFS. Parameters with the biggest impacts on quality of life were the relative effectiveness on EFA and OS, the utility benefits from risdiplam or nusinersen for the “sitting” health-state.

Figure 22: Deterministic sensitivity analysis on incremental costs: risdiplam versus nusinersen (type 1)



Abbreviations: EFS = event-free survival; HR = hazard ratio; OS = overall survival; RDI = relative dose intensity

Figure 23: Deterministic sensitivity analysis on incremental QALYs: risdiplam versus nusinersen (type 1)



Abbreviations: EFS = event-free survival; HR = hazard ratio; HSUV = health state utility value; OS = overall survival

Risdiplam compared to OA

The parameters with the largest impact on costs were the drug costs of OA and risdiplam, respectively, the relative dose intensity of risdiplam, and patient costs at the “sitting” state. For quality-of-life, parameters with the largest impact were relative effectiveness on EFS, and patient utility benefits from risdiplam and OA in the “sitting” states.

Figure 24: Deterministic sensitivity analysis on incremental costs: risdiplam versus OA (type 1)



Abbreviations: EFS = event-free survival; HR = hazard ratio; OA = onasemnogene abeparvovec; RDI = relative dose intensity

Figure 25: Deterministic sensitivity analysis on incremental QALYs: risdiplam versus OA (type 1)



Abbreviations: EFS = event-free survival; HR = hazard ratio; HSUV = health state utility value; OA = onasemnogene abeparvovec; QALY = quality-adjusted life year;

7.3.3.12.2 Company's scenario analysis (type 1)

Risdiplam [redacted] across all scenarios when compared independently to nusinersen, and to OA. When compared to BSC, scenarios that had the largest impact on the ICER were using the health-state related costs from TA588, using the PV costs from TA588, and using alternative health-state utility values from TA588.[2]

Table 7.27: Scenario analyses from Roche submission (type 1)

Scenario	BSC	% ICER change*	Nusinersen	OA
Base case	[redacted]	-	[redacted]	[redacted]
Efficacy scenarios				
Comparative efficacy vs. OA: Source for OA set to STC STR1VE-US	[redacted]	[redacted]	[redacted]	[redacted]
Risdiplam transition probabilities informed by bootstrapped multi-state model 5	[redacted]	[redacted]	[redacted]	[redacted]
Source for % scoliosis: based on fixed proportions over time based on FIREFISH	[redacted]	[redacted]	[redacted]	[redacted]
Source for % respiratory support: on fixed proportions over time based on FIREFISH	[redacted]	[redacted]	[redacted]	[redacted]
Source for % bulbar dysfunction: on fixed proportions over time based on FIREFISH	[redacted]	[redacted]	[redacted]	[redacted]
HCRU scenarios				
Alignment with TA588 source for HCRU	[redacted]	[redacted]	[redacted]	[redacted]
Alignment with TA588 source for HCRU and PV health state costs: 175% increase from the "Not Sitting" health state	[redacted]	[redacted]	[redacted]	[redacted]
Utility values scenarios				
Source for patient utility values: EQ-5D-3L (NICE ERG TA588)[2]	[redacted]	[redacted]	[redacted]	[redacted]
Source for patient utility values: EQ-5D-Y (Lloyd et al. 2019)[69]	[redacted]	[redacted]	[redacted]	[redacted]
Source for caregiver utility values: Roche utility survey (96)	[redacted]	[redacted]	[redacted]	[redacted]
Source for caregiver utility values: UK Burden of Illness Study[46]	[redacted]	[redacted]	[redacted]	[redacted]

Scenario	BSC	% ICER change*	Nusinersen	OA
Other scenarios				
Changing time horizon to 20 years	[redacted]	[redacted]	[redacted]	[redacted]
Changing time horizon to 40 years	[redacted]	[redacted]	[redacted]	[redacted]
Inclusion of VAT saving from risdiplam homecare	[redacted]	[redacted]	[redacted]	[redacted]
Changing baseline characteristics to REACH UK patient population	[redacted]	[redacted]	[redacted]	[redacted]
Number of carers lowered to 2	[redacted]	[redacted]	[redacted]	[redacted]
Number of carers increased to 3	[redacted]	[redacted]	[redacted]	[redacted]
Discount rate for both costs and benefits is lowered to 1.5%	[redacted]	[redacted]	[redacted]	[redacted]
Discount rate for benefits is lowered to 1.5%, discount rate for costs remains 3.5%	[redacted]	[redacted]	[redacted]	[redacted]

*Relative to the base-case ICER
Abbreviations: ERG = External Review Group; HCRU = health care resource use; ICER = incremental cost-effectiveness ratio; NICE = National Institute for Health and Care Excellence; OA = onasemnogene abeparvovec; UK = United Kingdom; VAT = value added tax

7.3.4 Type 2 and 3 population

7.3.4.1 Model structure

Type of model: Roche used a Markov model to represent the natural history of type 2/3 5q SMA which was primarily informed by the previous NICE TA755 (see Figure 17).[3]

7.3.4.1.1 Health states and transitions*:*

The Markov model was built in Microsoft Excel with five mutually exclusive health states: Four were defined following MFM32 scores as: “not sitting”, “sitting with support”, “sitting unsupported”, “standing (with or without support)”.[46] The definition of the “walking (with or without support)” health state was derived from the HFMSE scoring measure using the ‘level of independent mobility: highest current level of independent mobility’ as neither the MFM32 nor the HFMSE were able to accurately capture this dimension.[46] Table 7.28 presents the model motor milestone-related states with their respective definitions.

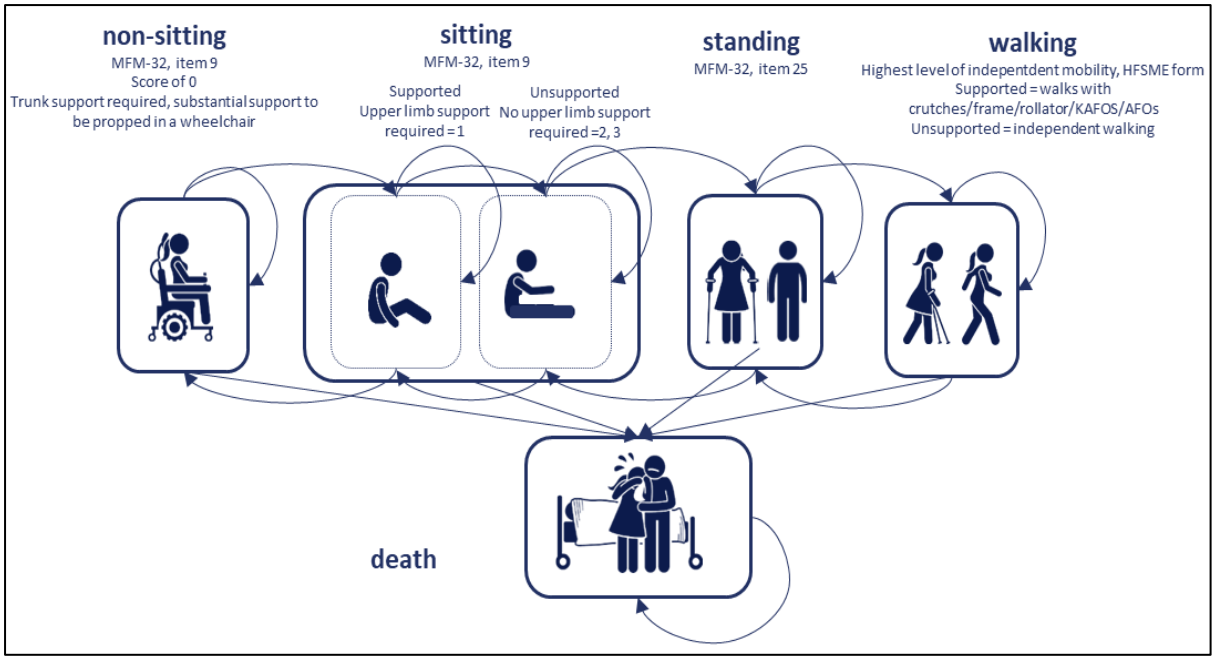
Table 7.28: Model health state definitions based on MFM-32/HFMSE scores

Health state	MFM-32 item and score
Not sitting	Item 9 (maintain seated position) = 0 (not able to maintain)
Sitting with support	Item 9 (maintain seated position) = 1 (able to perform but not finish)

Health state	MFM-32 item and score
Sitting without support	From Item 9 (maintain seated position) = 2 (able to perform with some help) to Item 25 (maintain standing position) < 1 (able to perform but not finish)
Standing (with or without support)	From Item 25 (maintain standing position) = 1 (able to perform but not finish) but HFMSE score not in highest current level of independent mobility
Walking (with or without support)	HFMSE 'level of independent mobility: highest current level of independent mobility'
Abbreviations: HFMSE = Hammersmith Functional Motor Scale Expanded; MFM=32 = 32-item Motor Function Measure	

Patients start the model distributed across the motor milestone states based on proportions from the SUNFISH trial,[49] and it was assumed that each model cycle with a duration of one month, patients could either maintain their motor milestone state, improve to a higher motor milestone or lose mobility and decline to a previous motor milestone. Death was the absorbing state to which patients could move into from any state at any cycle. The arrows in the Figure 26 indicate the direction of transitions across model health states.

Figure 26: Model structure for the later-onset SMA population used by Roche (type 2/3)



Source: company submission[46]
Abbreviations: AFO: ankle-foot orthosis; HFMSE: Hammersmith Functional Motor Scale Expanded; KAFOS: knee-ankle-foot-orthosis; MFM32: 32 Item Motor Function Measure

Transition probabilities for the risdiplam arm were based on a subgroup population of the SUNFISH trial (excluding patients from Asia), over the 60-month trial follow-up.[55] This subgroup was selected due to concerns from clinical experts around differences in standard of care from the UK clinical practice. Data from the placebo arm of SUNFISH were available for a 52-week follow-up,[49] a subgroup of this data excluding patients from Asia was used to calculate the motor milestone transition probabilities for BSC. Table 7.29 presents the motor

milestone transitions from risdiplam, and Table 7.30 presents the motor milestone transitions for BSC. Figure 27 and Figure 28 present the modelled motor-milestone predictions based on the probabilities for risdiplam and BSC, respectively.

Table 7.29: Transition probabilities for risdiplam (type 2/3 model)

From\To	Not Sitting	Sitting (supported)	Sitting (unsupported)	Standing	Walking
Not Sitting	[redacted]	[redacted]			
Sitting (supported)	[redacted]	[redacted]	[redacted]		
Sitting (unsupp)		[redacted]	[redacted]	[redacted]	
Standing			[redacted]	[redacted]	[redacted]
Walking				[redacted]	[redacted]

Table 7.30: Transition probabilities for BSC (type 2/3 model)

From\To	Not Sitting	Sitting (supported)	Sitting (unsupported)	Standing	Walking
Not Sitting	[redacted]	[redacted]			
Sitting (supported)	[redacted]	[redacted]	[redacted]		
Sitting (unsupp)		[redacted]	[redacted]	[redacted]	
Standing			[redacted]	[redacted]	[redacted]
Walking				[redacted]	[redacted]

Abbreviations: BSC = best supportive care

Figure 27: Modelled motor-milestone predictions for risdiplam over four years (type 2/3)

[redacted]

Figure 28: Modelled motor-milestone predictions for risdiplam over one year (type 2/3)



Abbreviations: BSC = best supportive care

After 24 months (2 years), the model assumes patients do not lose the motor milestones gained from a DMT, and after the [55]26 months the model assumes that patients reach long-term stability and can only maintain their motor milestones, the equivalent long-term assumption is applied to nusinersen. BSC patients are assumed to either maintain or decline their motor-milestones after 24 months.

EAG comment: The EAG considered the model structure to represent an adequate picture of the primary outcome trial data available, while also acknowledging the existence of further mobility improvements in SMA that may not have been captured by the motor milestone-based health states as defined in the economic model, but that will have an impact on patient health-related quality of life and were not being captured due to gaps in the quantitative evidence.

Although the EAG understands the pragmatic reasons to exclude the Asian population from the data, it was unclear how much this affected the baseline characteristics of the subgroup dataset as the EAG was unable to corroborate this from the documents submitted. Moreover, although the approach to fit trial data to the Markov chain likely followed a similar procedure as with the type 1 data (based on information criteria coefficients), the EAG could not access this information or the visual plots for type 2/3.

Finally, as with the presymptomatic and type 1 model, long-term assumptions of maintenance of motor milestones under treatment were of concern to the EAG, as clinical feedback suggested that long-term risks of motor decline may be present even during treatment.

The EAG decided to align the approach to long-term effectiveness in the Roche model with that of the Biogen model to maintain consistency in the assumptions of disease progression over the long-term. This meant that the effect of disease modifying therapies was not lifelong, instead DMTs allow patients to reach motor milestone improvements for a duration of time that matches the available clinical trial evidence. After this period, patients either maintain their

motor milestones or are at risk of losing them over the long-term. For risdiplam the EAG assumed 96 months of motor milestone improvement using SUNFISH trial data for transitions.

Patients receiving BSC were assumed to gain improvements in motor milestones over the first 12 months based using SUNFISH placebo data for transitions. After 12 months the rate of motor milestone decline corresponds to the natural history of SMA disease reported by Wadman et al. 2018.[41] The relative rate of motor milestone decline for risdiplam was extracted from Oskuoi et al. 2023,[50] which reports that after 2-years of SUNFISH data 58% of risdiplam patients showed stabilisation of motor milestones from MFM-32 scores.

7.3.4.2 Population

The population modelled in the type 2/3 model reflected the ITT patient characteristics of the global population in SUNFISH presented in Table 7.31.

Table 7.31: Type 2/3 SMA patient characteristics in the Roche model

Baseline characteristics	Value
Mean start age, years	10
Female (SE)	50.6%
SMA type	
Type 2	71.1%
Type 3	28.9%
Motor milestones	
Not sitting	0%
Sitting (supported)	13%
Sitting (unsupported)	74%
Standing	6%
Walking	7%

7.3.4.3 Interventions and comparators

The type 2/3 SMA model compared risdiplam against nusinersen and BSC in a population with the characteristics like those reported above in section 7.3.4.2.

Intervention: Same as the presymptomatic model (see Section 7.3.2.3).

Comparators: The company modelled nusinersen and BSC as the comparators for type 2/3 SMA populations.

EAG comment: In line with the critique of the clinical evidence and the limitations in the comparative effectiveness analysis, the base-case economic analysis by the EAG focused on comparing risdiplam with BSC.

7.3.4.4 Perspective, time horizon and discounting

The analysis was conducted from the perspective of the NHS and Personal Social Services (taking account of costs directly related to the medical treatment of SMA patients, and the quality of life of SMA patients and their carers) and with a time horizon of [redacted] (considered to cover the lifetime) in the base case. The costs and benefits were discounted at annual rate of 3.5% in accordance with the NICE methods guidelines NICE methods guidelines.[42]

EAG comment: To fully capture the impact of the disease and the interventions across time, the EAG considers a lifetime horizon covering 90 years to be more appropriate but that this may have little impact on the results.

7.3.4.5 Treatment effectiveness and extrapolation

As detailed above, relative effectiveness in motor milestone changes between risdiplam and BSC were informed by the SUNFISH trial data excluding the patient population from Asia to account for differences in standard of care. The risdiplam arm had a follow-up of 60 months (5 years) while the follow-up for the placebo arm informing BSC had a follow-up of 52 weeks (1 year).[49]

An unanchored MAIC was used to compare RULM scores for risdiplam from the SUNFISH trial with RULM scores for nusinersen from the CHERISH trial and presented them as odds ratios (ORs). Although the company reported high uncertainties around the estimated results from the MAIC, these were used to estimate the relative effectiveness between risdiplam and nusinersen in the economic model. The economic model assumes a monthly relative risk of nusinersen versus risdiplam for improving to a higher motor milestone of [redacted] applied to the probability of improving in all health states except "walking". Crucially, uncertainty around this estimate is not explored, instead, the model only explores uncertainty around transition probabilities with standard errors based on mean values.

EAG comment: As detailed previously, the base-case analysis conducted by the EAG focused on the comparison between risdiplam and BSC given the gaps in high-quality evidence comparing both drugs. The EAG considered the evidence available comparing risdiplam and nusinersen as a scenario analysis caveated by the limitations in the data. This comparison also focused on the relative effectiveness available in a publication by Ribero et al. 2022,[66] and explored the uncertainty around the relative effectiveness estimate given the published evidence, in addition to uncertainty around transition probabilities. The model also assumes that disease-modifying therapies do not remove the risk of long-term motor milestone decline, therefore the same assumptions of long-term decline were applied between risdiplam and nusinersen.

7.3.4.6 Health related quality of life

The company collected EQ-5D-5L data from the ITT population in the SUNFISH part 2 trial.[49] These data were used to derive utility estimates, and were presented to a group of clinical experts, along with utility values from a vignette study by Lloyd et al. 2019,[69] and utility values preferred by the EAG team appraising TA588.[2] The company base-case used estimates from Lloyd et al. 2019 due to them being preferred by clinical experts and explored the alternative utilities in its scenario analysis.[69] Table 7.32 reports the patient utility estimates used in the economic model.

Table 7.32: Utility values used in the Roche type 2/3 economic model

Base-case utility values			**Utilities from TA588[2]**		**Utilities from SUNFISH part 2**	
Model state	**Mean**	**Source**	**Mean**	**Source**	**Mean**	**Source**
Not sitting	-0.17	Based on	0.2	TA588[2]	[redacted]	
Sitting (supported)	0.04		0.4		[redacted]	

Base-case utility values			Utilities from TA588[2]		Utilities from SUNFISH part 2	
Model state	**Mean**	**Source**	**Mean**	**Source**	**Mean**	**Source**
Sitting (unsupported)	0.04	Lloyd et al.[69]	0.5		[redacted]	SUNSHINE part 2 internal data
Standing	0.56		0.7		[redacted]	
Walking	0.56		0.85		[redacted]	
Disutilities						
Bulbar function	-0.17		-		-	
Severe scoliosis	-		-		[redacted]	
Respiratory support	-		-		[redacted]	
Age ≥ 12 years old	-		-		[redacted]	
Abbreviations: TA = technology appraisal						

As with the Roche presymptomatic and type 1 models, the type 2/3 model combined health-related quality of life estimates from patients and informal carers. The company base-case used estimates from TA755[3] and explored alternative utility estimates from a burden of illness study and a utility survey both conducted by Roche.[46] Table 7.33 presents the informal carer utilities used in the company model. The model assumed an average of 2.2 carers per patient across all states except the "not sitting" state, where it assumed an average of 3 carers.

Table 7.33: Informal carer utilities used in the economic model

Base-case carer utilities			Scenario 1		Scenario 2	
Model state	**Mean**	**Source**	**Mean**	**Source**	**Mean**	**Source**
Not sitting	0.70	TA755[3]	0.75	Roche BoI study[46]	0.40	Roche utility survey study[46]
Sitting (supported)	0.77		0.74		0.40	
Sitting (unsupported)	0.84		0.74		0.66	
Standing	0.92		0.72		0.87	
Walking	0.92		0.75		0.87	
Abbreviations: TA = technology appraisal						

The economic model also included an increase in patient utility from receiving a disease-modifying therapy of 0.2 in the "not sitting", "sitting (supported)", and "sitting (unsupported)" health states. Similarly, an increase in carer utility of 0.05 was assumed for the same health states.

EAG comment: As with the previous models, the EAG recognises the challenges around methodological approaches for collecting data from young children in this patient population. Due to concerns around face validity of patient utility in this area in previous appraisals (TA588 and TA755[2,3]) the EAG decided to adopt the approach of the most recently published appraisal in this area, assessing OA in presymptomatic patients (HST24[17]), aiming to reach a degree of consistency across economic models.

The EAG was also concerned about the presence of negative utility values in some of the scenarios and have thus adopted an approach where negative utility health-states are assumed to be equivalent to the death state. For further details see the discussion in Section 7.3.2.6.

Regarding the direct impact of disease-modifying therapies, the EAG has assumed these provide an increment of 10% above the mean utility across all health-states, to make our analysis consistent across both company submissions.

The EAG was concerned about the approach for combining both patient and informal carer quality of life in the base-case analysis. The data on informal carer utility was not the result of data collection in the clinical trials, and it was difficult to ratify its validity beyond clinical expert opinion. Moreover, as the critique from the Biogen submission showed, there was a lack of a standardised methodology to include carer quality of life.

The EAG understands the importance of the perspective of informal carers in SMA and the value of including the impact on informal carers in this appraisal. For transparency and clarity in our analyses the EAG focused its base-case analysis exclusively on patient quality of life. An additional scenario analysis was presented including treatment impacts on patient and informal carer quality of life with the aim of exploring the potential impact of treatment on informal carers.

Regarding the values of informal carer utilities, the EAG noted discrepancies between values used from Lloyd et al. 2019 in this population,[69] and the models in the presymptomatic and type 1 population, and thus strove to make this consistent across all populations.[69]

7.3.4.7 Resource use and costs

Risdiplam resource use: Drug list price and confidential price assumptions, as well as delivery costs were consistent with Section 7.3.2.7. Relative dose intensity was assumed at [redacted] based on data part 2 of the SUNFISH trial. Furthermore, since the patient starting age in the model was 10 years, patients were expected to have reached a bodyweight above 20 kg and thus all patients received a regular monthly dose of risdiplam of 5 mg.

Comparator interventions resource use: The same assumptions around drug costs and delivery for nusinersen in the presymptomatic and type 1 model were applied in the type 2/3 model. For more details see Section 7.3.2.7.

Health-state related resource use: Roche reported the results of its own Delphi panel study collecting expert opinion on quantitative estimates for health-care resource use (HCRU) related to the management of SMA type 1 and type 2/3.[46] Results showed that resource use was high in SMA patients, particularly regarding disease-related healthcare visits, surgeries, and procedures. Costs from NHS reference values were used to derive monthly costs for each motor milestone-related health state. Resource use values from TA588 were used as a scenario analysis.[2] Table 7.34 reports the health state related costs used on the Roche economic model for patients with type 2/3 SMA.

Table 7.34: Health state-related costs in the Roche type 2/3 model

Costs per cycle: base-case				Costs per cycle from TA588
Health state	**Paediatric patient**	**Adult patient**	**One-off costs**	**Paediatric and adult**
Unable to sit	£1,581	£697	£15,586	£13,284
Sitting with support	£1,315	£521	£9,456	£13,284
Sitting without support	£1,315	£521	£9,456	£9,704
Standing	£660	£189	£2,372	£1,951
Walking	£222	£121	£715	£1,951

Source: company submission[46]
Abbreviations: TA = technology appraisal

7.3.4.8 Adverse events

The company did not include the costs associated with adverse events in the model. This was informed by RAINBOWFISH[59], FIREFISH, [58] and SUNFISH,[55] where the incidence of treatment-related severe adverse events was fewer than 5%. The economic model did include the impact of non-permanent respiratory support, severe scoliosis, and bulbar dysfunction as disease-related events across all treatments using data from an SMA natural history study conducted by Roche.[46] Their occurrence depends on motor milestone health-states in the model (i.e. by improving motor milestones disease modifying therapies decrease the occurrences of these events).

EAG comment: The EAG was concerned about double counting disease-related events in patient HRQoL, as the health-state utility values are expected to include the impact of the disease on the general SMA patient population. Moreover, the data used to model their impact on patient HRQoL is not derived from clinical trial data and have not been validated by clinicians, and therefore risks further underestimating the HRQoL values of the patient population. To maintain consistency across economic models, the EAG assumed that the utility values for each motor milestone capture the impact of the disease and disease-related events. The EAG explored the impact of adding an additional disutility for bulbar dysfunction based on SUNFISH part 2 data and Lloyd et al 2019 in the scenario analysis.[49,69]

7.3.4.9 Survival

As with the CHERISH trial for nusinersen,[29] data from part 2 in the SUNFISH trial lacked sufficient events to perform a survival analysis that compared survival outcomes between treatment arms.[55] Instead, Roche used different assumptions around mortality for type 2 and for type 3 patients respectively.

For type 2 patients, the company selected six studies identified from their systematic review and digitised the Kaplan-Meier curves to create a pooled pseudo-individual patient dataset.[46] Survival analysis was conducted, and parametric survival functions were fitted to the pooled pseudo-IPD data, with the Gompertz distribution considered the most appropriate according to the goodness of fit statistics and clinical experts' feedback. However, the company explored the Weibull distribution in a scenario analysis. These survival probabilities were applied to

Type 2 patients in the “not sitting”, “sitting (supported)”, and “sitting (unsupported)” health states in the model.

For type 3 patients, the company took evidence from the literature[76] and assumed overall survival similar to that of the general population taken from Office for National Statistics (ONS) for England.[44] In addition, in line with the previous NICE technology appraisals and clinical expert opinion, the company assumed that type 2 patients who reach advanced motor milestone of standing or walking, also had a survival equivalent to that of the general population. The economic model also assumed a 0.75 hazard ratio reducing the risk of mortality for disease-modifying therapies compared to BSC.

EAG Comment: The EAG acknowledges the existence of gaps in the data from the clinical trials in SMA types 2 and 3 regarding patient overall survival. Nonetheless, the EAG was not able to find published evidence backing the 0.75 hazard ratio in the overall risk of death for patients receiving DMTs and was unable to assess the uncertainty around this parameter. The EAG acknowledges that disease-modifying therapies may impact survival, yet the primary role of treatment for type 2 and type 3 patients is on improving health-related quality of life through improvements in mobility and the avoidance of disease-related adverse events, therefore the EAG did not assume a 0.75 relative probability of survival for patients receiving BSC.

In order to maintain consistency across the submissions in this disease area and considering the current gaps in the evidence, the EAG adopted the approach used in the latest submission to NICE for SMA (HST24[17]) and assumed that patients in the “not sitting”, “sitting (supported)”, and “sitting (unsupported)” faced a higher mortality risk, based on HST24,[17] to reflect the severity of the condition.[17] Patients at the “standing” and “walking” health states were assumed to follow the mortality of the general UK population, therefore therapies had the potential of impacting survival by decreasing the severity of the condition. The approach to survival used by the Roche base-case was explored as a scenario analysis.

7.3.4.10 Discontinuation

No assumption of treatment-related discontinuation was applied for risdiplam and nusinersen; see section 7.3.2.10 for details and EAG comment.

7.3.4.11 Decision modifier: Severity

The company analysed the proportional and absolute shortfall of BSC, and nusinersen separately, and applied a severity multiplier of 1.7 to the incremental QALY results across all pairwise comparisons.

EAG comment: In the submission, the company compared risdiplam versus nusinersen, and BSC applying the severity modifier, respectively, to their base-case scenario which included carer utilities. This was considered an erroneous approach, as the severity modifier should only be based on and applied to patient utilities. The EAG has reported the company results, as well as separate results for informal carers and the severity modifier on patient utilities only.

7.3.4.12 Company’s cost-effectiveness results (types 2 and 3)

In the company’s base-case scenario analysis including the patient and informal carer quality of life estimates, severity modifiers, and using PAS discount prices for risdiplam against the comparator’s list price, risdiplam was [redacted] against nusinersen, and it was more effective and more costly compared to BSC. The increase in

costs per QALY gained for risdiplam compared to BSC was [redacted] higher than NICE's £20,000/QALY threshold. Correcting by removing the severity modifier from patient and carer utility data led to an ICER of [redacted]. Applying the severity modifier exclusively to patient utilities led to an ICER of [redacted].

The probability of risdiplam being cost-effective at a WTP of £30,000/QALY was [redacted].

Table 7.35: Deterministic and probabilistic results for the type 2 and 3 population reported in the Roche submission (using risdiplam PAS price)

Technologies	Total costs (£)	Total LYs	Total QALYs	Inc. costs (£)	Inc. LYs	Inc. QALYs	ICER (£/QALY)
Deterministic							
Risdiplam	[redacted]	21.63	[redacted]	-	-	-	-
Nusinersen	[redacted]	21.51	[redacted]	[redacted]	0.13	[redacted]	[redacted]
BSC	[redacted]	20.29	[redacted]	[redacted]	1.34	[redacted]	[redacted]
Probabilistic							
Risdiplam	[redacted]		[redacted]				
Nusinersen	[redacted]		[redacted]	[redacted]		[redacted]	[redacted]
BSC	[redacted]		[redacted]	[redacted]		[redacted]	[redacted]

Source: company submission[46]
Abbreviations: BSC = best supportive care; ICER = incremental cost-effectiveness ratio; LY = life year; QALY = quality-adjusted life year

Table 7.36: Deterministic results using carer utilities without the severity modifier (using risdiplam PAS price)

Technologies	Total costs (£)	Total LYs	Total QALYs	Inc. costs (£)	Inc. LYs	Inc. QALYs	ICER (£/QALY)
Deterministic							
Risdiplam	[redacted]	21.59	[redacted]				
Nusinersen	[redacted]	21.46	[redacted]	[redacted]	0.12	[redacted]	[redacted]
BSC	[redacted]	20.29	[redacted]	[redacted]	1.30	[redacted]	[redacted]

Source: company submission[46]
Abbreviations: BSC = best supportive care; ICER = incremental cost-effectiveness ratio; LY = life year; QALY = quality-adjusted life year

Table 7.37: Deterministic results using patient utilities only with the severity modifier (using risidiplam PAS price)

Technologies	Total costs (£)	Total LYs	Total QALYs	Inc. costs (£)	Inc. LYs	Inc. QALYs	ICER (£/QALY)
Deterministic							
Risdiplam	[redacted]	21.59	[redacted]	-	-	-	-
Nusinersen	[redacted]	21.46	[redacted]	[redacted]	0.12	[redacted]	[redacted]

Technologies	Total costs (£)	Total LYs	Total QALYs	Inc. costs (£)	Inc. LYs	Inc. QALYs	ICER (£/QALY)
BSC	[redacted]	20.29	[redacted]	[redacted]	1.30	[redacted]	[redacted]

Source: company submission[46]
Abbreviations: BSC = best supportive care; ICER = incremental cost-effectiveness ratio; LY = life year; QALY = quality-adjusted life year

7.3.4.12.1 Deterministic sensitivity analysis (types 2 and 3)

Risdiplam compared to BSC

The parameters with the most impact on the ICER between risdiplam and BSC were carer utilities for “sitting without support”, the cost of risdiplam, caregiver utilities a “not sitting” and risdiplam treatment benefit at “sitting without support”. For costs those with the greatest impact were risdiplam costs, the proportion of type 2 relative to type 3, and HR of mortality for risdiplam versus BSC. For quality of life this was caregiver utility for “sitting without support” and “not sitting”, and risdiplam treatment benefit at “sitting without support”.

Figure 29: Deterministic sensitivity analysis on the ICER: risdiplam versus BSC (type 2/3)



Abbreviations: BSC = best supportive care; HSUV = health state utility value; ICER = incremental cost-effectiveness ratio; QALY = quality-adjusted life year

Risdiplam versus nusinersen

Parameters with the biggest impacts on costs were the drug costs of nusinersen and the cost of risdiplam, as well as the HR for mortality for nusinersen and the percentage of type 2 over type 3 patients. Parameters with the biggest impacts on quality of life were treatment-related benefits for risdiplam and nusinersen on patient and carer utilities for “sitting without support” and “not sitting”.

Figure 30: Deterministic sensitivity analysis on incremental costs: risdiplam versus nusinersen (type 2/3)



Figure 31: Deterministic sensitivity analysis on incremental QALYs: risdiplam versus nusinersen (type 2/3)



Abbreviations: HR = hazard ratio; HSUV = health state utlity value; QALY = quality-adjusted life year

7.3.4.12.2 Company's scenario analysis (types 2 and 3)

Risdiplam [redacted] across all scenarios when compared independently to nusinersen. When compared to BSC, scenarios that had the largest impact on the ICER were using the health-state related costs from TA588,[2], using alternative carer utility values from the Roche study, and using alternative health-state utility values from TA588 or utility values from the SUNFISH trial.[2,55]

Table 7.38: Company reported scenario analysis results for the type 2/3 SMA model

Scenario	ICER vs BSC	% ICER change	ICER vs nusinersen
Base case	[redacted]	-	[redacted]
Efficacy scenarios			
Comparative efficacy vs. BSC: set to natural history study	[redacted]	[redacted]	[redacted]
Risdiplam efficacy informed by non-imputed 5-year SUNFISH (excl. Asia)[55]	[redacted]	[redacted]	[redacted]
Risdiplam efficacy post follow-up set to the extrapolations as seen in the SUNFISH trial period	[redacted]	[redacted]	[redacted]
Weibull used for type 2 OS extrapolation	[redacted]	[redacted]	[redacted]
Source for % scoliosis: change to Wijngaarde et al. 2019[38]	[redacted]	[redacted]	[redacted]
Source for % bulbar dysfunction: change to Wadman et al. 2017[41]	[redacted]	[redacted]	[redacted]
Source for % respiratory support: change to van der Heul et al. 2019[75]	[redacted]	[redacted]	[redacted]
HCRU scenarios			
Alignment with TA588 source for HCRU[2]	[redacted]	[redacted]	[redacted]
Utility values scenarios			
Source for patient utility values: TA588 ERG clinical advisors[2]	[redacted]	[redacted]	[redacted]
Source for patient utility values: EQ-5D-3L values from SUNFISH[55]	[redacted]	[redacted]	[redacted]
Source for caregiver utility values: Roche utility survey	[redacted]	[redacted]	[redacted]
Source for caregiver utility values: UK Burden of Illness Study	[redacted]	[redacted]	[redacted]
Other scenarios			
Inclusion of VAT saving from risdiplam homecare	[redacted]	[redacted]	[redacted]
Changing baseline characteristics to REACH UK patient population	[redacted]	[redacted]	[redacted]
Number of carers lowered to 2	[redacted]	[redacted]	[redacted]
Number of carers increased to 3			
Discount rate for both costs and benefits is lowered to 1.5%	[redacted]	[redacted]	[redacted]

Scenario	ICER vs BSC	% ICER change	ICER vs nusinersen
Discount rate for benefits is lowered to 1.5%, discount rate for costs remains 3.5%	[redacted]	[redacted]	[redacted]

Source: company submission[46]
Abbreviations: BSC = best supportive care; HCRU = health care resource use; ICER = incremental cost-effectiveness ratio; NICE = National Institute for Health and Care Excellence; OS = overall survival; TA = technology appraisal; UK = United Kingdom

7.3.5 Model validation and face validity check

The company reported that all models were subject to external quality assurance procedure which involved technical validation of key model inputs and calculations. In addition, face validity of the models was examined by seeking patient and clinical experts' opinion on appropriateness and relevance of the model structure and inputs to ensure the model approach appropriately captured the costs and outcomes in UK clinical practice. An ad-board was run with academic health economics experts to discuss the appropriateness and potential adaptations of the original model from TA755.[3]

EAG comment: Although the EAG considered the model structure to be appropriate for the decision problem, the EAG has highlighted concerns around the approach used to model uncertainty around relative effectiveness parameters in the Roche model. Moreover, the EAG found multiple small errors across the model files, including an error in the calculation of "not sitting" utilities in the type 2/3 model or assumed differences in disease-related events between risdiplam and OA in the type 1 model. To ensure transparency, the EAG recreated the Markov trace in the Roche models and changed the approach of uncertainty in relative effectiveness using the same model files provided by Roche.

8 Summary and comparison of company submissions

8.1 SLR comparison

The search strategy for the SLR by Biogen (nusinersen) was assessed using the PRESS checklist and met the criteria for reporting. In contrast, the SLR by Roche (risdiplam) did not provide the search strategy and the EAG were unable to assess whether the search strategy lead to a complete overview of the literature.

The Biogen SLR originally considered type 0 and 4 patients, however due to clinical advice and lack data, respectively, they were not assessed further. These subgroups of SMA were not considered in the Roche SLR. The Roche SLR did identify further treatments outside the scope (i.e. reldesemtiv, apitegromab, RO7204239 and Branaplam) as interventions. This means there would be no missing data from this aspect. An issue with the Biogen inclusion criteria was the restriction of sample size (minimum 100 participants). This led to the exclusion of smaller studies, but not controlled studies. The Roche SLR did not make such exclusions. Some concerns are present regarding data extraction for the Roche SLR as there was a lack of detail surrounding the methods used. Additionally, some concerns are raised regarding the Roche SLR quality appraisal methods, due to lack of details.

Overall, there were some concerns regarding the reporting standards of the Roche SLR, while the Biogen SLRs main concern was regarding eligibility criteria.

8.2 ITC comparison

Biogen and Roche both attempted to perform MAIC analyses. Biogen only compared nusinersen with OA in presymptomatic patients using an unanchored MAIC, not with risdiplam. While Roche did compare risdiplam against both nusinersen and OA, these analyses were naïve and utilised only t-tests.

For type 1, Roche and Biogen both compared risdiplam and nusinersen using unanchored MAICs. However, Roche utilised an STC when comparing to OA, whilst Biogen continued using an unanchored MAIC for nusinersen. For type 1 SMA patients, Biogen controlled for the following factors, which Roche did not; sex; age at screening; age at symptom onset; weight; SMN2 copy number; baseline ventilation support (yes/no); and baseline feeding issues (yes/no). Roche stated that sex was not included as a previous prognostic review suggested this variable was not a statistically significant factor. Weight was not included due to lack of data availability. Mean age at symptom onset was not included due to correlations with age at first dose, which was selected in the base case. Ventilatory and/or nutritional support were deemed not viable to use for matching due to differences in practice. The reasons for excluding age at screening and SMN2 copy number as covariates were not provided. Covariates for the modelling were specifically reduced in the Biogen models, if necessary, using a LASSO regression. Roche did not report this.

For type 2/3 patients, Biogen utilised an STC only, as they suggested that the cohorts were not easily comparable. Roche implemented an anchored MAIC and reported the limitations of this, mainly due to lack of comparability between the two cohorts and reduced ESS leading to increased uncertainty. Type 2/3 SMA analyses for both companies utilised the same covariates for matching. The EAG believes that indirect comparisons for the type 2/3 patients is difficult to conduct due to differences in patient eligibility and baseline characteristics. While IPD could potentially balance some of this confounding it is unclear if this would be adequate

to overcome these inherent differences in eligibility and patient characteristics. This opinion of the EAG is also supported by a recent draft report of the same treatments conducted by the Institute for Clinical and Economic Reviews.[77]

8.3 MAA comparison

For the paediatric MAAs nusinersen conducted more MMRMs compared to risdiplam (n = 5 vs 2, respectively), this was likely due to data availability. The main difference was the lack of type 1 MMRM analyses (e.g. CHOP-INTEND, RHS). There were also differences in model covariates, nusinersen included baseline score and duration of disease at baseline, which the risdiplam MMRMs did not. Additionally, for type 2/3 patients nusinersen analyses included baseline function of non-sitters, sitters and walkers. While risdiplam analyses categorised patients as walkers/sitters or non-sitters in type 2/3 models. Overall, both MAAs conducted analyses when feasible and, if not feasible, descriptive statistics were reported.

For the adult MAAs nusinersen and risdiplam conducted the same MMRMs. Efforts were also made to consider the type 2/3 patients as separately as possible. Overall, the analyses are conducted using appropriate methods.

8.4 Cost-effectiveness analysis

Biogen and Roche both conducted cost-effectiveness analyses of treatments for presymptomatic, type 1, and type 2/3 SMA populations separately.

Biogen only compared nusinersen with BSC across all the three population groups citing the reason that it was not appropriate to assess the relative effectiveness of nusinersen against DMTs given the lack of robust evidence on relative effectiveness. The economic model structure in the Biogen submission was based on TA588 and focused on a set of motor-milestones gains and loses defined by the WHO-MM instrument.[2] For both the presymptomatic and type 1 populations, the model included a transition to permanent ventilation. For the presymptomatic population, Biogen used data from the single-arm NURTURE study and conducted a naïve comparison against BSC using control arm motor milestones data from ENDEAR and CHERISH trials.[28,29,36] Due to a lack of events, survival assumptions were informed by the approach in HST24.[17] For the type 1 population, Biogen used data from the ENDEAR-SHINE controlled trial and its extension, which informed transitions in motor-milestones, risk of death and risk of permanent ventilation for both nusinersen and BSC.[28,37] For the type 2/3 population, data were drawn from the CHERISH-SHINE controlled trial and extension study to inform motor milestone transitions for both nusinersen and BSC.[29,37] Due to a lack of events, survival assumptions in this model were informed by the approach in HST24, as well as general UK population survival.[17,44]

Trial results from NURTURE indicated that nusinersen [redacted] In the ENDEAR-SHINE study [redacted]. Results from CHERISH-SHINE suggested that nusinersen [redacted]

Patient health-related quality of life (HRQoL) data was not collected from either the NURTURE or ENDEAR trials.[28,36] Instead, the model adopted the HRQoL approach used in HST24 and applied it across the presymptomatic, type 1, and type 2/3 population models.[17] In the base-case analysis patient and informal carer HRQoL were pooled together using an approach consistent with that applied in TA755.[3] As the base-case approach combined HRQoL for both patients and carer, a severity modifier was not applied to the results. Biogen also used cost estimates from HST24 to inform NHS and personal social services costs.[17] The approach to modelling the disease included a long-term risk of motor-milestone decline, based on available clinical trial evidence.[41] Additionally, patients receiving nusinersen were also at risk of treatment discontinuation and moving to BSC, as observed in the trial data.[33]

Biogen's base-case analysis indicated that [redacted] for treating the presymptomatic population. A subgroup analysis further suggested that [redacted]. However, [redacted] compared to BSC in the treatment of type 1 and type 2/3 SMA populations. Similar findings were reported in the company's subgroup analyses for the type 2 and type 3 populations.

Roche compared risdiplam with nusinersen and OA for the presymptomatic population. BSC was not deemed an appropriate comparator for the presymptomatic population, as this approach is rarely used in clinical practice for presymptomatic patients. For the type 1 population, risdiplam was compared with nusinersen, OA, and BSC, while for the type 2/3 risdiplam was compared with nusinersen and with BSC. The economic model structure in the Roche submission was based on TA755 and focused on a set of motor milestones gains and loses defined by the HINE-2 instrument for presymptomatic and type 1 patients,[3] while the type 2/3 model focused on motor milestones from the MFM-32 and HFMSE instruments.[46] The presymptomatic and type 1 models also included the risk of permanent ventilation.

For the presymptomatic population, Roche used data from the RAINBOWFISH[59] single-arm study and assumed equivalence in effectiveness across risdiplam, nusinersen and OA. Data for BSC from an internal, unpublished natural history study was included in the model, but the Roche submission did not consider the BSC results to be a relevant comparator in the decision problem.[46] For the type 1 population, Roche used data from FIREFISH, [58] a single-arm trial for risdiplam, and applied the estimates from the unanchored MAIC with ENDEAR to estimate the relative effectiveness of nusinersen and BSC, as well as STR1VE-EU for OA.[46,67] These data informed model transitions for motor milestones, overall survival, and the risk of death or permanent ventilation (from EFS data). For the type 2/3 population, Roche used data from the SUNFISH study,[55] a controlled trial informing transitions between motor milestones for nusinersen and BSC. Due to a lack of events, survival assumptions were informed by pooled survival data from published studies identified in the literature review for type 2 patients, and general population survival for type 3 patents, and an assumption of lower overall survival for BSC.[44]

Trial results from RAINBOWFISH[59] suggested risdiplam [redacted]. Results from FIREFISH suggested risdiplam

[redacted]. Results from SUNFISH suggested risdiplam [redacted]. These key results had the largest implications for disease-related health care costs, patient quality of life and carer quality of life. Patient health-related quality of life (HRQoL) data was not collected from either RAINBOWFISH[59] or FIREFISH. [58] Instead, the model adopted the approach to patient HRQoL from TA755,[3] applying it through the presymptomatic and type 1 population models. HRQoL for type 2/3 patients was informed by estimates from Lloyd et al. 2019 and trial data on the EQ-5D from SUNFISH was explored as a scenario analysis.[55,69] The base-case analysis pooled together patient and informal care HRQoL based on an approach used in TA755.[3] As the base-case approach combined patient and carer HRQoL, a severity modifier should not be applied to the results.

The submission by Roche used an expert elicitation exercise conducted by the company across type 1, type 2, and type 3 patients to inform NHS-related costs and personal social services costs.[46] Costs for presymptomatic patients were assumed to be equivalent to type 1 patients. The approach to modelling the disease assumed no long-term risk of motor-milestone decline for patients treated with DMTs. Based on evidence from the trials, the models assumed no risk for treatment discontinuation for risdiplam and extended this assumption to nusinersen; this approach is not clinically plausible for OA and BSC.

Roche's base-case analysis showed that risdiplam would [redacted] when treating the presymptomatic population. Even though the comparison with BSC was not deemed appropriate, the company model showed that [redacted] when compared to BSC for the presymptomatic population. The company did not conduct a subgroup analysis in the population with 2 or 3 copies of SMN2 due to a lack of comparative evidence. The company's base-case analysis showed that [redacted] when compared to nusinersen or OA. However, [redacted] treatment when compared to BSC. Risdiplam was [redacted] in the treatment of type 2/3 population when compared to nusinersen [redacted]

The economic model structures used by the companies were appropriate conceptualisations of the decision problem and disease progression. However, important differences in patient characteristics and the clinical definitions of motor milestones made it difficult to compare the effectiveness of therapies across models. This limitation also affected the interpretation of results from the MAA data, further reducing their applicability to the cost-effectiveness models. Table 8.1 highlights differences in motor milestone definitions for the presymptomatic and type 1 populations and Table 8.2 for the type 2 and 3 populations.

Table 8.1: Motor milestone definitions for presymptomatic and type 1 patient models

Economic model: Biogen submission			Economic model: Roche submission	
Model states	**WHO motor milestones**	**HINE-2 definitions**	**Model states**	**HINE-2 definitions**
Not sitting	-	< 3 in the HINE-2 sitting dimension	Not sitting	< 1 in the HINE-2 sitting dimension

Economic model: Biogen submission			Economic model: Roche submission	
Model states	**WHO motor milestones**	**HINE-2 definitions**	**Model states**	**HINE-2 definitions**
Sitting without support	Sitting without support	≥ 3 in the HINE-2 sitting dimension to < 2 in the standing dimension	Sitting (with or without support)	≥ 1 in the HINE-2 sitting dimension to < 2 in the standing dimension
Standing with support	Standing with assistance	≥ 2 in the HINE-2 standing dimension to < 3 in the walking dimension	Standing (with or without support)	≥ 2 in the HINE-2 standing dimension to < 2 in the walking dimension
Walking independently	Walking alone	≥ 3 in the HINE-2 walking dimension	Walking (with or without support)	≥ 2 in the HINE-2 walking dimension
Abbreviations: HINE-2 = Hammersmith Infant Neurological Examination-2; WHO = World Health Organization				

Table 8.2: Motor milestone definitions for type 2/3 patient models

Economic model: Biogen submission		Economic model: Roche submission	
Model states	**WHO motor milestones**	**Model states**	**MFM-32/ HFMSE item and score**
Not sitting	-	Not sitting	Item 9 (maintain seated position) = 0 (not able to maintain)
Sitting without support	Sitting without support	Sitting with support	Item 9 (maintain seated position) = 1 (able to perform but not finish)
		Sitting without support	From Item 9 (maintain seated position) = 2 (able to perform with some help) to Item 25 (maintain standing position) < 1 (able to perform but not finish)
Standing with support	Standing with assistance to standing alone	Standing (with or without support)	From Item 25 (maintain standing position) = 1 (able to perform but not finish) but HFMSE score not in highest current level of independent mobility
Walking independently	Walking alone	Walking (with or without support)	HFMSE 'level of independent mobility: highest current level of independent mobility'
Abbreviations: HFMSE = Hammersmith Functional Motor Scale - Expanded; MFM-32 = Motor Function Scale – 32 Item; WHO = World Health Organization			

Beyond the limitations arising from differences in clinical outcome measures, the quality of relative effectiveness data available from ITCs further restricted the EAG's ability to assess the relative effectiveness of DMTs in the base-case. As a result, these comparisons had to be explored through scenario analyses. Patient HRQoL was a major source of uncertainty in both submissions, largely due to the challenges of measuring HRQoL in children and the rarity and severity of SMA. The greatest uncertainty stemmed from HRQoL estimates associated with severe health states, such as permanent ventilation, non-sitting and sitting-related states.

Indeed, another major source of uncertainty in the cost-effectiveness analysis across both company submissions was the estimation of disease-related costs for the most severe health states, including permanent ventilation, non-sitting and sitting-related states. At these levels of severity, the cost of care can be close to the maximum willingness-to-pay threshold of the healthcare system. As a result, any treatment that increases costs, regardless of its effectiveness, risks exceeding this willingness to pay threshold. The EAG identified substantial variation in cost estimates for the model health states, driven by a lack of robust data.

Furthermore, the EAG acknowledges that the perspective of informal carers is an important consideration in this disease area, and that NICE guidelines permit the inclusion of carer health-related quality of life (HRQoL) in appraisals. Indeed, discussions between the EAG and patient organisations as part of the MTA process emphasised the impact of SMA on carer HRQoL. However, the company submissions adopted markedly different approaches to incorporating informal carer HRQoL, relying on data elicited outside the clinical trials. Due to these limitations in both data quality and methodology, the EAG adopted the patient perspective to better reflect the severity of the disease, while also presenting a scenario analysis that included both patients and carers.

Overall, clinical results indicated that, in presymptomatic patients, both risdiplam and nusinersen had the potential to improve motor milestones to the least severe levels of the disease and reduce the risk of permanent ventilation. However, the evidence was insufficient to draw strong conclusions compared to BSC. For type 1 patients, both treatments appeared to reduce the risk of permanent ventilation and maintain motor function around sitting-related health states, although significant evidence gaps remained for risdiplam. In patients with type 2 and 3 SMA, there was stronger evidence that both treatments helped maintain motor milestones related to sitting when compared to BSC. These findings have important implications for the economic analysis, as the costs of care in sitting-related health states are substantial and must be weighed against gains in patient quality of life. However, this also constrains the analysis to motor milestones measured by instruments that may lack sensitivity to fully capture the disease's complexity.

Although the economic analyses submitted by both companies combined patient and carer quality of life meaning that results were not eligible for the severity modifier criteria, Table 8.3 presents the eligibility for nusinersen and risdiplam across each patient population to the severity modifier criteria based on QALYs in standard care.

Table 8.3 Severity modifier eligibility based on the economic evidence presented by each company

Population	Expected QALYs	BSC QALYs	Absolute shortfall	Proportional Shortfall	Eligible severity modifier
Biogen - nusinersen					
Presymptomatic	24.89	[redacted]	[redacted]	[redacted]	1.2
Type 1	24.87	[redacted]	[redacted]	[redacted]	1.7
Type 2&3	24.55	[redacted]	[redacted]	[redacted]	1.2
Roche - risdiplam					
Presymptomatic	24.87	[redacted]	[redacted]	[redacted]	1.7
Type 1	24.87	[redacted]	[redacted]	[redacted]	1.7
Type 2&3	24.02	[redacted]	[redacted]	[redacted]	1.7

Abbreviations: QALY = quality adjusted life year; BSC = best supportive care

8.4.1 Addendum addressing NICE and manufacturers' changes to the economic models during the consultation process

Following the submission of the EAG assessment report, an online meeting was held between NICE, the EAG, and the manufacturers (Biogen and Roche) to discuss alternative approaches to caregiver quality of life and the severity modifiers. In response to a request from NICE, Biogen and Roche submitted additional results.

Biogen used the EAG adapted models to run additional scenarios on caregiver quality of life and severity modifiers. However, the overall conclusions on the cost-effectiveness of nusinersen across the three SMA subpopulation types (presymptomatic, type 1 and type 2/3), as reported by the EAG later in Section 15.1, remain unchanged even when Biogen applied different methodological approaches (utility decrement or increment) to carer utility calculations.

Roche similarly submitted a revised version of the models used to run the EAG's analyses including additional scenarios on caregiver quality of life. However, the overall conclusions of the cost-effectiveness of risdiplam across the three SMA subpopulation types (presymptomatic, type 1 and type 2/3), as reported by the EAG later in Section 15.2, remain unchanged even when Roche applied different methodological approaches (utility decrement or increment) to carer utility calculations. Roche also pointed to an error in the EAG's type 2/3 model which the EAG has corrected, but the EAG's conclusions remained robust to these changes.

Please refer to the addendum of economics results from companies alongside this report for the detailed results, as well as the results of additional analyses requested by NICE.

9 Involvement and engagement with companies, professionals and patients

Throughout the MTA process, the EAG consulted with both Biogen and Roche, representatives of professional organisations, representatives of patient organisations and individual clinicians. Three meetings each were held separately with each of Biogen and Roche, representatives of professional organisations, and representatives of patient organisations. The discussions in these meetings informed the overall approach to the MTA and the methods the EAG proposed to use, as well as providing feedback on high-level, interim results. The EAG met with other clinicians on an individual, ad-hoc basis to help validate clinical assumptions made.

An overall summary of the meeting dates with each stakeholder and a brief overview of the agenda for each meeting is provided in Table 9.1.

Table 9.1: Overview of meetings between the EAG and key stakeholders

Date	Who the EAG met with	Key discussion points
18.03.2025	Biogen	• Exploration of additional PfC
26.03.2025	Roche	• Exploration of additional PfC
31.03.2025	Clinicians and professional organisations	• High level overview of the overall approach and methods being taken by the EAG • Key considerations to inform the review question • Early economic modelling designs and considerations • Qualitative data reflections • Discussion and agreeing next steps
04.04.2025	Patient organisations	• High level overview of the overall approach and methods being taken by the EAG • Key considerations to inform the review question • Early economic modelling designs and considerations • Qualitative data reflections • Discussion and agreeing next steps
10.04.2025	Clinician	• Prognostic factors • Reasons for delay in diagnosis • Choices of treatment • Discussion of different outcomes and their lack in picking up important factors • Reasons for discontinuation • Rate of loss of function
28.04.2025	Specialist physiotherapist	• Experience of treating patients with different types of SMA and their characteristics, impact on quality of life
06.05.2025	Roche	• Overview of the EAG assessment of the Roche submission and changes made by the EAG to the Roche decision problem, the clinical evidence, and the economic model. • Discussion of the EAG changes to the Roche submission.

Date	Who the EAG met with	Key discussion points
06.05.2025	Patient organisations	• Reflection on major points from previous meeting and what the EAG have considered surrounding these • Presenting an overview of the structure of the economic models, including the anticipated outcomes, costs and utilities feeding into each model • Overview of the EAG's approach to the qualitative analyses and interim results • Discussion and space for questions and answers on each of the key points covered
07.05.2025	Biogen	• Overview of the EAG assessment of the Biogen submission and changes made by the EAG to the Biogen decision problem, the clinical effects, and the economic model. • Discussion of the EAG changes to the Roche submission.
07.05.2025	Professional organisations	• Reflection on major points from previous meeting and what the EAG have considered surrounding these • Presenting an overview of the structure of the economic models, including the anticipated outcomes, costs and utilities feeding into each model • Overview of the EAG's approach to the qualitative analyses and interim results • Discussion and space for questions and answers on each of the key points covered
09.05.2025	Specialist physiotherapist	• Differences between type, with consideration of natural history, in adult patients • Timing of assessments for patients • Changes in motor milestones and the large spectrum of potential motor changes • Impact of fatigue and how treatment may improve this
20.05.2025	Registry	• Availability of data and updating of modelling where possible • Timeframes for getting any further updates, if available
10.06.2025	Clinician	• Follow-up meeting to discuss permanent ventilation and drug side effects
16.06.2025	Biogen	• Recap of the EAG base-base models and scenarios surrounding nusinersen • Presentation of interim ICER results and discussion

Date	Who the EAG met with	Key discussion points
17.06.2025	Clinicians and professional organisations	• Reflection on major points from previous meeting and what the EAG have considered surrounding these • Update on methods used for the qualitative analysis following previous meeting • Summary of the approach to the SLR and comparison of information used to inform SLRs for nusinersen and risdiplam • Recap of the EAG base-case economic models and scenarios for both nusinersen and risdiplam • High-level presentation of overall results for the economic models • Discussion and space for questions and answers on each of the key points covered
18.06.2025	Roche	• Recap of the EAG base-base models and scenarios surrounding risdiplam • Presentation of interim ICER results and discussion
18.06.2025	Patient organisations	• Reflection on major points from previous meeting and what the EAG have considered surrounding these • Update on methods used for the qualitative analysis following previous meeting • Summary of the approach to the SLR and comparison of information used to inform SLRs for nusinersen and risdiplam • Recap of the EAG base-case economic models and scenarios for both nusinersen and risdiplam • High-level presentation of overall results for the economic models • Discussion and space for questions and answers on each of the key points covered
Abbreviations: EAG = Evidence Assessment Group; ICER = incremental cost-effectiveness ratio; SLR = systematic literature review; SMA = spinal muscular atrophy		

10 EAG qualitative analysis methods

10.1 Data sources

To identify areas of key concern surrounding living with SMA, as well as surrounding the benefits of nusinersen and risdiplam from the perspective of those with a lived experience of SMA, the EAG conducted qualitative analyses. Insofar as possible, the process was guided by the principles of the CLIP-Q approach to rapid qualitative research, particularly the principles surrounding data collection and analysis.[78]

The EAG used the following sources to inform the analyses.

- Transcripts of meetings the EAG have had with professional and patient organisations, arranged by NICE
- Patient organisation submissions to NICE[79-81]
- Professional organisation submissions to NICE[82]
- Professional expert submissions to NICE[83]
- Patient expert submissions to NICE[84-86]
- Case studies included as part of the appendix provided by SMA UK, Muscular Dystrophy UK and SMA Reach[87]
- Select quotations included as part of the appendix provided by SMA UK, Muscular Dystrophy UK and SMA Reach[87]
- Free-text data for adult and paediatric populations provided to the EAG by SMA REACH UK[88-91]

10.2 Coding framework

As much as possible, the EAG adopted the principles of the CLIP-Q approach for rapid qualitative research, taking a pragmatic approach to data analysis that utilised both deductive and inductive approaches.[78] As such, a framework analysis was undertaken, focusing on identifying the issues of most importance to people with a lived experience of SMA, as well as the impacts of treatment with nusinersen and risdiplam.

Following discussions with patient and professional groups, the EAG sought to develop an initial coding framework. Two members of the EAG (EEJ and NOC) iteratively developed the final framework over two phases of piloting. The framework included all outcomes from the NICE decision problem for the MTA,[6] as well as themes that were raised as important issues in initial meetings the EAG held with professional and patient groups. Inductive codes could also be added to the framework if new concepts and themes arose during the coding process; these were discussed and agreed upon by the two researchers.

The final coding framework was as follows.

- Ability to socialise
- Activities of daily living
- Adverse events
- Bulbar function
- Complications of SMA (e.g. scoliosis, contractures)
- Economic considerations (e.g. resource use, use of health or social services)
- Equality considerations
- Hospitalisation

- Impact on ability to work
- Impact on education
- Impact on families and carers
- Independence
- Looking to the future (e.g. increased hope for the future, anticipatory grief)
- Maintenance or stability of condition
- Mortality
- Motor function
- Need for non-invasive or invasive ventilation
- Patient choice
- Psychological impact (e.g. impact on mental health or wellbeing)
- Quality of life
- Respiratory function
- Spectrum of SMA (e.g. differences in functional ability within SMA types)
- Stamina and fatigue

Because independence and quality of life could be impacted by many aspects of living with SMA and treatments for SMA, these were considered to be themes that cut across many of the other domains. As such, the pragmatic decision was taken to only utilise these codes when independence, dependency or quality of life were explicitly mentioned within any of the sources.

10.3 Data coding

The coding framework was transferred to the software Nvivo for coding. File classifications were created within Nvivo to identify the following characteristics for each piece of data coded.

- Source: as listed above
- Respondent: PPI group; professional group; patient expert; professional group; patient – adult; patient – child; carer; not known
- SMA type: Type 0; Type 1; Type 2; Type 3; Type 4; not known
- Treatment: nusinersen; risdiplam; Zolgensma (OA); nusinersen, risdiplam and OA; nusinersen and OA; not known

In accordance with CLIP-Q guidance, a team-based, collaborative approach to coding was undertaken.[78] First, two members of the EAG (EEJ and NOC) undertook two pilot coding phases, independently coding three data sources each within Nvivo. The results of the pilot coding phase were discussed to help establish concordance between the coders and identify areas where the coding framework could be modified.

Subsequently, both members of the EAG independently coded a third of the sources independently, comparing coding upon completion of this batch to further ensure a level of agreement. The level of agreement between reviewers for each file and code was compared by generating coding reports within Nvivo. If agreement was below 80%, the two researchers would examine and discuss the difference, noting these in a coding log. The remaining sources were then coded by a single EAG researcher (EEJ) and checked by other (NOC). Any potentially missing or erroneous codes identified by the second researcher were discussed and agreed prior to analysis.

10.4 Analysis and reporting

Following coding, both EEJ and NOC worked to interrogate the data coding, identifying key subthemes from the framework inductively; these related to the impact of SMA on patients' and carers' lives, as well as the impact of treatment. A collaborative approach between researchers was taken to identify the main connections and subthemes from the coded data.

An initial, visual analysis of the coded data were taken to two further meetings with professional and PPI groups in May 2025; this interim analysis did not contain any qualitative data from registries as these data had not been received at that point. The findings were discussed to validate the findings at an interim stage, make any adjustments to wording or analysis approach, and to more broadly discuss what had been found through the qualitative analysis to that point.

Following this step, both researchers wrote narratives surrounding the major themes and subthemes identified from the coding phase, including illustrative quotations where appropriate. The narratives were written from a pragmatic perspective to present the findings of the qualitative data without additional theory generation or interpretation. This step was repeated when free-text data from the registry was received to fully update the qualitative analysis and ensure comprehensiveness. Where quotations were included, contextualisation was added by noting who provided the quotation (e.g. a person with SMA or their carer, patient or professional group submission, or discussion with the EAG) and the type of SMA the individual or the individual they were caring for had (if known). For quotations derived from registry data, the age of the patient and the length of time they had been on treatment when the comment was submitted were presented. For the paediatric registry data, we also included information about their functional status (e.g. sitter, walker) and their SMA type, where possible. This information was not available for the adult registry data.

Once written, researchers read, commented on and discussed the written narratives together, in order to ensure that there were no potentially missing sub-themes, that the narratives were written from the aforementioned pragmatic standpoint, and that the narratives and direct quotations used were adequately contextualised (e.g. by source and demographic information) wherever possible.

10.5 Role of reflexivity

The qualitative component of the EAG report was undertaken by two researchers. Both researchers had some experience of qualitative coding and analysis from prior research projects. One of the reviewers had no prior experience of research within the SMA community, while the other had previously worked on research relating to the condition. Neither of the researchers involved in the qualitative coding had a clinical background. Both researchers regularly met to debrief regarding the data coding and analysis processes, allowing room to reflect on their perspectives and interpretations when drawing any conclusions from the data.

10.6 Limitations of the qualitative analyses

The qualitative analysis had several limitations. Firstly, the use of a framework analysis, while appropriate for the timescale of the project and linking the qualitative analysis to the decision problem for the MTA, meant that a deeper exploration of the data through thematic analysis was not undertaken.

The information taken from the case studies and quotations provided by SMA UK, Muscular Dystrophy UK and SMA Reach were not originally intended for the purpose of this MTA.[87] There were also often very few details reported about the respondents' demographics or the treatment that they were undergoing. This meant that it was often challenging to be able to directly connect any changes in the respondents' health and wellbeing with either nusinersen or risdiplam. A similar issue was present for the registry data. In discussion with the EAG, members of the registries noted that some of the symptoms and experiences of those providing free-text were not always attributable to nusinersen or risdiplam. As such, the EAG did not attribute any treatment effects to either nusinersen or risdiplam where this information was not explicit, instead commenting on these instances as the effects of treatment more generically. However, this meant that it was not always possible to differentiate between the treatments and peoples' experiences of both nusinersen and risdiplam.

Furthermore, the registry data used had other caveats. Firstly, the adult registry data was limited by a lack of demographic information. While we attempted to contextualise any quotations and narratives using the information provided, it was not possible to include details such as their SMA type, functional status and age at diagnosis. In discussions between the registries and the EAG, it was also noted that the people providing free-text data for the paediatric data were not always the primary caregiver for the child. As it was not possible to discern when this was the case, the EAG were not able to provide this context within the analyses and report.

Finally, the EAG had originally planned to weave the results of the qualitative analysis consistently throughout the full report. However, as the EAG decided that the evidence for nusinersen and risdiplam were not directly comparable (see Section 11.6.2 for an explanation), the resulting report structure meant it was not possible to feed the qualitative analysis through the results. As such, the qualitative analysis is presented in two standalone sections within the clinical effectiveness and cost-effectiveness results (see Sections 13.5 and 15.3).

11 EAG clinical effectiveness SLR methods

11.1 Objective and methods

The EAG ran update searches and incorporated newly published data into the original systematic review;[1] the previous work was not repeated, except to screen previously excluded studies for eligibility, and to critically appraise the main company trials.

Systematic review methods were based as far as possible on those in the Cochrane Handbook, with the caveat of time limitations.[92]

11.2 Inclusion and exclusion criteria

The eligibility criteria for the EAG review are reported in Table 11.1.

Table 11.1: Inclusion and exclusion criteria for EAG SLR

Domain	Inclusion criteria	Exclusion criteria
Population	People with types 0, 1, 2, 3 or 4 5q SMA, or presymptomatic 5q SMA confirmed with genetic testing with 1 to 4 SMN2 copies.	• Received spinal fusion surgery following a diagnosis of scoliosis (prohibits safe administration of nusinersen) • Hospitalisation or respiratory conditions history or planned at the time of screening or tracheostomy. • History of surgery for scoliosis or hip fixation • Presence of clinically relevant ECG abnormalities before study drug administration • Unstable gastrointestinal, renal, hepatic, endocrine or cardiovascular system diseases • Any in vitro studies
Interventions	• Nusinersen • Risdiplam Interventions are monotherapies in addition to existing clinical services and established clinical management. Onasemnogene abeparvovec	• Concomitant or previous participation in any investigational drug • Any history of cell therapy
Comparators	• Established clinical management • Best supportive care	None

Domain	Inclusion criteria	Exclusion criteria
	In addition, for children aged 12 months and under with a bi-allelic mutation in the SMN1 gene and present with a clinical diagnosis of type 1 5q SMA or presymptomatically with up to 3 copies of the SMN2 gene • Onasemnogene abeparvovec • Placebo control • Sham control	
Outcomes	• Motor function (including, where applicable, both age-appropriate gross motor milestones and fine motor skills) • Bulbar function (including, for example, swallowing and ability to communicate) • Frequency and duration of hospitalisation • Respiratory function • Complications of spinal muscular atrophy (including, for example, scoliosis and muscle contractures) • Need for non-invasive or invasive ventilation • Stamina and fatigue • Mortality • Adverse effects of treatment • Health-related quality of life (for patients and carers) • Ability to socialise[a] • Activities of daily living[a] • Psychological impact[a] • Impact on ability to work[a] • Impact on education[a] • Impact on family and carers[a] • Independence[a] • Looking to the future[a] • Maintenance or stabilisation of disease[a] • Patient choice[a] • Spectrum of SMA[a]	No exclusion criteria

Domain	Inclusion criteria	Exclusion criteria
Subgroups	• Number of SMN2 gene copies in people with presymptomatic SMA • Functional status (non-sitter, sitter, walker) • People who have had prior active treatment for SMA	
Study design	Controlled studies: RCT, non-randomised studies, case/control, cohort studies Non-controlled studies: before-after studies, longitudinal observational studies	• Case series • Case reports • SLRs[b] • Studies containing fewer than 20 participants
Publication types	• Journal articles • Conference abstracts	• Editorials • Commentaries

[a] Outcomes added after consultation with patients, for the update only
[b] SLRs and meta-analyses were included past the abstract screening stage to enable reference checking but were excluded at full-text stage.
Abbreviations: ECG = electrocardiogram; HRQoL = health-related quality of life; RCT = randomised controlled trial; SLR = systematic literature review

Qualitative studies were not formally included. However, stakeholder insights were incorporated into the review from stakeholder submissions and the free text fields of quality of life tools (see Section 9 above).

The following differences exist between the previous review eligibility criteria and the update review eligibility criteria:

- The interventions were not compared directly to each other (Section 11.6.2).
- Conference abstracts were included in the update if they reported results from eligible studies and provided sufficient data for extraction (these were not included in the previous SLR).
- Following consultation with key stakeholders (e.g. patient advisors, carers, professionals) to ensure that the most relevant outcomes and outcome measures were captured, and a list of extra outcomes not specified in the decision problem but considered to be important were added (Table 11.1).

11.3 Identification of studies

Literature searches implemented for the previous SLR were critiqued to ensure they were comprehensive before re-running the searches to include studies published up to March 2025.

Searches for effectiveness evidence were implemented in: biomedical databases (Medline and Embase); an interdisciplinary database (Web of Science); clinical trial registries (Cochrane Central Register of Controlled Trials (CENTRAL) and ClinicalTrials.gov); and the

Cochrane Library, which indexes systematic reviews of medical interventions. Search terms pertained to the population, interventions and outcomes of interest.

Based on the previous searches, databases were searched from 2017 for publications reporting data on nusinersen and from 2020 for publications reporting data on risdiplam, which corresponds to the dates when the technology appraisal (TA) submissions were made by the companies for each drug. The pivotal clinical trials for these drugs were registered pre- 2017/ 2020, therefore search restrictions were not applied in ClinicalTrials.gov. Searches were limited to studies published in English language.

The search critique and Medline search strategy are available in Appendix 1 (Section 19).

The reference lists of relevant systematic literature reviews and meta-analyses captured in the searches were screened to identify primary studies that were eligible for inclusion in this systematic review update.

The excluded studies list from the previous review was scrutinised for studies meeting the edited eligibility criteria.

11.4 Data collection

11.4.1 Screening

Multiple reviewers independently assessed the relevance of a sample of retrieved records based in stage 1 on title and abstract, and in stage 2 on full text in relation to the eligibility criteria. Any conflicts at each stage were resolved via a discussion between the screening team; the remaining records were then screened by one reviewer, who discussed with a second reviewer in case of uncertainty.

11.4.2 Data extraction

A data extraction form was created in Excel and piloted on a sample of included studies and included items from the previous systematic review: study characteristics; participant characteristics; intervention details; outcomes; and results. One person extracted data from each study, while a second reviewer checked the extracted data for accuracy.

11.5 Critical appraisal

The methodological quality of RCTs and non-randomised studies was assessed using the Risk of Bias 2 (RoB2) and the Risk of Bias in Non-randomised Studies – of Interventions (ROBINS-I) V2 tools, respectively.[93,94] Critical appraisal was undertaken by one reviewer and checked for accuracy by a second reviewer. Any disagreements between the reviewers were resolved by discussion with adjudication by a third reviewer. Risk of bias assessments were not undertaken for uncontrolled studies; timelines did not allow for formal assessment of risk of bias for the volume of uncontrolled studies found, and they were assumed to be at high risk of bias.

11.6 Data synthesis

11.6.1 Narrative synthesis

Data were grouped within a narrative synthesis according to the type of intervention, comparator and outcomes assessed. Within those groupings, a best available evidence approach was used, with data from the highest quality studies reported first.

11.6.2 Indirect treatment comparison

The EAG considered that conducting an ITC to evaluate the effectiveness of nusinersen versus risdiplam was inappropriate. The trials that would have provided the most robust patient data for comparative evaluation are CHERISH and SUNFISH, both of which recruited type 2/3 patients who could sit independently and included a 'control' arm to provide the indirect data. However, patients were excluded from the CHERISH trial if they had severe contracture or scoliosis (Cobb angle > 40). Patients with these characteristics were not excluded from the SUNFISH trial: 28% and 38% of the risdiplam and placebo group respectively would not have been eligible for CHERISH due to their scoliosis. Participants in the SUNFISH trial recorded lower HFMSE scores than those in CHERISH and were older on average. An ITC assumes that patients would be equally as eligible and as likely to be allocated to any of the candidate arms, but in reality the administration routes and settings are so different for risdiplam and nusinersen that the EAG considered that this was not the case. It is also unclear that an oral liquid placebo is comparable to a sham injection.

12 EAG economic assessment methods

12.1 Systematic review of existing cost-effectiveness evidence

A previously conducted systematic review of studies evaluating the cost-effectiveness of disease modifying therapies (DMTs) (e.g. risdiplam, nusinersen, onasemnogene abeparvovec) used in the treatment of SMA was updated following standard guidelines.[92] The following sections describe methods undertaken in the previous systematic review conducted in January 2024, and in this update (January 2024 to present). The results from the original systematic review are summarised in Section 1414, along with the results from this review update.

12.1.1 Objectives

In the original systematic review, the first objective was to summarise the evidence identified on modelling techniques, structures and inputs (including clinical, survival analysis methods, resource use and costs, utility estimates) that were required to generate the models, assumptions and key outcomes. The second objective was to identify key issues that should be considered in model-based economic analyses conducted in the future.

In this review update, the same objectives were applied to evidence identified after January 2024, evaluating the cost-effectiveness of DMTs used in the treatment of SMA.

12.1.2 Inclusion and exclusion criteria

The eligibility criteria applied in the original systematic review are described in the following sections below and were applied in this update without any amendments. The eligibility criteria are presented in Table 12.1.

Table 12.1: Eligibility criteria for the SLR of economic evaluations

Eligibility domain	Criteria
Population	• People with types 0, 1, 2, 3 or 4 5q SMA, or presymptomatic 5q SMA confirmed with genetic testing with 1 to 4 SMN2 copies.
Intervention(s)	• Nusinersen monotherapy • Risdiplam therapy
Comparator(s)	• Established clinical management • Best supportive care • The interventions will be compared to each other Additionally, for children aged 12 months and under with a bi-allelic mutation in the SMN1 gene and present with a clinical diagnosis of type 1 5q SMA or presymptomatically with up to 3 copies of the SMN2 gene: • onasemnogene abeparvovec
Outcome(s)	• LYG • QALYs
Study design(s)	• All types of economic evaluations (cost-effectiveness, cost-utility, cost-benefit, cost-consequence, or cost minimisation analyses).

Eligibility domain	Criteria
	• Only full publications in the English language were considered, although relevant non-English studies were mentioned.
Abbreviations: LYG = life years gained; QALY = quality adjusted life year; SLR = systematic literature review; SMA = spinal muscular atrophy; SMN2 = survival motor neuron 2	

12.1.3 Identification of studies

In the previous review, searches were conducted in January 2024 and were reported to comprise searching electronic bibliographic databases and other online sources and contacting experts in the field, followed by examining included studies and a selection of recent, relevant systematic reviews. An information specialist alongside the review team, was reported to have developed the search strategy including terms for SMA, onasemnogene abeparvovec, nusinersen, and risdiplam, with a validated economic evaluation filter where relevant. The searches used incorporated both free-text and thesaurus terms (MeSH/EMTREE), which were initially developed in Embase (Ovid) and stated to be peer-reviewed by a second specialist before being translated to other databases.

In the original review, the searches were conducted between 30 and 31 January 2024 in the following bibliographic databases: Embase (Ovid); MEDLINE All (Ovid); International HTA database (INAHTA); Science Citation Index and Conference Proceedings (Web of Science); CEA Registry (Tufts Medical Center); and EconPapers (RePec). Additionally, database searches were stated to be supplemented by a targeted Google search (31 January 2024) and by a review of selected international HTA and regulatory agency websites (25 January 2024), including: NICE, the Scottish Medicines Consortium, Canadian Agency for Drugs and Technologies in Health, the Institute for Clinical and Economic Review, U.S. Food and Drug Administration, Medicines and Healthcare Products Regulatory Agency and European Medicines Agency.

For this review update, the EAG re-ran the searches on 11 March 2025 to identify new publications since January 2024. Full details of the Medline search are provided in Appendix 1 (Section 19.1).19 Searches for the economics review were run in: The International Network of Agencies for Health Technology Assessment (INAHTA); Research Papers in Economics (RePEc); and Cost-Effectiveness Analysis (CEA) Registry. No search limits were placed.

12.1.4 Data collection

12.1.4.1 Screening

In the previous systematic review, a pilot screen was performed using the predefined inclusion criteria. Two independent reviewers identified relevant records by first screening the titles and abstracts of all records retrieved from the searches. Potentially relevant records were then screened at full text. Any conflicts between reviewer decisions were reported to be resolved by discussion or by consultation with a third reviewer. The progression of records in during screening and reasons for their exclusion at full text was documented using a PRISMA flow diagram.[95]

In this review update, after deduplication 2472 records retrieved in the updated searches were uploaded to an Excel spreadsheet. Then, the same process as described above for identifying relevant records in the previous review were followed.

12.1.4.2 Data extraction strategy

In the previous systematic review, an a priori pre-piloted data extraction sheet 19in tabular form using items recommend by Wijnen et al. was used to extract data from all included records (see Appendix 3, Section 19.3).[96] Information was extracted on items including: study details and funding; patient characteristics; types of intervention; methods; and outcomes of economic evaluations. The original review stated that if data was found to be missing or not clearly stated, the corresponding author was contacted. Data was assumed to be unavailable if no response was received. Data extraction was performed by one reviewer and cross-checked by a second reviewer. Any disagreements were reported to be resolved by discussion or consultation with a third reviewer.

In this review update, the same data extraction sheet uploaded to Excel was used to extract relevant information from included records. One reviewer carried out the data extraction, which was checked by a second reviewer.

12.1.5 Reporting and methodological quality assessment

In the previous systematic review, the critical appraisal strategy involved assessing all included economic evaluations using the Consolidated Health Economic Evaluation Reporting Standard (CHEERS) 2022 checklist,[97] as well as appraising records against the Philips' checklist.[98] Each record was assessed by one reviewer and checked by a second reviewer, with any disagreements being resolved by discussion or consultation with a third reviewer.

In the current review update, for consistency and transparency, included records were evaluated using the CHEERS and Philips' checklist. The EAG acknowledges that the CHEERS 2022 checklist was developed for guiding the reporting of identifiable, interpretable and useful health economic evaluations, not as critical or quality appraisal tool.[97]

12.1.6 Methods of data synthesis

In the original review, a narrative summary of the included economic evaluations was presented alongside summary tables. An overview of the evidence across studies, including their economic modelling approach, key drivers of cost-effectiveness and sources of uncertainty, was presented with recommendations for future economic modelling. In this update, the findings from the previous systematic review were summarised, with relevant new evidence added to the existing summary table and narrative summary.

12.2 EAG cost-effectiveness analysis

The EAG assessed the economic evaluation models submitted by Biogen and Roche for presymptomatic, type 1 and type 2/3 SMA populations. Considering the differences in population characteristics for nusinersen and risdiplam, and to avoid any bias arising out of these differences, the EAG base-case analysis utilised the models submitted by Biogen to compare nusinersen versus BSC, and the models submitted by Roche to compare risdiplam versus BSC.

Based on the considerations in the preceding sections of this EAG report, the EAG defined an EAG base-case for each of the SMA populations. This EAG base-case models included several adjustments to each of the company base-case and these adjustments are summarised in sections 12.2.1 and 12.2.2 below. These adjustments have been broadly categorised into three categories (derived from Kaltenthaler 2016) below.[99]

- Fixing errors (correcting the model where the company's submitted model was unequivocally wrong)
- Fixing violations (correcting the model where the EAG considered that the NICE reference case, scope or best practice had not been adhered to)
- Matters of judgement (amending the model where the EAG considers that reasonable alternative assumptions are preferred)

12.2.1 Nusinersen using Biogen models

12.2.1.1 Presymptomatic population

The key changes made by the EAG to the Biogen presymptomatic model are summarised in Table 12.2.

Table 12.2: Changes made by the EAG to the Biogen presymptomatic model

Input	Biogen base-case	EAG changes	Section
Decision problem	Nusinersen vs BSC	Same as company submission, however exploratory analysis for nusinersen vs OA undertaken.	6.3.1
Time horizon (years)	100	Same as the company submission.	6.3.2.4
Model state transitions	Nusinersen: Based on NURTURE[36] trial BSC: Based on ENDEAR[28] and CHERISH[29] trials.	Same as the company submission	6.3.2.1
Relative effectiveness	BSC- ENDEAR[28] and CHERISH[29] trials	Same as the company submission for BSC, however for the exploratory nusinersen vs OA, the	6.3.2.5

Input	Biogen base-case	EAG changes	Section
		difference in proportions of state occupancy taken from unanchored MAIC of SPR1NT data[33]	
Treatment effect duration*	Nusinersen: 72 months (Relative rate of decline after this period from treatment response in ENDEAR[28] and CHERISH[29]) BSC: 15 months (Baseline probability of decline from Wadman et al.[41] after this period.)	Same as the company submission, however for the exploratory nusinersen vs OA, the treatment effect duration and the relative rate of decline for OA was considered equal to nusinersen.	6.3.2.5
Survival	Overall survival for health states, "sitting without support", "not sitting" and "permanent ventilation" taken from HST24[17]. The overall survival for health states "'standing without support' and 'walking independently' was informed by the UK general population mortality data from 2017-19. Both the nusinersen and BSC were assumed to have equal survival data.	Same as the company submission, however the most recent UK general population mortality estimates (2021-23) were used.[44] In the exploratory analysis, it was assumed that OA survival data equivalent to nusinersen.	6.3.2.10
Discontinuation	Treatment discontinuation for nusinersen based on MAA)[19] data	Same as company submission, however most recently updated MAA)[19] data was used.	6.3.2.11

Input	Biogen base-case	EAG changes	Section
		In the exploratory analysis, it was considered inappropriate to have discontinuation from OA, as it is a one-off treatment.	
Health related quality of life	Health state utility values from HST24[17], and it was assumed that disease modifying therapy increases utility by 10%	Same as company submission. In the exploratory analysis, OA was also assumed to have a utility increment of 10%.	6.3.2.6
Carer health related quality of life	Carer utility increments from TA755[3] were considered in the base-case analysis	Carer utility from TA755[3] was not considered in the base-case analysis; however its impact was assessed in the scenario analyses using utilities from Lo et al, 2022.[73] as they were more recent UK data. In addition, carer utility decrements were used as an alternative methodological approach to calculate impact on carer quality of life.	6.3.2.7
Health care resource utilisation	Health state costs informed by HST24[17] and TA755[3]	Same as the company approach; however, the costs were inflated to the most recent price year.	6.3.2.8

*After the treatment effect period, patients are assumed to maintain the motor milestones achieved to that point and are at risk of losing motor milestones but cannot gain higher motor milestones after this period.

Abbreviations: BSC = Best supportive care; OA = onasemnogene abeparvovec; MAA = Managed Access Agreement; MAIC = matching-adjusted indirect comparison; NICE = National institute for

Input	Biogen base-case	EAG changes	Section
health and care excellence; TA = technology appraisal; HST = highly specialised technology; UK = United Kingdom			

12.2.1.2 Type 1 population

The key changes made by the EAG to the Biogen type 1 model are summarised in Table 12.3.

Table 12.3: Changes made by the EAG to the Biogen type 1 model

Input	Biogen base-case	EAG changes	Section
Decision problem	Nusinersen vs BSC	Same as company submission, however exploratory analysis for nusinersen vs OA undertaken.	6.3.1
Time horizon (years)	100 years	Same as the company submission	6.3.3.4
Model state transitions	For both nusinersen and BSC: based on data from ENDEAR[28] and SHINE[37] trials	Same as the company submission	6.3.3.1.2
Relative effectiveness	BSC-ENDEAR[28] trial	Same as the company submission for BSC, however for the exploratory nusinersen vs OA, the difference in proportions of state occupancy taken from unanchored MAIC of STR1VE data[33].	6.3.3.5
Treatment effect duration*	Nusinersen: 60 months (Relative rate of decline after this period from treatment response in ENDEAR[28]) BSC: 12 months (Baseline probability of decline from Wadman et al[41] after this period)	Same as the company submission, however for the exploratory nusinersen vs OA, the treatment effect duration and the relative rate of decline for OA was considered equal to nusinersen.	6.3.3.5
Survival	Overall survival for health states, “sitting	Same as the company submission,	6.3.3.9

Input	Biogen base-case	EAG changes	Section
	without support", "not sitting" and "permanent ventilation" from ENDEAR[28] and SHINE[37]. The data for these states in BSC came from ENDEAR[28]. The overall survival for health states "'standing without support' and 'walking independently' was informed by the UK general population mortality data from 2017-19. Joint Weibull model was used for overall survival; and for permanent ventilation log normal model was used in the nusinersen arm, while log-logistic was used in the BSC arm.	however the most recent UK general population mortality estimates (2021-23)[44] were used. In the exploratory analysis, it was assumed that OA survival data equivalent to nusinersen.	
Discontinuation	Treatment discontinuation for nusinersen based on MAA)[19] data	Same as company submission, however most recently updated MAA)[19] data was used. In the exploratory analysis, it was considered inappropriate to have discontinuation from OA, as it is a one-off treatment.	6.3.3.10
Health related quality of life	Health state utility values from	Same as company submission.	6.3.3.6

Input	Biogen base-case	EAG changes	Section
	HST24[17], and it was assumed that disease modifying therapy increases utility by 10%	In the exploratory analysis, OA was also assumed to have a utility increment of 10%.	
Carer health related quality of life	Carer utility increments from TA755[3] were considered in the base-case analysis	Carer utility from TA755[3] was not considered in the base-case analysis; however, its impact was assessed in the scenario analyses using utilities from Lo et al, 2022[73] as they were more recent UK data. In addition, carer utility decrements were used as an alternative methodological approach to calculate impact on carer quality of life.	6.3.2.7
Health care resource utilisation	Health state costs informed by HST24[17] and TA755[3]	Same as the company approach; however, the costs were inflated to the most recent price year.	6.3.3.7

*After the treatment effect period, patients are assumed to maintain the motor milestones achieved to that point and are at risk of losing motor milestones but cannot gain higher motor milestones after this period.

Abbreviations: BSC = Best supportive care; OA = Onasemnogene Abeparvovec (Zolgensma); MAA = managed access agreement data from REACH registries; NICE = National institute for health and care excellence; TA = NICE technology appraisal; HST = NICE highly specialised technology.

12.2.1.3 Type 2/3 population

The key changes made by the EAG to the Biogen type 2/3 model is summarised in Table 12.4.

Table 12.4: Changes made by the EAG to the Biogen type 2/3 model

Input	Biogen value	EAG changes	Section
Decision problem	Nusinersen vs BSC	Same as company submission	6.3.1
Time horizon (years)	100 years	Same as the company submission	6.3.4.4
Model state transitions	For both nusinersen and BSC: based on data from CHERISH[29] and SHINE[37] trials	Same as the company submission	6.3.4.1.2
Relative effectiveness	BSC-CHERISH and SHINE[37] trials	Same as the company submission.	6.3.4.5
Treatment effect duration*	Nusinersen: 96 months (Relative rate of decline after this period from treatment response in CHERISH[29]) BSC: 15 months (Baseline probability of decline from Wadman et al[41] after this period)	Same as the company submission.	6.3.4.5
Survival	Overall survival for health states, “sitting without support”, “not sitting” from HST24[17],. The overall survival for health states “‘standing without support’ and ‘walking independently’ was informed by the UK general population mortality data from 2017-19. Both the	Same as the company submission, however the most recent UK general population mortality estimates (2021-23)[44] were used.	6.3.4.9

Input	Biogen value	EAG changes	Section
	nusinersen and BSC were assumed to have equal survival data.		
Discontinuation	Treatment discontinuation for nusinersen based on MAA[19] data	Same as company submission, however most recently updated MAA[19] data was used.	6.3.4.10
Health related quality of life	Health state utility values from HST24[17], and it was assumed that disease modifying therapy increases utility by 10%	Same as company submission, however exploratory analyses including impact of bulbar dysfunction using data from Roche submission[46], utilities used in Roche base-case model[46], and utilities from SUNFISH[50] used in Roche model was conducted.	6.3.4.6
Carer health related quality of life	Carer utility increments from TA755[3] were considered in the base-case analysis	Carer utility from TA755[3] was not considered in the base-case analysis; however, its impact was assessed in the scenario analyses using utilities from Lo et al, 2022[73] as they were more recent UK data. In addition, carer utility decrements were used as an alternative methodological approach to calculate impact on carer quality of life.	6.3.2.7
Health care resource utilisation	Health state costs informed by HST24[17], and TA755[3]	Same as the company approach; however, the costs were inflated to the most recent price year.	6.3.4.7

Input	Biogen value	EAG changes	Section
*After the treatment effect period, patients are assumed to maintain the motor milestones achieved to that point and are at risk of losing motor milestones but cannot gain higher motor milestones after this period. Abbreviations: BSC = best supportive care; MAA = Managed Access Agreement; NICE = National Institute for Health and Care Excellence; TA = technology appraisal; HST = highly specialised technology.			

12.2.2 Risdiplam using Roche models

12.2.2.1 Presymptomatic population

The key changes made to the Roche presymptomatic model is summarised in Table 12.5.

Table 12.5: Changes made by the EAG to the Roche presymptomatic model

Input	Roche base-case	EAG changes	Section
Decision problem	Risdiplam versus OA; Risdiplam versus nusinersen	Risdiplam versus BSC. Scenario analysis: Risdiplam versus OA; Risdiplam versus nusinersen	7.3.2.1
Time horizon (years)	[redacted]	Lifetime (100 years)	7.3.2.1
Model state transitions	Risdiplam: based on RAINBOWFISH[59]	Risdiplam: based on RAINBOWFISH[59]; BSC based on internal natural history data.	7.3.2.1.2
Relative effectiveness	Cost-comparison analysis.	Scenario analysis: CUA for risdiplam versus OA and risdiplam versus nusinersen assuming equivalence on average. CUA for risdiplam versus nusinersen based on results from the naïve comparison	7.3.2.5
Treatment effect duration*	After 10 years receiving DMTs only maintained the motor milestones achieved.	Assumption of long-term risk of losing motor milestones based on Roche internal natural history data and Wadman et al. 2018[41] using the higher risk estimate available. Relative risk of decline for risdiplam based on average treatment estimates from the Type 1 and Type 2/3 models. Assumption of 72 months of treatment effect duration for risdiplam before long-term decline, and 15 months for BSC	7.3.2.5
Survival	General UK population	OS for sitting without support, not sitting, and permanent ventilation from HST24[17]	7.3.2.9
Discontinuation	No discontinuation assumed across DMTs.	Same as company submission.	7.3.2.10

Input	Roche base-case	EAG changes	Section
Health related quality of life	Based on TA755.[3]	Same approach as HST24[17], Assumption that DMT increases utility by 10%. Approach to adjust utility values for age and gender updated to the latest NICE approach.	7.3.2.6
Adverse events	No treatment-related adverse events. Non-permanent respiratory support and bulbar dysfunction assumed as disease-related events for BSC patients using internal data from a natural history study by Roche.	Assumption that patient reported health-related quality of life for SMA includes the impact of disease-related events to avoid double-counting events in the BSC arm.	7.3.2.8
Carer health related quality of life	Base-case analysis combined the impact on patients and informal carers. Carer utilities from TA588.[2]	Base-case analysis focused on patient utilities only, scenario analyses include the impact on both patients and informal carers; using carer utilities from Lo et al, 2022.[73] as they were more recent UK data In addition, carer utility increments were used as an alternative methodological approach to calculate impact on carer quality of life.	7.3.2.6
Health care resource utilisation	Based on an expert opinion elicitation exercise from Roche.	Same approach as HST24[17] and TA755.[3]	7.3.2.7

*After the treatment effect period, patients are assumed to maintain the motor milestones achieved to that point and are at risk of losing motor milestones but cannot gain higher motor milestones after this period.
Abbreviations: BSC = best supportive care; MAA = Managed Access Agreement; NICE = National Institute for Health and Care Excellence; TA = technology appraisal; HST = highly specialised technology.

12.2.2.2 Type 1 population

The key changes made to the Roche type 1 model are summarised in Table 12.6.

Table 12.6: Changes made by the EAG to the Roche type 1 model

Input	Roche base-case	EAG changes	Section
Decision problem	Risdiplam versus OA; risdiplam versus nusinersen; risdiplam versus BSC.	Risdiplam versus BSC. Scenario analyses: risdiplam versus OA; risdiplam versus nusinersen.	7.3.3.1
Time horizon (years)	[redacted]	Lifetime (100 years).	7.3.3.1
Model state transitions	Risdiplam: based on FIREFISH. [58]	Same as company submission.	7.3.3.1.2
Relative effectiveness	Internal results using an unanchored MAIC for risdiplam with nusinersen and BSC using results from ENDEAR[28], and risdiplam with OA using results from STRIVE-EU.[67]	BSC: based on Ribero et al. results for uMAIC between FIREFISH[58] and ENDEAR.[28] Scenario analyses: OA based on internal STRIVE-EU[67] uMAIC results; nusinersen based on Ribero et al.[66] results.	7.3.3.5
Treatment effect duration*	After 5.5 years receiving DMTs only maintained the motor milestones achieved.	Risdiplam: 60 months; BSC: 12 months. BSC long-term risk of decline based on data from FIREFISH[58] and Wadman et al. 2018[41] using the higher risk estimate from the two after this period. Relative risk for risdiplam based on HINE-2 motor milestone response results from Ribero et al. Scenario analysis: OA and nusinersen assumption of 60 months, relative risk assumed the same for all DMTs.	7.3.3.5
Survival	OS: exponential; EFS: exponential. OS from FIREFISH[58] informed survival for "not sitting" and "sitting" states only.	FIREFISH[58] survival adjusted by General UK population mortality over the long term. Mortality at permanent ventilation assumed the same as mortality under BSC across all DMTs.	7.3.3.9
Discontinuation	No discontinuation assumed across DMTs.	Same as company submission.	7.3.3.10

Input	Roche base-case	EAG changes	Section
Health related quality of life	Based on TA755.[3]	Same approach as HST24[17], assumption that DMT increases utility by 10%. Approach to adjust utility values for age and gender updated to the latest NICE approach.	7.3.3.6
Adverse events	No treatment-related adverse events. Non-permanent respiratory support, permanent ventilation, and bulbar dysfunction assumed as disease-related events using additional data from the literature.	Assumption that patient reported health-related quality of life for SMA includes the impact of disease-related events to avoid double-counting events.	7.3.3.8
Carer health related quality of life	Base-case analysis combined the impact on patients and informal carers. Carer utilities from TA588.[2]	Base-case analysis focused on patient utilities only, scenario analyses include the impact on both patients and informal carers; using carer utilities from as they were more recent UK data. In addition, carer utility increments were used as an alternative methodological approach to calculate impact on carer quality of life.	7.3.2.6
Health care resource utilisation	Based on an expert opinion elicitation exercise from Roche.	Same approach as HST24[17] and TA755.[3]	7.3.3.7

*After the treatment effect period, patients are assumed to maintain the motor milestones achieved to that point and are at risk of losing motor milestones but cannot gain higher motor milestones after this period.
Abbreviations: BSC = best supportive care; MAA = Managed Access Agreement; NICE = National Institute for Health and Care Excellence; TA = technology appraisal; HST = highly specialised technology.

12.2.2.3 Type 2/3 population

The key changes made to the Roche type 2/3 model are summarised in Table 12.7.

Table 12.7: Changes made by the EAG to the Roche type 2/3 model

Input	Roche base-case	EAG changes	Section
Decision problem	Risdiplam versus nusinersen; risdiplam versus BSC.	Risdiplam versus BSC. Scenario analyses: risdiplam versus nusinersen.	7.3.4.1
Time horizon (years)	[redacted]	Lifetime (90 years).	7.3.4.1
Model state transitions	Risdiplam: based on SUNFISH[55] risdiplam arm (excluding Asian population)	Same as company submission.	7.3.4.1.1
Relative effectiveness	Risdiplam: based on SUNFISH[55] control arm (excluding Asian population)	Same as company submission. Scenario analysis: nusinersen based on CHERISH[29] uMAIC RULM responders OR (Bucher ITC) published in Ribero et al. (2022)[66]	7.3.4.5
Treatment effect duration*	After 60 months receiving DMTs patients only maintained the motor milestones achieved.	Risdiplam: 96 months; BSC: 15 months. BSC long-term risk of decline based on the BSC arm of SUNFISH and Wadman et al.[41] using the higher risk estimate from the two after this period. Relative risk for risdiplam based on probability of stabilisation in SUNFISH from Oskuoi et al. 2023.[50] Scenario analysis: nusinersen assumption of 96 months, relative risk assumed the same for all DMTs.	7.3.4.5
Survival	Survival curves from the systematic literature review digitised and pooled together applied to type 2 patients at "not sitting" and "sitting (with and without support)". For type 3 the company assumed equivalent survival to the general population. Assumption of a hazard ratio of 0.75 in OS for risdiplam and	OS for "not sitting" and "sitting (with and without support)" from HST24. General UK population mortality applied to "standing" and "walking". No OS difference between DMTs and BSC, survival gains directly dependent on disease severity improvements from therapy.	7.3.4.9

Input	Roche base-case	EAG changes	Section
	nusinersen compared to BSC.		
Discontinuation	No discontinuation assumed across DMTs.	Same as company submission.	7.3.4.10
Health related quality of life	Vignette study from Lloyd et al. 2019[69]	Same approach as HST24[17], assumption that DMT increases utility by 10%. Approach to adjust utility values for age and gender updated to the latest NICE approach.	7.3.4.6
Adverse events	No treatment-related adverse events. Non-permanent respiratory support, permanent ventilation, and bulbar dysfunction assumed as disease-related events using additional data on disease history from Roche.	Assumption that patient reported health-related quality of life for SMA includes the impact of disease-related events to avoid double-counting events. Scenario analysis explicitly modelled the impact of bulbar dysfunction for type 2 and 3 patients.	7.3.4.8
Carer health related quality of life	Base-case analysis combined the impact on patients and informal carers. Carer utilities from TA588.[2]	Base-case analysis focused on patient utilities only, scenario analyses include the impact on both patients and informal carers; using carer utilities from Lo et al, 2022.[73] as they were more recent UK data. In addition, carer utility increments were used as an alternative methodological approach to calculate impact on carer quality of life.	7.3.2.6

Input	Roche base-case	EAG changes	Section
Health care resource utilisation	Based on an expert opinion elicitation exercise from Roche.	Same approach as HST24[17] and TA755.[3]	7.3.4.7

*After the treatment effect period, patients are assumed to maintain the motor milestones achieved to that point and are at risk of losing motor milestones but cannot gain higher motor milestones after this period.
Abbreviations: BSC = best supportive care; MAA = Managed Access Agreement; NICE = National Institute for Health and Care Excellence; TA = technology appraisal; HST = highly specialised technology.

12.2.3 Caregiver Health-Related Quality of Life and the EAG's approach:

The EAG considers there is an important gap in the evidence measuring the size of the financial and health-related quality of life (HRQoL) impact of SMA on caregivers, whether the impact varies significantly across disease subtypes, and whether there are and therefore the size of treatment-related differences across the therapy arms assessed. Furthermore, there is currently methodological uncertainty regarding the best methods for quantifying the caregiver burden for health technology assessments[100], and this is in part reflected by the diverging methods presented by the manufacturers.

Considering these uncertainties, the EAG preferred to focus its base-case assessment on patient HRQoL alone, while the inclusion of carer utilities was explored as an alternative scenario in the scenario analysis. As caregiver HRQoL data could not be sourced from the main clinical trials, the EAG used Lo et al. 2022[73] to inform our assumptions for caregiver utilities across the decision models submitted by Biogen and Roche. Lo et al. (2022) was a Roche funded study using decision choice experiments and surveys to measure caregiver utilities from a UK sample of the general population.[73]

Caregiver characteristics were based on the Lo et al. (2022)[73] sample of carers (mean age = 36 years, 52% male). The economic models assume that carer utilities are determined by improvements in motor milestone-related health-states only, with no additional treatment-related differences modelled explicitly. In addition, the model assumes that patients have access to an average of one 36-year-old caregiver during their life-expectancy. This was a pragmatic approach that prevented imposing additional assumptions about the average number of carers and their life expectancy in relation to the patient due to limitations in the models; and while it is an oversimplification, quantitatively it is likely to over-estimate rather than under-estimate the impact of SMA on carer HRQoL. Scenarios with caregiver HRQoL also included any severity or decision modifiers in patient HRQoL based on NICE guidance. Scenarios also tested the decremental and incremental utility approaches presented by the Roche submission and the Biogen submission across both economic models, the disutilities used are reported in Table 12.8.

Table 12.8 Caregiver disutilities used in the EAG's scenario analyses

Model state	Decrements approach	Increments approach
Permanent ventilation	-0.408	Baseline
Not sitting	-0.408	0.000
Sitting (supported)	-0.222	0.186
Sitting (unsupported)	-0.222	0.186
Standing	-0.068	0.340

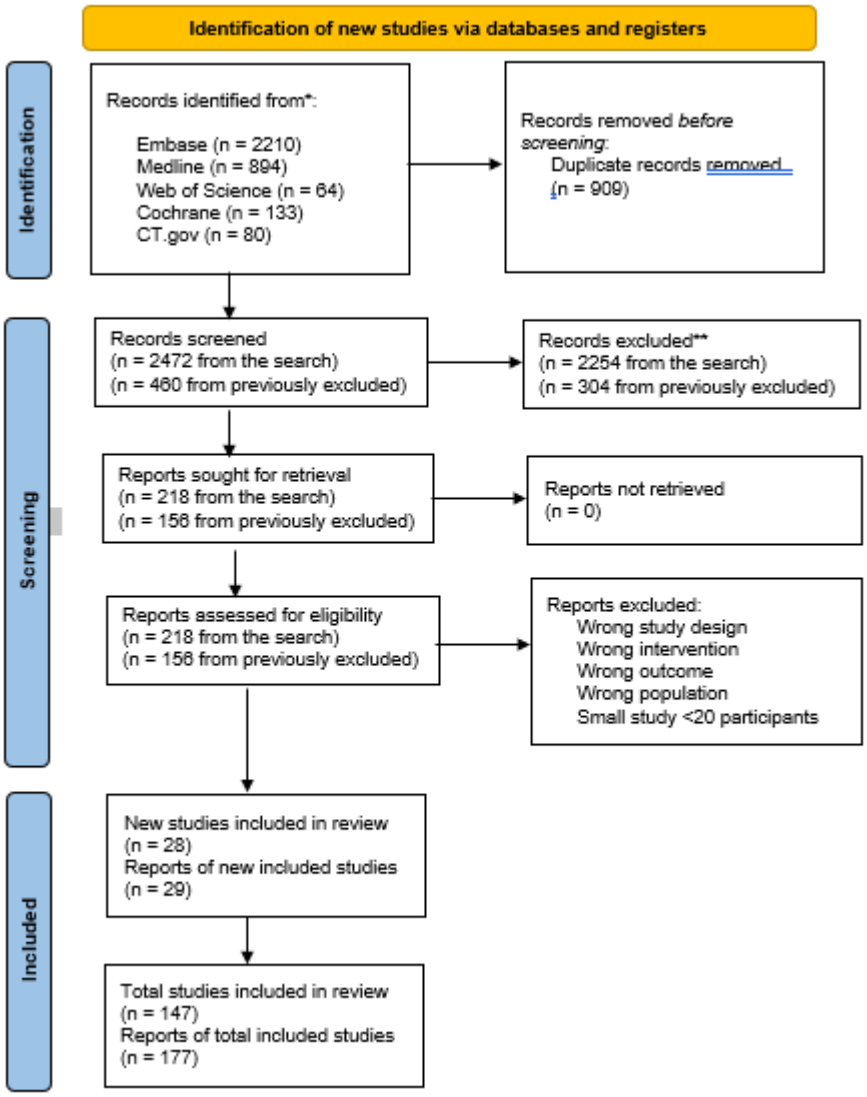
Model state	Decrements approach	Increments approach
Walking	Baseline	0.408
Source: produced by the EAG based on health utilities from Lo et al. 2022[73]		

13 Clinical effectiveness results

The results of the update of the EAG SLR are presented below. These results should be read in the context of the qualitative analysis exploring experiences of those living with SMA, their carers and wider network of family and friends, as well as their experiences of treatment. The qualitative analyses related to the clinical effectiveness can be found in Section 13.5.

A total of 2932 records from the update searches and from the list of previously excluded studies were retrieved for screening, of which 374 were selected for full text review. We included 29 new studies, reported in 30 references. Newly published data from previously included studies, or data that had previously been excluded due to publication type, were added from 51 references. A total of 154 studies reported in 185 reports are reported in this review update.

Figure 32: PRISMA diagram for updated clinical systematic literature review



13.1 Characteristics of all evidence/data for each drug

13.1.1 Nusinersen

Selected references are given here in the text; please see Appendix 4 (Section 19.4) for full table of included studies with full references.

A total of 130 studies in 168 reports evaluating the effectiveness of nusinersen were included, of which 22 reports were new in the update,[101-122] and two were updated with newly published data (NURTURE, SHINE).[31,123]

Three studies were RCTs (CHERISH, EMBRACE, ENDEAR)[28-30] and eight had a controlled design of which four compared to treatment-naïve patients, two compared to natural history, and two recruited health control patients.[102,118,124-129] The rest were single-arm studies (appendix 4).

Studies were conducted across the world: in Europe (n = 73 of which 6 in the UK; TA588 was listed as included in the previous review);[2,111,112,118,130,131] Asia (n = 18); North America (n = 10); Middle East (n = 4); Australia (n = 3); and South America (n = 2). Seventeen studies took place internationally (including NURTURE, CHERISH, ENDEAR, SHINE), and location was unclear or not reported in three studies.

One study included only presymptomatic patients.[117] Eighteen studies focused on patients with type 1 SMA.[28,106,111,112,118,130-142] Two studies each recruited only patients with type 2[143,144] or type 3[145,146] respectively. SMA type was not reported in five studies.[140,147-150] The rest of the studies included people with different types of SMA.

13.1.2 Risdiplam

A total of 13 studies evaluating the effectiveness of risdiplam were included, three of which were new in the update,[151-153] and three of which were updated with newly published data (SUNFISH, FIREFISH and RAINBOWFISH).[49,56,59] One was a randomised controlled trial (SUNFISH),[49] whilst the rest were single arm studies. Five studies were international,[49,56,59,64,154] two were from each of the USA[151,155] and Germany,[156,157] and one came from each of China,[153] Croatia,[158] Spain[152] and the UK.[159] One study included presymptomatic patients only (RAINBOWFISH),[59] one included patients with type 1 SMA only (FIREFISH),[56] one included type 2 patients only,[152] and the rest included multiple SMA types (including SUNFISH with types 2 and 3)[49] or were not reported.[64,151,153-158]

13.1.3 Mixed interventions

The evidence base for studies that included patients taking more than one treatment comprised one non-randomised controlled study[160] and three single-arm studies.[161-163]

13.2 Critical appraisal results (where applied)

13.2.1 Nusinersen

Three randomised controlled trials (RCTs) were assessed using the Cochrane risk of bias tool (ROB 2.0): CHERISH,[29] ENDEAR,[28] and EMBRACE.[30] Two of these trials (CHERISH and ENDEAR) were judged overall to have high risk of bias, one (EMBRACE) was judged overall to have some concerns. A summary of all RoB 2.0 assessments is presented in Table 13.1.

For the domain “bias arising from the randomisation process”, studies were rated as having some concerns due to imbalances in several prognostic factors between groups, including disease symptoms (ENDEAR), disease duration and a motor milestone (ability to walk with support) (CHERISH), and age at first dose and SMN2 copy numbers (EMBRACE) (> 5% or 5-point difference in mean/ median value between the intervention and control groups). These differences between groups were not necessarily incompatible with chance, therefore the studies were not rated as being at high risk of bias for this domain.

All three trials were rated as being at low risk of bias for the domain ‘effect of assignment to intervention’. It should be noted that trial personnel delivering the intervention were not blinded to each participant’s allocation status. However, patients, parents/carers and outcome assessors were blinded. Co-interventions may also have been delivered to treat adverse effects of the intervention. However, this was in line with the trial protocol for each study and this isn’t marked down for in the RoB 2.0 guidance.

For the domain ‘missing outcome data’, both ENDEAR and CHERISH were judged to have some concerns, and EMBRACE was judged to be at low risk. For ENDEAR, all randomised participants were included in time-to-event (death or use of permanent assisted ventilation) analyses. However, < 95% of participants were included in analyses of motor response variables. For the CHERISH study, missing data were imputed.

All three studies were rated as being at low risk of bias for ‘measurement of the outcome’, as outcome measures seemed appropriate. For ‘selection of the reported result’, all three studies were reported as being at low risk of bias. However, the EAG notes that only interim data were available in the publications, which may mean that the data are immature.

Twenty-four non-randomised controlled studies were assessed using the ROBINS-I V2 tool. None of the studies were judged overall to have low risk of bias; nine were rated as having moderate overall risk of bias[124,129,140,147,149,162-165] and fifteen were rated as having serious overall risk of bias.[75,118,123,125,127,134,148,166-173]. A ROBINS-I V2 assessment could not be implemented for one study,[128] due to inadequately reported methods. A summary of all ROBINS-I V2 assessments is presented in Table 13.2.

The most common domains for which risk of bias was demonstrated, were “bias due to confounding” and “bias in measurement of the outcome”. The former of these domains (“bias due to confounding”) was rated moderate in 10 studies[124,127,129,140,149,162,164-166,172] and serious in 10 studies.[75,118,125,134,147{Schneider, 2021 #1425,148,167,168,171,173] The latter domain (“bias in measurement of the outcome”) was rated as moderate in 20 studies[75,124,127,129,134,140,147,149,162-173] and serious in one study.[123]

Table 13.1: Risk of bias assessments of nusinersen RCTs

Study ID	Study design	Overall RoB rating	Bias arising from the randomisation process	Effect of assignment to intervention	Missing outcome data	Measurement of the outcome	Selection of the reported result
ENDEAR[28]	Parallel-group RCT	High	Some concerns	Low	High	Low	Low
CHERISH[29]	Parallel-group RCT	High	Some concerns	Low	High	Low	Low
EMBRACE[30]	Parallel-group RCT	Some concerns	Some concerns	Low	Low	Low	Low
Abbreviations: RCT = randomised controlled trial; RoB = risk of bias							

Table 13.2: Risk of bias of non-randomised controlled studies of nusinersen (incorporating Table 8 from original review)

Author and year	Study design	Overall RoB rating	Bias due to confounding	Bias in selection of participants into the study	Bias in classification of interventions	Bias due to deviations from intended interventions	Bias due to missing data	Bias in measurement of outcomes	Bias in selection of the reported result
Alruthia 2021	Cross sectional Questionnaire	Moderate	Moderate	Low	Moderate	Low	Low	Moderate	Low
Alves 2021	Longitudinal cohort study	Serious	Moderate	Low	Serious	Low	Low	Moderate	Serious

Author and year	Study design	Overall RoB rating	Bias due to confounding	Bias in selection of participants into the study	Bias in classification of interventions	Bias due to deviations from intended interventions	Bias due to missing data	Bias in measurement of outcomes	Bias in selection of the reported result
Chiriboga 2016	Open-label, escalating dose phase 1 study	Serious	Serious	Low	Low	Low	Low	Moderate	Low
Duan 2022*	Non-randomised observational trial	Moderate	Moderate	Moderate	Low	Low	Low	Moderate	Moderate
de la Banda 2020	Prospective study	Serious	Serious	Low	Low	Low	Low	Moderate	Low
Finkel 2021	Phase 2, open-label, multicentre, dose-escalation clinical trial	Serious	Serious	Moderate	Low	Low	Moderate	Moderate	Moderate
Freigang 2021b*	Prospective, multicentre observational study	Moderate	Moderate	Low	Low	Low	Low	Moderate	Low
Kroksmark 2023	Prospective study	Serious	Low	Low	Moderate	Low	Low	Moderate	Low

Author and year	Study design	Overall RoB rating	Bias due to confounding	Bias in selection of participants into the study	Bias in classification of interventions	Bias due to deviations from intended interventions	Bias due to missing data	Bias in measurement of outcomes	Bias in selection of the reported result
Lee 2022	Retrospective study	Moderate	NI	Low	Low	Low	Low	Moderate	Moderate
Li 2024*	Single-centre retrospective case–control study	Serious	Moderate	Low	Serious	Low	Low	Moderate	Moderate
Mirea 2021	Observational study	Moderate	NI	Low	Low	Low	Low	Moderate	Low
Mirea 2022	Retrospective observational study	Serious	Moderate	Low	Low	Low	Low	Moderate	Serious
Pane 2022	Real-world data	Serious	Serious	Low	Low	Low	Low	Moderate	Low
Pechmann 2023	SMArtCARE registry of longitudinal data used	Moderate	Moderate	Low	Low	Moderate	Low	Moderate	Moderate
Pandey 2025*	Prospective cohort	Serious	Serious	Moderate	Moderate	Low	Low	Low	Low

Author and year	Study design	Overall RoB rating	Bias due to confounding	Bias in selection of participants into the study	Bias in classification of interventions	Bias due to deviations from intended interventions	Bias due to missing data	Bias in measurement of outcomes	Bias in selection of the reported result
Rich 2022	Retrospective analysis of samples collected during two trials (NCT04139343 and NCT04591678)	Moderate	Serious	Low	Low	Low	Low	Moderate	Low
Schneider 2021	Single-centre cross-sectional and longitudinal study	Serious	Serious	NI	Low	Low	Low	Low	Moderate
SHINE (Dunaway Young 2023)	Uncontrolled Before and After Study/Time Series	Serious	Low	Low	Low	Low	Low	Serious	Serious
Trancho 2024	Observational study	Moderate	Moderate	NI	NI	NI	Low	Moderate	Low
Trucco 2023*	Multicentre cross-sectional prospective study	Moderate	Moderate	Moderate	Low	Low	Low	Moderate	Low

Author and year	Study design	Overall RoB rating	Bias due to confounding	Bias in selection of participants into the study	Bias in classification of interventions	Bias due to deviations from intended interventions	Bias due to missing data	Bias in measurement of outcomes	Bias in selection of the reported result
van der Heul 2020	Prospective study	Serious	Serious	Serious	Moderate	Low	Low	Moderate	Low
Vazquez-Costa 2022	Prospective observational study	Serious	Moderate	Low	Low	Low	Low	Moderate	Serious
Weaver 2021	Observational cohort study	Serious	Serious	Serious	Moderate	Low	Low	Moderate	Low
Weststrate 2021*	Retrospective audit	Serious	Serious	Low	Low	Moderate	Low	Low	Low

*Study added in the update

Abbreviations: NI = no information; RoB = risk of bias

13.2.2 Risdiplam

The SUNFISH RCT[49] was assessed using the Cochrane RoB 2.0 tool as having some concerns, due to imbalances in motor function between intervention and control group at baseline as shown in Table 13.3. For the domain ‘bias arising from the randomisation process’, SUNFISH was rated as having some concerns; although the reported randomisation process was robust, there were nevertheless some imbalances at baseline in motor scores. For the rest of the domains the SUNFISH trial was judged to be at low risk of bias.

Table 13.3: Risk of bias assessment of risdiplam RCT

Study ID	Study design	Overall RoB rating	Bias arising from the randomisation process	Effect of assignment to intervention	Missing outcome data	Measurement of the outcome	Selection of the reported result
SUNFISH[49]	Randomised parallel-group trial	Some concerns	Some concerns	Low	Low	Low	Low
Abbreviations: RCT = randomised controlled trial; RoB = risk of bias							

13.2.3 Risdiplam versus nusinersen

One controlled study,[160] which compared the effectiveness of risdiplam and nusinersen, was critically appraised using the ROBINS-I V2 tool. As shown in Table 13.4, the study was rated as having serious risk of bias overall due to having multiple (n=4) domains rated as moderate risk of bias.

Table 13.4: Risk of bias of non-randomised controlled study of risdiplam compared to nusinersen

Author and year	Study design	Overall RoB rating	Bias due to confounding	Bias in selection of participants into the study	Bias in classification of interventions	Bias due to deviations from intended interventions	Bias due to missing data	Bias in measurement of outcomes	Bias in selection of the reported result
Ashrafi, 2024	Prospective cohort	Serious	Low	Moderate	Low	Moderate	Moderate	Moderate	Low

13.3 Effectiveness

This section covers outcomes for which data could be included in either the base case models for nusinersen and risdiplam or the scenario analyses, and also outcomes where data could not be modelled. Many outcomes were represented by data which could not be incorporated into the models; many of these were highlighted to the EAG as being important to patients and carers. Additional outcomes which were not in the original scope, but which were highlighted as important by patient and professional groups are included in the updated SLR and represented in the MAA, where data allows. All the effectiveness data should be considered in the context of the qualitative analysis of information provided by patients and professionals.

13.4 Narrative synthesis of all results by outcome incorporating critical appraisal/source as caveats

The narrative synthesis includes all outcomes from the NICE decision problem and the extra outcomes as defined during patient consultation where reported. If an outcome is not reported below, it can be assumed that it was not included in any of the studies for that particular SMA type.

13.4.1 Nusinersen

13.4.1.1 Motor function

The clinical trials reporting data for the effects of nusinersen on motor function were NURTURE for patients with presymptomatic SMA, CS3A and ENDEAR for type 1 patients, CS12A and CHERISH for types 2-3 patients, and SHINE which was an open label extension study following the ENDEAR and CHERISH studies for patients with types 1-3 SMA. This updated review contains newly published data for each of these studies, which suggests improved or maintained motor function on average across the spectrum of SMA for each of the outcomes assessed, relative to a control group of before-after observations, for follow-up timepoints of up to 5 years. Some studies reported differences in effectiveness between population sub-groups, in relation to age (e.g., one study reported greater increases in CHOP INTEND scores amongst non-sitters with 2 copies of SMN2 who were aged ≤ 9 months compared to those aged > 9 months[174]). Another study that used standardised data from three measures of motor function reported significant increases in type 1 and 2 patients. Type III patients, who had higher baseline motor function than type 1 and 2 patients overall, showed a trend towards improvement on motor scales, albeit that statistical significance was not reached (p = 0.051). [175] A third study reported that higher dosage of nusinersen was associated with greater improvements in CHOP INTEND scores.[176]

13.4.1.1.1 WHO motor milestones

SLR evidence

Presymptomatic

Two records,[31,177] reported in the earlier review, reported data for the effects of nusinersen on WHO MM assessments in presymptomatic patients. In NURTURE, patients were able to sit without support and all children who achieved milestones retained them at the last visit.[31] Additionally, 5/7 patients were able to sit independently, 1/5 was able to stand unaided and one was able to walk with support. Amongst younger patients, two were able to stand with support (SM201).[177] The updated review identified one further uncontrolled study (i.e., a study without an independent control group), which aimed to assess the impact of screening on early treatment of SMA.[117] The study reported that asymptomatic patients who received early treatment, via nusinersen, achieved timely acquisition of WHO MMs.[117]

Additional data from NURTURE further supports the long-term benefit of nusinersen in presymptomatic patients.[178],[179] At the last study visit (~5 years), all 15 participants with 2 SMN2 copies achieved the WHO motor milestones of sitting without support and standing with assistance. All 10 participants with 3 SMN2 copies achieved all six WHO motor milestones. Among those with 2 SMN2 copies, the majority also achieved hands-and-knees crawling (93%), walking with assistance (93%), standing alone (93%), and walking alone (87%). Importantly, all participants who achieved a milestone during the study retained that milestone at the final assessment.[178,179]

Type 1

No studies reported WHO motor milestones in type 1 patients specifically. However, data for this outcome and patient sub-group were reported in one record [180] that is included in the section “Multiple types”, below.

Types 2 and 3

Two records,[29,181] reported in the earlier review, included data for the effects of nusinersen on WHO MM in type 2/3 patients. There was an observed 20% gain in at least one motor milestone for those treated with nusinersen, compared to 6% in the control group (CHERISH).[29] Additionally, 14.9% of young sitters and 1.3% of older sitters gained the ability to walk independently following treatment. Furthermore, no motor milestones were lost during nusinersen treatment.[181]

Multiple types

Two records,[123,180] included in the earlier review, reported data for the effects of nusinersen on WHO MM in patients with mixed types of SMA. Significant increases[180] and stable or higher milestones in all patients (SHINE)[123] were observed. Three new uncontrolled studies were identified in this update.[120,182,183] One study also identified stabilisation or improvement in WHO MM between baseline and follow-up in patients (n = 45).[182] Another study reported that 54 patients gained new motor skills after three years of nusinersen treatment, while two lost a motor ability and one remained stable.[183] Finally, a retrospective assessment of SMA type 1 (n = 8) and 2 (n = 30) patients showed improvements in sitting without support and crawling.[120]

SMA type not reported

Two studies, reported in the earlier review,[134,140] assessed patients receiving nusinersen where the SMA type was not reported. One study reported that 1/4 (25%) patients achieved developmental motor milestones in cohort 1 compared to 8/15 53% in cohort 2.[134] In a further study, n=29 (33%) in the younger cohort and n=6 (10.9%) in the older cohort gained the ability to sit independently, and no milestones were lost in any patients.[140]

MAA evidence

Paediatric registry

The data for the WHO MM was updated by the paediatric registry in April 2025 from the original submissions in December 2023. The updated data are presented and discussed for this outcome, as it is more mature than the original report.

Data were presented reporting the number of patients for each SMA type that either maintained or attained motor milestones. Two versions of the data were presented: one of which excluded those with missing data; and another which used linear interpolation for missing data. The MAA data suggests that longer follow-up led to maintenance and improvement for a number of patients (see Table 13.5 and Table 13.6) The registry highlights the significance of these descriptive data compared to natural history. The natural progression of the condition means motor function, as well as respiratory and bulbar function, deteriorates over time. This is especially true for type 1 patients but is also inevitable for type 2/3 patients. As such, stabilisation can be considered a treatment effect and potentially lead to better long-term outcomes and quality of life. In this real-world dataset, where patients were heavily symptomatic and chronically affected by the condition at baseline, there is clear evidence of stabilisation for a number of patients across each SMA type.

[redacted]Table 13.5: Nusinersen paediatric registry WHO MM attainment or maintenance of motor milestones

Nusinersen paediatric WHO MM		Time point (n/N)							
Measure	**Type**	**6 months**	**1 year**	**1.5 years**	**2 years**	**2.5 years**	**3 years**	**3.5 years**	**4 years**
Attainment of a motor milestone	1 (EAP)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Attainment of a motor milestone	1 (Non-EAP)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Attainment of a motor milestone	2/3 non-sitters	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Attainment of a motor milestone	2/3 sitters	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Attainment of a motor milestone	2/3 walkers[b]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Attainment or maintenance of a motor milestone	1 (EAP)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Attainment or maintenance of a motor milestone	1 (Non-EAP)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Attainment or maintenance of a motor milestone	2/3 non-sitters	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Attainment or maintenance of a motor milestone	2/3 sitters	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Attainment or maintenance of a motor milestone	2/3 walkers[b]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: WHO MM = World Health Organisation Motor Milestones; N = overall number of patients; n = number of patients achieving; MM = Motor Milestone; EAP = Expanded Access Programme[a]

[a] EAP patient data represents only data collected during the MAA and not since initiation of treatment

[b] type 2/3 walkers cannot attain motor milestones beyond walking

Table 13.6: Nusinersen paediatric registry WHO MM attainment or maintenance of motor milestones with linear interpolation for missing data.

Nusinersen paediatric WHO MM		**Time point: interpolation used (n/N)**							
Measure	**Type**	**6 months**	**1 year**	**1.5 years**	**2 years**	**2.5 years**	**3 years**	**3.5 years**	**4 years**
Attainment of a motor milestone	1 (EAP)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Attainment of a motor milestone	1 (Non-EAP)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Attainment of a motor milestone	2/3 non-sitters	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Attainment of a motor milestone	2/3 sitters	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Attainment of a motor milestone	2/3 walkers[b]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Attainment or maintenance of a motor milestone	1 (EAP)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Attainment or maintenance of a motor milestone	1 (Non-EAP)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Attainment or maintenance of a motor milestone	2/3 non-sitters	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Attainment or maintenance of a motor milestone	2/3 sitters	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Attainment or maintenance of a motor milestone	2/3 walkers[b]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: WHO MM = World Health Organisation Motor Milestones; N = overall number of patients; n = number of patients achieving; MM = Motor Milestone; EAP = Expanded Access Programme[a]

[a] EAP patient data represents only data collected during the MAA and not since initiation of treatment

[b] type 2/3 walkers cannot attain motor milestones beyond walking

Adult registry

The results for this outcome are taken from the updated April 2025 report.

The registry reported data split by type 2/3 non-sitters, sitters, and walkers. Non-sitters had one patient gain a motor function status, becoming a sitter. This patient scored one on the WHO assessment (item 1) on months 18 to 36, increasing from WHO item 0 to 1 at 18 months. In the sitters, five patients declined in motor function status (became a non-sitter). Three patients gained WHO motor function status, becoming a walker. Forty-four sitter patients remained a sitter. The five patients who lost WHO motor function (became a non-sitter), scored 1 on WHO scale and dropped to 0 at the time of loss of motor function, or had missing data. Patients who gained WHO walker motor function scored 3-5 on previous visits as a sitter before gaining walker status (score = 6). For the walkers, three patients lost motor function status (became a sitter). Forty-six patients remained as walkers (for a breakdown of motor milestones at follow-up see Table 13.7).

The registry stated that the results are similar to natural history in the adult SMA population. They show maintenance with limited transition between functional groups. Overall, four patients gained a motor milestone, eight lost one, and 105 were stable throughout the study period. The stability captured on the WHO motor scale demonstrates the known stability of this group. However, it is important to note the lack of sensitivity of this scale; it does not capture important subtle changes. For example, the sitters group can score 1-5 on the WHO motor scale and not change classification. Therefore, a change from sitter to walker implies a significant change in their motor function, which was experienced by three patients.

Table 13.7: Type 2/3 number of patients who attained a motor milestone or attained or maintained motor milestone whilst on nusinersen treatment

Nusinersen adult WHO MM		Time point (n/N)								
Measure	**Type**	**6 months**	**1 year**	**1.5 years**	**2 years**	**2.5 years**	**3 years**	**3.5 years**	**4 years**	**4.5 years**
Attainment of a motor milestone	2/3 non-sitters	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Attainment of a motor milestone	2/3 sitters	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Attainment or maintenance of a motor milestone	2/3 non-sitters	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Attainment or maintenance of a motor milestone	2/3 sitters	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Remained in the same motor milestone category	2/3 walkers[a]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: WHO MM = World Health Organization Motor Milestones; n = number of patients who met criteria; N = number of patients overall; NA = Not Applicable (due to no data being available for this time point)

[a] type 2/3 walkers cannot attain motor milestones beyond walking

13.4.1.1.2 CHOP-INTEND

SLR evidence

Presymptomatic

Two records, reported in the earlier review,[31,177] included data for the effects of nusinersen using CHOP INTEND assessments in presymptomatic patients. Improvements were seen on CHOP INTEND following nusinersen, with mean scores of 62.1 for patients with two copies of SMN2 and 63.4 for patients with three copies of SMN2 in the NURTURE trial,[31] while 7/18 patients achieved maximum scores in SM201.[177]

New data from NURTURE provides additional long-term evidence of CHOP INTEND outcomes in presymptomatic patients treated with nusinersen.[178,179] At baseline, CHOP INTEND scores ranged from 25 to 60, with a median of 50.0 overall (45.0 in participants with two SMN2 copies and 53.5 in those with three copies). All 25 participants in the ITT population demonstrated improvement from baseline to the last visit (up to Day 2891). Twelve of 15 participants (80%) with two SMN2 copies and all 10 participants (100%) with three SMN2 copies achieved the maximum score of 64, after which assessments were discontinued per protocol. At the final visit, mean CHOP INTEND scores were 63.3 for the 2-copy group and 64.0 for the 3-copy group. These findings were supported by longitudinal plots showing consistent increases over time.[178,179]

Type 1

Fifteen records, seven of which were reported in the earlier review,[28,136-139,162,184] examined the effect of nusinersen on CHOP INTEND in Type 1 patients. These seven records reported data from the ENDEAR trial. Overall, scores on CHOP INTEND increased amongst the majority of patients but some also showed stabilisation of scores.[138,139,162] Further results from a newly identified uncontrolled study[134] extracted for this review update, found that, at the final visit response rates were 52/73 (71%) vs 1/37 (3%) (P <.001; ≥4-point increase), respectively for the intervention and control groups.

Nine uncontrolled studies[101,106,111,112,116,120,121,128,185] were newly included in this review update.

Three studies[106,111,112] reported data from EAPs. One of these studies[106] reported median progress on the CHOP INTEND scale was 4 points at 6 months (n=17). In another study,[111] it was reported that 75% of the patients showed an improvement of the CHOP Intend total score after the 4th or 5th injection. The third study[112] reported that, from baseline to follow-up, most patients showed improved CHOP INTEND scores (between 1-17 points, with a mean of 36/64 at the 5th injection). Additionally, few patients remained stable and one dropped from 52 at baseline to 46 at the 5th injection due to limited mobility secondary to a bone fracture, but scored 58 after the 4th injection.

Of the remaining studies, one[185] reported that CHOP INTEND scores increased from 25.6 ± 15.4 at baseline to 33.0 ± 23.4 at follow-up amongst n=8 participants with type 1 SMA. Another study[116] found that during the first year of treatment, there was a significant increase in CHOP INTEND

score in type 1 patients. Results from a different study[128] suggested that, for type 1 patients, CHOP INTEND scores increased 14.8 points per year (n=29; median follow-up 12 months, range 7.8-15.0 months). Additionally, another study[101] reported that CHOP INTEND scores in SMA type 1 patients increased significantly after loading treatment compared to baseline, and this improvement progressively increased with subsequent doses. Another study[120] reported changes in CHOP INTEND scores amongst in six patients with type 1 SMA from mean 19.5 ± 11.9 at baseline to mean 20.5 ± 12.1 at day 63 (P = 0.416). Finally, a different study[121] reported median CHOP INTEND scores of 23 (range 0-38) at baseline and 41 (range 3-64) at follow-up (median duration 37.7 months) amongst nusinersen recipients.

Types 2 and 3

One study[136] reported data for the effects of nusinersen on CHOP INTEND in type 2 and type 3 patients. As reported in the earlier review, the results showed an overall mean increase of 2.37 points.

Multiple types

Twenty-four records reported data for the effects of nusinersen on mixed types of SMA. Twenty of these studies[123,170,175,176,180,185-199] were included in the earlier review. Four additional, uncontrolled studies were identified in this review update.[101,109,120,174]

One study,[123] from the Warwick review, reported results from the SHINE trial, which suggested increased CHOP INTEND scores amongst patients treated with nusinersen. Another study,[174] identified in this review update, reported data from the RESPOND trial (in post-OA use), showing that, at day 183 following nusinersen treatment, there were mean changes (SD) in CHOP INTEND scores of +6.7 ± 6.76 for people aged ≤ 9 months with 2 copies of SMN2 and +0.6 ± 5.50 for patients aged > 9 months with 2 SMN2 copies. Among non-sitters, the mean changes were +6.7 ± 6.76 for people aged ≤ 9 months with 2 copies of SMN2 and+3.6 ± 3.91 for those aged > 9 months with 2 copies of SMN2. Additional results reported in the earlier review were as follows. Two studies showed varied results, with one suggesting unclear effectiveness[189] and the other suggesting 67% patients remained clinically stable.[192] Patients receiving higher doses of nusinersen showed higher increases in CHOP INTEND scores,[176] scores for non-sitters increased by six points.[199] Another study that used standardised data from three measures of motor function reported significant increases in type 1 and 2 patients. Type III patients, who had higher baseline motor function than type 1 and 2 patients, showed a trend towards improvement on motor scales, albeit that statistical significance was not reached (p = 0.051). [175] The remaining studies observed increased CHOP INTEND scores.[170,180,185,187,188,190,191,193-198]

The results from an additional study[109] included in this review update showed that 23 patients (85.2%) (denominator not reported) demonstrated the clinical effectiveness of nusinersen based on the CHOP INTEND score after receiving treatment. Of these, seven were type 1 SMA patients (58.3%), 15 were type 2 SMA patients (57.7%), and 1 was a type 3 SMA patient (25.0%) who demonstrated clinical improvement.

Unreported type

Four studies examined CHOP INTEND in patients with unreported SMA type following nusinersen.[130,140,186,200] As reported in the earlier review, all four studies showed an improvement.

MAA evidence

Paediatric registry

The results for this outcome are taken from the original December 2023 report.

Two MMRMs were conducted: one assessing the whole type 1 cohort and the other a sensitivity analysis for those who were non-EAP and EAP type 1 patients. Of the original covariates, weight was not statistically significant. Coupled with its poor data collection, leading to reduced sample size, the analysis without weight as a covariate was preferred.

In the first model, there was a statistically significant interaction between visit and CHOP INTEND score. For the sensitivity analysis, non-EAP and EAP categorisation also significantly interacted with visit. The results suggested a consistent increase in CHOP INTEND scores from baseline up to four years, with the majority showing statistically significant improvements. The sample size reduced from 54 patients at baseline to three patients at 4 years follow-up within the main analysis.

Adult registry

This outcome is not applicable for adult patients as CHOP INTEND is used for those aged 1-38 months.[201]

13.4.1.1.3 HINE-2

SLR evidence

Presymptomatic

One study, which was included in the earlier review,[177] reported data for the effects of nusinersen on HINE-2 assessments in presymptomatic patients. As reported in the original review, all patients had age-appropriate motor development and 5/5 patients developed additional milestones at day 302 following nusinersen treatment. At the last study visit, 13/18 patients had achieved the maximum score for this assessment in the SM201 trial.

New data from NURTURE provided updated long-term HINE-2 data for presymptomatic patients treated with nusinersen.[178,179] All 25 participants achieved the maximum level for head control, sitting, voluntary grasp, kicking, and rolling. Eleven of 15 participants (73%) with two SMN2 copies and all 10 participants (100%) with three SMN2 copies achieved the maximum level for crawling and standing. Additionally, 10 of 15 participants (67%) with two SMN2 copies and all participants with three SMN2 copies achieved the maximum level for walking. At the final assessment, all participants with three SMN2 copies reached the maximum HINE-2 total score of 26. The mean total score in the two-copy group was 23.9 (range: 16–26).[178,179]

Type 1

Seven records, four of which were included in the earlier review,[28,137-139] and three newly identified records reporting data from uncontrolled studies,[106,112,185] examined motor function using HINE-2/HINE in type 1 patients following nusinersen treatment.

One record[28] reported data from the ENDEAR trial. The results from this study indicated that, in the interim analysis, a significantly higher percentage of infants in the nusinersen group than in the control group had a motor-milestone response (21 of 51 infants [41%] vs. 0 of 27 [0%], P<0.001). Furthermore, in the final analysis, a significantly higher percentage of infants in the nusinersen group than in the control group had a motor-milestone response (37 of 73 infants (51%) vs. 0 of 37 (0%)).

Among the other studies reported in the earlier review, the majority of patients remained stable,[137] 21/68 patients reached the ability to sit,[138] and 44.5% patients improved from baseline to 48 months.[139]

Results extracted for the updated review from a newly identified study[106] showed that median progress on the modified HINE-2 score was 1.5 points after 6 months of treatment (P<0.0001) regardless of SMN2 copy number. In the same study, patients who scored ≥ 2 points on the modified HINE-2 at baseline presented with an improvement two times higher than patients scoring < 2, although the difference did not reach statistical significance. Another newly identified study reported an increase in HINE score from 2.5 ± 3.1 to 5.5 ± 7.1 in eight type 1 patients. The follow-up timeframe was unclear and could be either 6 or 12 months.[185] The remaining newly identified study reported an improvement of at least 2 points in 9/17 patients at the 5th injection with no cases of motor regression.[112]

Multiple types

Twelve records reported data that examined HINE-2 in patients with multiple types of SMA following nusinersen.[30,110,123,174,180,182,185,187,189,202-204] Eight of these[123,180,185,187,189,202-204] were reported in the earlier review.

One newly identified record reported data from the EMBRACE trial (a controlled study; rated ‘some concerns’ using the ROB 2.0),[30] showed that the percentages of HINE-2 responders in the nusinersen and sham group were 78% vs 0%, respectively. Results from the RESPOND trial of

patients who previously received OA, reported by two records and included in the earlier review[110,174] showed that the mean change in HINE-2 score at day 183 was 8.6 in group 1 (patients with two SMN2 copies, aged ≤ 9 months) and 13.5 in group 2 (patients with two SMN2 copies, aged > 9 months). Another record from the earlier review[182] reported results from the PANDA trial, showing that mean change from baseline in HINE-2 scores were 7.3 and 3.2 for the infantile-onset and later-onset groups at day 423. Furthermore, the proportion of HINE-2 responders was seven of nine (77.8%) evaluable participants in the infantile-onset SMA subgroup and 30/32 (93.8%) evaluable participants in the later-onset SMA subgroup.

Unreported type

Three records,[132,134,200] which were included in the earlier review, reported data that examined HINE-2 following nusinersen treatment in patients where SMA type was not reported. One of the studies reported that, in patients with two copies of SMN2, 63% showed incremental improvements in scores.[134] Additionally, sitters had more improvement than non-sitters (3 vs 1 point increase).[132] Finally, amongst patients with two copies of SMN2, all showed improvement, eight presymptomatic patients remained symptom free, and, amongst those with three copies of SMN2, one patient had delayed milestones, whilst all other patients remained asymptomatic with normal milestones.[200] One newly identified uncontrolled study[110] reported mean change from baseline to follow-up (day 183) values of 5.4 for patients aged ≤ 9 months with two copies of SMN2, and 5.2 for patients aged > 9 months with two SMN2 copies. Mean scores at day 183 were 8.6 in patients aged ≤ 9 months with two copies of SMN2 and 13.5 for patients aged > 9 months with two SMN2 copies.

MAA evidence

Paediatric registry

The results for this outcome are taken from the updated April 2025 report.

An MMRM was conducted in type 1 patients; weight had missing values and the preferred model did not include weight as it allowed for patient data to be included in the analysis. The interaction between visit and baseline HINE score was statistically significant. The results suggest an improvement in HINE score from baseline (n = 50) over the follow-up period, up to four years (n = 5). A sensitivity analysis of non-EAP and EAP patients was conducted. The interaction between non-EAP and EAP groups and visit was statistically significant. Both groups showed positive results, with increases in HINE scores from baseline up to 4 years.

Adult registry

This outcome is not applicable for adult patients as HINE is used for those aged 2-24 months.[201]

13.4.1.1.4 BSID-III

No evidence for this outcome was identified for any SMA type in the original or updated review for patients treated with nusinersen.

13.4.1.1.5 RHS

SLR evidence

There was no reported evidence for presymptomatic or type 1 patients.

Types 2 and 3

Three records reported data for the effects of nusinersen on motor function assessed using the RHS. One study,[205] which was included in the earlier review, reported a significant increase in RHS score at six months but not beyond.[205] Two new studies were identified during this review update.[122,125] The results from one of the newly identified studies,[125] an RCT (ROB 2.0 rating: serious), showed that the mean RHS score in the nusinersen group increased from 35 (± 18) at baseline to 38.9 (± 19) and 39.9 (± 17) at 6 and 12 months, respectively (P = 0.001). In the standard of care (SoC) group, the scores increased from the baseline of 28.8 (± 15) to 29.6 (± 16) and 29.9 (± 17) at 6 and 12 months, respectively (P = 0.35). The mean gain in the RHS score over 12 months in the nusinersen group was significantly higher compared to the SoC group (P = 0.02). Another uncontrolled study reported results from the NICE SMA evaluation.[122] The results showed a mean change of 0.8 ± 4.1 (P > 0.05) from baseline to 14 months for 31 participants. Additionally, the number of patients gaining 3 or more points on RHS at 14 months was 8/31 (26%), while the number who lost 3 or more points was 4/31 (13%).

Multiple types

One study,[195] reported in the earlier review, which included people with different types of SMA, showed that following nusinersen treatment, there was no significant increase in RHS score for 12/17 type 3 patients.

MAA evidence

Paediatric registry

The results for this outcome are taken from the original December 2023 report.

Type 1

RHS is used in type 1 only if the CHOP INTEND ceiling effect is observed, or if a patient has achieved such skills as rolling and sitting (not assessed in CHOP INTEND). Weight was again not a statistically significant predictor and excluded from the analysis. As these patients are originally measured on the CHOP INTEND, a new baseline was created using the RHS. The interaction between visit and the new baseline was significant. The MRMM included 30 patients and there are differences in when the baseline occurred, therefore the registry suggests extreme caution when interpreting the results. The results do suggest a positive impact, with an increase or maintenance (i.e. no statistically significant decreases) in RHS score up to 2.5 years follow-up from baseline (n = 3). The registry also highlighted that there are no expected milestones in the natural history for this patient population and that the RHS was initially developed for type 2/3 patients. The registry did consider a sensitivity analysis with the non-EAP and EAP groupings. However, due to when the EAP patients received nusinersen (i.e. prior to MAA inclusion), and being a more severely affected group of patients, it was less likely they would achieve a ceiling effect. The groups were therefore not considered comparable and the analyses were not conducted.

Types 2 and 3

An MMRM was conducted in type 2/3 patients for changes in RHS assessments. Similar to CHOP INTEND, weight was not a statistically significant predictor and was removed from the analysis. Additionally, visit and baseline RHS score did not have a significant interaction, which were also removed to simplify the model. There was evidence of an increased RHS score over time from baseline to four years. At baseline there were 96 patients and at four years 11 patients.

Adult registry

The results for this outcome are taken from the updated April 2025 report.

The adult registry reported a MRMM for RHS in type 2/3 data for sitters and walkers. For sitters, no statistical significance was observed. However, the numerical trend of improvement suggests potentially positive outcomes for these patients. Potential improvement was suggested but should be interpreted with caution due to lack of data, with only 15 patients available at baseline and six patients with follow-up data at 2.5 years.

Similar results were observed for the walkers. No statistical significance was observed. However, the numerical trend suggests maintenance over the follow-up period, with small improvements in the first 2.5 years and non-statistically significant decreases from 2.5 to 4 years. Data was limited in the longer follow-up periods, with 39 patients available at baseline but only 10 at four years follow-up. Nevertheless, maintenance may be represented in this data, this should be considered a good outcome.

13.4.1.1.6 RULM

SLR evidence

There was no reported evidence for presymptomatic or type 1 patients.

Type 2

One study,[144] included in the earlier review, reported a significant increase in RULM scores between baseline and month 12, as well as a significant difference between the number of clinically meaningful improvements between treated and untreated patients.

Another study,[128] which included a treatment naïve group (risk of bias could not be assessed due to limited information reported) and was identified in this review update, reported that nusinersen-treated type 2 patients had increased RULM scores of 2 points per year (4.8 months follow-up; range 3.3-12.2 months), while treatment-naïve patients, also with type 2 SMA, had decreased RULM scores, by -0.75 points per year.

Type 3

One study,[206] reported in the earlier review, examined RULM in type 3 patients following nusinersen. Increases in scores were found up to 12 months of treatment.

Types 2 and 3

Ten records, seven of which were included in the earlier review,[29,125,171,181,207-209]and three newly identified uncontrolled studies,[120,122,210]examined the effects of nusinersen on RULM in patients with types 2-3 SMA.

Results reported in the earlier review are as follows. One record reported results from the CHERISH trial, showing that RULM scores increased by 4.2 points in the nusinersen group and by 0.5 in the control group. A record that was newly included in this review update reported results from the NICE SMA study, in which gains in RULM scores were higher in the nusinersen group (baseline mean 29.0 ± 8.3; 12-month mean 31.3 ± 6.6; P= 0.022) compared to the SoC group (baseline mean 25.7 ± 7.5; 12-month mean 26.3 ± 7.2; P=0.539).[125]

Another record from the earlier review reported results from the CS2/12 trial, showing an increase in RULM scores following nusinersen treatment.[207] The remaining studies from the earlier review showed a significant increase in RULM scores in type 2 patients, but not in type 3,[171] and an increase in clinically meaningful improvements following nusinersen treatment.[181,208,209]

Of the remaining (newly identified) studies, one[210] reported that there was no statistically significant change in the average RULM score from baseline to the fourth, fifth and sixth treatments. However, a positive trend was observed, with more marked improvements in the non-ambulatory group. A different study[122] reported mean changes of 1.4 ± 1.8 (P=0.0004, n=29), 0.9 ± 2.0 (n=26, P≤0.02) and 1.0 ± 2.4, (P≤0.02, n=23) at 15 days, 6 and 14 months, respectively, after nusinersen treatment. At 14 months, 9/23 (39%) gained 2 or more points and 3/23 (13%) lost 2 or

more points on the RULM scale. Another study[120] reported that mean RULM scores increased from 15.8 ± 8.7 at baseline to 17.6 ± 9.3 at day 63 (P=0.004) amongst 20 patients with type 2 SMA. For people with type 3 SMA, mean RULM scores were 29.3 ± 4.8 at baseline and 32.7 ± 2.7 at day 63 (P=0.042).

Multiple types

Fifteen records reported data from studies that examined RULM in patients with mixed types of SMA following nusinersen treatment. Thirteen of these were included in the earlier review,[123,172,185,188,193,196,198,199,211-215] while two, uncontrolled studies were newly identified in this review update.[104,109]

Amongst the records included in the earlier review, one reported results from the SHINE trial, which showed increases in RULM following nusinersen treatment.[123] One study showed improvement amongst paediatric patients and stabilisation in adult patients[212] and one study showed increases in five type 2 patients and decreases in five patients, with increases in two type 3 patients, stabilisation in two patients and decreases in one.[193] Another study showed a decrease of -2.40 points amongst patients who discontinued treatment.[213] The remaining studies showed increases in RULM scores following nusinersen treatment.[172,185,188,196,198,199,211,214,215] A further study[185] reported changes in mean RULM scores of 5.0 ± 4.2 at baseline to 10.0 ± 9.9 at follow-up (timescale not reported) in two type 1 SMA patients; mean changes of 10.0 ± 8.6 at baseline to 12.6 ± 9.9 at follow-up in seven type 2 SMA patients; and changes in mean values from 28.6 ± 6.2 baseline to 30.4 ± 5.8 at follow-up in seven type 3 patients.

Amongst the studies that were newly included in this review update, one study[104] reported changes in mean RULM scores from baseline (25, n=67) to six months (28, n=47) and 10 months (31, n=38) (P=0.0000). The other study[109] found that the numbers of patients in which nusinersen was shown to be clinically effective (improvement shown in at least one outcome measure) were three (25%), 10 (38.5%), and one (25%) for patients with types 1, 2 and 3 SMA, respectively, as well as 14 (51.9%) for the total sample (P=0.668). The number of patients who showed clinically meaningful improvement (an increase of ≥2 points in the RULM score) following nusinersen treatment were: two (66.67%), 10 (100%) and one (100%), respectively, for patients with types 1, 2 and 3 SMA, with 13 (92.86%) for the total sample (P=0.139). The median and interquartile range (IQR) scores after nusinersen treatment were: 2 (1.5, 3.0; n= 12), 5.5 (3.3, 8.8; n= 26), 2 (2.0, 2.0; n= 2) for patients with types 1, 2 and 3 SMA, respectively, and 4 (2.3, 7.5; n=42) for the whole sample (P=0.086).

MAA evidence

Paediatric registry

The results for this outcome are taken from the original December 2023 report.

Type 1

The RULM was developed for patients aged 2.5 years and over who can sit supported or unsupported and have functional use of their upper limbs. Historically, this scale would not have been considered for type 1 patients. However, due to disease modifying therapies, these assessments are beginning to be utilised. Similar to the RHS type 1 analysis, the baseline was adjusted to the new RULM scale from CHOP INTEND. The MRMM, excluding weight, showed a statistically significant interaction between post new baseline and visit. Similarly, as baseline varies between patients and there are limited patient numbers (n=20), the registry suggests extreme caution when interpreting results. The evidence suggests a positive impact on RULM scores in this population from baseline to 2.5 years (n=3). No non-EAP and EAP group sensitivity was conducted due to the groups not being considered comparable, as per the analysis for the RHS.

Types 2 and 3

An MMRM was conducted in type 2/3 patients for changes in RULM score. As with the previous analyses, weight was not a statistically significant predictor and was excluded from the model. There was a statistically significant interaction between visit and baseline RULM score, which was included in the model. There was evidence of an increase in RULM scores over time, from baseline to four years. At baseline, there were 58 patients and, at four years, six patients.

Adult registry

The results for this outcome are taken from the updated April 2025 report.

The adult registry reported a MMRM for RULM in type 2/3 non-sitters and sitters. For non-sitters, the mean change suggests improvement, however, there is minimal data. No statistical significance is observed; however, the numerical trend of improvement suggests potentially positive outcomes for these patients. The limited data suggests potential improvement but should be interpreted with caution due to lack of data, with data for 13 patients available at baseline and five at 2.5 years follow-up.

Similar results are observed for the walkers. No statistically significant changes occurred but the numerical trend suggests maintenance/small improvements in RULM scores over time. Again, data is limited at follow-up, with 34 patients at baseline and five patients at 4 year follow-up.

13.4.1.1.7 Motor Function Measure (MFM)

SLR evidence

There was no reported evidence for individual SMA types.

Multiple types

Two studies, reported in the earlier review,[168,186] examined MFM in patients with either type 1 or type 2 SMA following nusinersen treatment. In one study, one subscale showed a non-statistically significant increase from 55% at baseline to 61% at follow-up.[168] The other study showed an increase in the median total score by 6 points.[186] These two studies reported the MFM32, while the updated review identified a further study using the MFM20 in an uncontrolled study. The mean change during nusinersen treatment, standardized over a 4-month period, was improved for both SMA1 (+4.1%, standardised response mean (SRM) 1.5) and SMA2 (+2.8%, SRM 0.89) patients.[108]

13.4.1.1.8 Hammersmith Functional Motor Scale - Expanded (HFMSE)

SLR evidence

Presymptomatic

One study included in the previous review examined the impact of nusinersen on HFMSE in presymptomatic patients.[31] However, the original review did not report these results. For patients with 2 SMN2 and 3 SMN2 copies, continued improvement was observed.[31]

New data from NURTURE provided detailed long-term HFMSE data for presymptomatic patients.[178,179] At the first evaluable HFMSE assessment after two years of age, mean total scores were 34.5 for participants with two SMN2 copies and 46.4 for those with three SMN2 copies. At 48 months after this initial assessment, mean scores had increased to 52.3 in the 2-copy group (mean change from baseline of +18.7) and 64.9 in the 3-copy group (mean change of +20.0), out of a maximum possible score of 66. At the final study visit (Day 2891), the mean score was 56.1 (range: 30–66) for participants with two SMN2 copies and 65.9 (range: 65–66) for those with three SMN2 copies.[178,179]

Type 1

Two studies, both reported in the earlier review,[136,139] examined HFMSE in type 1 patients following nusinersen treatment. Both showed a significant increase in scores, one a mean increase from 14.7 to 18.8 at 48 months,[139] and the other an increase of 1.60 points compared to a mean decline in control group (-3.93 points) at 24 months.[136]

Types 2 and 3

The previous review identified 17 records examining HFMSE in type 2/3 patients following treatment with nusinersen.[29,116,127,136,144,171,181,209,216,217]

Four records reported data showing no change, or a stabilisation in scores of HFMSE following nusinersen,[209,217-219] while one showed initial improvements which were not sustained at 12 months.[156] Improvements were observed from data in the remaining 11 records, with treated

patients showing more improvements than control groups (CHERISH[29] and two other studies[136,169]) and improvements reported following nusinersen treatment (eight studies, including CS2/12).[127,167,171,181,207,208,216,220]

The current review identified six more studies examining HFMSE in type 2/3 patients.[103,113,120,121,128,210] One of these studies included a control group.[128] (risk of bias could not be assessed for this study due to limited reporting of the methods). Two of the studies identified a statistically significant improvement in HFMSE score from baseline.[103,210] Similarly, another study reported statistically significant increases in scores from baseline to 26 months.[113] One retrospective controlled study observed increases in type 2 patients in HFMSE scores (+3.25 points per year) while the naïve control group decreased (-2.67 points per year). In type 3 patients both the treatment and naïve groups' scores increased, however, the increase in the treated group was numerically greater (+5.4 points per year vs +1 point per year, respectively).[128] Similarly, another retrospective cohort reported that type 2 patients showed a statistically significant increase from baseline to day 63 (12.5 vs 15, respectively). Type 3 patients' scores also increased over the same timeframe, but this was not statistically significant (44.2 to 47.2).[120] Another study[121] reported median (range) HMFSE scores and baseline and (median 134 month) follow-up of 4 (1-26) and 8 (4-30), respectively, for people with type 2 SMA. For people with type 3 SMA, the median (range) HMFSE scores were 41 (17-62) at baseline and 48 (28-64) at the (median 41 month) follow-up, respectively.

One study reported in the earlier review,[144] examining type 2 patients only using nusinersen, reported a significant increase in mean HFMSE scores and a significant difference between the number of clinically meaningful increases in treated and untreated patients.[144]

The current review identified two further retrospective studies that were not previously reported, with both studies showing significant increases in HFMSE scores for type 2 patients.[101,116]

One study reported in the earlier review,[206] examined HFMSE in type 3 patients only following treatment with nusinersen. Treated patients showed statistically significantly improvements from baseline.[206]

Multiple types

The previous review identified 27 records reporting data assessing HFMSE in people with different SMA types following nusinersen. As reported in the earlier review, six studies showed stabilisation of scores amongst most or all of patients.[180,189,191,192,211,212] One study showed both improvements and decline in HFMSE scores.[193] The remaining studies (including SHINE)[123] showed increases in HFMSE scores.[123,170,172,175,176,185,187,188,194-199,202-204,213-215]

The updated review identified a further three uncontrolled studies examining HFMSE in people with different types of SMA type following nusinersen.[104,109] A retrospective cohort reported on the clinical effectiveness of nusinersen, including clinically meaningful improvement, which

was observed from two type 1 patients (100%), 11 type 2 patients (84.62%), and 2 type 3 patients (66.67%).[109] The other retrospective cohort reported statistically significant improvements from baseline to 14 months for patients on nusinersen treatment.[104] Finally a prospective cohort observed similar findings, with improvements in scores for type 1, 2 and 3 patients (statistical significance is not reported).[185]

13.4.1.1.9 Responder analysis

MAA evidence

Paediatric registry

The results for this outcome are taken from the updated April 2025 report.

The results of a responder analysis, defined as a 1 point increase in HINE score or 9 point increase in CHOP-INTEND score, was included. The results of this are reported in Table 13.8. The registry provides some context on the results regarding the inclusion of those in the EAP. These patients were older and heavily symptomatic, while some were treated under compassionate use. Patients treated through the EAP were symptomatic at treatment initiation, however, they were younger and therefore less likely to have deteriorated as much as older patients, which means they may respond better to treatment. By the time the younger patients transitioned from the EAP to the MAA, they had already improved their CHOP-INTEND and HINE scores. This meant a higher baseline at MAA initiation. After an initial more rapid response, with increased scores of the motor scales, a plateau or slower response is common. A proportion of patients who had already achieved a relatively high baseline score at the time of starting nusinersen under the MAA, have been already treated with this drug for some time, but gains in scores have been missed. As expected, stabilisation is observed in these patients. The EAG would like to again highlight that a maintenance of motor function is equally important as gaining motor function, given the natural history and potentially rapid deterioration of motor functions that can be experienced.

Table 13.8: Responder analysis for nusinersen paediatric MAA patients

Nusinersen paediatric responders		Time point: patients achieved important improvement (n/N)							
Measure	**Type**	**6 months**	**1 year**	**1.5 years**	**2 years**	**2.5 years**	**3 years**	**3.5 years**	**4 years**
CHOP-INTEND	1 (EAP)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
CHOP-INTEND	1 (Non-EAP)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
CHOP-INTEND	2/3 non-sitters	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
CHOP-INTEND	2/3 sitters	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
CHOP-INTEND	2/3 walkers	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Nusinersen paediatric responders		Time point: patients achieved important improvement (n/N)							
Measure	**Type**	**6 months**	**1 year**	**1.5 years**	**2 years**	**2.5 years**	**3 years**	**3.5 years**	**4 years**
HINE-2	1 (EAP)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
HINE-2	1 (Non-EAP)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
HINE-2	2/3 non-sitters	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
HINE-2	2/3 sitters	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
HINE-2	2/3 walkers	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: CHOP INTEND = Children's Hospital Of Philadelphia Infant Test Of Neuromuscular Disorders; N = number of patients with evaluable data; n = number of patients who achieved important improvement; EAP = Expanded Access Programme[a]; HINE-2 = Hammersmith Infant Neurological Examination 2

[a] EAP patient data represents only data collected during the MAA and not since initiation of treatment

Adult registry

The adult registry report did not include a responder analysis. The CHOP-INTEND and HINE-2 outcomes used in the responder analysis are not applicable to adults, as previously stated.

13.4.1.1.10 ATEND

SLR evidence

No evidence from the original or updated review was identified for this outcome.

MAA evidence

Paediatric registry

The paediatric registry did not report on this outcome. The intended age range for this tool is still to be confirmed.[201]

Adult registry

The results for this outcome are taken from the updated April 2025 report.

The adult registry reported a MMRM for ATEND left and right in type 2/3 non-sitters and sitters. For non-sitters, the mean change suggests improvement. There is minimal data with short follow-up (12 months) due to number of patients available. No statistical significance is observed. However, the numerical trend of improvement suggests potentially positive outcomes for these patients. The limited data suggests potential improvement but should be interpreted with caution due to lack of data, with data for five patients available at baseline and four at 12 months.

The ATEND was utilised in less functional sitters (RHS <6); these individuals show an unusual degree of symptomatic progressions. Baseline included 12 patients, with follow-up to 2.5 years showing varying mean scores. The results show no statistically significant reductions or improvement and numerical trends are less obvious than for the non-sitter patients. The limited data means the results should be interpreted with caution.

13.4.1.1.11 Sitting position

SLR evidence

Type 1

The review update identified a single, uncontrolled study that examined sitting position in type 1 patients when treated with nusinersen.[106] This study was part of the EAP and reported that 5 of 30 patients acquired a stable, support-free sitting position (> 30 seconds).[106]

There was no reported evidence for any other SMA types.

13.4.1.1.12 Compound Motor Action Potential (CMAP)

SLR evidence

Presymptomatic

The original review identified a record reporting data from the NURTURE trial, examining the effectiveness of nusinersen on CMAP; scores remained stable.[31] They also reported information from a previous European Medicines Agency assessment report (study: SM201). However, this data is from the NURTURE trial and is therefore not reported separately.[177]

New data provided long-term CMAP findings from the NURTURE study, including assessments of both ulnar and peroneal nerves in presymptomatic patients treated with nusinersen.[178,179]

Ulnar nerve

At baseline, the mean (SD [range]) ulnar nerve CMAP amplitude was 2.69 (1.516 [1.0–6.7]) mV in participants with two SMN2 copies (n=14) and 3.11 (1.119 [1.8–4.9]) mV in those with three SMN2 copies (n=10). At Day 2891, mean amplitudes had increased to 7.23 (4.466 [2.3–16.7]) mV for the two-copy group (n=8) and 9.01 (3.658 [4.2–16.0]) mV for the three-copy group (n=8). Improvements in ulnar CMAP amplitudes were consistently greater in participants with three SMN2 copies throughout the study.[178,179]

Peroneal nerve

Baseline mean (SD [range]) peroneal nerve CMAP amplitude was 3.52 (2.159 [1.1–9.7]) mV in participants with two SMN2 copies (n=12) and 3.75 (2.188 [0.2–7.0]) mV in those with three SMN2 copies (n=10). While peroneal CMAP amplitudes fluctuated over time, the mean values did not decrease relative to baseline. Up to Day 1611, mean amplitudes were similar between the two groups. After Day 1611, values stabilized in participants with three SMN2 copies but continued to increase in the two-copy group.[178,179]

Type 1

One record in the original review reported data examining CMAP in type 1 patients following nusinersen; 36% of the treatment group were classified as responders compared to 5% of the control group (ENDEAR).[28]

Types 2 and 3

The original review identified two records that reported data examining CMAP in type 2/3 patients following nusinersen.[127,207] One reported an increase of 0.4 mV in type 2 patients and 0.3 mV in type 3 patients (CS2/12),[207] whilst the other showed no significant changes after nusinersen treatment.[127] The original review also identified one study examining CMAP in type 3 only patients following nusinersen and found no significant differences between SMA patients and healthy individuals.[148]

The current review identified two further studies assessing CMAP in type 2/3 patients treated with nusinersen.[125,210] One of these was a controlled prospective study (ROBINS-I rating: serious) that reported no statistically significant differences between groups at 12 months for median and ulnar nerve.[125] The other, uncontrolled, prospective study reported a CMAP value of the trapezius muscle ≥ 1.76 mV, suggesting that patients were more likely to respond to treatment by day 300 (sensitivity 84.6%, specificity 85.7%).[210]

Multiple types

The original review identified three studies that assessed CMAP in patients with different types of SMA following nusinersen treatment. Increases were seen across all three.[166,191,192] Scores were higher in patients with 4 SMN2 copies compared to 2 or 3 SMN2 copies.[166] The largest improvements in CMAP values were recorded in SMA type 1 patients, which were statistically correlated with scores on CHOP scales ($p < 0.001$).[191]

Unreported type

The original review identified three studies that assessed CMAP in patients with an unreported SMA type following nusinersen treatment. All studies reported some increase in CMAP,[134,200,221] with scores plateauing after day 568 in one study,[134] and increases in symptomatic patients not reaching levels of asymptomatic patients in another.[200]

13.4.1.1.13 Motor Unit Index (MUNIX)

SLR evidence

There was no reported evidence for presymptomatic or type 1 SMA.

Types 2 and 3

The current review identified one study which examined MUNIX in type 2/3 patients receiving nusinersen. This prospective, uncontrolled, study reported that upper limb improvements were superior to lower limb improvements. As this is a conference abstract, no further details are provided.[210]

13.4.1.1.14 Revised Amyotrophic Lateral Sclerosis Functional Rating Scale (ALSFRS-R)

SLR evidence

There was no reported evidence for presymptomatic or type 1 SMA.

Types 2 and 3

In the original review, three studies reported on ALSFRS-R in type 2/3 patients following nusinersen. All three reported an increase of one point.[205,209,220] In one of these, the increase was observed in type 3 patients only,[220] and in one the increase was observed in type 2 patients only.[205]

Multiple types

In the original review two studies examined ALSFRS-R in mixed SMA types following nusinersen. One reported a 67.3% improvement in scores, with 32.7% remaining unchanged.[204] The other observed that treated patients experienced clinically meaningful improvements.[172]

13.4.1.1.15 Medical Research Council Sum Score (MRC-SS)

SLR evidence

There was no reported evidence for presymptomatic or type 1 SMA.

Types 2 and 3

The original review identified two studies examining MRC-SS in type 2/3 patients following nusinersen.[216,220] Increases were seen in type 3 patients only in one study,[220] with an average change of 3.9 points at 24 months in treated patients[218] and significant increases in ambulatory patients only.[216]

Multiple types

The original review identified one study examining MRC-SS in people with different SMA types following nusinersen. MRC sum scores improved on average 2.4–2.5 points at months 6–14, respectively.[211]

13.4.1.1.16 Manual Muscle Testing (MMT)

SLR evidence

There was no reported evidence for presymptomatic or type 1 SMA.

Types 2 and 3

The original review identified one study which included 37 patients examined using MMT of type 2/3 SMA type following nusinersen treatment. The scores increased at six months and 14 months.[205]

13.4.1.1.17 Motor Unit Number Estimation (MUNE)

SLR evidence

There was no reported evidence for presymptomatic or type 1 SMA.

Types 2 and 3

The original review identified two records that reported data for the assessment of MUNE in type 2/3 patients treated with nusinersen.[148] One of these records, which reported data from the CS2/12 trial, examined MUNE in type 2 and 3 following nusinersen and showed an increase for type 2 patients by 2.0 points, and a decrease for type 3 patients by 29.6 points.[207] One study examined MUNE in type 3 patients only following nusinersen and showed no significant differences overall.[148]

Multiple types

The original review identified one study examining MUNE scores in people with different types of SMA following nusinersen, and showed increased scores.[192]

13.4.1.1.18 Grip and Finger Flexion Strength (GFFS)

SLR evidence

There was no reported evidence for presymptomatic or type 1 SMA.

Types 2 and 3

The original review identified two studies reporting GFFS in type 2/3 patients following nusinersen.[218,219] GFFS increased in all cohorts at follow-up[219] and three patients reported increased hand strength.[218]

Multiple types

The original review identified one study examining GFFS in a range of SMA types following nusinersen and showed a significant increase in scores, and a significantly higher dominant hand score.[211]

13.4.1.1.19 6 minute walk test

SLR evidence

Presymptomatic

One study included in the original review examined the impact of nusinersen on the 6MWT in pre-symptomatic patients,[31] however, the original review did not report these results. In 11 presymptomatic children (two SMN2 copies = 5; three SMN2 copies = 6) there was evidence of sustained independent walking (ranges: 150-325 metres and 238-444 metres, respectively).[31]

New final analysis data from NURTURE (2024) provided further detail on 6MWT outcomes in presymptomatic patients treated with nusinersen in study 232SM201. Participants who achieved independent ambulation were able to perform the 6MWT at various time points throughout the study (up to Day ~2892), with distances ranging from 50 to 594 metres. Mean walking distances generally increased over time, and overall, distances were consistently higher in participants with three SMN2 copies compared to those with two. These findings support the durability of ambulatory function in this cohort following early treatment.[178,179]

Type 1

The original review included one study examining the effectiveness of nusinersen in the 6MWT. One participant improved and was able to walk 165 metres at 48 months.[139]

Types 2 and 3

The original review included four records that reported 6MWT assessments in type 2/3 patients following nusinersen.[206,207,220]

In one study, it was reported that 78% of patients showed a clinically meaningful improvement.[220] Another record, which reported data from the CS2/12 trial, reported that 100% patients achieved a clinically meaningful improvement by day 1050, but 1/11 type 2 patients gained the ability to walk independently, and in type 3, 2/4 lost the ability to walk at baseline and regained it during treatment.[207] Distance walked in the 6MWT increased significantly, with the rate of patients achieving a clinically meaningful improvement increasing from 53% to 69% of patients.[208]

The updated review identified two further, uncontrolled studies assessing type 2/3 patients.[122,210] Both studies were prospective cohorts. One showed a non-statistically significant improvement in 6MWT from baseline to 14 months (11.9 metres, n = 11).[122] The other reported improvements in 6MWT at visits, however, the timeframe is not explicitly stated: at visit four, 5/15 improved; at visit five, 9/15 improved; and at visit six 12/15 improved.[210]

One study reported in the original review assessed 6MWT in type 3 patients only following nusinersen, showing no significant increase in scores.[206] The updated review identified one prospective cohort study reporting 6MWT in type 3 patients only following nusinersen, in which five patients increased the average distance from baseline (100.9 metres) to follow-up (158 metres).[185] The updated review also identified a retrospective cohort study reporting the impact of nusinersen on the 6MWT in type 3 patients.[120] The results suggested no statistically significant improvements between baseline and 63 days follow-up (199.9 vs 226.3 metres, respectively).[120]

Multiple types

The original review identified 12 studies examining 6MWT in mixed SMA types following nusinersen treatment.[172,185,193,195,198,203,204,211,212,214,215] The majority of these studies showed improvement. Studies reported no significant increase in ambulatory patients,[211] no significant increase in four patients,[195] a worsening in 33% patients (along with a clinically meaningful increase of 50%).[188] One study showed an increase in distance amongst later-onset patients.[204] The remaining studies reported increases in 27.2% paediatric patients and 26.5% adult walkers,[212] and overall improvements or clinically meaningful increases.[172,185,193,198,203,214,215]

The updated review identified two further, uncontrolled studies assessing the 6MWT in a group of people with mixed SMA types following nusinersen treatment.[104,222] One of these was a conference abstract for the SHINE study, which reported that three patients (of five) improved their 6MWT (range of improvement: 24 to 81 metres).[222] The other study was a retrospective cohort which showed stabilisation of the 6MWT from baseline to 14 months (339.2 to 343.3 metres, respectively).[104]

Unreported type

The original review identified two studies that examined 6MWT in unreported SMA type following nusinersen.[149,221] One study showed a variable increase in distance walked,[221] whilst the other reported that SMA patients achieved half the distance walked by control patients.[149]

MAA evidence

Paediatric registry

The paediatric registry did not report on this outcome. However, the 10 metre run test was conducted as part of the RHS, results of which can be seen in section 13.4.1.1.5.

Adult registry

The results for this outcome are taken from the updated April 2025 report.

The adult registry conducted MMRM in type 2/3 walkers for the 6 minute walk test (6MWT). No statistically significant changes are reported. The data trends towards maintenance and the registry suggest that this test captures performance fatigability, which is not captured in other functional groups. Stabilisation of a 6MWT is a good outcome as it could represent no changes in muscular fatigue. Data availability is low, with 21 patients with data available at baseline and five patients with data at 4 years follow-up.

13.4.1.1.20 Timed Up and Go (TUG)

SLR evidence

There was no reported evidence by individual SMA type.

Multiple types

The original review identified one study examining TUG in people with a range of SMA types following nusinersen and showed that scores became faster over time.[223]

Unreported type

The original review identified one study reporting TUG following nusinersen where SMA type was unreported. SMA patients completed TUG in 21.3 seconds compared to control patients completing in 4.3 seconds.[149]

13.4.1.1.21 Unspecified motor function assessments

SLR evidence

There was no reported evidence by individual SMA type.

Multiple types

The current review identified five uncontrolled studies that considered unspecified tools for motor function assessments for patients with different types of SMA receiving nusinersen (i.e. tools that were not explicitly named).[105,109,185,224,225]

Motor function status (non-sitter, supported sitter, independent sitter, supported walker, and independent walker) was considered by one prospective, non-comparative, study.[185] The results were reported as number of patients in each category at baseline and follow-up (with the time-point unclear, at either 6 or 12 months). It stated that type 1 patients were all non-sitters at baseline (n = 8), while at follow-up three remained non-sitters, three became supported sitters, and two became independent sitters. For type 2 patients, at baseline all were independent sitters (n = 7), five remained independent sitters, one became a supported sitter, and one became a supported walker. Finally, at baseline one type 3 patient was a supported walker and seven were independent walkers. At follow-up, one remained a supported walker and another became a supported walker, with the remaining six patients maintaining independent walker status (see Table 13.9).

Table 13.9: Overview of the results from Ip and colleagues 2024[185] of changes in motor functions status

Motor Function Status	Baseline n	Follow-up n
Non-sitter	• Type 1: 8 • Type 2: 0 • Type 3: 0	• Type 1: 3 • Type 2: 0 • Type 3: 0
Supported Sitter	• Type 1: 0 • Type 2: 0 • Type 3: 0	• Type 1: 3 • Type 2: 1 • Type 3: 0
Independent sitter	• Type 1: 0 • Type 2: 7 • Type 3: 0	• Type 1: 2 • Type 2: 5 • Type 3: 0
Supported Walker	• Type 1: 0 • Type 2: 0 • Type 3: 1	• Type 1: 0 • Type 2: 1 • Type 3: 2
Independent Walker	• Type 1: 0 • Type 2: 0 • Type 3: 7	• Type 1: 0 • Type 2: 0 • Type 3: 6
Abbreviations: n = number of patients		

Another prospective, non-comparative, study reported that 66% of patients improved in muscle strength or in QoL. Additionally, there was evidence of stabilisation of respiratory and swallowing function. Information was from a conference abstract and no further details are provided, which makes interpretation of the results difficult.[105] A further comparative prospective study only provided baseline data (number of non-sitters, sitters, and walkers) and no follow-up information, therefore, no results from this study can be included.[224]

A retrospective cohort identified motor milestone response. For type 1, four participants (33.3%) responded, in type 2 13 participants (50%) responded, and three type 3 participants (75%) responded. This equates to 20 patients responding to treatment in terms of motor milestones overall (74.1%). However, this result was not statistically significant.[109] Finally, a retrospective comparative chart review reported that improvement or maintenance in motor milestones was achieved by 5 of 10 patients receiving nusinersen monotherapy (mean time to initial improvement in any motor milestone: 7.3, standard error = 3.8 months).[161]

13.4.1.2 Bulbar function

SLR evidence

13.4.1.2.1 Nutritional support including nasogastric feeding and gastrostomy

Presymptomatic

One study from the earlier review,[31] examining the effect of nusinersen on the bulbar function in those with presymptomatic SMA, reported that the majority of participants maintained their ability to swallow, as most never gagged or choked on liquid or solids. In addition, participants' parents were also reportedly not concerned about choking or aspiration during meals.

New final analysis data from NURTURE (2024) further evaluated bulbar function in presymptomatic patients treated with nusinersen in study 232SM201, using both HINE-1 and the Paediatric Functional Oral Intake and Swallowing Assessment (PASA).[178,179] Based on HINE-1 (suck/swallow) assessments up to Day 778, 12 of 15 participants with two SMN2 copies maintained normal suck/swallow function from baseline to the last assessment. None of the participants with three SMN2 copies experienced a decline in suck/swallow function. Dysphagia symptoms were infrequent and generally mild throughout the study.[178,179]

According to PASA outcomes up to Day 2891, five of the 15 participants with two SMN2 copies demonstrated consistent bulbar disability. The remaining 10 participants in this group retained more consistent normal function and did not require gastric tube support. All 10 participants with three SMN2 copies showed predominantly normal bulbar function.[178,179]

Type 1

Seven studies[75,133,135,136,138,139] in the earlier review examined the effects of nusinersen on bulbar function in type 1 SMA. As reported in the review, one study[139] showed some improvement in feeding following nusinersen treatment. Two studies showed either no change[133] or stability,[136] while three studies[75,135,138] showed a decline in the ability to feed orally following treatment.

One new study was identified in this review update[118] which reported that the numbers and rates of gastronomy-fed patients were 18 (64%) in the nusinersen group and 2 (6%) in the treatment-naïve (control) group. Furthermore, the numbers (%) who were nasogastric tube fed were 4 (14%) and 31 (86%) in the treatment and control groups, respectively. Finally, two (7%) of the nusinersen-treated patients were nasogastric tube fed (NGT) with some oral intake (n/% NR for the control group). Another newly identified study[121] reported that two patients required feeding with percutaneous gastrostomy and one with a nasogastric tube.

Types 2 and 3

Two studies[165,181] from the earlier review reported bulbar function in type 2 and 3 SMA patients. Mastication and swallowing was reported to be stable among those treated after 16 months in one study.[165] In another study,[181] an increased need for tube feeding was reported following nusinersen treatment.

Multiple types

Nine studies[107,124,161,183,186,187,193,195,226] reported on the impact of nusinersen treatment on bulbar function in relation to nutritional support in individuals with mixed types of SMA. In the original review, four studies[124,187,193,195] indicated a general decline in bulbar function following nusinersen treatment, particularly in relation to feeding, with these studies noting an increased number of patients requiring tube feeding or additional support. Additionally, one study[186] specifically reported a non-significant increase in the number of patients needing feeding support after nusinersen treatment in SMA types 1 and 2.

Four newly identified studies[107,183,226] provided further insights into nutritional support among patients with mixed types of SMA. In one study,[226] investigators observed that while most patients showed no change, some experienced notable improvements in swallowing or feeding ability following nusinersen treatment.

In another study,[107] the need for gastrostomy was reported in relation to treatment adherence among patients with different types of SMA. The need for gastrostomy was higher in non-adherent participants compared to adherent ones (SMA type 1 58.3% for non-adherent vs. 36.4% for adherent; SMA type 2 44.8% for non-adherent) vs. 0% for adherent; SMA type 3 21.4% for non-adherent vs. 18% for adherent). The highest need was observed in non-adherent SMA type 1 patients (n=12), with seven (58.3%) requiring gastrostomy, followed by non-adherent SMA type

2 patients (n=29), with 13 (44.8%) requiring gastrostomy. No gastrostomy was reported among adherent SMA type 2 patients (n=12). Similarly, another newly identified study,[183] reporting on the impact of nusinersen on the need for gastrostomy support, showed increased need for gastrostomy from four participants at baseline to 14 after three years.

Also, as reported by another newly identified study,[107] the need for nasogastric or other non-oral feeding support assessed between adherent and non-adherent groups showed a higher need among non-adherent participants (SMA Type 1 33.3% for non-adherent) vs. 27.3% for adherent; SMA type 2 37.9% for non-adherent) vs. 0% for adherent; SMA type 3 21.7% for non-adherent vs. 18% for adherent). The highest need was among non-adherent SMA type 2 patients (n=29), with 11 (37.9%) requiring support, followed by non-adherent SMA type 1 patients (n=12), with 4 (33.3%). No nasogastric tube feeding was reported among adherent SMA type 2 patients (n=12). Like the adherent SMA type 2 results, no patients needed nasogastric feeding support another newly identified study[183] following three years of nusinersen treatment.

Finally, another newly identified study[161] reporting real-world outcomes in patients with multiple types SMA treated with either nusinersen monotherapy or OA monotherapy found that half of the patients receiving nusinersen experienced either improvement or maintenance in eating function. This outcome was more pronounced in those receiving OA, with 5 out of 6 showing positive results.

Unreported type

Two studies examined feeding in patients with unreported SMA type receiving nusinersen. The need for a feeding tube increased during treatment in one study,[140] while another study[130] showed a decline in feeding score.

13.4.1.2.2 Swallowing function

Type 1

One study[133] in the original review observed a reduced deterioration in swallowing following nusinersen treatment in type 1 SMA participants, while in another study[75] from the existing review, a decline in swallowing function was observed.

Types 2 and 3

One study[217] included in the earlier review showed a preservation of swallowing function without further significant decline in bulbar function in participants with type 2/3 SMA.

13.4.1.2.3 Speech therapy support

Multiple types

Two newly identified studies[105,161] reported on the need to receive speech therapy support in the participants with different types of SMA receiving nusinersen. In one newly identified study[107] the distribution of the speech therapy support received was assessed between those who were adherent and non-adherent to nusinersen therapy. The study showed that higher number of non-adherent participants received speech therapy support than the adherent participants (SMA Type 1 50% for non-adherent vs. 9.1% for adherent; SMA Type 2 34.5% for non-adherent vs. 0% for adherent; SMA Type 3: 9.0 % for non-adherent vs. 8% for adherent). The highest need was among non-adherent SMA type 1 participants (n=12), with half (50%) requiring some form of speech therapy support. No speech therapy was reportedly needed among adherent SMA type 2 patients (n=12).

13.4.1.2.4 Miscellaneous

Presymptomatic

One new study,[117] reporting on presymptomatic patients who received early treatment which achieved timely acquired World Health Organization motor development milestones and did not experience feeding problems.

Multiple types

One newly identified study[161] reporting real-world outcomes in patients with multiple types SMA treated with either nusinersen monotherapy or OA monotherapy found that half of the patients receiving nusinersen experienced either improvement or maintenance in cry function. This outcome was more pronounced in those receiving OA treatment, with all of them showing positive results. The same newly identified study[161] found that 7 of 8 participants receiving nusinersen experienced either improvement or maintenance in speech function while all those receiving OA treatment showed either improvement or maintenance in speech function.

Another new study[102] reported that, amongst 7/37 nusinersen-treated patients for whom 10-month follow-up data were available, there were no significant changes in the decline of three measures of facial nerve vulnerability, namely the CMAP amplitude (from 2.13 ± 0.97 to 1.49 ± 0.97, P=0.1094), the MUNIX of orbicularis oculi (from 31.31 ± 14.52 to 29.51 ± 23.42, P=0.5781), and the MUSIX (from 66.68 µV ± 18.23 to 49.27 µV ± 8.98, P=0.0625).

13.4.1.3 Hospitalisation
SLR evidence

Presymptomatic

New final analysis data from NURTURE by Tichler et al. (2024) provide long-term hospitalisation outcomes for presymptomatic patients treated with nusinersen in study 232SM201. Hospitalisations were infrequent and primarily related to acute, self-limiting respiratory infections. No long-term hospitalisation or intensive care unit (ICU) admission was required. Additionally, among participants with two SMN2 copies, the rate of hospitalisation due to respiratory events decreased over time.[178,179]

Type 1

New data extracted from a conference abstract by Arjunji et al. (2019) compared patients treated with OA (CL-101 study) to those treated with nusinersen (ENDEAR study), using a retrospective model of projected healthcare resource utilisation[227]. The reported unadjusted annualised rate of hospitalisations was 4.5 per patient-year for nusinersen-treated patients (up to 13 months follow-up), compared with 2.1 per patient-year for OA-treated patients (up to 24 months follow-up). The mean proportion of time spent hospitalised was also higher in the nusinersen group (11.4%; range 0–50%) compared to the OA group (4.4%; range 0–18.3%). Additionally, 18% of nusinersen-treated patients spent ≥ 20% of their follow-up period in hospital, whereas no patients in the OA group reached this threshold.[227]

Types 2 and 3

Hospitalisation outcomes for later-onset SMA were primarily informed by the CHERISH trial, which assessed nusinersen in children with SMA Types 2 and 3. Although hospitalisation was not a prespecified endpoint, serious adverse events (SAEs), many of which necessitate inpatient care, were used as a proxy measure.[1] As reported by Mercuri et al (2018) and cited in the EMA assessment (2023), SAEs occurred in 17% of nusinersen-treated participants, compared with 29% in the control group over the 15-month treatment period.[29]. Moreover, no SAEs were considered by the Investigator to be related or possibly related to the study treatment.[70]

13.4.1.4 Respiratory function

13.4.1.4.1 FVC

SLR evidence

Presymptomatic

New final analysis data from NURTURE (2024) provide long-term respiratory function outcomes for presymptomatic patients treated with nusinersen in study 232SM201. Overall, respiratory parameters improved across participants. The average phase angle—a surrogate measure of thoracoabdominal synchrony—remained within normal ranges for both SMN2 groups (2-copy group: 16.56 to 24.40 degrees; 3-copy group: 13.27 to 18.54 degrees). Most participants remained off respiratory support throughout the study.[178,179] Five of 15 participants (33%) with two SMN2 copies met the predefined primary endpoint, which was defined as receiving invasive or non-invasive ventilation for ≥6 hours/day

continuously for ≥7 days, or requiring tracheostomy. Notably, none of the 10 participants with three SMN2 copies met this endpoint. Importantly, no participants died or required a tracheostomy. Among the five participants who met the ventilation endpoint, four events were associated with acute, reversible infections. All five participants continued to gain motor milestones. None of the participants required permanent ventilation, defined as ≥16 hours/day continuously for >21 days in the absence of an acute reversible event or tracheostomy.[178,179]

Types 2 and 3

Three studies,[115,122,228] two newly identified and one from an earlier review, examined the impact of nusinersen treatment on forced vital capacity (FVC) in individuals with type 2 or 3 SMA. The study included in the earlier review reported no significant change in FVC after treatment.[228]

One of the new studies[115] reported a slower annual decline in FVC among treated participants compared to the expected natural progression of the disease. Specifically, the decline was 2.2% per year versus 4.2% in type 2 SMA, and 1.4% versus 6.3% in type 3 SMA. In the other new study,[122] FVC remained stable following nusinersen treatment, with no significant change in the percent predicted FVC (mean change 0.1 ± 8.6, P>0.05).

Multiple types

Ten studies, eight from the previous review and two newly identified records, examined the effects of nusinersen on respiratory function in individuals with different types of SMA. Among the studies included in the earlier review, four reported improvements in FVC and overall respiratory function,[172,180,211,223] while three found no significant change in FVC following treatment.[196,212,229] One study[195] noted a decline in respiratory function in a single patient after treatment.

Of the two new studies, one study[119] found that overall FVC remained stable over a 22-month follow-up period (mean monthly change −0.047, 95% CI −0.115 to 0.020; P=0.17), though outcomes varied by SMA type. Patients with type 2 SMA showed a significant increase in FVC (+0.144, 95% CI 0.086 to 0.202; P<0.0001), while those with type 3 or type 4 SMA experienced a significant decrease (−0.142, 95% CI −0.239 to −0.044; P=0.005). The second new study[230] evaluated a paediatric cohort with different types of SMA and found no significant improvement in mean FVC over approximately 13 months of nusinersen treatment (+0.4; P=0.90).

One study[168] included in the earlier review examining respiratory function in patients with type 1 and 2 following treatment with nusinersen, reported better respiratory muscle strength and significantly better forced vital capacity (FVC) in patients with type 2 SMA compared to control.

13.4.1.4.2 PFVC

SLR evidence

No evidence was reported for presymptomatic or type 1 patients.

Types 2 and 3

One new study[122] examining the impact of nusinersen treatment in type2 and 3 SMA patients reported stability but no significant mean change in the % of predicted FVC (0.1 ± 8.6, P>0.05).

13.4.1.4.3 FEV1

SLR evidence

No evidence was reported for SMA types separately.

Multiple types

One new study[230] examined the impact of nusinersen treatment in patients with different types of SMA on FEV1, and showed a significant increase in the mean values of FEV1 (+4.4; P=0.03) in all patients at approximately 13 months following nusinersen treatment.

13.4.1.4.4 Maximum inspiratory pressure

SLR evidence

No evidence was reported for presymptomatic or type 1 patients.

Types 2 and 3

One newly identified study[122] assessed the impact of nusinersen on maximum inspiratory pressure (MIP) in patients with type 2 and 3 SMA. The study reported stable respiratory performance with no significant mean change in MIP from baseline through to month 14 (−0.6 cm H_2O ± 16.4; P>0.05).

13.4.1.4.5 Maximum exploratory pressure

SLR evidence

No evidence was reported for presymptomatic or type 1 patients.

Types 2 and 3

One newly identified study[122] examined the impact of nusinersen treatment on maximum exploratory pressure in type 2/3 SMA patients. The study reported stable respiratory function with no significant mean change in the maximum exploratory pressure from baseline through to month 14 (11.1 cm H_20 ± 41.2; P>0.05)

Multiple types

One newly identified study[114] investigating the effect of nusinersen treatment in different types of SMA showed that a significant improvement in maximum expiratory pressure was observed in participants over 18 months, with a significant increase of 12.74 cm H_2O (t(32) = -3.18; P=0.003)

13.4.1.4.6 Sniff nasal inspiratory pressure

SLR evidence

No evidence was reported by individual SMA type.

Multiple types

One newly identified study[114] investigating the effect of nusinersen treatment in SMA types SMA 2, 3 and 4 showed a significant improvement in sniff nasal inspiratory pressure in participants aged over 18 months, with a significant mean increases of 11.82 cm H_2O (t(32) = -4.14, P<0.001)

13.4.1.4.7 Peak expiratory flow (PEF)

No evidence was reported by individual SMA type.

Multiple types

Two newly identified studies[114,230] examined the impact of nusinersen treatment on PEF in individuals with different types of SMA. One study[114] reported a non-significant improvement in PEF among participants over an 18 month period (t(32) = 1.87, P=0.071). In the second study, the overall mean PEF percentage remained stable and showed no further decline in patients with mixed SMA type. However, a significant increase in average PEF was observed in the type 2 SMA subgroup (2.9%, p = 0.03).[230]

13.4.1.4.8 Miscellaneous

Type 1

Three studies from the original review[131,135,136] investigated the effectiveness of nusinersen on other markers of respiratory function in patients with type 1 SMA. One study[131] reported improvements in respiratory function in most patients. Another study[135] found that all patients required respiratory support, and a third study[136] observed a reduction in the duration of ventilatory support in most patients.

Types 2 and 3

Two studies[205,208] included in the earlier review reported that no improvement was seen in other measures of respiratory function.

Multiple types

One study[105] with an updated result from the earlier review showed that an improvement in muscle strength or quality of life and stabilisation of respiratory function were seen in 66% of patients.

13.4.1.4.9 Tracheostomy

SLR evidence

No evidence was identified for this outcome in the review process.

MAA evidence

Paediatric registry

The results for this outcome are taken from the updated April 2025 report.

The registry stated that only two type 1 EAP patients had tracheostomies.

Adult registry

This outcome was not reported in the adult registry report.

13.4.1.5 Complications of SMA

Presymptomatic

New final analysis data from NURTURE (2024) provide long-term safety data on complications in presymptomatic patients with genetically confirmed 5q SMA treated with nusinersen. Over the five-year follow-up period, there was a low incidence of failure to thrive, dysphagia, and

orthopaedic complications. Growth parameters either remained stable or showed improvement throughout the study, supporting a favourable long-term safety and developmental profile in this population.[178,179]

Types 2 and 3

All data in this section are drawn from previously published sources and were also referenced in the Warwick EAG report. According to the previous MTA report, complications in patients with later-onset SMA (Types 2 and 3) were most prominently reported in studies related to the CHERISH (NCT02292537) and SHINE (NCT02594124) trials.[1] Mercuri et al (2018), based on the CHERISH trial, reported the occurrence of respiratory complications including pneumonia and respiratory distress. These complications were observed in both nusinersen and control groups, suggesting they may reflect the natural course of the disease rather than being treatment-related adverse effects. Importantly, the overall safety profile remained favourable throughout the study period.[29]

As noted in the previous MTA report, further longitudinal insights were provided by Dunaway Young et al (2023), based on results from the SHINE extension study, which explored scoliosis progression in participants treated with nusinersen. An analysis of changes in Cobb angle revealed progressive scoliosis in a proportion of participants, which was associated with lower improvements in motor function as measured by HFMSE and RULM scores. Although not a direct adverse event of the treatment, scoliosis progression remains a known complication of SMA that may influence the functional outcomes of therapeutic interventions.[1,123]

Multiple types

One newly-identified study by Masson et al reported that three patients with type 1, 14 with type 2 and three with type 2 developed scoliosis before treatment. During treatment, eight patients with type 1 SMA and three patients with type 3 SMA developed scoliosis. Scoliosis surgery was performed for two patients with type 2 SMA.[110]

13.4.1.6 Need for non-invasive or invasive ventilation

SLR evidence

Presymptomatic

New final analysis data from NURTURE (2024) assessed the need for ventilatory support among presymptomatic patients with 5q SMA treated with nusinersen. Over the course of the study (up to Day 2892), 5 out of 15 participants with two SMN2 copies met the composite primary endpoint of death or need for ≥6 hours/day of respiratory support for at least seven consecutive days, or tracheostomy. No participants with three SMN2 copies met this endpoint. Importantly, no deaths or tracheostomies occurred in either group. Among the five participants who required non-invasive ventilation, four events were related to acute, reversible infections. One participant required ≥16 hours/day of ventilation for over 21 days

but subsequently recovered, and did not progress to permanent ventilation. At the final study visit (Days 2878–2917), all five participants remained on non-invasive ventilation (6–10 hours/day), but none required permanent ventilation.[178,179]

Furthermore, recent long-term follow-up data from Crawford et al. (2023) reported that, over five years of treatment, none of the children with type 1 or 2 SMA required permanent ventilation.[31]

Type 1

As noted in the previous MTA report, data from Finkel et al. (2021) reported results from the ENDEAR trial (NCT02193074), which evaluated nusinersen in infants with symptomatic type 1 SMA.[1] Participants in the nusinersen group had a 47% lower risk of requiring permanent ventilation or death compared to the control group (HR 0.53, 95% CI 0.32–0.89; P=0.005).[134] Although the overall rate of permanent assisted ventilation use was lower in the nusinersen group, the result did not reach statistical significance (HR, 0.66; P=0.13). Long-term follow-up data from the SHINE extension supported this trend, with lower-than-expected rates of ventilatory support reported over time.[134]

New data from an additional evaluation by Arjunji et al (2019), comparing OA and nusinersen, showed that no participants required permanent ventilation in the OA group during a follow-up of more than 24 months. Ventilation outcomes were also favourable among nusinersen-treated participants, although specific comparative figures were not fully detailed.[227]

Another newly identified study[118] reported that the number (%) of patients who received NIV was 26 (93%) in the nusinersen group and 15 (41%) in the treatment-naïve control group. The same study reported that cough assist was administered to 25 (96%) in the nusinersen group and two (6%) in the treatment-naïve group.

Finally, another newly identified study[112] reported that, at baseline, 36/69 patients received NIV, while on treatment seven more patients started NIV.

Types 2 and 3

As mentioned in the previous MTA report, no participants in the nusinersen group required permanent ventilation during the trial period within the CHERISH trial.[1,29] This pattern was consistent in CHERISH-related extension studies and in the NICE company submission based on NCT02462759.

Multiple types

A newly identified study[121] reported that ventilatory support was required by six and two type 1 SMA patients at baseline and follow-up, respectively, and by two type 2 SMA patients at baseline and follow-up.

Newer data from Acsadi et al. (2021) reported a significant reduction in cumulative ventilation support time among nusinersen-treated patients compared to sham-treated controls.[30]

MAA evidence

Paediatric registry

The results for this outcome are taken from the updated April 2025 report.

The registry defined permanent ventilation as any ventilation type for ≥ 16 hours/day continuously for > 21 days or tracheostomy. There was not enough data to conduct a formal analysis. Three patients have been permanently ventilated but details specifying when this happened are lacking for two of them. Another patient from the EAP, not included in the analysis due to lack of baseline data, was also on permanent ventilation. It is worth noting that these patients were part of the EAP and, therefore, had more chronic type 1 SMA. Compared to the natural history, where approximately 90% were either deceased or needing permanent ventilation, the number of patients represented in the MAA who needed permanent ventilation is very small number.

Adult registry

The results for this outcome are taken from the updated April 2025 report.

No patients had events of permanent ventilation since commencing nusinersen treatment. It is worth noting that the registry reported descriptive statistics for lung function, which suggest stabilisation for type 2/3 non-sitters, sitters and walkers over the study period.

13.4.1.7 Stamina and fatigue

13.4.1.7.1 *Individualized Neuromuscular Quality of Life Questionnaire (INQoL) - fatigue score*

No evidence was reported by individual SMA type.

Multiple types

One newly identified study[104] examined the effect of nusinersen on fatigue in individuals with different types of SMA type followed up at months 6, 10 and 14 using INQoL fatigue domain scores. The study reported a significant improvement in the fatigue domain of the INQoL scores throughout the follow-up periods (P=0.0137)

13.4.1.7.2 *Fatigue*

No evidence was reported by individual SMA type.

Multiple types

Two studies identified in the earlier review reported fatigue following nusinersen.[212,229] One study reported increased fatigue during treatment,[229] whilst the other reported improvement in fatigue.[212]

13.4.1.8 Mortality

SLR evidence

Presymptomatic

New final analysis data reported in the clinical study report (CSR) for the NURTURE study by Tichler et al. (2024) provide updated long-term survival outcomes for nusinersen in patients with genetically confirmed, presymptomatic 5q SMA. Survival status was assessed over the entire study period (from baseline to the last assessment, up to Day 2891—approximately eight years). No deaths were reported during the study, further supporting the long-term survival benefit of nusinersen in this patient population.[178,179]

As noted in the previous report, the integrated analysis of the NURTURE and ENDEAR–SHINE studies investigated the continued benefit of nusinersen initiated presymptomatically. In this analysis, 100% survival was reported among the 25 children in the NURTURE cohort, with no deaths occurring over a median treatment duration of nearly four years.[1,134]

As previously reported, an early-phase trial (NCT02386553) involving infants likely to present with type 1 or 2 SMA also reported complete survival at the five-year mark, with all 25 children alive at last follow-up.[1,31] A subsequent evaluation by Crawford et al (2023), involving patients transitioning to long-term follow-up, reported complete survival over five years in all 25 participants.[31]

Type 1

The ENDEAR study (NCT02193074) and its extension SHINE assessed nusinersen in infants with symptomatic type 1 SMA. According to Finkel et al (2021), and as mentioned in the previous MTA report, approximately 75% of participants in cohort 2 remained alive at the last reported follow-up. The median time to death or permanent ventilation was longer in the nusinersen arm compared to controls.[1,134]

New data from Arjunji et al (2019), comparing OA and nusinersen among patients with type 1 SMA, found that all participants in the OA group were alive during the 56-week follow-up period. Among the nusinersen-treated group, 66% of participants were reported to be alive during the

same follow-up period.[227] Another newly identified study[118] reported that the numbers of patients who died following nusinersen treatment was 2/28 compared to 37/38 in a treatment-naïve group. An additional study,[112] also newly identified in this review, reported that four patients died due to causes considered non-related to the drug or lumbar puncture procedure.

Types 2 and 3

For types 2 and 3 SMA, mortality outcomes were drawn from the CHERISH study (NCT02292537) and associated analyses; no new data were reported. As noted in the previous review, the results reported by Mercuri et al (2018) showed no deaths in either the nusinersen or control groups during the 15-month follow-up period.[1,29] These findings were consistent across other CHERISH-related analyses, including the CS2/CS12 cohorts (NCT01703988), in which no deaths were reported among participants.[207]

Multiple types

In an additional study by Acsadi et al (2021), one death occurred in the sham-treated group, while no deaths were reported among nusinersen-treated participants, although this study was not powered specifically for mortality outcomes.[30]

MAA evidence

Paediatric registry

The results for this outcome are taken from the updated April 2025 report.

All patients who died were reportedly type 1 patients: [redacted]

Adult registry

The results for this outcome are taken from the updated April 2025 report.

No occurrence of death occurred after starting nusinersen.

13.4.1.9 Adverse events
SLR evidence

It is noteworthy that most adverse events (AEs) reported across the included documents appear to be attributable to the underlying disease or the method of administration (e.g., lumbar puncture), rather than the treatment itself.

Presymptomatic

As noted in the NURTURE study population, comprising presymptomatic infants with genetically confirmed SMA, no adverse events led to treatment discontinuation in this target group. Safety outcomes remained favourable over the follow-up period.[70]

New data from the final analysis reported in the CSR for the NURTURE study demonstrated that, over a follow-up period of up to Day 2891 (approximately eight years), there were no treatment-related discontinuations or deaths. Most adverse events were mild to moderate in severity, and no new safety signals emerged during long-term follow-up.[178,179]

As reported in the previous MTA report, Darras et al (2019) observed that all participants experienced AEs, with common events including post-lumbar puncture syndrome (57%), headache (46%), respiratory tract infections (43%) and gastrointestinal complaints such as vomiting (21%). SAEs were reported in 18% of participants but none were considered to be related to treatment. No discontinuations occurred due to AEs and no laboratory abnormalities or neurological worsening were attributed to nusinersen.[1,207]

As noted in the previous MTA report, Crawford et al (2023) followed infants at high genetic risk for SMA over an additional two years. No AEs were judged study-drug related, although 40% had AEs possibly linked to nusinersen. Most AEs were non-serious and consistent with underlying disease presentation, such as constipation and vomiting.[1,231]. All resolved without discontinuation except for isolated cases of proteinuria and clonus. Serious AEs occurred in 48% of participants, but none were considered drug-related[1,231]

Type 1

According to the EMA (2023) and based on the findings of Finkel et al (2017; 2021), AEs were common in both nusinersen and control groups.[28,70,134] The most frequently reported AEs included respiratory infections, feeding difficulties and constipation. Finkel et al (2017) reported that the overall AE incidence was similar between groups (96% in nusinersen vs. 98% in control), but the rate of severe AEs (56% vs. 80%), serious AEs (76% vs. 95%), and treatment discontinuation due to AEs (16% vs. 39%) was notably lower in the treatment group.[28]

In follow-up analyses, Finkel et al (2021) reported that there were five deaths attributable to SMA and 101 SAEs in 80% of patients, although none of these were considered to be treatment-related. The incidence of respiratory and gastrointestinal AEs declined over time (from 69% to 20% and 63% to 30%, respectively).[134] **Type 1 previously treated with OA**

New data from the RESPOND study, reported by Masson et al (2024), Proud et al (2024) and Kuntz et al (2023), details adverse events in children with type 1 SMA previously treated with OA. Masson et al (2024) reported that 82% (31/38) of participants experienced AEs, the most

common being infections (63%) and respiratory disorders (26%). Two participants developed mild, treatment-related proteinuria, which resolved. Thirteen patients (34%) experienced serious AEs, none of which were attributed to nusinersen during the 183-day follow-up.[110]

Proud et al (2024) reported that 82% of participants reported AEs. Infections and infestations were the most common (63.2%), followed by respiratory (26.3%), gastrointestinal (13.2%), general disorders including injection-site reactions (13.2%), and skin-related AEs (13.2%). Two mild AEs (proteinuria) were considered related to nusinersen but no serious AEs were drug-related. All AEs resolved during the median 230.5 day follow-up.[226]

Kuntz et al (2023) reported upper respiratory tract infections in six participants and viral upper respiratory tract infections in five. Mild proteinuria in two cases was identified as treatment-related but resolved. Nine serious AEs were reported, none of which were related to nusinersen. There were no deaths or post-lumbar puncture syndromes during the median 183-day follow-up.[232]

Types 2 and 3

As reported by the EMA (2023), in patients with SMA types 2 and 3, data from the CHERISH trial and its extensions served as the primary safety evidence.[29,70] Mercuri et al (2018) reported that 93% of patients in the nusinersen group and 100% in the control group experienced AEs. SAEs occurred in 17% of nusinersen-treated participants compared to 29% of controls.[29]

New data extracted from the SHINE study, as reported by Day et al (2020), confirmed that most adverse events were mild or moderate in severity and were primarily related to the underlying disease or to lumbar puncture procedures. Only one SAE (appendicitis) was reported, which was judged by investigators to be unrelated to nusinersen treatment.[222]

Multiple types

Acsadi et al (2021), in a study of children excluded from ENDEAR and CHERISH, reported pyrexia, cough, pneumonia, and vomiting as the most frequent AEs. No treatment-related discontinuations occurred. One participant in the sham treatment arm withdrew due to AEs.[30,70]

New data from Darras et al (2020) evaluated adverse event profiles across presymptomatic (NURTURE) and symptomatic (ENDEAR–SHINE) cohorts. In the NURTURE group (median follow-up: 33.9 months), the most frequently reported AEs were pyrexia (84%), upper respiratory tract infections (76%), and vomiting (40%). In the ENDEAR–SHINE cohort (median follow-up: 997.5 days), similar patterns were observed, with pyrexia (66%) and pneumonia (31%) among the most common events.[233]

Another study[121] that was newly identified in this review reported that 10 patients experienced AEs, which included proteinuria, thrombocytosis and intracranial hypotension, though cessation of treatment was not required.

Unreported type

One study[110] reported that the overall number (%) of adverse effects that occurred in nusinersen recipients was 31/38 (82%). Of the 31 children who experienced adverse effects, infections/infestations occurred in 63% of the children, respiratory, thoracic and mediastinal disorders occurred in 26%, mild proteinuria in 5% and SAEs in 34%.

13.4.1.10 Health-related quality of life and Patient Reported Outcomes

SLR evidence

New data on health-related quality of life for patients with genetically confirmed 5q SMA and their caregivers have been identified in the studies detailed below. These findings—drawn from both presymptomatic and symptomatic populations—offer additional insights not previously captured in earlier evidence syntheses.

Presymptomatic

In the final analysis of the NURTURE study, health-related quality of life using the Pediatric Quality of Life Inventory (PedsQL) was reported in presymptomatic patients treated with nusinersen.[178,179] Data collection was conducted between approximately day 1800 and day 2880. PedsQL scores, where available, indicated improvements in patients' mobility and overall quality of life, with many families reporting positive changes in daily functioning. However, substantial variability in HRQoL scores was observed over time.[178,179]

Subgroup analysis by SMN2 copy number showed that participants with three SMN2 copies generally reported slightly higher median scores at certain time points, particularly in the Neuromuscular Module. A discrepancy was also observed between participant-reported and parent-reported outcomes: while participants with two SMN2 copies reported relatively stable scores between Day 1800 and Day 2880, their parents reported a decline in median total scores over the same period. These findings highlight the importance of capturing both self-reported and proxy perspectives when evaluating quality of life in SMA.[178,179]

Types 2 and 3

Day et al. (2020) evaluated caregiver-reported outcomes in families of patients with SMA types 2 and 3 using the ACEND (Assessment of Caregiver Experience in Neuromuscular Disease) tool. Over a median follow-up period of approximately 1952 days [range: 1860–2121 days], most caregivers reported stable or improved scores across seven assessed domains, suggesting sustained or enhanced caregiver well-being during long-term nusinersen treatment.[57]

13.4.1.10.1 EQ-5D-L

MAA evidence

Paediatric registry

The results for this outcome are taken from the original December 2023 report. It is important to note that data reported here is from a pilot study aiming to recruit 50 paediatric patients. There was insufficient data to assess separate groups (i.e. SMA type). Additionally, the limited amount of data means the results require cautious interpretation. Furthermore, pilot studies often do not present comparative data due to imprecision and unreliability.

Only two patient responses were recorded as being available for this outcome and therefore no data was presented.

Adult registry

The results for this outcome are taken from the updated April 2025 report.

The registry highlighted potential limitations of the PROMs evidence. The patient-reported nature of PROMs carries the risk of voluntary response bias and recall bias. PROMs data has been obtained from the registry and displayed in the report as a representation of a smaller proportion of the entire SMA population. As such, results must be interpreted with care.

Utilising a Pareto Classification of Health Change method, the registry reported whether patients' health status was better, worse, the same or mixed (i.e. better on one dimension but worse on another). Data was available with for 11 non-sitters with a baseline and a follow-up submission. [redacted]

[redacted] **Table 13.10** [redacted] **For the EQ VAS, the registry compared the first response of a patient to next response. The registry reported the number of patients who had an increase of +≥ 10 or +≥ 1 points, stayed the same, or -≥ 1 or -≥ 10 points. An increase in this metric is desirable as it equates to higher quality of life** [redacted]

[redacted]

[redacted]Table 13.10: Number of type 2/3 patients reporting changes in EQ-5D-L for nusinersen from the adult registry at each follow-up time point

Nusinersen adult EQ-5D-5L		Time point (n/N)								
Measure	**Type**	**6 months**	**1 year**	**1.5 years**	**2 years**	**2.5 years**	**3 years**	**3.5 years**	**4 years**	**4.5 years**
Better	2/3 non-sitters	[redacted]								
Same	2/3 non-sitters	[redacted]								
Mixed	2/3 non-sitters	[redacted]								
Worse	2/3 non-sitters	[redacted]								
Better	2/3 sitters	[redacted]								
Same	2/3 sitters	[redacted]								
Mixed	2/3 sitters	[redacted]								
Worse	2/3 sitters	[redacted]								
Better	2/3 walkers	[redacted]								
Same	2/3 walkers	[redacted]								
Mixed	2/3 walkers	[redacted]								
Worse	2/3 walkers	[redacted]								

Abbreviations: NR = Not Reported as data was not available for this time point; n = number of patients who met the criteria for that category; N = overall number of responses for that time point

13.4.1.10.2 EQ-5D-Y

MAA evidence

Paediatric registry

The results for this outcome are taken from the original December 2023 report. It is important to note that data reported here is from a pilot study aiming to recruit 50 paediatric patients. There was insufficient data to assess separate groups (i.e. SMA type). Additionally, the limited amount of data means the results require cautious interpretation.

Registry data were available for EQ-5D-Y total score and EQ-5D-Y-VAS. The total score had 27 patients with available data at first entry and nine with a follow-up (latest available; see Table 13.11). The limited data suggests maintenance of total score, with a higher score representing more problems experienced.

Table 13.11: Change in EQ-5D-Y total score for those receiving nusinersen; from Paediatric MAA report December 2023

	Number of patients	Mean	SD	Median	Min	Max
First entry	27	10.9	1.4	11	9	13
Latest available	9	11	1.8	12	8	13
Change first to last available visit	9	0.3	1.2	0	-1	3
Abbreviations: SD = standard deviation						

The EQ-5D-Y VAS was available for 33 patients at first entry. Twelve patients had a data point from with the latest available visit. The limited data suggests an overall decrease in VAS, which would indicate worsening health status (see Table 13.12). However, the limited interpretation of the data needs to be considered.

Table 13.12: Change in VAS for those receiving nusinersen; from Paediatric MAA report December 2023

	Number of patients	Mean	SD	Median	Min	Max
First entry	33	78.8	17.9	80	20	100
Latest available	12	79.6	15.5	82.5	50	100
Change first to last available visit	12	-5.3	16.0	-5.5	-25	20
Abbreviations: SD = standard deviation						

Adult registry

The adult registry did not provide evidence for this outcome.

13.4.1.10.3 HRQoL measures from unreported tools

SLR evidence

Multiple types

The original review identified eight studies assessing HRQoL in patients treated with nusinersen where the tool measured was not reported. Of these, four studies showed no significant difference as a result of nusinersen treatment on HRQoL,[164,173,211,213,234] while three showed improvements compared to before nusinersen or to control group.[124,235,236]

13.4.1.10.4 PGI-S

MAA evidence

Paediatric registry

The results for this outcome are taken from the original December 2023 report. It is important to note that data reported here is from a pilot study aiming to recruit 50 paediatric patients. There was insufficient data to assess separate groups (i.e. SMA type). Additionally, the limited amount of data means the results require cautious interpretation.

Initial visit data was reported for 32 patients. However, data was only available for 10 patients at the latest available visit. Of these 10 patients, six had no change in severity and four had a reduction of one unit. This limited data suggests maintenance or improvement for this PROM.

Adult registry

The results for this outcome are taken from the original April 2024 report.

The registry highlights potential limitations of the PROMs evidence. The patient-reported nature of PROMs carries the risk of voluntary response bias and recall bias. PROMs data have been obtained from the registry and displayed in the report as a representation of a smaller proportion of the entire SMA population. Results must be interpreted with care.

Data was only available for 15 type 2/3 patients at last follow-up, with 33 available at first entry. There was a rise in percentage of moderate and severe levels (45.45 to 46.67 and 36.3 to 40%, respectively). This suggests deterioration in the patient condition, though data is extremely limited. Additionally, the means of the baseline (3.18 ± 0.73) and last follow-up (3.27 ± 0.70) are similar. A sensitivity analysis was presented for those who had a PROM in ±8 weeks visit window. This dataset had nine patients at last follow-up, with 22 patients available at first entry. Moderate level rose (27.7 to 33.3%), however severe level decreased (50 to 44.44%), representing improvement in patient condition. Additionally, the means of the baseline (3.27 ± 0.83) and last follow-up (3.22 ± 0.83) are similar. Unlike the paediatric registry, the adult registry did not report if the patients available at last entry available showed improvement, maintenance or worsening.

13.4.1.10.5 PGI-I

MAA evidence

Paediatric registry

The results for this outcome are taken from the original December 2023 report. It is important to note that data reported here is from a pilot study aiming to recruit 50 paediatric patients. There was insufficient data to assess separate groups (i.e. SMA type). Additionally, the limited amount of data means the results require cautious interpretation.

Initial visit data was reported for 35 patients. However, data was only available for 13 patients at the latest available visit. Of these 13 patients, seven had no change in improvement level. Worsening on the scale was experienced by two patients, one had a reduction of one unit, and

another had a reduction of three units. Three had an improvement of one unit and one an improvement of two units. This limited data suggested mixed results for this PROM.

Adult registry

The results for this outcome are taken from the original April 2024 report.

The registry highlighted potential limitations of the PROMs evidence. Due to their patient-reported nature, PROMs hold the risk of voluntary response bias and recall bias. PROMs data has been obtained from the registry and displayed in the report as a representation of a smaller proportion of the entire SMA population. Results must be interpreted with caution.

Data was available for 49 type 2/3 patients at first entry and 38 at last follow-up. There was an increase in the proportion of people reporting they were much improved, minimally improved, had experienced no change, or were minimally worse. This coincided with a decrease in the proportion of patients ranking as much worse and very much worse, which suggests an overall improvement. Additionally, the means at baseline (3.63 ± 1.35) and last follow-up (3.50 ± 1.13) are similar but show a small decrease on average. A sensitivity analysis was presented for those who had a PROM in the ±8 week visit window. This dataset had 30 patients at last follow, with 43 patients available at first entry. Proportions of much improved and minimally improved decreased between the two data points. While proportions of no change and minimally worse increased. Proportions of much worse and very much worse decreased. Overall, it appears that the condition was slightly better or similar. Additionally, the means of the baseline (3.39 ± 1.33) and last follow-up (3.53 ± 1.11) are similar, with a slight increase. Unlike the paediatric registry, the adult registry did not report if the patients available at last entry available showed improvement, maintenance or worsening.

13.4.1.10.6 Egen Klassification-2 (EK-2)

SLR evidence

Type 1

The original review identified one study examining EK2 in type 1 SMA patients treated with nusinersen, reporting that 5/41 patients showed a change of at least two points.[136]

Type 2/3

The original review identified one study examining EK-2 in patients with type 2/3 following nusinersen treatment, reporting improvement by at least two points in five patients.[237]

Multiple types

The original review identified one study examining EK-2 in people with different types of SMA following nusinersen treatment, showing a significant increase.[172]

MAA evidence

Paediatric registry

The results for this outcome are taken from the updated April 2025 report.

The EK-2 scale assesses activity and participation in individual with non-ambulatory SMA. The scale covers eight daily life categories including wheelchair use and transfers, trunk mobility, eating, swallowing, breathing, coughing and fatigue. A higher EK-2 score indicates a greater level of functional impairment. No formal analysis was conducted and individual participant data was provided in graphical format. Most individuals maintained their level of function. Type 1 patients showed a trend towards improvement. However, some patient scores increased (i.e. worsened) over time. Data was not available for type 1 non-EAP. It is important to note that this data was not mandated and has not been cleaned to the same degree as mandated items.

Adult registry

The results for this outcome are taken from the updated April 2025 report.

The adult registry conducted MRMMs for type 2/3 non-sitters and sitters. For non-sitters the mean change suggested improvement. There was minimal data with short follow-up due to the number of patients available. No statistical significance was observed but the numerical trend of improvement suggests potentially positive outcomes for these patients. The limited data suggests potential improvement but should be interpreted with caution due to lack of data, with 13 patients available at baseline and five available at 2.5 years follow-up.

Similar results are observed in the patients classified as sitters, with no statistically significant changes occurring but the numerical trend suggesting maintenance or small improvements in EK-2 scores over time. At baseline data for 34 patients were available and five patients had data at 4 year follow-up. As with other outcomes, the data is sparser the longer the follow-up.

13.4.1.10.7 SMA Independence Scale-Upper Limb Module (SMAIS-ULM)

SLR evidence

Type 2/3

One newly identified study[222] reported data from the SHINE trial for the effects of nusinersen on SMAIS-ULM scores on types 2-3 SMA, reporting stable scores in three out of five participants (i.e. 0 point change).

MAA evidence

Paediatric registry

The results for this outcome are taken from the original December 2023 report.

It is important to note that data reported here is from a pilot study aiming to recruit 50 paediatric patients. There was insufficient data to assess separate groups (i.e. SMA type). Additionally, the limited amount of data means the results require cautious interpretation.

Table 13.13 shows data at first entry to the patient registry whilst on nusinersen and for the most recent visit. In addition, a summary of changes from first to last available assessment is shown. Where individual items are missing, an adjustment was been made to the total score so that the total is expressed out of the total number of items (similar to the approach for motor outcomes).

Table 13.13: Change in SMAIS for patients on nusinersen treatment; from Paediatric MAA report December 2023

	Number of patients	Mean	SD	Median	Min	Max
First entry	31	21.4	11.2	21	4	44
Latest available	11	25.6	8.9	25	9	44
Change first to last available visit	11	1.6	4.4	2	-8	7

Abbreviations: MAA = Managed Access Agreement; SMAIS = Spinal Muscular Atrophy Independence Score; SD = standard deviation

Adult registry

The results for this outcome are taken from the updated April 2025 report.

The registry highlighted potential limitations of the PROMs evidence. The patient-reported nature of PROMs carries the risk of voluntary response bias and recall bias. PROMs data has been obtained from the registry and displayed in the report as a representation of a smaller proportion of the entire SMA population. Results must be interpreted with caution.

The registry reported whether type 2/3 patients reported an increase, the same, or decrease in the SMAIS-ULM. Data was available with for nine non-sitters, with baseline and follow-up submissions. [redacted].

For a breakdown over the follow-up period see Table 13.14.

Table 13.14: Number of type 2/3 patients reporting changes in SAMIS-ULM for nusinersen from the adult registry at each follow-up time point

Nusinersen adult SMAIS-ULM		Time point (n/N)							
Measure	**Type**	**6 months**	**1 year**	**1.5 years**	**2 years**	**2.5 years**	**3 years**	**3.5 years**	**4 years**
Increased	2/3 non-sitters	[redacted]							
Same	2/3 non-sitters								
Decrease	2/3 non-sitters								
Increased	2/3 sitters								
Same	2/3 sitters								
Decrease	2/3 sitters								
Increased	2/3 walkers								
Same	2/3 walkers								
Decrease	2/3 walkers								

Abbreviations: SMAIS-ULM = Spinal Muscular Atrophy Independence Scale-Upper Limb Module; n = number of patients meeting this criterion; N = overall number of responses for that time point; NR = not reported as data was not available for this time point

13.4.1.10.8 Impact on carers and families

13.4.1.10.9 SLR evidence

No evidence was reported for carers of presymptomatic or type 1 patients.

Types 2 and 3

The current review identified three studies that reported the impact of nusinersen on ACEND.[125,222] One trial reported longer term outcomes for five adolescent patients with type 2/3 SMA. Most caregivers reported to be stable or improved in all seven domains of the ACEND.[222] One comparative prospective study showed no statistically significant differences of the score between or within both groups between baseline and 12-month follow-up (nusinersen n = 16; standard of care n = 26).[125]

13.4.1.10.10 Pediatric Quality of Life Inventory (PedsQL)

SLR evidence

No evidence was reported for presymptomatic or type 1 patients.

Types 2 and 3

The original review identified two studies assessing PedsQL changes when patients received nusinersen. No significant change in the PedsQL were reported in either study.[167,238]

13.4.1.10.11 SF-36

SLR evidence

No evidence was reported according to individual SMA type.

Multiple types

The original review identified one study assessing the impact of nusinersen treatment on the SF-36. The study showed a change of -4.8 points on the SF-36 scale.[229]

13.4.1.10.12 Individualized Neuromuscular Quality of Life (INQoL)

SLR evidence

No evidence was reported according to individual SMA type.

Multiple types

The current review identified one study assessing the impact of nusinersen treatment on INQoL.[104] This retrospective cohort study of 78 patients showed statistically significant lowering of scores (i.e. improved quality of life) from baseline to 14 months for the over INQoL score and weakness score. No statistically significant differences were observed for INQoL total score or weakness score between walkers and on-walkers, with both groups showing decreases (improvements) over time.[104]

13.4.1.10.13 Ability to socialise

SLR evidence

No evidence was reported according to individual SMA type.

Multiple types

The current review identified two studies that assessed socialisation in patients with different types of SMA receiving nusinersen, both of which were retrospective cohorts.[104,183] One study assessed children's (n = 16) social integration via interview.[183] After three years of nusinersen treatment, 11 of 16 children socialised in school or daycare. Four of the five children who did not socialise were non-invasively ventilated and/or had gastrostomy, whereas the socialised children were free of ventilatory and nutritional support.[183] The other study provided data from the INQoL social relationships sub theme, which was measured at baseline (n=70), 6 months (n=48), 10 months (n=41) and 14 months (n=30). They observed an initial increase in the subscale score from baseline to 6 months (24 vs 32, respectively), however the results at 10 months (sub score: 21) and 14 months (sub score: 24) showed a statistically significant reduction from baseline.[104] A lower score is to be interpreted as improved socialisation, with a higher score suggesting more issues within the subscale.

13.4.1.10.14 Impact on Activities of Daily Living (ADLs), Independence and Emotions

SLR evidence

Presymptomatic

New final analysis data from NURTURE (2024) demonstrate that presymptomatic patients with genetically confirmed 5q SMA treated with nusinersen were able to achieve and maintain key markers of independence, particularly independent ambulation—an outcome rarely observed in untreated SMA. Of the 25 participants, 23 (13/15 with two SMN2 copies and all 10 with three SMN2 copies) achieved independent walking, with median ages of 23.7 months and 13.7 months, respectively. Additionally, retrospective comparison with seven untreated siblings (all with two SMN2 copies) highlighted substantial differences in disease progression: none of the siblings were able to sit or walk independently, four required ventilation, and four died. These findings reinforce the significant impact of early nusinersen treatment on functional independence and developmental outcomes in presymptomatic SMA.[178,179]

Multiple types

The current review identified one study assessing ADLs, employment and independence for mixed type SMA patients treated with nusinersen.[104] The INQoL activities sub theme, which was measured at baseline (n=70), 6 months (n=48), 10 months (n=41) and 14 months (n =30), showed a statistically significant reduction from baseline. The study showed a decrease at each follow-up time point for the subscale score: baseline was 59.5 points, 6 months 57.2 points, 10 months was 53.6 points, and 14 months was 50.4 points. The same pattern was observed when considering a subgroup of walkers and non-walkers, which showed a statistically significant reduction in score.[104] A lower score is to be interpreted as improved socialisation, with a higher score suggesting more issues with that sub scale.

Similarly, for the independence subscale there was a statistically significant reduction from baseline to follow-up (baseline: 59; 6 months: 54.8; 10 months: 54.3; 14 months: 50.8 points). This finding did not extend to the subgroup analysis of walkers and non-walkers, where there was a numerical trend of decreasing scores but this was not statistically significant.[104]

The same study showed a statistically significant reduction in the emotional impact sub scale.[104] Specifically at baseline the score was 32 points, 6 months it was 29 points, 10 months

28 points, and 14 months it was 27 points.[104] Similar results were observed for body image (baseline: 54.8; 6 months: 50.1; 10 months: 46.5; 14 months: 46.7 points), which also was recorded as having a statistically significant reduction.[104]

13.4.1.11 Other outcomes

13.4.1.11.1 Clinical Global Impression-Improvement scale (CGI)

SLR evidence

No evidence was reported according to individual SMA type.

Multiple types

The previous review identified three studies which presented evidence for the Clinical Global Impression-Improvement scale (CGI-I) in people with different types of SMA type receiving nusinersen.[30,172,203] One study examined CGI-I following nusinersen in type 1 and 2 patients. More patients receiving nusinersen improved compared to those initially in the sham condition (EMBRACE).[30] One of the other studies reported that 62.3% of patients' scores improved and 37.7% were unchanged;[203] 64.1% and 61.5% treated patients improved in the other study.[172]

13.4.2 Risdiplam

13.4.2.1 Motor function

Three studies reported motor function outcomes for risdiplam: RAINBOWFISH for patients with presymptomatic SMA,[60,70] FIREFISH for type 1 patients,[56,57] and SUNFISH for types 2/3 patients.[49,51,52] This updated review contains newly published data for each of these studies, which suggests most patients continued to improve or maintained their motor function in all measured outcomes up to two years (presymptomatic) and five years (types 1-3) .

[redacted] Data for type 2/3 SMA were also reported in two prospective studies,[156,158] as well as one retrospective single arm study.[152] Only 1 of 85 patients across these three studies declined in RULM score at 16 months. No published data was found for WHO Motor Milestones or ATEND outcomes in studies reporting on risdiplam, though MAA data was available for both.

MAA evidence was available for some outcomes from the original December 2023 report and as an updated report obtained in April 2025 from both paediatric and adult registries. Much of the paediatric data is limited but is reported alongside the adult data below. From the adult data, most patients improved or maintained their motor function as measured by RULM, 6MWT, WHO Motor Milestones, HINE-2 and ATEND. For type 2/3 sitters, there was a trend to worsening RHS outcomes after a year.

13.4.2.1.1 WHO Motor Milestones

None of the SLR evidence reported on WHO motor milestones.

MAA evidence

Paediatric registry

The data for the WHO MM was updated by the paediatric registry in April 2025 from the original submissions in December 2023.

WHO MM data for risdiplam in the paediatric registry MAA was reported in a manner dissimilar to that for nusinersen (see Section 13.4.1.1.1). The data is reported by SMA type and, within each type, the number of patients in each classification (e.g. non-sitters, sitting without support, crawling) for baseline and every 6 months up to 3 years. Information regarding attaining or maintaining is not directly reported and challenging to disentangle.

Adult registry

The results for this outcome are taken from the updated April 2025 report.

All type 1 patients remained non-sitters from baseline throughout the follow-up timepoints.

Type 2/3 patients were categorised by status of either non-sitter, sitter, or walker. For non-sitters, [redacted], see Table 13.15.

The registry provided further context to the results by stating the results are like natural history in the adult SMA population. They show maintenance with limited transition between functional groups.

[redacted] **The stability captured on the WHO motor scale demonstrates the known stability of this group. However, it is important to note the lack of sensitivity of this scale, as it does not capture important subtle changes. For example, the sitters group can score 1-5 on the WHO motor scale and not change classification. Therefore, a change from sitter to walker implies a significant change in their motor function, [redacted].** **Table 13.15: Risdiplam adult registry WHO MM attainment or maintenance of motor milestones**

Risdiplam adult WHO MM		Time point (n/N)								
Measure	**Type**	**6 months**	**1 year**	**1.5 years**	**2 years**	**2.5 years**	**3 years**	**3.5 years**	**4 years**	**4.5 years**
Attainment of a motor milestone	1	[redacted]								
Attainment of a motor milestone	2/3 non-sitters	[redacted]								
Attainment of a motor milestone	2/3 sitters	[redacted]								
Attainment of a motor milestone	2/3 walkers	[redacted]								
Maintenance of a motor milestone	1	[redacted]								

Maintenance of a motor milestone	2/3 non-sitters	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Maintenance of a motor milestone	2/3 sitters	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Maintenance of a motor milestone	2/3 walkers	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Abbreviations: WHO MM = World Health Organization Motor Milestones; n = number of patients who met criteria; N = number of patients overall; NA = Not Applicable (due to no data being available for this time point); NR = Not Reported as there is no data for this time point; *one patient's status was unknown										

13.4.2.1.2 CHOP-INTEND

SLR evidence

Presymptomatic SMA

Results extracted for this review update from the single arm (uncontrolled) RAINBOWFISH study showed that patients achieved high levels of motor function prior to month 12 on the CHOP-INTEND, with 10 of 13 patients (76.9% of patients analysed) achieving scores of ≥ 60 at month 4 (week 16). Four of 7 patients achieved the maximum score of 64 at month 12.[70] At month 24, 22 out of 23 infants (96%) met the CHOP-INTEND stopping criteria for assessment: they were able to sit without support and achieved a total CHOP-INTEND score of ≥60 at two consecutive visits.[239]

Type 1

Results were extracted for this review update from three uncontrolled studies reporting the effects of risdiplam on CHOP-INTEND score. The FIREFISH study reported an increase in the proportion of infants achieving a CHOP-INTEND score of at least 40 points by month 12. After 12 months of treatment, 23 out of 41 infants (56%) achieved a CHOP-INTEND score of 40 or higher.[56] Additionally, 37 out of 41 infants (90%) showed an increase of at least four points from baseline in the CHOP-INTEND score. The proportion of infants who achieved an increase of at least four points from baseline on the CHOP-INTEND was maintained at month 24.[56] At the 36-month follow-up, 78% (36/46) of participants achieved a CHOP-INTEND score ≥ 40.[57] At 5-year follow-up, 81% achieved a score of ≥ 40 and 62% attained a score of ≥50.[58]

Types 2 and 3

No evidence was reported for types 2 and 3 SMA.

MAA evidence

Paediatric registry

The results for this outcome are taken from the original December 2023 report.

An MRMM was not possible for CHOP-INTEND for type 1 patients due to limited data. Data from eight patients were available for this outcome. The mean scores suggest improvement over time. However, due to small number of patients and lack of statistical analysis, the interpretation of these results is limited.

Adult registry

This outcome is not applicable for adult patients as CHOP INTEND is used for children aged 1-38 months.[201]

13.4.2.1.3 HINE-2

SLR evidence

Presymptomatic

Two records, one that was cited in the earlier review[70] and a newly included study,[62] reported data from the uncontrolled RAINBOWFISH trial. Outcome data were reported for the 12 month follow-up in both records. Data from one record[70] suggested that all participants (n=7

participants for which data were available out of 18 enrolled) developed motor abilities, including the ability to sit without support. The other record[62] reported that 24/26 infants (92%) were able to sit without support, 21/26 (81%) were able to stand and 16/26 (62%) were able to walk. When assessed with the HINE-2 at month 24, a total of 21 of 23 infants (91%) could stand unaided and 20 of 23 (87%) walked independently.[239]

Type 1

Three records, including two that were included in the earlier review,[56,240] and one newly identified record,[57] reported data from the FIREFISH single arm trial. The results from one record[240], as reported in the original review, suggested that patients demonstrated an overall increase in HINE-2 score, with higher doses leading to higher proportions of responders and more patients with greater head control at the 12-month follow-up. The results from another record,[56] also reported in the original review, indicated an increased number of patients achieving the highest motor milestone category at the 24-month follow-up. Additional data extracted from the same study for this review update showed that, although no infants could walk or stand independently at month 24 following treatment initiation, more infants achieved a higher motor milestone category in the HINE-2 compared with month 12. For example, more infants achieved “standing with support” and one infant (2% of the sample) achieved “cruising.” Furthermore, more infants were reported to be able to achieve the highest motor milestone category. For instance, more infants were able to “pivot (rotate)” as recorded within the sitting milestone, more infants were able to “roll from supine to prone”, and two infants were recorded for the crawling milestone as able to “crawl on their hands and knees” at month 24 compared to month 12.

Results from another record,[57] from which data were extracted for this review update, showed that the following numbers and proportions of participants achieved milestones from the HINE-2 assessment at 24 months: head control (37/58 participants, 64%); sitting (16/58 participants, 28%); rolling (23/58, 40%); standing (7/58, 12%); and walking (1/58, 2%). Between months 24 and 36, the numbers of participants who gained, maintained and lost each skill out of 49 participants for whom data were available were: 3 gained, 36 maintained and 0 lost for head control; 2 gained, 4 maintained and 2 lost for sitting; 3 gained, 22 maintained and 0 lost for rolling; 5 gained, 6 maintained and 1 lost for standing; and 2 gained, 1 maintained and 0 lost for walking.

The FIREFISH study reported that, at five years, 69% of children achieved head control (compared to 47% before), 59% achieved sitting (including stable sit and pivot, previously 28%), 50% could roll supine to prone (10%), 12% could stand (aided or unaided, previously 3%), and 10% were cruising where previously none had.[58]

No evidence was reported for types 2 and 3 SMA.

MAA evidence

Paediatric registry

The results for this outcome are taken from the updated April 2025 report.

There was insufficient data to conduct an MRMM in the type 1 patients for this outcome. However, the proportion of patients in type 1 and types 2/3 showing improvement (i.e. a 1-point increase in the HINE-2 score) was reported (see Table 13.16). The registry provided some context for this data, stating it was noticeable with longer follow-up that maintenance, and in some cases improvement, are documented. This may show long lasting treatment effects, even with expected disease progression (i.e. increased contractures or scoliosis). The natural history of SMA is characterised by progressive deterioration in motor function, as well as respiratory and bulbar function. This will be more rapid in SMA type 1 but will inevitably happen in SMA type 2 and 3 as well. Stabilisation needs therefore to be considered a treatment effect, leading to better long-term outcomes and quality of life. Even in this heterogeneous cohort of real-world data, where patients started treatment when heavily symptomatic and chronically affected by the disease, there is a clear treatment effect resulting in stabilisation.

Table 13.16: Proportion of patients achieving a 1 point increase in HINE-2 at latest visit, adapted from the updated (April 2025) paediatric MAA report

	Type 1	Type 2/3 non-sitters	Type 2/3 sitters/walkers
N	[redacted]	[redacted]	[redacted]
No improvement	[redacted]	[redacted]	[redacted]
1 point increase	[redacted]	[redacted]	[redacted]
> 1 point increase	[redacted]	[redacted]	[redacted]
Missing	[redacted]	[redacted]	[redacted]

Abbreviations: HINE-2 = Hammersmith Infant Neurological Examination; MAA = Managed Access Agreement

Adult registry

This outcome is not applicable for adult patients as HINE-2 is used for children aged 2-24 months.[201]

13.4.2.1.4 BSID-III

SLR evidence

Presymptomatic

New data from a 12-month follow-up of the uncontrolled RAINBOWFISH study showed that, at month 12, 80% of infants (n=5) were able to sit without support for ≥ 5 seconds, and 7/8 infants with two SMN2 copies were able to sit without support for ≥ 30 seconds, including all infants with CMAP amplitude < 1.5 mV (n=3).[62] At month 24, 21 of 23 infants (91%) were able to stand alone (BSID-III Item 40) and walk alone (BSID-III Item 42).[239]

Type 1

New data from the uncontrolled FIREFISH study, reported that, after 24 months of treatment, all 12 infants who had previously attained the ability to sit without support for ≥ 5 seconds at month 12 maintained this ability.[56] Additionally, at month 24, 35 (60%) of infants met the

endpoint of sitting without support for ≥ 5 seconds, 23 (40%) of infants were sitting without support for ≥ 30 seconds, and 18 infants (44%) were able to sit without support for at least 30 seconds. However, no infants could stand alone or walk alone after 24 months of treatment. New data showed that, up to 36 months, four infants gained sitting without support for at least 5 seconds, 32 infants maintained this and none lost from 24 months measurement.[57] Furthermore, 15 infants gained sitting without support ability for at least 30 seconds, 20 infants maintained this ability and 0 lost this ability from the 24-month measurement. At five years, the FIREFISH study reported that 62% and 59% of children could sit without support for five and 30 seconds, respectively (previously 33% and 19%), while 7% of them achieved standing without support (previously 0%).[58]

No evidence was reported for types 2 and 3 SMA.

13.4.2.1.5 MFM32

SLR evidence

No evidence was reported for presymptomatic SMA.

Type 1

No evidence was reported for presymptomatic or Type 1 SMA.

[56]**Types 2 and 3**

Ten records, six of which were included in the earlier review[24,85,232,241-243] and four which were newly identified,[51,52,55],[46] reported data from the SUNFISH RCT (RoB assessment: some concerns). The results from the earlier review reported that the MFM32 total score from baseline increased by 1.8 (95% CI: 0.7–2.9); 58% of patients experienced stabilisation (change of ≥ 0) and 32% achieved an improvement (change of ≥ 3) in MFM32 total score after 24 months of risdiplam treatment.[232,241] Amongst patients initially assigned to the placebo group, change from adjusted baseline (month 12, before switching to risdiplam) in MFM32 total score was 0.3 (95% CI –0.7 to 1.3) after 12-months of risdiplam treatment; 59% experienced stabilisation, and 16% demonstrated improvement (change of ≥ 3) in MFM32 total score at month 24. Newly extracted data showed a statistically significant difference in change from baseline in MFM32 total score at month 12 in patients treated with risdiplam (n = 120) versus placebo (n = 60), favouring risdiplam.[51,52] The gains observed with risdiplam treatment at month 12 were maintained between months 12 and 36. Other newly identified outcome data from the SUNFISH trial in the initial submission[46] and another study[55] reported mean change from baseline in MFM32 total score of -0.08(7.38) at 60 months and of these patients, 52.1% (49/94) achieved a change of ≥ 0 and 31.5% (33/94) achieved an improvement of ≥ 3 in MFM32 total score. The evidence further showed that though, there was an initial increase in change in baseline MFM32 total score, it remained stable generally in in trial participants compared to a sharp decline observed in an untreated population from the MFM-Lyon database.

Multiple types

As reported in the earlier review, the results from JEWELFISH study showed stabilisation of the MFM32 total score from baseline (mean total score = 39.93, 95% CI 37.07–42.80) to month

12 (mean total score = 40.41, 95% CI 37.30–43.52) and month 24 (mean total score = 40.67, 95% CI = 37.60–43.74).[64]

13.4.2.1.6 HFMSE

SLR evidence

No evidence was reported for presymptomatic or type 1 SMA.

Types 2 and 3

Data reported in the earlier review from the SUNFISH RCT (RoB assessment: some concerns) showed a mean change from baseline in total HFMSE score at month 12 of 0.95 for the intervention group, with a treatment difference of 0.58 in favour of risdiplam versus placebo.[49,50,241] Recent studies report that these increases were sustained between months 12 and 36 in the risdiplam arm.[51,52] The original review also reported that 22.6% of patients improved on at least one motor scale,[158] whilst a new study reported that "clinical stability in motor function was observed" based on the HFMSE and RULM.[152]

Other newly identified outcome data from the SUNFISH trial in the initial submission[46] and another study[55] showed that participants followed up for 5 years, including those who received placebo for 12 months followed by risdiplam for 4 years, had HFMSE total scores that increased up to year 2 but returned to baseline by year 4. The mean change from baseline in HFMSE total score was -0.77(6.96) with 48.4% (46/95) of these participants achieving a change of ≥0 and 30.5% (29.95) achieving an improvement of ≥2 in HFMSE total score. Additionally, 49(40.8%) participants receiving risdiplam, 25 (41.7%) placebo and 74(41.4%) of All SUNFISH participants had HFMSE total score of <10.

Multiple types

As reported in the original review, in the JEWELFISH study the HFMSE total score was stable at month 24 compared with baseline (mean change from baseline in HFMSE total score: –0.11, 95% CI –0.98 to 0.76).[64]

13.4.2.1.7 RULM

SLR evidence

No evidence was reported for presymptomatic or type 1 SMA.

Types 2 and 3

The SUNFISH RCT (RoB assessment: some concerns) reported significant improvements in RULM score at 12 months.[49,50,241] New SUNFISH evidence extracted for this review update reported that motor function increases (including RULM) were sustained at the 36 month follow-up.[46,51,52,55]

Of two further studies that were reported in the original review, one showed no significant improvements at 12 months[156] and the other showed increases of more than 1 point in 5 patients and decreases in one patient at 16 months.[158]

A newly identified uncontrolled study reported that, at the eight month follow-up, “clinical stability in motor function was observed” based on assessments using the HFMSE and RULM tools.[152]

Newly identified outcome data from the SUNFISH trial in the initial submission[46] and another study[55] showed that the mean change from baseline in RULM total score was 2.11 at 5 years with 63.3% (62/98) of these participants achieving a change of ≥0 and 48% (37/98) achieving an improvement of ≥2 in RULM total score. Additionally, in participants followed up for 5 years including those who received placebo for 12 months followed by risdiplam for 4 years, the mean total RULM score was 19.7 (7.2) in those who received risdiplam, 20.9 (6.4) in placebo and 20.1 (7.0) across All SUNFISH participants.

Multiple types

As reported in the earlier review, data from the 24 month follow-up of the JEWELFISH study showed functional stabilisation of upper limb ability, assessed using the RULM, with a mean change of 0.71 (95% CI 0.17 to 1.26).[64]

13.4.2.1.8 MAA evidence

Paediatric registry

The results for this outcome are taken from the original December 2023 report.

An MRMM was not plausible for the type 1 patients in this outcome due to limited data. Data from nine patients were available for the RULM. The mean scores are uninformative due to variation and low patient numbers. From baseline, there is an initial drop at six months' follow-up (11.8 vs 9.1, respectively) in seven patients. At 1 year and 1.5 years, only one patient is available at each time point. Interpretation of these results is therefore extremely limited.

MMRM was possible for type 2/3 patients. The interaction between visit and baseline RULM score was not statistically significant. The analysis suggests some improvement from baseline at six months, with maintenance for the remaining two time points (1 and 1.5 years).

Adult registry

The results for this outcome are taken from the updated April 2025 report.

The registry conducted MMRM for type 2/3 non-sitters and sitters. For non-sitters, from the baseline including 70 patients, there was an increase from baseline observed to 2.5 years (n=13). The mean change suggests improvement but no statistical significance is observed. However, the numerical trend of improvement suggests potentially positive outcomes for these patients. For sitters, the baseline data included 84 patients, of which 16 had data with a 2.5 year follow-up. No statistically significant changes occurred but the numerical trend suggests maintenance or small improvements in RULM scores over time.

13.4.2.1.9 6MWT

SLR evidence

No evidence was reported for presymptomatic or types 1 or 2 SMA.

Type 3

As reported in the earlier review, the JEWELFISH study reported that, of 13 ambulant patients at baseline aged ≥ 6 years, all maintained their ability to walk. Among eight patients aged ≥ 6 years who were ambulant at baseline, previously treated with nusinersen, and evaluated both

at baseline and at month 24, there was a mean increase in the total distance walked of 30.88 metres (95% CI –5.54 to 67.29).[64]

MAA evidence

Paediatric registry

The paediatric registry did not report on this outcome. However, the 10 metre run test was conducted as part of the RHS, results of which can be seen in Section 13.4.2.1.11.

Adult registry

The results for this outcome are taken from the updated April 2025 report.

For type 2/3 walkers there were 24 patients at baseline and at 2.5 years follow-up data were available for six patients. The numerical trend suggests improvement over the follow-up period, with an initial increase that is maintained over time. Data is limited in the longer follow-up periods. However, maintenance may be represented in the results, and this should be considered a good outcome.

13.4.2.1.10 CMAP amplitude

SLR evidence

Presymptomatic

One record, which reported results from the RAINBOWFISH trial and was included in the earlier review, reported an increased CMAP in 5/7 patients after 12 months.[70] Another record, which reported data from the RAINBOWFISH trial up to month 24, reported a mean change from baseline in ulnar CMAP amplitude of 1.76 (±1.76) at 12 months and 2.43 (±2.01) at 24 months.[239]

No evidence was reported for types 1, 2 or 3 SMA.

13.4.2.1.11 RHS

SLR evidence

No evidence was reported for presymptomatic or type 1 SMA.

Types 2 and 3

One study[158] included in the original review reported an increase in RHS score for 2/6 patients, a meaningful improvement in three patients and a decrease of one point for one patient after 16 months.

MAA evidence

Paediatric registry

The results for this outcome are taken from the original December 2023 report.

An MRMM was not plausible for the type 1 patients for this outcome due to limited data. Nine patients' data were available for this outcome. The mean scores suggest improvement over time. At the 1 year follow-up, the mean score drops from baseline (5.0 vs 6.4, respectively),

though this data is from only one patient. Due to the small number of patients and lack of statistical analysis, the interpretation of these results is limited.

An MMRM was possible for type 2/3 patients. The interaction between visit and baseline RULM score was not statistically significant. The analysis suggests no statistically significant changes from baseline to 1.5 years follow-up. These results imply that maintenance may be occurring, which should be considered a good outcome.

Adult registry

The results for this outcome are taken from the updated April 2025 report.

The adult registry conducted MMRMs for type 2/3 sitters and walkers. For sitters, the baseline included 19 patients and, for 1 year follow-up, eight patients had data. No statistical significance was observed, though the numerical trend suggests potential worsening of this outcome for these patients at 1 year. Data is limited and should be interpreted with caution. For walkers, the baseline data includes 24 patients and at 2.5 years follow-up six patients had data. The numerical trend suggests improvement over the follow-up period, with an initial increase that is maintained over time. Data is limited for the longer follow-up periods. However, maintenance may be represented and this should be considered a good outcome.

13.4.2.1.12 ATEND

No SLR evidence was found reporting ATEND as an outcome.

MAA evidence

Paediatric registry

The paediatric registry did not report on this outcome. The intended age range for this tool is still to be confirmed.[201]

Adult registry

The results for this outcome are taken from the updated April 2025 report.

The adult registry reported an MMRM for ATEND left and right in type 2/3 non-sitters and sitters. For non-sitters, at baseline 48 patients were included the analyses and six had data at the 36-month follow-up. The mean change suggests maintenance in the ATEND, with no statistically significant reductions or increases from baseline. Data is limited in the longer-term follow-up (i.e. 30 and 36 months; < 20 patients). The registry also noted an unusual asymmetry between the left and right ATEND, which has not been previously observed in large cohort studies.

The ATEND was utilised in sitters who were less functional patients (RHS < 6); these individuals show an unusual degree of symptomatic progressions. The baseline included 61 patients, with seven being followed up to 2.5 years. The results show no statistically significant reductions in improvement and numerical trends show maintenance with some potential improvements. However, patient numbers are limited in the later follow-up timepoint.

13.4.2.2 Bulbar function

SLR evidence

Presymptomatic

Data from the RAINBOWFISH trial indicated that all of the 23 infants who completed 24 months of treatment with risdiplam were able to feed without support.[239] A new study reported that, 8.5 months following initiation of risdiplam, all newborns following positive newborn screening or prenatal testing for SMA were alive and without feeding support.[151]

Type 1

The FIREFISH study reported improved swallowing following risdiplam treatment.[240] Another found that, over the course of the study, there was an improvement in ability to feed orally. At month 12, 34 infants (82.9%) were able to feed orally, which increased to 35 (85%) by month 24, while no infant lost the ability to swallow.[56]

New data showed that 50/52 infants were alive at the 12-month follow-up and were able to swallow; at 36 months the numbers of infants who gained, maintained and lost the ability to swallow were 0, 48 and 1, respectively.[57] Also at 36 months, the numbers of participants who gained, maintained and lost the ability to feed orally were 1, 33 and 2 respectively (out of 50 participants), whilst 2, 28 and 1 participants gained, maintained and lost the ability to exclusively feed orally respectively (out of 38 participants). At five years, the FIREFISH study reported that 96% were able to swallow (compared to 94% beforehand), while the number feeding orally had stayed at 91%, and the number feeding exclusively orally had risen from 76% to 80%.[58]

No evidence was found for types 2 or 3 SMA.

13.4.2.3 Hospitalisation
SLR evidence

Presymptomatic

RAINBOWFISH reported that there were no overnight hospitalisations for presymptomatic patients.[70] There was no new evidence for hospitalisation in presymptomatic patients.

Type 1

Data from FIREFISH showed that the rate of hospitalisations per person year was 0.94 (95% CI 0.76 to 1.14) by month 24.[56] Updated data showed this rate to be 0.7 per person year after 36 months (no CI reported),[244] with natural history range of hospitalisations for type 1 SMA reported as between 4.2 and 7.6 every year[244,245,246] At five years, hospitalisations were down to 0.55 per person year, while 22% of children had not required any hospitalisation since starting risdiplam treatment.[58]

Type 2/3

No evidence was found for types 2 or 3 SMA.

13.4.2.4 Respiratory function

13.4.2.4.1 FVC
SLR evidence

No evidence was found for presymptomatic or type 1 SMA.

Types 2 and 3

One study[50], as reported in the earlier review, showed that there were no significant changes in the forced vital capacity (FVC) among the participants in the assessment of respiratory function over 24 months. Further evidence, from an earlier company submission,[46] at 60 months showed a non-significant decline in the mean change from baseline in FVC {18.5% (17.29%)}

Multiple types

The JEWELFISH study reported a mean change of 0.14% (95% CI –2.64 to 2.92, n = 113) from baseline to month 24 for the sniff nasal inspiratory pressure test.[64]

13.4.2.4.2 Respiratory plethysmography

SLR evidence

No evidence was found for presymptomatic SMA.

Type 1

One study[56] reported results from the FIREFISH trial on the effects of risdiplam on respiratory plethysmography in type 1 SMA patients. Fourteen infants (34%) achieved a phase angle reduction of at least 30 degrees from baseline at 24-months follow-up.

No evidence was found for types 2 and 3 SMA.

13.4.2.5 Complications

Nothing reported.

13.4.2.6 Need for non-invasive or invasive ventilation

SLR evidence

Presymptomatic

Two records, one from the earlier review[70] and a newly identified record,[61] both from the RAINBOWFISH trial, reported on ventilation support. Results from both studies indicated that no patients required permanent ventilation, as all patients were alive without permanent ventilation at the clinical cut-off date.

Type 1

Data from FIREFISH, reported in the original review, indicated that, at month 12, 85% of infants remained permanent ventilation event-free (n=41).[56,240] Although 70.7% of infants did not require any form of ventilatory support, a proportion of patients were still receiving ventilation support with 14.3% receiving bilevel positive airway pressure (BiPAP) for fewer than 16 hours per day and 19% receiving prophylactic ventilation. Additionally, 24% (10 infants) were receiving neither invasive nor non-invasive respiratory support. At month 24, the permanent ventilation event-free rate decreased to 83%, as one additional infant required permanent ventilation. The percentage requiring any form of ventilatory support remained unchanged at 70.7%, although 11 of 12 infants receiving pulmonary care were receiving prophylactic ventilation while the number of infants with neither invasive nor non-invasive respiratory support decreased to eight. Further evidence from the uncontrolled FIREFISH

study[240] reported in the earlier review showed that 19 of 21 infants enrolled had no need for permanent ventilatory support after 12 months.

No evidence was found for types 2 and 3 SMA.

Unreported type

One newly identified single arm study of newborns[151] evaluating infants who had positive newborn screening or prenatal testing for SMA and receiving risdiplam showed that all patients were without any ventilatory support at 8.5 months follow-up.

MAA evidence

Paediatric registry

The results for this outcome are taken from the updated April 2025 report.

Permanent ventilation was defined as any ventilation type for ≥ 16 hours/day continuously for > 21 days or tracheostomy. No patient was recorded as being on permanent ventilation, either at baseline or the most recent visit.

Adult registry

The results for this outcome are taken from the updated April 2025 report.

No patients had events of permanent ventilation since commencing risdiplam treatment.

13.4.2.7 Stamina and fatigue
Nothing reported.

13.4.2.8 Mortality
SLR evidence

Presymptomatic

One study,[60] not reported in the earlier review, showed that all infants were alive at 12 months' follow-up.

Type 1

The FIREFISH study, including two reports from the earlier review[56,240] and two newly identified reports,[57,58] reported data on mortality among participants receiving risdiplam. One of the reports[56] from the earlier review showed that 38 of 41 (93%) infants were alive at 12 months, which remained unchanged at the 24 month follow-up. The other earlier study[240] reported four deaths, including one in the interim and three deaths from SMA-related complications at 12 months. Further evidence from the newly identified report[57] showed that the percentage of patients who were alive decreased to 91% at 36 months. At 5 years, 91% of children were still alive and 81% were event-free (defined as alive with no permanent ventilation). Event-free survival was reported to be much better than natural history. Untreated infants from an alternative study had a median age for reaching death or permanent ventilation of 10.5 months (IQR 8.1 to 13.6), whereas this was inestimable at five years in FIREFISH due to a lack of events. [58]

No evidence was found for types 2 and 3 SMA.

Unreported type

One newly identified study[151] of newborns who had positive newborn screening or prenatal testing for SMA and were receiving risdiplam stated that all patients were alive at 8.5 months follow-up.

MAA evidence

Paediatric registry

The results for this outcome are taken from the updated April 2025 report.

There were no additional deaths reported since the December 2023 report. One type 1 patient died before any follow-up visits due to a hypoxic head injury (primary) and SMA type 1 (secondary cause). One type 2/3 non-sitter died after 1 year follow-up from an unknown cause.

Adult registry

The results for this outcome are taken from the updated April 2025 report.

Five patients died after commencing risdiplam. For three the primary cause of death was reported to be diseases of the respiratory system, one was due to spontaneous bacterial peritonitis and one had an unknown cause. The patients were on treatment for a mean of 1.59 years (range: 0.95 to 2.75).

13.4.2.9 Adverse events
SLR evidence

Of note, the majority of adverse events (AEs) reported for this treatment also appear to be linked to the underlying condition or the method of administration, rather than to the treatment itself.

Presymptomatic

A newly included abstract (Servais 2024) reported data from the RAINBOWFISH clinical trial (NCT03779334).[62] According to EMA (2023), at the 12-month follow-up, 77.8% of participants experienced at least one AE, with a total of 81 events reported. The most frequently affected systems were the skin and subcutaneous tissue (38.9% of participants) and the gastrointestinal system (50.0%).[70] One Grade 3 AE, cystoid macular oedema, was observed but assessed as being unrelated to risdiplam treatment. No SAEs, deaths, or Grade 4 AEs were reported, and no Hy's law cases or liver-related abnormalities were identified. Seven of the 18 participants underwent Spectral-Domain Optical Coherence Tomography (SD-OCT) assessments for at least 12 months.[70] Two TEAEs, diarrhoea and skin discoloration, were reported in two participants, both graded as non-serious and Grade 1.[70] One event of skin discoloration was considered treatment-related by the investigator.[70] Additionally, one SAE of gastroenteritis due to norovirus was downgraded to non-serious following review. The overall AE rate in the study was 558.2 events per 100 patient years. A higher AE rate of 681.0 events per 100 patient years was observed in the first six months of treatment, decreasing to 401.1 events per 100 patient years in the subsequent 6 months.[70] There were isolated shifts in vital signs, including diastolic and systolic blood pressure, temperature and pulse rate, but these were not considered clinically significant. Retinal abnormalities, attributed to immaturity rather than treatment, were reported in one participant.[70]

The findings reported in the Servais (2024) abstract were consistent with EMA (2023), confirming that no AEs led to withdrawal or treatment discontinuation.[70] Most AEs were mild and resolved over time. The safety profile in presymptomatic infants was comparable to that observed in older treated populations, with upper respiratory tract infections and diarrhoea among the most common events.[62]

Type 1

Adverse event outcomes for symptomatic Type 1 SMA were drawn from the FIREFISH clinical trial (NCT02913482). Data from Masson et al (2022), cited in the earlier review, indicated that at the 24-month follow-up, 86 disease-related AEs were reported in 32 infants (78%), most of which were mild to moderate. Upper respiratory tract infection was the most common AE, reported in 54% of participants. The Canadian Agency for Drugs and Technologies in Health (CADTH) summary of FIREFISH Part 2 reported that all enrolled infants experienced at least one AE, with the most frequently reported being upper respiratory tract infection (46.3%), followed by pneumonia (39.0%), pyrexia (39.0%), and constipation (19.5%).[56]

Day (2022) presented new data from the same study, reporting SAEs including pneumonia, respiratory tract infections, and acute respiratory failure. Upper respiratory tract infection remained the most common AE (55%), while pneumonia was the most frequently reported SAE (34%), followed by respiratory distress (9%). In total, 68 SAEs were reported among 28 infants (68%). Post-hoc analyses highlighted 48 SAEs, with pneumonia affecting 13 infants, and bronchiolitis, hypotonia and respiratory failure each affecting two infants. According to CADTH data, 58.5% of infants (24/41) experienced SAEs, primarily respiratory-related. A further 24 SAEs were reported as of the data cut-off, with pneumonia and various forms of respiratory infection and distress occurring most frequently. AE rates per 100 patient years at 12, 24, and 36 months were 614.96, 432.14, and 216.21, respectively. Rates of pneumonia-specific AEs over the same timepoints were 34.37, 15.16, and 7.86 per 100 patient years. All 58 infants experienced at least one AE, with a total of 731 AEs reported. Six deaths (10%) occurred, with five infants (9%) experiencing at least one AE with a fatal outcome. Three infants (5%) experienced AEs that led to dose modification or interruption. Ten infants (17%) had TEAEs and 36 infants (62%) experienced Grade 3–5 AEs. No AEs led to treatment withdrawal. The most common AEs in more than 10 infants at 36 months were pyrexia (60%), upper respiratory tract infection (57%), pneumonia (43%) and constipation (26%). Serious AEs were reported in 74% of infants. Two infants (3%) experienced SAEs that led to dose modification or interruption and two (3%) had treatment-related SAEs. Pneumonia (36%) and respiratory distress (10%) were the most frequent SAEs, occurring in more than three infants.[57]

Types 2 and 3

Safety data for patients with Type 2 or 3 SMA were primarily drawn from the SUNFISH trial (NCT02908685), which included a placebo-controlled phase followed by an open-label extension. Data from Mercuri et al (2022; 2023) and Oskoui et al (2023), all cited in the earlier review, were used to describe AE outcomes at both 12 and 24 months. In the risdiplam arm, 91.7% of patients experienced at least one AE between months 12 and 24.[1,49,50,241] Between months 0 to 12, 20.0% of patients experienced at least one SAE and, during months 12 to 24, 20.8% reported at least one SAE. Among those initially in the placebo arm, 91.7% reported AEs while receiving placebo and 80.0% after switching to risdiplam. Grade 3–5 AEs occurred

in 15.8% of patients in the risdiplam arm and 13.3% in the placebo arm between months 12 to 24.[1]

Additional data extracted from Mercuri (2022 and 2023) for this review update showed consistent SAE rates in risdiplam-treated participants, ranging from 19.4 to 36.1 events per 100 patient year. Between months 0 to 12, 17.5% of participants in the risdiplam arm experienced Grade 3–5 AEs.[75,241]

Safety data for patients with type 2 or 3 SMA were updated with new five-year follow-up findings from Servais (2025), reporting on the SUNFISH Parts 1 and 2 trials. The updated data indicated that the overall rates of AEs and SAEs per 100 patient years decreased over the five-year treatment period.[55] In SUNFISH Part 1, 98% of patients (50/51) experienced at least one AE and 26 SAEs were reported in total. The most common SAEs (≥ 25%) were pyrexia (64.7%), vomiting (39.2%), cough (37.3%), upper respiratory tract infection (35.3%), nasopharyngitis (31.4%), COVID-19 (27.5%), gastroenteritis (27.5%) and oropharyngeal pain (25.5%).[55] In SUNFISH Part 2, 98.9% of patients (177/179) experienced at least one AE, and 173 SAEs were recorded in total. The most common SAEs (≥5%) included upper respiratory tract infection (41.9%), nasopharyngitis (40.8%), pyrexia (34.1%), COVID-19 (33.0%), headache (26.3%), vomiting (25.7%), and diarrhoea (25.1%).[55] Pneumonia occurred in 9.8% of Part 1 and 10.6% of Part 2 participants. TEAEs were reported in 25.5% (13/51) of Part 1 participants and 20.7% (37/179) of Part 2 participants. Treatment-related SAEs occurred in two patients (1.1%) in Part 2 and none in Part 1. No participants discontinued due to TEAEs. AEs led to dose modification in 15.7% of Part 1 and 17.9% of Part 2 participants.[55] Grade 3–5 AEs were observed in 21.6% of Part 1 and 38.0% of Part 2 patients. The total number of AEs was 1026 in Part 1 and 2800 in Part 2. TEAEs leading to dose modification or interruption occurred in one Part 1 patient (2.0%) and two Part 2 patients (1.1%).[55]

Multiple types

Safety outcomes in previously treated patients with types 1, 2 and 3 SMA were assessed in the JEWELFISH trial (NCT03032172). Data from Chiriboga et al (2023; 2024) were cited in the earlier review, with additional findings extracted from the 2024 publication.[63,64,70]

In Chiriboga et al (2023), the most commonly reported AEs were upper respiratory tract infection and pyrexia, each affecting 17% of participants (n=30). Pneumonia was the most frequently reported SAE, occurring in four participants (2%). The overall AE rate decreased from 648.0 events per 100 person-years during months 0–6 to 270.2 events per 100 person years during months 6–12. Similarly, the rate of SAEs declined from 33.9 events per 100 person years (95% CI 22.7–48.7) to 18.3 per 100 person years (95% CI 10.2–30.1). In total, 159 participants (92%) experienced at least one AE and 923 AEs were reported overall. Twenty-four participants (14%) experienced SAEs, one of which was treatment-related. Six participants had SAEs that led to dose modification or interruption, although none were attributed to risdiplam. One participant discontinued treatment due to an AE. A treatment-related SAE, supraventricular tachycardia, was reported in one patient previously treated with olesoxime and resolved without requiring modification to risdiplam.[63]

In Chiriboga et al (2024), the overall AE rate at 24 months was 323.40 events per 100 person years in participants with type 1 SMA (95% CI 263.69–392.58), and 335.63 events per 100 person years in those with types 2/3 (95% CI 317.11–354.95). The most frequently reported AEs were pyrexia (24%), upper respiratory tract infection (21%) and headache (18%). These

findings suggest a favourable and stable safety profile of risdiplam in previously treated SMA populations.[64]

13.4.2.10 Health-related quality of life and Patient Reported Outcomes

13.4.2.10.1 *EQ5DL (HRQoL)*

No SLR evidence was found reporting EQ5DL.

MAA evidence

Paediatric registry

This outcome was not reported in the December 2023 or April 2025 MAA report.

Adult registry

The results for this outcome are taken from the updated April 2025 report.

The adult registry highlighted the limitations of the PROMs evidence. Patient-reported data holds the risk of voluntary response bias and recall bias. PROMs data has been obtained from the registry and displayed in the report as a representation of a smaller proportion of the entire SMA population. Results must be interpreted with care.

Utilising a Pareto Classification of Health Change method, the registry reported whether a patient's health status was better, worse, the same or mixed (i.e. better on one dimension but worse on another). Data was available for 45 non-sitters with a baseline and a follow-up submission. [redacted] (for a breakdown over the follow-up period see Table 13.17).

For the EQ VAS the registry compared the first response of a patient to next response. The registry reported the number of patients who had an increase of +≥ 10 or +≥ 1 points, stayed the same, or -≥ 1 or -≥ 10 points. An increase in this metric is desirable as it equates to higher quality of life.

[redacted]

Table 13.17: Changes in EQ-5D-5L for patients using risdiplam treatment at each timepoint over the follow-up period

Risdiplam adult EQ-5D-5L		Time point (n/N)					
Measure	**Type**	**6 months**	**1 year**	**1.5 years**	**2 years**	**2.5 years**	**3 years**
Better	2/3 non-sitters	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Same	2/3 non-sitters	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Mixed	2/3 non-sitters	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Worse	2/3 non-sitters	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Better	2/3 sitters	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Same	2/3 sitters	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Mixed	2/3 sitters	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Worse	2/3 sitters	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Better	2/3 walkers	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Same	2/3 walkers	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Mixed	2/3 walkers	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Worse	2/3 walkers	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: NR = not reported as data was not available for this time point; n = number of patients who met the criteria for that category; N = overall number of responses for that time point

13.4.2.10.2 EQ5DY

No SLR evidence was found reporting EQ5DY.

MAA evidence

Paediatric registry

The results for this outcome are taken from the original December 2023 report. It is important to note that data reported here is from a pilot study aiming to recruit 50 paediatric patients. There was insufficient data to assess separate groups (i.e. SMA type). Additionally, the limited amount of data means the results require cautious interpretation.

Registry data was available for EQ5DY total score and VAS. The total score had six patients with available data at first entry and two were with a follow-up (latest available; see Table 13.18). No conclusions can be drawn from this data.

Table 13.18: Change in EQ5DY total score for those receiving risdiplam; from Paediatric MAA report December 2023

	Number of patients	Mean	SD	Median	Min	Max
First entry	6	11.5	2.3	11	9	15
Latest available	2	11.0	1.4	11	10	12
Change first to last available visit	2	0	1.4	0	-1	1
Abbreviations: MAA = Managed Access Agreement; SD = standard deviation						

The VAS was available for six patients at first entry. Two patients had a data point from with the latest available visit. No conclusions can be drawn from this data (see Table 13.19).

Table 13.19: Change in VAS for those receiving risdiplam; from Paediatric MAA report December 2023

	Number of patients	Mean	SD	Median	Min	Max
First entry	6	81.5	12.7	82.5	61	100
Latest available	2	74.5	23.3	74.5	58	91
Change first to last available visit	2	1.5	6.4	1.5	-3	6
Abbreviations: MAA = Managed Access Agreement; SD = standard deviation						

Adult registry

The adult registry did not report on this outcome in either report.

13.4.2.10.3 ITQoL-SF47

SLR evidence

No evidence was found for presymptomatic SMA.

Type 1

As reported in the earlier review, one FIREFISH record[56] examined the impact of risdiplam on HRQOL using the Infant and Toddler Quality of Life Questionnaire (ITQoL-SF47) at month 24. The results showed improvement in emotional health, temperament and mood, growth and development domains, with no change in bodily pain/discomfort, parent impact on time limitation, family cohesion, overall health domains, and a decline in physical abilities and general health perceptions.

No evidence was found for types 2 and 3 SMA.

13.4.2.10.4 INQoL

SLR evidence

No evidence was found for presymptomatic or type 1 SMA.

Types 2 and 3

Included in the earlier review, one study[247] examined the impact of risdiplam on quality of life using Individualized Neuromuscular Quality of Life questionnaire (INQoL), stating that all patients reported improvement in the quality of life the quality-of-life following treatment with risdiplam.

13.4.2.10.5 *PGI-S*

No SLR evidence was found reporting PGI-S.

MAA evidence

Paediatric registry

The results for this outcome are taken from the original December 2023 report. It is important to note that data reported here is from a pilot study aiming to recruit 50 paediatric patients. There was insufficient data to assess separate groups (i.e. SMA type). Additionally, the limited amount of data means the results require cautious interpretation.

There were six patients available at first entry and only two with data from a latest visit. For these two patients, one had no change in severity and one has an increase of 1 unit (higher scores are worse). No conclusions can be drawn from this.

Adult registry

The results for this outcome are taken from the original December 2023 report. The adult registry highlighted the limitations of the PROMs evidence: patient-reported nature holds risk of voluntary response bias and recall bias. PROMs data has been obtained from the registry and displayed in the report as a representation of a smaller proportion of the entire SMA population. Results must be interpreted with caution.

Data was available for 68 patients at first entry and 27 patients at a latest follow-up. Similar percentages between baseline and latest follow-up for moderate and severe levels were reported (26.47 to 22.22 and 72.06 to 74.07%, respectively). This suggests potential maintenance in the patient condition, though data is limited. Additionally, the means of the baseline (3.69 ± 0.55) and latest follow-up (3.70 ± 0.54) are similar. A sensitivity analysis was presented for those who had a PROM in ±8 weeks visit window. This dataset had nine patients at latest follow-up, with

46 patients available at first entry. Moderate level rose slightly (30.34 to 33.33%), while severe levels decreased slightly (67.39 to 66.67%), representing probable maintenance in patient condition. Additionally, the means of the baseline (3.63 ± 0.60) and last follow-up (3.66 ± 0.50) are similar. Unlike the paediatric registry, the adult registry did not report if the patients available at last entry available showed improvement, maintenance or worsening.

13.4.2.10.6 PGI-I

No SLR evidence was found reporting PGI-I.

MAA evidence

Paediatric registry

The results for this outcome are taken from the original December 2023 report. It is important to note that data reported here is from a pilot study aiming to recruit 50 paediatric patients. There was insufficient data to assess separate groups (i.e. SMA type). Additionally, the limited amount of data means the results require cautious interpretation.

There were six patients available at first entry and only two with data from a latest visit. For these two patients, one had no change in severity and one had an increase of two units (higher scores are worse). No conclusions can be drawn from this.

Adult registry

The results for this outcome are taken from the original December 2023 report. The adult registry highlighted the limitations of the PROMs evidence: patient-reported data holds risk of voluntary response bias and recall bias. PROMs data has been obtained from the registry and displayed in the report as a representation of a smaller proportion of the entire SMA population. Results must be interpreted with care.

Data was available for 45 patients at latest follow-up, with 80 available at first entry. The proportion of patients reported for each level (from very much improved to very much worse) was similar at first entry and for those with the latest available data. This coincided with extremely similar means at baseline (4.02 ± 1.24) and last follow-up (4.02 ± 1.07), though these means showed a small decrease on average level. A sensitivity analysis was presented for those who had a PROM in ±8 weeks of the visit window. This data set had 22 patients at last follow-up, with 59 patients available at first entry. Proportion of minimally improved showed an increase between the two data points, although so did minimally worse. Overall, it appears that the patients reported their condition to be slightly better, similar or slightly worse. Additionally, the means of the baseline (3.78 ± 1.21) and last follow-up (3.81 ± 1.13) are similar, with a slight increase. Unlike the paediatric registry, the adult registry did not report if the patients available at last entry available showed improvement, maintenance or worsening.

13.4.2.10.7 SMAIS

SLR evidence

No evidence was found for presymptomatic or type 1 SMA.

Types 2 and 3

Seven records[46,49-51,55,57,241] reported data from the SUNFISH trial. Results from three records[49,50,241] showed a numerical increase from baseline in SMAIS-ULM score in the risdiplam group compared to a decline in the placebo group at the 12-month follow-up, though this was not statistically significant (adjusted P=0.39). The results from two other records[51,57] showed that patients and caregivers reported stabilisation or continuous improvements in the SMAIS-ULM total score change from baseline with risdiplam treatment over 36 months.

Newly identified outcome data from the SUNFISH trial in the initial submission[46] and another study[55] showed that the mean change from baseline in caregiver-reported SMAIS-ULM total score at 5 years was 2.65 whilst that of patient reported (>-12 years old) was 0.94 (4.22) indicating that patient and caregivers reported continuous improvements in the change from baseline in SMAIS-ULM score over 5 years.

Multiple types

One record[64] reporting data from the JEWELFISH trial showed an increase in the caregiver-reported SMAIS–ULM total score from baseline to month 24. At month 24, the mean change from baseline in caregiver-reported SMAIS–ULM total score was 1.90 (95% CI 0.70–3.10; n=110).

One newly identified study[153] investigating the effectiveness of risdiplam in type 1 and 2 SMA patients for 3 years using the SMAIS showed that most patients reported clinically meaningful improvement, except for two patients. The reported SMAIS scores showed a positive correlation to RULM scores at 12 months and 24 months. All three patients with zero RULM scores at baseline did not show improvement in motor function but had improvement in SMAIS, including drinking or using a keyboard.

MAA evidence

Paediatric registry

The results for this outcome are taken from the original December 2023 report. It is important to note that data reported here is from a pilot study aiming to recruit 50 paediatric patients. There was insufficient data to assess separate groups (i.e. SMA type). Additionally, the limited amount of data means the results require cautious interpretation.

Table 13.20 shows data at first entry to the patient registry whilst on risdiplam and for the most recent visit. In addition, a summary of changes from first to last available assessment is shown. Where individual items are missing, an adjustment has been made to the total score, so that the total is expressed out of the total number of items (similar to the approach for motor outcomes). Due to the limited data, no conclusions can be drawn.

Table 13.20: Change in SMAIS for those receiving risdiplam; from Paediatric MAA report December 2023

	Number of patients	Mean	SD	Median	Min	Max
First entry	5	22.4	5.0	22	17	30
Latest available	2	26.5	6.4	26.5	22	31
Change first to last available visit	2	3	2.8	3	1	5

Abbreviations: MAA = Managed Access Agreement; SD = standard deviation; SMAIS = Spinal Muscular Atrophy Independence Scale

Adult registry

The results for this outcome are taken from the updated April 2025 report. The adult registry highlights the limitations of the PROMs evidence: patient reported nature holds risk of voluntary response bias and recall bias. PROMs data has been obtained from the registry and displayed in the report as a representation of a smaller proportion of the entire SMA population. Results must be interpreted with care.

The adult registry reported whether patients reported an increase, the same, or decrease in SMAIS-ULM. Data was available with for 42 non-sitters, with a baseline and a follow-up submission. [redacted]

(for a breakdown over the follow-up period see Table 13.21).[redacted]Table 13.21: Changes in SMAIS-ULM for risdiplam users at each timepoint over the follow-up period

Risdiplam adult SMAIS-ULM		Time point (n/N)					
Measure	**Type**	**6 months**	**1 year**	**1.5 years**	**2 years**	**2.5 years**	**3 years**
Increased	2/3 non-sitters	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Same	2/3 non-sitters	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Decreased	2/3 non-sitters	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Increased	2/3 sitters	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Same	2/3 sitters	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Decreased	2/3 sitters	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Increased	2/3 walkers	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Same	2/3 walkers	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Decreased	2/3 walkers	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: SMAIS-ULM = Spinal Muscular Atrophy Independence Scale-Upper Limb Module; n = number of patients meeting this criterion; N = overall number of responses for that time point; NR = not reported as data was not available for this time point

13.4.2.10.8 EK-2

No SLR evidence was found reporting EK-2.

MAA evidence

Paediatric registry

The results for this outcome are taken from the updated April 2025 report.

The EK-2 scale assesses activity and participation in individual with non-ambulatory SMA. The scale covers eight daily-life categories including wheelchair use and transfers, trunk mobility, eating, swallowing, breathing, coughing and fatigue. A higher EK-2 score indicates a greater level of functional impairment.

No formal analysis was conducted and individual participant data was provided in graphical format. Most individuals maintained their level of function. Type 1 patients showed a trend towards improvement. However, some patient scores increased over time (i.e. worsened). It is important to note that this data was not mandated and has not been cleaned to the same degree as mandated items.

Adult registry

The results for this outcome are taken from the updated April 2025 report.

The adult registry conducted MMRMs for type 2/3 non-sitters and sitters. For sitters, the baseline includes 81 patients, with a decrease in EK-2 scores (positive impact) observed over the follow-up timepoints. At 2.5 years, 13 patients were included in the analysis, which is the last data point with enough patients to report a result. There are no statistically significant changes, but the numerical trend suggest improvement in the scores. For sitters, there were 85 patients at baseline and six at 2.5 years follow-up. No statistically significant changes are reported. Numerically, there is initial maintenance in the EK2 score, however, this is not maintained over the follow-up with small increases from 1.5 to 2.5 years, which suggests some degree of worsening. However, data is limited at the later timepoints.

13.4.2.11 Other outcomes

13.4.2.11.1 Clinical Global Impression Scale (CGI-S)

SLR evidence

No evidence was found for presymptomatic or type 1 SMA.

Types 2 and 3

One newly identified study[152] reported that "no patient showed worsening in CGI-S at 8 months."

13.4.3 Nusinersen, risdiplam and OA (comparative evidence)

No comparative evidence was found for nusinersen versus risdiplam for bulbar function, hospitalisation, respiratory function, complications, ventilation, or stamina and fatigue.

13.4.3.1 Motor function

No comparative evidence was found for nusinersen versus risdiplam for WHO motor milestones, CHOP-INTEND, HINE-2, BSID-III, RHS, or MFM.

13.4.3.1.1 RULM

SLR evidence

No evidence was found for type 1 SMA.

Types 2 and 3

The current review identified one study assessing the impact of both nusinersen (n=52) and risdiplam (n=73) treatment on type 2/3 patients.[160] This prospective, multicentre cohort study of children (aged 2-10 years) in Iran reported statistically significant improvements in RULM scores from baseline to follow-up (3 and 6 months) for both treatments. When comparing both treatments, no statistically significant differences were observed.

Two models were conducted to compare effectiveness between the drugs. In the first model, HMFSE and RULM score before medication therapy and medication type were included. In the second model, HFMSE and RULM scores before medication therapy, medication type, age at SMA diagnosis, age at start of treatment, sex, SMN2 copy number, scoliosis and use of an assistive device were included.[160]

As previously stated in Section 11.6.2, making comparisons between the two treatments is difficult due to differences in population characteristics. This study further exemplifies this as, at baseline and after employing the eligibility criteria, there were statistically significant differences in the risdiplam and nusinersen groups for age at start of treatment (mean 92.2 ± 29.4 vs 80 ± 31.9, respectively), sex (female = 51 vs 24, respectively), scoliosis (no = 30 vs 52, respectively), using an assistive device (no = 46 vs 51), HFMSE (mean 20.64 ± 17.56 vs 31.3 ± 17.86), and RULM (mean 17.75 ± 11.5 vs 26.18 ± 11.02). This shows clear differences, including supporting the previous narrative that those receiving risdiplam generally have a worse condition at baseline than those receiving nusinersen, as evidenced by the higher motor function scores for nusinersen patients.

It is also worth noting that, in the demographics table and the flow diagram of patient numbers, the numbers do not always equate to each other. For example, there were 46 people who did not use an assistive device for risdiplam and 49 who did (total = 95). The same demographic for those treated with nusinersen reported that 51 did not use a device and 18 did (total = 69). Both numbers are larger than the number of patients reported to be included in both groups at baseline (73 and 52, respectively). It is unclear why these discrepancies exist.

A positive of this research is that it is the first to compare the drugs directly in the same clinical setting. However, it was deemed implausible to randomise the groups due to the differences in eligibility for each drug.

13.4.3.1.2 HFMSE

The current review identified one study assessing the impact of both nusinersen (n=52) and risdiplam (n=73) treatment on type 2/3 patients.[160] This prospective, multicentre cohort study of children (aged 2-10 years) in Iran reported statistically significant improvements in HFMSE

scores from baseline to follow-up (3 and 6 months) for both treatments. When comparing both treatments, no statistically significant differences were observed.

Two models were conducted to compare effectiveness between the drugs. In the first model, HMFSE and RULM score before medication therapy and medication type were included. In the second model, HFMSE and RULM scores before medication therapy, medication type, age at SMA diagnosis, age at start of treatment, sex, SMN2 copy number, scoliosis and use of an assistive device were included.[160] The caveats to this study regarding differences in treatment groups and reporting indifferences reported in the RULM section above also apply here.

13.4.3.1.3 Tool not reported

One newly identified, uncontrolled study[161] reported data for the effects of both nusinersen and OA on motor function in type 1 SMA patients, where the tool was not reported. Improvements/maintenance from baseline in motor milestones were observed in 5/10 patients treated with nusinersen monotherapy, in 8/8 patients treated with OA monotherapy and in 7/9 patients who switched from nusinersen to OA. The mean time to initial improvement in any motor milestone in months (mean, SE) were 7.3 ± 3.8 for (n=10) patients treated with nusinersen monotherapy, 1.5 ± 0.7 for (n=8) recipients of OA monotherapy and 3.9 ± 1.4 for (n=9) patients who switched from nusinersen to OA.

13.4.3.2 Mortality

SLR evidence

No evidence was found for presymptomatic or type 1 SMA.

Types 2 and 3

The current review identified one new study that reported mortality of patients receiving either risdiplam or nusinersen treatments.[160] Across both treatment groups, one death was reported, which occurred in the nusinersen group. The patient was type 2 and had a history of respiratory problems with decreased FVC and mild scoliosis. The patient developed a severe respiratory infection, leading to respiratory arrest.[160]

13.4.3.3 Adverse events

SLR evidence

No evidence was found for presymptomatic or type 1 SMA.

Types 2 and 3

The current review identified one new study that reported AEs of patients receiving either risdiplam or nusinersen treatments.[160] Two patients had minor complications, with one patient experiencing abdominal cramps after risdiplam, which resolved spontaneously. The other patient had back pain and nausea after a nusinersen injection, which was managed with hydration and anti-nausea medication in subsequent injections.[160]

13.4.3.4 Health related quality of life

SLR evidence

No evidence was found by individual SMA type.

Multiple types

The original review identified one study reporting HRQoL following nusinersen, risdiplam or OA treatment.[10] The study was a prospective cohort study including patients with type 1 (n=7), type 2 (n=9) and type 3 (n=11) SMA. The PedsQL was utilised and the sub scales of school functioning, emotional functioning, social functioning and physical functioning were presented along with the total score.

While the results are not reported separately by drug type, meaning comparisons are not possible, the impact of the disease modifying therapies overall is considered here. The results show that 15 patients had an improved quality of life, while the other patients had the same or a lower level of quality of life at follow-up (18 months). SMA type 3 appeared to maintain their level of quality of life, with minimal changes in scores across all domain and total score. Those with type 1 appeared to have less consistent quality of life ratings, with decreases for school (-5.56 points), social (-2.38 points), physical (-2.08 points) and total scores (-2.03 points). However, emotional functioning scores did show some improvement (2.38 points). Finally, those with type 2 SMA appeared to have the most consistent increases in quality of life, showing improvements for each sub scale and total score; point score increases ranged from 1.85 for school functioning to 6.02 for physical functioning.[10]

13.4.3.5 Bulbar function

Type 1 SMA

One newly identified study[161] reported evidence for the effects of nusinersen compared to OA on cry function, swallowing function and eating function in type 1 SMA patients. The proportions of patients showing maintenance or improvements in cry function were 5/10 for those who received nusinersen monotherapy, 8/8 for people who received OA monotherapy and 6/9 for those who switched from nusinersen to OA. Maintained or improved speech function was observed in 7/8 patients who received nusinersen monotherapy, 6/6 who received OA monotherapy and 6/8 who switched from nusinersen to OA. Eating function was maintained or improved in 4/8 patients who received nusinersen monotherapy, 5/6 who received OA monotherapy and 5/9 who switched from nusinersen to OA.

13.5 Qualitative analyses

The following section presents results from the qualitative framework analyses described in Section 9. Qualitative analyses relating to economics is presented in Section 15.3.

13.5.1 Ability to socialise

People living with SMA and their carers expressed that the impact of the condition left them feeling isolated and less able to socialise with other people. Some people who lived with SMA described that they struggled to find other people to speak to. Others noted that that they would isolate themselves because they had lost physical functions, such as being able to feed themselves. In turn, this contributed to anxiety surrounding socialising with other people. The impact of poor bulbar function on the ability to communicate was also highlighted by one parent of a child with SMA. Furthermore, people with SMA can feel their ability to interact with others is impacted by their need to self-isolate. People mentioned that lockdown made them feel isolated, though others spoke more generally about self-protecting.

“Desperately looking to be an active member of society as I have always been for myself and my family, I Have developed a hermit personality as you are self protecting which is not living.” – Case study from appendix of SMA UK/ MD UK/ Treat SMA joint organisation submission; adult with Type 4 SMA

[redacted]

Carers of those with SMA also suggested that their social lives were diminished, either due to their caring responsibilities or because of a lack of support and not being able to ask others to take on their caring roles. This not only impacted friendships but also familial and intimate relationships. Carers and parents of people with SMA often cited that the nature of their relationships with partners and spouses had changed or even ended as a result of the caring responsibilities required. They expressed that they could not spend quality time together to maintain their relationships.

“Marriage of 25 years ended because caring for a child/young person/adult has a massive impact on relationships. Making sure a younger sibling is able to enjoy life too creates a huge strain and leaves you juggling many balls in the air.” – Quotation from SMA UK/ MD UK/ Treat SMA joint organisation submission; carer of a child with SMA

“It has changed the marriage between my husband and I to the point where we exist as carers only. We work together to care for our children but are separate at night due to one of us on night shift in another room. We are handling daily stress and sadness about our child and it makes us argue/ feel frustrated with each other.” – Quotation from SMA UK/ MD UK/ Treat SMA joint organisation submission; carer of a child with SMA

Both people with SMA and carers of those with SMA noted that treatment had a positive impact on their social lives. One adult noted that this was because their condition had stabilised as a result of treatment with nusinersen.

“But what Spinraza does, it helps to stabilise the condition and I’ve noticed that stabilisation in my condition. That has enabled me to hold a bit of hope for the future, hope that I will be able to live a full life, go on lots of holidays and continue to work, continue my social life and my hobbies and activities.” – Case study from appendix of SMA UK/ MD UK/ Treat SMA joint organisation submission; adult with Type 3 SMA

[redacted]

Carers for children with SMA noted the positive impacts of treatments on both themselves and their children. They noted that their children were able to play with friends and that, because the need to avoid infection had reduced, they and their families also socialised more. One carer suggested that if their child was not receiving any treatment, the fear and anxiety they would feel would have a negative impact on their own social life.

13.5.2 Activities of daily living

Activities of daily living were often impacted by the symptoms and complications associated with SMA, such as reduced bulbar and respiratory function, as well as motor function. [redacted]

[redacted]

People talked about not being able to undertake activities independently. Carers in particular noted that they needed to help the people they were looking after to eat, drink, dress, go to the toilet and wash themselves. The impact of poor bulbar muscle function on being able to eat safely without choking was often a concern. Furthermore, the amount of assistance needed with regards activities of daily living could be substantial.

“His physical needs consisted of dressing, toileting, bathing, washing, assisting with meals and snacks throughout the day, getting [my child] anything he needed, changing his position throughout the day from the floor, to wheelchairs or turning him throughout the night. Ultimately, being there to assist him 24 hours a day.” – Patient expert submission 2 (carer for child with SMA)

[redacted]

There was also a financial impact on people with SMA, their families and carers on facilitating activities of daily living, due to the need for adaptations and equipment. These included wheelchairs to help with mobility, but also adaptive beds, hoists, adapted toilets, transfers and standing frames. Some people also talked about the need to adapt their vehicles or to have wheelchair-accessible vehicles to enable to them to travel beyond their own homes.

The impact of treatment on activities of daily living were highlighted by people with SMA and their carers. Adults with SMA noted that they could enjoy their life more following treatment. Being able to eat and drink independently was a common theme, which was particularly highlighted by carers and patient experts. Adults taking either nusinersen or risdiplam noted that the treatments allowed them to cut up and eat more than soft foods as the fear of choking had been reduced.

[redacted]

A case study from one adult with type 3 SMA noted that only needing to have nusinersen administered every four months was convenient, as they were able to forget about the need for medication and continue with their life in-between doses. A patient expert (submission 2, carer for a child) noted that taking risdiplam did not impact on their daily lives and so their child's needs could be more easily met.

13.5.3 Adverse events

Experiences of adverse events from nusinersen, risdiplam and OA were described by some people with SMA, as well as some carers for those with SMA. Some reflected on anecdotal evidence that adults using nusinersen have experienced headaches and fatigue, with gastrointestinal side-effects reported in adults taking risdiplam. One professional expert noted that, although rare, some patients discontinue risdiplam due to the side-effects. One patient organisation submission noted the potential for serious side-effects for those undertaking OA if they had an underlying infection, as this could lead to a systemic immune response. This possibility often led to families shielding themselves from infection for either all or part of the three-month monitoring phase post-administration. One professional submission noted that side-effects linked to treatment could potentially be a reason for discontinuing or switching treatments.

However, people with SMA and their carers often noted that they did not experience adverse events due to treatment either with nusinersen or risdiplam.

"We are usually in and out of the hospital within about 4 hours with no side-effects." – Patient expert submission 3 (carer for a child with SMA)

"[My child] has never had any side effects from this treatment." – Patient expert submission 2 (carer for a child with SMA)

[redacted]

Although nusinersen requires administration through a lumbar puncture, some also suggested that they found the procedure to be acceptable and were willing to accept minor side-effects of the treatment. However, one person noted that they particularly disliked the process of a lumbar puncture.

"Looking back, I would not have changed my decision to get Spinraza, I find the lumbar punctures completely fine, a couple of minor side effects but they are not really noticeable" – Case study from appendix of SMA UK/ MD UK/ Treat SMA joint organisation submission; adult with Type 3 SMA using nusinersen

[redacted]

13.5.4 Bulbar function

The negative impact on the lives of people with SMA due to weakened bulbar function was a common theme across submissions and case studies. As previously noted, bulbar function is

inherently connected to both the ability to eat and drink independently and safely, but also to be able to communicate and socialise with others. Several of the submissions and case studies highlighted the difficulties associated with the loss of bulbar function, including not being able to chew or swallow, needing to modify diets to ensure safety, and the potential for tube feeding. The potential for aspiration was also highlighted. One parent noted that their child's weakening ability to swallow meant that they had been aspirating, while another had been told to start thickening powder.

Submissions often spoke of the positive impacts of treatment on bulbar function, both in terms of their ability to communicate and to swallow.

"I can now talk to people and they understand every word because my voice box works again." – Quotation from SMA UK/ MD UK/ Treat SMA joint organisation submission; adult with SMA

"My swallow ability is stable and it is very important for me too. Because it is in a rather poor condition and if it progresses, I could lose the ability to eat tough food." – Quotation from SMA UK/ MD UK/ Treat SMA joint organisation submission; adult with SMA

However, one adult with SMA noted that they had experienced little improvement in bulbar function from treatment, other than less aspiration.

Some people spoke about the specific effects of risdiplam on bulbar function. One adult noted that they no longer had to worry about choking, one parent noted their child had regained their swallowing function, while another carer highlighted how their child had improved from being completely tube fed to mostly eating orally since taking the medication. [redacted]

Despite these improvements, many of the submissions and the EAG's discussions with PPI and professional groups highlighted that data surrounding the impact of treatment on bulbar function is currently lacking. In discussion with the EAG, some members of patient groups noted that the monitoring of bulbar function in children is not always extensive. One submission noted that although the tests are used to measure bulbar function in response to treatment within clinical settings, these often show as non-significant despite the patient and carer perception that their function and quality of life have improved. One carer told the EAG that their child had no further clinical follow-up or tests regarding bulbar function after one video fluoroscopy and they were reliant on their own perception to know whether their child's function had stabilised or improved. Professionals noted in discussion with the EAG that it has only been more recently that clinical trials have begun capturing the impacts of treatment on bulbar function in people with SMA, leading to gaps within the current evidence.

13.5.5 Complications of SMA

There was some brief discussion on complications associated with SMA within the submissions and case studies, particularly surrounding scoliosis and contractures. One parent in a patient expert submission (submission 3) noted that their child's contractures restricted their overall mobility in their knees, ankles, hips and shoulders, highlighting the interconnected nature of complications and physical function in those with SMA. Scoliosis was noted by one submission to be a common occurrence in people with SMA, which impacted on mobility but also had the potential to compress the internal organs and cause the person pain.

[redacted]

13.5.6 Equality considerations

As previously noted, the submissions highlighted geographical inequalities in care and provision of equipment across the UK. Beyond these service and resource use factors, the submissions also highlighted delays in access to treatment and the impact that these waiting times had on the condition. This included difficulties in accessing treatment through the current MAA.

"Took a long time to be offered MAA. I think because there weren't many people of my age and the hospital wanted to offer the drug simultaneously to a meaningful sample." – Quotation from appendix of SMA UK/ MD UK/ Treat SMA joint organisation submission; adult (SMA type and treatment unknown)

"And then it was YEARS before I could get my hands on the drug, my hands started to go, I couldn't drive my car any more, I couldn't even drive my chair reliably any more." – Case study from appendix of SMA UK/ MD UK/ Treat SMA joint organisation submission; adult (SMA type and treatment unknown)

[redacted]

The lack of availability of treatment and care for adults compared with children with SMA was also highlighted within the submissions. One professional expert submission highlighted the differences in access to treatment and care between adults and children with SMA.

“There is a notable difference in the access of adults to standard of care compared to children. In a recent patient survey, a 59% difference for access to physiotherapy (100% in paediatric, 41% in adults) was observed between adult and paediatric populations. Similar patterns were seen with access to interventions, including a 46% difference for access to supported standing (53% paediatric, 7% adult) and 45% difference for access to splints (59% paediatric, 14% adult).” – Association of British Neurologists submission

Adults with Type 4 SMA currently do not have access to treatment via the MAA. In discussion with the EAG, patient groups noted that treatments are still as valuable for adults than presymptomatic patients, with one patient expert noting that a lack of access to treatment options means that people with Type 4 SMA can be left unable to work and increasingly reliant on their families and friends to care for them.

As this issue highlights, the difficulty adults had in accessing treatment was often connected to the strict eligibility criteria linked with treatments. The limited eligibility criteria for OA was highlighted within submissions, noting that most of the SMA population within the UK are ineligible for the gene therapy. One patient organisation submission also noted that access to OA was further limited by geographic location, as there are currently only seven infusion centres in the UK. Furthermore, others highlighted that the difficulty of administering nusinersen to those who had spinal fusions means it may not be a viable option for adults with SMA.

The issues surrounding eligibility for the different treatments emphasised the need for a range of treatments to be available to the SMA community to meet different needs. Expert submissions and patient organisations emphasised that both nusinersen and risdiplam needed to be accessible to ensure that all people with SMA could have access to treatment.

“Both should be available as some patients cannot tolerate or access one (for example after spinal fusion). Operating on the principle that those who are long term ventilated unnecessarily have a less good quality of life is an equality issue.” – Professional expert submission

“Patients have seen benefits from treatment across the severity spectrum. Access for all from those fully ventilated to those living with type 4 is the only way to ensure equity of access for the whole SMA community.” – SMA UK/ MD UK/ Treat SMA joint organisation submission

13.5.7 Hospitalisations

The need to be hospitalised or to visit A&E within the submissions was often due to declining respiratory function. Two patient expert submissions noted that their children had been hospitalised because of respiratory issues that, in one example, also led to the need for further intervention and ventilation.

"I also had to watch his respiratory system decline which resulted in multiple hospital admissions" – Patient expert submission 2 (carer for child with SMA)

"Unfortunately, the remainder of 2017 saw three further long PICU admissions throughout which we were trained how to use a bi-pap ventilator, a cough assist machine and how to administer aggressive respiratory physiotherapy and invasive deep suction." – Patient expert submission 3 (carer for child with SMA)

Another submission highlighted good respiratory health as being a major factor in preventing people with SMA from being hospitalised. Undertaking treatment was stated to have improved

respiratory function, which subsequently reduced or eliminated the need to be hospitalised. This was highlighted by patients, carers and professional experts.

"I'm so much stronger and haven't had a hospital admission for a common cold in 4 years" - Quotation from SMA UK/ MD UK/ Treat SMA joint organisation submission; adult (SMA type and treatment unknown)

"Since [my child] has been on risdiplam, he has not had a hospital admission" – Patient expert submission 2 (carer for child with SMA)

[redacted]

13.5.8 Impact on education and ability to work

The physical symptoms and complications of SMA, as well as the need to care for people with SMA and assist them with daily activities, was noted to have a profound effect on the ability to attend school and go to work.

"I was diagnosed approx 5 years ago where I had to leave a job I loved for 25 years as manager of local Airport for Loganair as I couldn't do the hours due to extreme fatigue and experience anxiety which was very new to me being a very calculated person before SMA." – Case study from SMA UK/ MD UK/ Treat SMA joint organisation submission; adult with Type 4 SMA

[redacted]

Parents and carers for children with SMA stated that they often did not feel supported by the education system. They spoke about how the physical impact of SMA hindered access to mainstream education. Some people in the submissions appeared frustrated by the lack of physical accessibility within nurseries and schools, particularly as SMA does not affect children's intellect.

"We have faced issues with [child's] nursery & him not being able to be with his peer group due to the class being upstairs and health and safety issues with no 121 support being offered by the council, so he has to stay in the baby class until we can get him into pre-school. This is detrimental to his cognitive and communicational skills as SMA does not affect his intelligence, he has struggled seeing his peers move up to the next class." – Case study from SMA UK/ MD UK/ Treat SMA joint organisation submission appendix; carer for child with Type 2 SMA

It was not only people with SMA whose education and working lives were affected by the condition but also that of their families and carers. Carers for children noted the significant impact on siblings' education, including absences due to the need to shield and compounded anxiety during already stressful periods, such as during exams.

"[…] She also had to try the steroids on drip for 3 days, but we knew this could be a side effect from Zolgensma, it can be hard with having other children who still need to go school I feel

like it's pretty hard going on them" – Quotation from SMA UK/ MD UK/ Treat SMA joint organisation submission; carer for child with SMA

"My eldest daughters went through GCSE's and A-levels, revising at [my child's] bedside, managing the trauma of his condition and the impact on their daily lives, alongside exam stress." – Patient expert submission 3 (carer for child with SMA)

The working lives of parents and carers for those with SMA were also impacted. Some feared they would need to give up their jobs while others felt as if they were forced to leave their jobs to take on caring responsibilities. As previously described, this places a substantial financial strain on families.

"We had no idea if we could keep working, if we would lose our house and how were we going to cope watching our son deteriorate before our eyes." – Case study from SMA UK/ MD UK/ Treat SMA joint organisation submission appendix; carer for child with Type 2 SMA

"When my son was diagnosed with SMA Type 1 at 3 months old, I had no choice but to give up my job" – Quotation from SMA UK/ MD UK/ Treat SMA joint organisation submission; carer of a child with Type 1 SMA

"Electric, fuel for the van, insurance, food, extra hotel room for carer when we go away overnight impact us massively. I can't work apart from 10 hours per week I get paid as part of my son's care team as I'm always on call/ home alone with him." - Quotation from SMA UK/ MD UK/ Treat SMA joint organisation submission; carer for adult with SMA

The benefits of treatment both on education and ability to work were highlighted throughout the submissions. Some noted that the children they looked after were able to attend school more regularly, which also had an impact on their siblings' ability to attend. The stabilisation of the condition that receiving treatment provided for people was noted to increase the likelihood that they could keep working into the future. Some described this as one aspect of being able to live a normal and productive life.

"[…] now she is consistently attending school things have improved significantly." – Quotation from SMA UK/ MD UK/ Treat SMA joint organisation submission appendix; carer for a child with SMA

[redacted]

"This is making my working day so much easier! I used to want to cry in pain from a day at work, typing on laptop - not anymore. I no longer feel that 'withdrawing from work' is on the horizon and I can earn a good income for at least another 10-15 years provided the [treatment] benefits are maintained" – Quotation from SMA UK/ MD UK/ Treat SMA joint organisation submission appendix; adult with Type 2 SMA

However, measuring the impact of SMA and treatment on education was highlighted as problematic. In discussion with the EAG, one patient group representative queried whether the differences treatment makes to school attendance and attainment could be more regularly monitored and quantified.

“Say there’s no data, which I agree, there isn’t any that I know of, is is there any way in terms of education getting any data with attendance prior to treatment and after treatment, is there anything that can be done that way? Because I know for example, was 30% attendance, he’s now 96.” – Patient group representative in discussion with the EAG

Furthermore, patient representatives in discussion with the EAG also highlighted the financial impact on families and carers as being an important issue, suggesting that the economic model should include carer costs and the impact on the wider family as well.

“I was just quite pleased to see that the carers bit was in there as well. And I think we just got to be how that, how that is actually calculated within the cost modelling side of things because, like I said before, that kind of ripple effect, the carer, is quite wide and it could be the impact on siblings, parents, aunties, uncles, grandparents, and it gets bigger and bigger. School, you know. Everything else in between that. So I think it’s just how that is calculated as a number you know, is is quite key actually.” - Patient group representative in discussion with the EAG

13.5.9 Independence

Independence was a cross-cutting theme across the submissions, as it was often mentioned alongside the ability to do activities of daily living, the need for support from family, friends and carers, and the need for assistive devices and adaptations. The overall importance of independence and how encompassing it is for those living with SMA and those who care from them was summarised in a discussion between the EAG and PPI groups.

“I mean in terms of independence, independence to communicate, independence to usual wheelchair, independence enables you to type on a keyboard, independently to work, like independence is huge. I mean, that links into mental health that links things to impacts and siblings, on to carers, on to going into school on education. I mean, but that's huge. Independence is massive” – Patient group representative in second discussion with the EAG

[redacted]

An organisation submission noted that not allowing continued access to treatments would mean their level of dependence on others would increase. Indeed, when discussing independence directly, many people with SMA and their carers noted the specific impacts of treatment on how they could function without help from others. [redacted]

13.5.10 Looking to the future

Two clear sub-themes emerged, surrounding anticipatory grief and feeling greater hope for the future. Firstly, the concept of anticipatory grief was captured in experiences related to the life of an SMA patient and what it is like to live with a progressive condition. Anticipatory grief captured not only mourning premature mortality but also living in a state of ongoing anxiety and fear about what functional losses may occur next as the condition progresses. This could be a loss or decline in mobility, swallowing function, energy, independence, or multiple aspects simultaneously. One expert patient submission from an adult with SMA likened this experience to living with "chronic sorrow".

"SMA Being a progressive condition always means that individuals are often faced with the knowledge that you are soon to lose another everyday function, but without any indication as to when. For example, I may be able to clean their teeth myself today but I know at some point in the future this will be impossible. I often refer to this as having a constant "sword of Damocles" hanging over my head as to what function I am going to lose next, all of which has an indescribable impact on my mental health. It is often said that someone who is in an accident, and perhaps loses the ability to walk, there is a grieving process for the loss of that function. This can take months if not years to recover from. Those with SMA face this continuous grieving process over and over again throughout their entire life due to the progressive ongoing loss of different functions over time." - Patient expert submission 1 (adult with SMA)

Anxiety over the progression of the disease and potential functional decline was also reported within case studies, both from patients and carers for those of SMA."SMA is an evil condition, one that condemns you to lifelong grief and sadness due to your constant decline" – Case study from appendix of SMA UK/ MD UK/ Treat SMA joint organisation submission; adult taking risdiplam (SMA type unknown)

"Living with a child with SMA is emotionally draining, I have recently contacted the doctor for counselling and treatment for stress and anxiety. It is a constant worry about the future and his independence." - Case study from appendix of SMA UK/ MD UK/ Treat SMA joint organisation submission; carer for a child with Type 2 SMA (treatment unknown)

However, the data also captured the experiences of people's lives following treatment and the impact this had on their outlook for the future. Receiving treatment with either nusinersen or risdiplam allowed patients and families to feel reassured. They often described the pronounced differences in their outlook on the future due to receiving treatment, and how they were able to plan their lives and futures.

"There is hope and there is evidence via the assessments that I am not deteriorating" – Quotation from appendix of SMA UK/ MD UK/ Treat SMA joint organisation submission; adult with SMA Type 2 being treated with nusinersen

[redacted]

“Rather than continued deterioration, Risdiplam has given me a future.” - Case study from appendix of SMA UK/ MD UK/ Treat SMA joint organisation submission; adult taking risdiplam (SMA type unknown)

“I can plan for my future, thinking about the next 5 or 10 years without wondering if I'll be significantly weaker by then. I'm able to make decisions about my life based on how I feel now, instead of how I'll feel if things get worse.” – Quotation from appendix of SMA UK/ MD UK/ Treat SMA joint organisation submission; adult with Type 2 SMA (treatment unknown)

This hopefulness about the future due to treatment was not just felt by patients themselves but also by carers. Both people with SMA and their carers described how the psychological burden had been relieved on their wider families.

“It was hope for my wife, was hope for my children, hope for my friends and other relatives who, in some regard, all expected me to die” - Case study from appendix of SMA UK/ MD UK/ Treat SMA joint organisation submission; adult taking risdiplam (SMA type unknown)

“[Patient] has been on treatment for 4 years, it’s changed all our lives and lessened the burden on our mental health and anxiety for the future.” – Quotation from appendix of SMA UK/ MD UK/ Treat SMA joint organisation submission; carer for child with Type 2 SMA, treatment unknown

13.5.11 Maintenance or stabilisation of condition

Across patient, carer, and professional perspectives, there was a strong suggestion across submissions that stabilisation and maintenance of motor function, respiratory function, bulbar function, stamina, and fatigue are meaningful outcomes in the context of SMA. The Association of British Neurologists noted that, in the context of the natural history of decline for those with SMA, no change in condition is an “excellent outcome.” The ability to preserve current abilities such as controlling a powerchair or swallowing can have a profound impact on quality of life. It was suggested that maintenance and stabilisation of the condition can support greater independence, functional ability and relationships.

“It’s acknowledged that the majority of those on this particular treatment are likely to be of the older population and therefore the perceived efficacy may be somewhat less, but I can tell you from personal experience, that is far from the truth. This deliver stability and that is what we should be looking to deliver with regards to treatment. Yes improvements are a bonus, but stability maintains lives, livelihoods, relationships and everything else.” – Patient expert submission 1 (adult with SMA)

“However, the value to an older individual of not losing a critical ability such as the movement in a finger to control a powerchair or the ability to swallow food, cannot be emphasised enough.” - Patient expert submission 3 (carer for a child with SMA)

“young people or young adults are becoming stronger or maintaining their SMA, they’re able to go on to further education or go into mainstream education.” - Representative for a PPI group in discussion with the EAG

Maintenance or stabilisation in condition is also interlinked with emotional and psychological wellbeing (see Section 13.5.16). From the qualitative analysis, people who reported experiencing stabilisation of their condition also suggested a positive improvement in their

psychological wellbeing, including reduced anxiety about the future, decreased fear of deterioration and less concern about mortality.

“It’s been a real mental soother to know I’m not getting weaker in theory and my results prove it.” – Quotation from SMA UK/ MD UK/ Treat SMA joint organisation submission; person with Type 2 SMA aged between 15-20 years old

“There is hope and there is evidence via the assessments that I am not deteriorating.” – Quotation from appendix of SMA UK/ MD UK/ Treat SMA joint organisation submission; adult with SMA Type 2 being treated with nusinersen

The importance of stabilisation was also suggested to be particularly significant for symptomatic adults. Stabilising the condition can help prevent the need for costly and invasive interventions over time, such as increased respiratory support or nutritional measures like gastrostomy. The joint submission by SMA UK, MD UK and Treat SMA noted that the value of stabilisation for adults with the condition “cannot be underestimated,” while the Association of British Neurologists noted that stability in motor function as an adult in particular would mean people could continue to work and not need respiratory support or gastrostomy.

[redacted]

13.5.12 Mortality

Reduced mortality is a potential reality for many people living with SMA. The submission by the Association of British Neurologists highlighted how, without treatment, the life expectancy of someone with Type 2 SMA is between 30 and 50 years. In discussion with the EAG, a representative for a patient organisation noted most children with Type 1 SMA would die before the age of two.

Findings were closely linked with looking to the future, with adults describing their experiences of living with the knowledge of early mortality and how this impacted them throughout their life course.

“You need to understand little bit about what life growing up with SMA is like, when you are young you are told you will die in your teens… maybe… if you're lucky (or you were told this in my day), then you get through those years and you're told you might get to 30 odd… Then you get to that age and you start thinking "when am I going to die” - Case study from appendix of SMA UK/ MD UK/ Treat SMA joint organisation submission; adult taking risdiplam (SMA type unknown)

“I was told I would not live beyond the age of five, then in my 20s I was told probably not beyond 40, all of these have had massive impacts on my life constantly being concerned about getting close to dying.” – Patient expert submission 1 (adult with SMA)

Carers also shared their reflections on the impact of being told they would likely lose a child or loved one due to SMA.

“We were told the devastating news that he would not make it to his second birthday.” - Patient expert submission 3 (carer for a child with SMA)

The impact of access to treatment on patients’ lifespan was noted across the submissions. The submission by SMA Reach UK noted that DMTs could reduce mortality, particularly for those with Type 1 SMA, while the Association of British Neurologists noted that the stabilisation in functions (particularly respiratory function) associated with nusinersen and risdiplam treatment would lead to increased life expectancy. Adult SMA Reach also anticipated that life expectancy would increase due to the impacts of treatment on respiratory function, motor function and other outcomes.

Additionally, adults reported that access to treatment has resulted in the stabilisation of the condition, which has meant they have less fear of dying when participating in aspects of life that some may consider routine daily events, such as getting a cold or flu or eating food. Adults with SMA reported feeling less fear of impending or early death because of the stabilisation in their condition.

“I'm not quite sure how to put this. Risdiplam has improved every part of my life. I can now talk to people and they understand every word because my voice box works again. I no longer feel like I'm dying. At all. Let alone soon.” - Quotation from SMA UK/ MD UK/ Treat SMA joint organisation submission; adult with SMA

“Treatment has now given me hope that while I may not live to 100, there is now no predefined expiry date that I am living to.” - Patient expert submission 1 (adult with SMA)

Carers also reported that their fear surrounding the reduced life expectancy of the people they were looking after had been alleviated due to the impact of treatments.

“Since [patient] has been on risdiplam, he has not had a hospital admission, his lung capacity has increased, he has regained his swallow and the threat to his life is no longer as severe.” – Patient expert submission 2 (carer for child with SMA)

“If he had not finished those loading doses I’m certain he wouldn’t be here with us.” - Case study from appendix of SMA UK/ MD UK/ Treat SMA joint organisation submission; carer for a child with an unknown type of SMA who had been administered nusinersen and OA

13.5.13 Motor function

The impact of SMA on motor function was a common theme throughout the qualitative analyses but, from discussions with the EAG and within expert submissions to NICE, there was also an emerging focus on the way in which motor function as an outcome is measured and how this may not reflect the experience of those with SMA, that of their carers, or experiences of treatment. It was noted that, historically, efficacy measures have primarily focused on improvements in motor function and motor milestones. However, the qualitative analysis suggested that, with the availability of disease-modifying treatments and subsequent shift in the natural history, the patient and clinical community believe these measures do not fully capture all aspects of meaningful change for individuals living with SMA. In discussion with the EAG, clinicians highlighted the range of different measurement tools for motor function and their applicability to either adults or children, and to different SMA types. One clinician

noted that a measurement tool such as the RHS or HMFSE may be useful for sitters or walkers, but another tool would need to be used for those with more advanced progression or severity. Furthermore, representatives of patient organisations told the EAG that the current tools used to measure motor function do not capture what they considered to be meaningful milestones.

“the motor milestones. I don’t think they’re anywhere near sensitive enough to capture the benefits. I think the first motor milestone that my son achieved that was the biggest celebration was being able to hold his head up by himself, when in a supportive chair to just being able to do that was huge and a massive impact on his quality of life. Being able to hold his head up and look around. And then the whole sitting thing. You have sitting, but then you have supported sitting. Like, my son can sit in a brace, a spinal brace for, for quite a long time. Time the brace off, he can still do it, but he’ll have to prop himself. It’s like, there’s sitting and there’s supported sitting and there’s sitting with your head up” – Representative for a PPI group in discussion with the EAG

“And I think it’s really important from a patient organisation’s perspective that the weighting is really heavy on the stories and the kind of, like I said before, the little moments, those, those things that really make a difference. Lifting a head up is very important. Or, you know, if somebody’s using an electric wheelchair rather than a carer putting their hands on to the device, they can do that themselves. That’s a tiny, tiny, tiny difference. But in terms of independence and quality of life, it’s an absolutely massive outcome.” - Representative for a PPI group in discussion with the EAG

A key finding from the qualitative analysis, which aligns with clinical and patient perspectives on meaningful treatment outcomes, is the value of stabilising, maintaining and slowing the decline in motor function. The Association of British Neurologists noted that both nusinersen and risdiplam were “likely to be effective” in stabilising motor function in adults with SMA, subsequently also improving quality of life and participation. In their submission to NICE, a clinical expert also noted that, for symptomatic patients with SMA, slowing or stopping disease progression would be considered a clinically significant treatment response. The importance of stabilisation of motor function, as opposed to larger improvements in motor milestones, was also consistently described as an important treatment outcome by people with SMA and their carers.

I think that stabilisation is really the hidden benefit of this medication. Its not about helping me to walk again like I used to in my teenage years, but actually that stabilisation is so valuable to me as it keeps me independent which is actually such a full part of my identity and who I am.” – Case study from appendix of SMA UK/ MD UK/ Treat SMA joint organisation submission; adult with Type 3 SMA taking nusinersen

”I have maintained my strength and improved in some aspects. For example, putting on my headset is very important to me and I no longer strain as much as I did.” - Quotation from SMA UK/ MD UK/ Treat SMA joint organisation submission; teenager with SMA

“And then just to kind of clarify that for example, if we see that the patient is stable. For example, if we look at WHO motor function, if they remain as a sitter, that is a very good outcome for adult patients. So we also will try to emphasise that that it is a good outcome for adult patients to be remain stable. So we're not necessarily looking at gaining” - Professional group representative in discussion with the EAG

Further discussion surrounding maintenance and stabilisation of the condition can be found in Section 13.5.11.

An important emergent sub-theme closely linked to the preservation or stabilisation of motor function is the role of the fine motor skills. People with SMA discussed how smaller movements are crucial for enabling individuals to maintain independence, remain in their careers, attend school and participate in everyday activities. This includes vital tasks and activities of daily living, such as eating, drinking, operating electric wheelchairs, and using electronic devices without assistance.

“This means I am able to continue with my career with very limited functional use, for example, the ability to use a mouse with one hand. I no longer have the ability to type, I use voice recognition, but the ability to manipulate a computer easily using a mouse sustains my role. Yes, something as simple as that, these are the details that people do not understand.” - Patient expert submission 1

“I am now able to lift my hand from my lap to the control of my wheelchair without help” - Quotation from SMA UK/ MD UK/ Treat SMA joint organisation submission; adult with SMA

A submission from a clinical expert also noted that preserving fine motor function is especially important for individuals with SMA who are long-term ventilated, a group whose specific needs may not be fully addressed under the current MAA regulation.

Motor function is also closely tied to the experiences of carers, influencing their daily lives and having a psychological impact. It was suggested in the qualitative analysis that a person's ability to maintain as much independence as possible not only enhances their own quality of life but also greatly benefits their carers and wider families. Many carers described the emotional relief and improved wellbeing that comes from knowing treatment can help preserve their child’s abilities and slow further decline. This sense of stability also allows carers the space and capacity to support other children and family members, helping to restore some balance to family life.

“His physical abilities have got stronger in some areas and have maintained in the rest. I feel this is due to the medicine itself and as he is well the majority of time, he is able to participate in physical activities and physio. This improved strength has allowed me to be needed less and therefore I have more quality time with my daughter. Knowing your child’s condition will not deteriorate, is a heavy weight lifted on what I have to carry as a parent. This has eradicated the fear of wondering what [patient] may lose from one day to the next.” - Patient expert submission 2 (carer for a child with SMA)

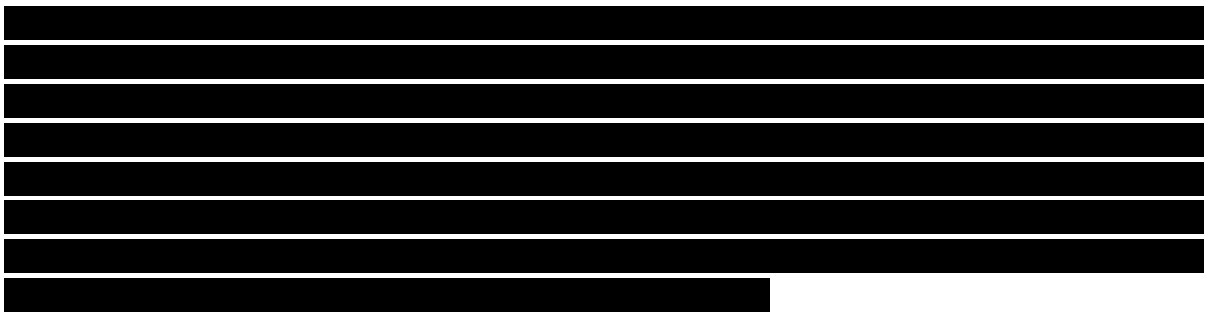
[redacted]

13.5.14 Need for invasive or non-invasive ventilation

Inherently related to respiratory function, SMA can lead to a need for either invasive or non-invasive ventilation. For some people, ventilation may be permanent. However, there were some occasions where people talked about the need for ventilation, particularly from carers of children. One case study from a carer of a child, submitted as part of the appendix from the SMA UK/ MD UK/ Treat SMA joint organisation submission, noted that their child was intubated a month after being born and was offered OA despite managing only eight hours without Bilevel Positive Airway Pressure (BiPAP) per day. Patient expert submission 3 also noted that their child was dependent on a BiPAP ventilator during the night.

Receiving treatment was noted to either improve the amount of time or type of ventilation needed by people with SMA. One carer, quoted as part of the appendix from the SMA UK/ MD UK/ Treat SMA joint organisation submission, noted that while their child had previously been intubated every time they caught a common cold, receiving treatment meant that they could manage colds at home with the help of chest physiotherapy and BIPAP. An adult noted that their treatment had greatly reduced their reliance on ventilation, from permanent to only during the night.

“I was ventilated 24 hours a day just to stay alive I now only need my ventilator when I’m asleep and can mange all naps off it.” - Quotation from SMA UK/ MD UK/ Treat SMA joint organisation submission; adult with SMA



Despite the noted effect of treatment on the need for ventilation, the submissions also raised specific issues relating to the accessibility of treatments when a person with SMA is ventilated. A clinical expert submission noted that people who are long-term ventilated are currently ineligible via the MAA. They argued that this denies these people a meaningful quality of life, given that long-term ventilation does not necessarily mean they are not independent. This sentiment was echoed within a patient organisation submission. A carer, quoted in a patient organisation submission, summarised their experience of having to fight to have their child with Type 1 SMA given treatment due to being intubated.

“Being a young parent and having a recent diagnosis of SMA 1 is stressful enough on its own without having the fight we have to go through. Due to my little girl being intubated no treatment was available until we pushed and pushed and eventually got a trial for 3 months of risdiplam (which has worked wonders) now because my daughter is still intubated and the 3 months is nearly up we have to wait for it to go back to a panel meeting to see if treatment can carry on. It is so so disappointing as a parent to have to fight so much” - Quotation from SMA UK/ MD UK/ Treat SMA joint organisation submission; carer for a child with SMA Type 1

13.5.15 Patient choice

The need for patient choice between different treatments links closely with the idea that the nature of SMA can vary between different types and SMN copy numbers, as described in 'Spectrum of SMA'. The need for patient choice arose in the qualitative analysis for different reasons. A submission by a clinical expert noted that potential reasons for discontinuing or switching treatments include no perceived response to treatment and increased burden on both patients and families. The Association of British Neurologists noted that choice been nusinersen and risdiplam was essential because of side effects and the potential impact on fertility. The joint submission by SMA UK, MD UK and Treat SMA also noted that choice of treatments was important because different people will respond to treatment in different ways.

"It is important for the SMA community to have a choice of all available treatments on the NHS. There is not one treatment that is effective for all, both clinical and real world evidence has shown that there are non-responders to all of the treatment options, where one treatment is ineffective, another might get better outcomes. Choice and trial and error is currently the only way to optimise treatment outcomes for SMA." - SMA UK/ MD UK/ Treat SMA joint organisation submission

In discussion with the EAG, representatives of patient organisations emphasised that "choice is key in the SMA community." People with SMA and carers also expressed the need for patient choice when considering treatment options. They stated reasons for why people may choose different treatments, including echoing issues surrounding perceived lack of efficacy, the potential for adverse events, and being acknowledging individual lifestyles and preferences. Alongside this, patient experts consistently highlighted the need for treatment choices for people with SMA.

"Every patient should be given the right to receive treatment in a way that best suits their own personal circumstances and lifestyle choices." - Patient expert submission 1 (adult with SMA)

"It is important that all three treatments are available. Firstly, so people have the right to choose their treatment. Secondly, to swap treatments if one no longer works, if there are any side effects and if administering the drug is impossible via lumbar puncture. The right to choose is very important." – Patient expert submission 2 (carer for a child with SMA)

"The perspective of the impact of treatment on daily life and quality of life is subjective and another reason for the importance of choice. Having three treatments available means that if a person does not get on with one or cannot have it there is the option of the other. For [patient] it will be vital that if his spinal curvature or any surgery prevents the use of nusinersen, he still has the option of risdiplam." – Patient expert submission 3 (carer for a child with SMA)

13.5.16 Psychological impact

The physical symptoms of SMA and its impact on daily life were often cited as having a profound psychological impact on people with SMA, their families and carers. People noted that, although SMA is a physical condition, the impact on mental health and wellbeing could not be ignored. Stress and anxiety were often associated with having the condition.

[redacted]

Sometimes these feelings co-existed with feelings of anticipatory grief, fearing for what functions may be lost next. One adult described their fear of having a fall in a public space.

“That caused me quite a lot of stress and anxiety thinking, if I’m going to public places, what would I be able to do?” – Case study from appendix of SMA UK/ MD UK/ Treat SMA joint organisation submission; adult with Type 3 SMA using nusinersen

[redacted]

The psychological impact on the family and carers of people with SMA was equally pronounced across submissions. A submission by patient organisations noted that, from a survey they conducted, 67% of carers reported feeling occasionally or frequently anxious, stressed or down because of their role. Carers for children with SMA expressed a range of emotions associated with the responsibility of looking after a child with the condition, including that the diagnosis is “devastating”, that they feel guilty that they are not doing enough to help their condition, and the immense stress of being a sole carer. Some carers turned to health services for support with their mental health, though there was some suggestion that this was not always available or offered.

“Living with a child with SMA is emotionally draining, I have recently contacted the doctor for counselling and treatment for stress and anxiety. It is a constant worry about the future and his independence.” – Case study from appendix of SMA UK/ MD UK/ Treat SMA joint organisation submission; carer for a child with Type 2 SMA (unknown treatment)

“We have not had any support for our mental health.” – Patient expert submission 3 (carer for child with SMA)

The wider family beyond those caring for people with SMA also described being affected psychologically and emotionally by having a family member with the condition. A submission from patient organisations noted that siblings reported feeling anxious and worried like the primary caregivers, but that they also feel that they receive far less attention from their parents as a result.

“I treat him like a normal brother. But it does make me sad that he cannot eat or walk and run. When he is poorly in hospital, I do feel very sad and worried, and I miss my mum a lot” - Quotation from SMA UK/ MD UK/ Treat SMA joint organisation submission; 10-year-old sister of child with SMA.

Although treatments for SMA are not designed to improve mental wellbeing, the benefits it brings to physical health were described as having a subsequent positive impact on psychological health. Even if treatment is not designed to cure or improve SMA, the stability surrounding the physical symptoms of the condition it provided helps to alleviate anticipatory grief and provides positivity and hope for the future.

“In terms of the emotional/mental health aspect, the benefits are immeasurable. While I acknowledge the treatment is unlikely to provide me with significant improvements in my condition, the fact that I can now look forward to stability and maintaining my current levels of energy and strength has had unbelievable impact on my mental health.” – Case study from appendix of SMA UK/ MD UK/ Treat SMA joint organisation submission; adult (SMA type and treatment unknown)

These positive impacts on psychological wellbeing were also described by the families and carers of people with SMA.

“I do get time to socialize I am more mindful to enjoy myself because as the back of my mind I know my child is having treatment & it is a positive impact. I feel if [child] was not on any treatment, fear, anxiety would over take me and I wouldn't be able to enjoy to socialize as much.” – Quotation from SMA UK/ MD UK/ Treat SMA joint organisation submission; carer of child with SMA

“If she was not on any treatments I would feel anxious and depressed - especially if I could see her declining. Her day to day care is something I don't choose to feel sad about - I remain positive and love watching her thrive. Her happiness and positive development through treatment has and IS helping me to be a strong, happy positive Mummy.” – Quotation from SMA UK/ MD UK/ Treat SMA joint organisation submission; carer of child with SMA

[redacted]

13.5.17 Quality of life

Like independence, QoL is a theme that cross-cuts all aspects of the lives of people with SMA and those of their families and carers. For example, as stated within the submission by the Association of British Neurologists, being able to maintain motor, bulbar and respiratory function all have a significant impact on QoL for people with SMA. However, a survey of both people with SMA and their carers conducted by SMA UK, MD UK and Treat SMA as part of their joint submission noted a range of potential reasons why someone’s QoL may be impacted. The themes from their analysis of the free-text data differed between people with SMA and carers. From free-text submissions to their work, increased independence (including in work and their social lives) was the most frequently-cited way in which the QoL of people SMA was said to be impacted (N=23). By contrast, carers perceived that physical health may have had the greatest impact on the QoL of people with SMA (N=37).

There were also some specific examples of people with SMA and their carers talking about the impact of the condition on their QoL within the submissions. [redacted]

[redacted]

As may be expected given the effects on outcomes such as motor, bulbar and respiratory function, people within the submissions highlighted beneficial impacts on their QoL from receiving treatment. The Association of British Neurologists and the submission to NICE from SMA Reach UK both stated that they expected the HRQoL of people with SMA treated with the technologies to increase in comparison to current care. The Association of British Neurologists also noted that, from real-world experience, the QoL of around 50% of patients was positively enhanced due to improvements in function and fatigue.

Individuals with SMA and their carers also noted the specific effects of nusinersen and risdiplam on their overall QoL. Sometimes this was linked to an improvement in physical function.

[redacted] This was summarised in a quotation from an adult with Type 3 SMA.

"What that data collection fails to capture is the global impact of treatment on the patient. This is not just a 'slicing up' of motor functions, or distanced walked, or coins picked up. Rather it is something greater than the sum of its parts - a life lived better and longer, with less fear, less risk, less pain." Quotation from SMA UK/ MD UK/ Treat SMA joint organisation submission; adult with Type 3 SMA being administered nusinersen

Representatives of PPI groups in their first discussion with the EAG noted that QoL was often improved in-between motor milestones, such as the ability to be able to use an electric wheelchair independently rather than be dependent on a carer. This was reflected in a submission from a clinical expert, who also highlighted that even if clinical scales did not detect any significant changes in function, patients often reported an enhanced ability to undertake activities of daily living, which in turn impacts QoL. Professionals speaking with the EAG also

noted that, although there are more recent initiatives to collect data on outcomes that may impact QoL, this may not be reflected in current data.

13.5.18 Spectrum of SMA

The qualitative data highlighted a strong emphasis by patient and professional groups on the heterogeneity across the spectrum of SMA. Some submissions emphasised the differences in trajectory of the condition, even between individuals who have been diagnosed with the same SMA type and have the exact SMN2 copy numbers. This was summarised in discussions between representatives of patient groups and the EAG.

“The spectrums are so big now. So even with a type 1, a, a type 1 to a type 1 is very, very different. At type 2 to a type 2 is very, very different. So where [patient] is talking about some of the, you know, aspirations and hospital visits, etc. My kids who have type 2 have a very, very, very, very different type of experience and have none of that. So I think it just needs to be wind into that narrative that the spectrum is massive.” - Patient group representative in discussion with the EAG

It was also noted by representatives of patient organisations that treatments do not impact individuals with SMA in the same way, and that there was not “one drug fits all SMA.” It was also noted by a joint submission to NICE that the effectiveness of treatment may differ between individuals with similar clinical features, underscoring the importance of ensuring that clinicians and patients have access to both treatment options.

“The data collected as well as experience supporting people through patient organisations, shows that the treatments do not impact individuals living with SMA in the same way. Two individuals with the same SMN2 copy numbers and presenting similarly clinically will not necessarily have the same treatment outcomes. For a minority of individuals, 2 in our data sample, treatment is not effective, or side effects decrease quality of life.” - SMA UK/ MD UK/ Treat SMA joint organisation submission

There was also concern that the diversity of the patient cohort meant that the assessments used to measure function, particularly motor function, were not sensitive enough. The submission by the Association of British Neurologists noted that there was no “single fit-all outcome measure to apply across the disease spectrum to define a clinically significant response to treatment.” The challenge of defining a clinically significant result for such a diverse cohort of patients was raised by the Adult SMA Reach submission, who noted that benefit from treatment can be variable as a result.

“The benefit is variable and outcome measures used in the MAAs may not capture all and consideration should be given to the challenges of the vast disease spectrum.” – Adult SMA Reach submission

13.5.19 Stamina and fatigue

The importance of the impact of SMA on stamina and fatigue to individuals is reflected in the regularity with which it is discussed for both adults and children. Patient experiences related to fatigue and stamina were varied, with some patients reporting its impact on activities of daily living such as ability to communicate and being able to talk more frequently without running out of breath when on treatment and being able to maintain employment and education.

“I was really tired every day, I found it really difficult to get out of bed, I didn’t really know what my fatigue level would be from day to day, what I wanted to do or what I could do. That provided a lot of uncertainty for me.” - Case study from appendix of SMA UK/ MD UK/ Treat SMA joint organisation submission; adult with Type 3 SMA being treated with nusinersen.

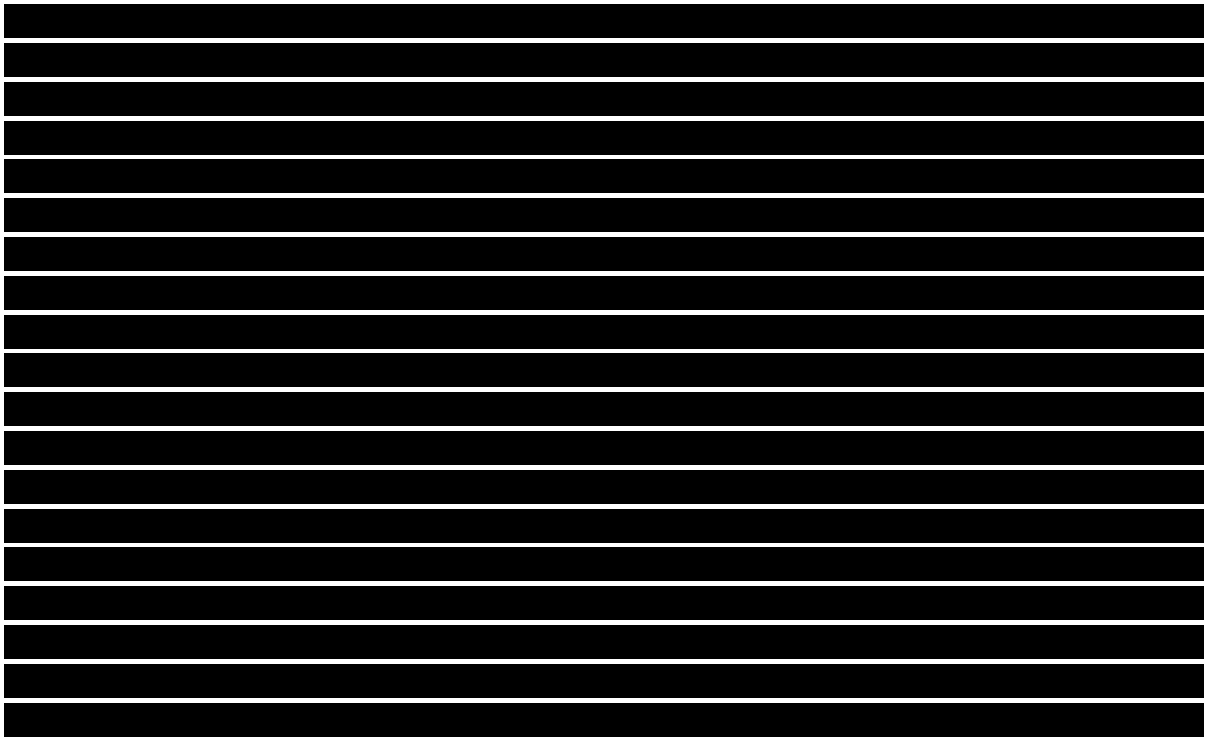
“I had little energy, little strength, I was struggling to drive my wheelchair and got extremely tired and suffered from extreme fatigue even just working for short periods.” - Case study from appendix of SMA UK/ MD UK/ Treat SMA joint organisation submission; adult with an unknown SMA type being treated with risdiplam.

As well as the direct impact of SMA on patients’ energy levels, the condition was also reported to affect the energy and stamina of the carers who support their loved ones. Many carers reported feeling overwhelmingly tired and emotionally drained due to the constant demands of ensuring the needs of the person they are caring for are fully met, as well as the broader impact in terms of strained relationships with other family members, such as their partners or other children.

“Tiredness is overwhelming and leaves you feeling it is too much effort to do anything else but care for your loved one.” – Quotation from appendix of SMA UK/ MD UK/ Treat SMA joint organisation submission; carer for a child with SMA.

“Exhausting always being the sole carer to someone” - Quotation from appendix of SMA UK/ MD UK/ Treat SMA joint organisation submission; carer for a child with SMA

The submission by the Association of British Neurologists indicated that one of the primary aims of treatment with both risdiplam and nusinersen and a clinically relevant treatment response is to improve levels of fatigue, subsequently improving quality of life. The Association of British Neurologists also confirmed a general positive experience in adults, with approximately 50% of patients experiencing improvement in function and fatigue. This reported improvement was further reflected in the qualitative data, with many adults receiving both nusinersen and risdiplam mentioning increases in energy and a drop in fatigue,



[redacted]

Throughout the various evidence used for the qualitative data analysis, including patient submissions, professional submissions and PPI group transcripts, stamina and fatigue were frequently referred to as a clinically relevant and highly meaningful outcome measure for adults and children across all types of SMA. Representatives of patient organisations told the EAG that stamina and fatigue were important outcomes to measure. In discussion with the EAG, professionals noted that there is ongoing work within the community to attempt to capture data on stamina and fatigue. This includes the EK-2, while the SMA EFFORT scale to capture perceived fatigue was also mentioned. In addition, a clinical expert emphasised in discussion with the EAG the importance of differentiating between perceived fatigue and performance fatigue.

Despite this, it was also said to the EAG that data surrounding stamina and fatigue were often not captured and that there are gaps in the evidence surrounding these outcomes. The submission by SMA Reach UK also noted that although fatigue was an important outcome, this is not captured within trials.

13.6 Key/summary effectiveness results

The evidence for the effectiveness of both nusinersen and risdiplam was found to be uncertain and at moderate risk of bias, mostly due to the small proportion of randomised controlled trials and other controlled designs. It should also be noted that little or no evidence was found concerning type 0 or type 4 SMA. However, with these caveats the EAG concludes the following.

The evidence suggested that nusinersen improved or maintained motor function on average across SMA types for up to five years. Some studies reported differences in effectiveness between population subgroups in relation to age and SMA type. Favourable results were also reported in relation to mortality, with higher survival rates amongst nusinersen-treated patients overall, especially for type 1 where children would usually survive no more than a few months without treatment. Stability or maintenance in respiratory function was generally suggested. Mixed results were reported regarding the effects on bulbar function and quality of life of carers and SMA patients. The long-term safety profile of nusinersen was found to be favourable, across a large number of real-world studies. Most adverse events were attributed to the injection or the disease, rather than the drug itself.

For risdiplam, patients continued to improve or maintain their motor function in all measures for all SMA types included. There was mixed evidence for the effects of risdiplam on bulbar function and ventilation. Evidence suggested maintenance or small increases or decreases in respiratory function, although the evidence was sparse. Due to the lack of controlled studies, the evidence on mortality was limited by the inability to compare longevity between people who were and were not treated with risdiplam. Adverse effects were generally not serious.

From the limited evidence available, nusinersen and risdiplam appeared to have comparable efficacy, although study limitations (e.g. baseline imbalances in prognostic factors) undermine the comparability of the data.

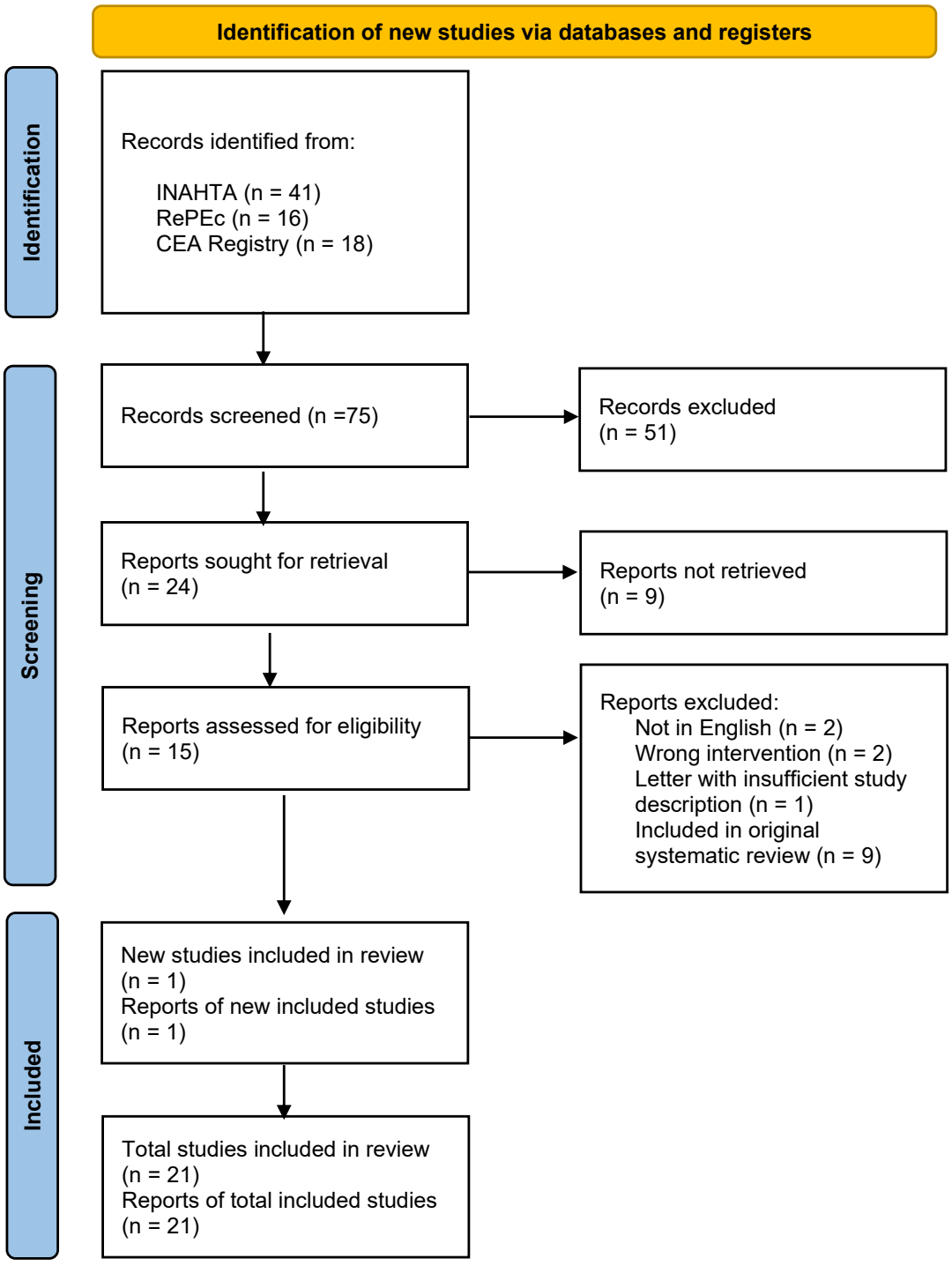
The MAA data showed a similar picture, suggesting that treatment with both nusinersen and risdiplam lead to maintenance or improvement for motor outcomes, across all SMA types assessed. From the paediatric registry, nusinersen had longer follow-up data available than risdiplam for motor outcomes (~4+ years vs ~3 years, respectively). While the adult registry for risdiplam extended to ~4 years, the patient numbers were smaller at this point than those in the nusinersen MAA. This is to be expected given that nusinersen was available earlier. Data for patient-reported outcome measures was lacking for both treatments and suggested some varying results. However, maintenance or improvement was reported for some scales for both nusinersen and risdiplam. Similarly, for both treatments separately, data surrounding QoL were also lacking but did suggest some improvement. Importantly, mortality rates in the MAA were generally low for both treatments and deaths that did occur appeared to be unrelated to the treatments.

14 EAG cost-effectiveness SLR: results

In the previous systematic review, 920 records were identified through database searches, while none were identified through other sources. After deduplication, 694 records were screened at title and abstract stage, out of which 71 records were assessed for eligibility at full text. In total, 20 records were considered relevant and included in the previous systematic review.

In this review update, 75 additional records were retrieved from databases searches for relevant economic evidence post-January 2025 to present. No duplicates were identified. At the title and abstract screening stage, 24 records were included as potentially relevant. At full text screening, one record was identified as new relevant evidence, while the remaining 23 records were excluded. The flow of records is depicted in Figure 33, with reasons for exclusion at full text.

Figure 33: PRISMA diagram for updated economic SLR



14.1 Characteristics of included studies

A summary of the characteristics of included studies in the previous SLR and in this update are provided in Appendix (see Appendix 7, Section 19.7).

In the original SLR, 20 economic analyses were included. This focused on patients with presymptomatic SMA, types 1, type 2 and type 3 SMA. There were no evaluations focusing on patients with type 0 or type 4 SMA. Across the included analyses, study populations and

subgroups were defined by the type of SMA, number of SMN2 gene copies, age of diagnosis or disease onset, duration of disease and treatment received.

In this review update, the one study included was a cost utility analysis by Khuntha et al. 2025[248] which focused on symptomatic SMA patients in Thailand. Patients were categorised into two groups: 1) SMA type 1 age onset at 3 months, and 2) SMA type 2 age onset at 12 months, and SMA type 3 age onset at 18 months, based on disease severity and treatment indications.

14.2 Intervention(s), comparator(s), outcome(s), study perspective, location and setting

In the initial SLR, the studies included reported costs for the following treatment comparisons:

- **OA versus BSC:** Ellis et al. 2019,[249] CADTH-OA, 2021,[250] Broekhoff et al. 2021,[251] Connock et al. 2020,[252] Dean et al. 2021,[253] Meijer at al. 2023,[254] Wang et al. 2022.[255]
- **Nusinersen versus BSC:** NICE-TA588,[2] Ellis et al. 2019,[249] CADTH-OA, 2021,[250] Broekhoff et al. 2021,[251] Connock et al. 2020,[252] Wand et al. 2022,[255] Zuluaga-Sanchez et al. 2019,[256] Thokala et al. 2020,[257] NCPE-2017,[258] CADTH-Nusinersen, 2019,[259] SMC-Nusinersen, 2018.[260]
- **Risdiplam versus BSC:** NICE-TA755,[3] CADTH-risdiplam, 2021.[261]
- **OA versus nusinersen:** NICE-OA HST 51,[262] Broekhoff et al. 2021[251], SMC-OA, 2021,[263] Connock et al., 2020,[252] Dean et al. 2021,[253] Malone et al. 2019,[264] Wang et al. 2022.[255]
- **Risdiplam versus nusinersen:** CADTH-risdiplam, 2021,[261] SMC-risdiplam, 2022.[265]

Across the included studies, the focus was on the health benefits in terms of LYGs and QALY gains. The study locations were located globally, including in the USA, UK, Australia and Canada, and all the studies were from high-income countries. Apart from SMC-risdiplam, 2022[265], all other studies adopted the viewpoint of the health system, societal perspective or both.

While all studies included in the previous SLR were all undertaken in high-income countries, Khuntha et al. 2025[248] included in this SLR update, evaluated the cost-utility of OA and risdiplam compared with SoC for SMA in Thailand (a middle-income country), thus providing some context for Southeast Asian and middle-income countries. Lifetime costs and outcomes expressed as QALYs gained were presented from both the provider and societal perspectives, which incorporated direct medical and non-medical care costs, as well as indirect costs incurred by caregivers.

14.3 Model structure and health states

All 20 studies included in the original SLR presented Markov models to simulate patient treatment outcomes for SMA and analyse the cost-effectiveness of the treatments for SMA. Half of the included studies included a single Markov model for the cost-effectiveness analysis,[250-255,257,262-264] while separate Markov models for assessing type 1 and type 2/3 SMA were used in seven included studies.[2,3,256,258,260,261,265] Furthermore, separate Markov models were also used in the NICE HST 24 surrounding treatment with OA[17] for modelling short- and long-term analyses, based on available trial data and the extrapolation of data respectively. In ICER 2019,[249] three separate Markov models were employed for patients with presymptomatic, type 1, type 2/3 SMA, while CADTH Nusinersen-2019[259] included three

distinct models to evaluate the cost effectiveness of treatments for type 1, type 2, and type 3 SMA.

In most of the studies included in the original SLR, the health states were defined by functional milestones (e.g. sitting, standing, walking, and ventilation support) which are indicators of functional abilities, disease progression and severity in SMA patients. Death was included as an absorbing state in all these models.

Comparable to the economic evaluations in the original SLR, in the new included report, Khuntha et al. 2025[248] constructed a Markov model to simulate the progression of SMA based on level of motor functioning, as measured by the CHOP INTEND. The model comprised the following five health states: a broad range of normal development; walking with support or equivalent; sitting; not sitting but living ventilation-free; and permanent assisted ventilation. These could all lead to the absorbing death state. To be consistent with the nature of the disease, patients entering the model could start at any health state except death. The models described the direction of health state transitions, which depended upon the treatment received.

14.4 Time horizon, cycle length and discount rate

The economic analyses conducted in the initial SLR considered life-long time horizons ranging from 60 years[2,250] to 100 years.[17,262] These studies attempted to capture the long-term effects of interventions in SMA patients in terms of the costs incurred and the benefits acquired through treatments. Meanwhile, some economic evaluations covered shorter-term time horizons like 36 months[254] or 25 years.[259] These variations in time horizon indicated the different approaches adopted by decision modellers to assess the cost effectiveness of SMA treatments.

Most of the included studies clearly stated that the costs incurred, and the benefits acquired over time were discounted with the annual discount rate varying between studies between 1.5% and 5%.[250,255] Therefore, some of the difference in costs and benefits between studies was a result of the choice of discount rate used.

The cycle length of the economic analyses in the included studies also varied, reflecting the dynamic nature of SMA disease progression and treatment outcomes. This largely depended upon the type of SMA, treatment intervention and specific trial endpoints (if trial data were considered). These were shown to vary from one month to specific time-periods to assess the treatment effect, which coincided with trial endpoints, with some modelled for up to a year. This further complicates comparisons between the results of different studies.

In the one study identified in the SLR update by Khuntha et al. 2025[248] the economic model generated included a lifetime horizon to capture the long-term benefits of the treatments. Additionally, as recommended by Thai HTA guidelines, a 3% annual discount rate for both costs and outcomes was applied. A six-month cycle length was also assumed based on the natural history of the disease and as defined by the CHOP INTEND.

14.5 Health state utility values

The health state utility values (HSUVs) used in the economic analyses in the original SLR were informed by various sources, such as literature reviews, expert opinions and clinical data from trials and registries. The values were assigned specifically based on the health states and the definition of these health states, which introduced some variability because of the

difference in sources of evidence used to inform these health states. Additionally, some studies favoured expert opinions while others relied more on the use of published literature or clinical data. Hence, there were differences in approach between studies as to the type of empirical evidence reinforcing the health state utilities of patients with SMA. Across the studies, the obtained values were regularly mapped to the EQ-5D, which demonstrates a standardised approach in the evaluation of health benefits of SMA treatments, making it easier to make comparisons between the utilities used across these studies.

Among the studies from the previous SLR, 5 studies included carer disutilities. But there were considerable differences in terms of the methods and data sources used to obtain the caregiver specific utilities, to incorporating caregiver utilities into the SMA models. NICE TA588 and TA755 considered the quality of life of caregivers by applying a utility decrement relative to the general population by comparing the utility estimates against a population score.[2,3] Meanwhile, CADTH-Nusinersen did not include caregiver utilities in its submission.[259] SMC-Risdiplam, 2022 sourced the burden on caregivers from published literature and relevant NICE submissions.[265] NICE HST24 used extensive expert opinion analyses and clinical trial data to source the carer utilities in SMA models.[17]. NICE HST15 explored the caregiver burden and its effect on their quality of life by modelling a scenario analysis.[262] The methods adopted in these studies gives an insight into the relevance of clinical data, how comprehensive these are in capturing the quality of life of caregivers with respect to the changes in patient health states, and the importance of eliciting expert opinions to substantiate caregiver utility estimates. The inferences drawn from these studies can help researchers make informed decisions about assumptions around the factors and considerations that can potentially influence the treatment outcomes in SMA patients.

The cost utility analysis identified in this SLR update utilised the EQ-5D-Y-3L questionnaire, translated into Thai, to interview patients and caregivers.[266] In the absence of an EQ-5D-Y valuation study for Thailand, the authors calculated utility values using a Japanese value set. However, due to a limited number of patients for two health states, utility estimates from a Chinese study, which used EQ-5D-3L for patients with SMA types 1-3, was used as proxy.

14.6 Health state resource use and costs, currency and conversion

In the original SLR, the data sources used in the included studies to obtain the resource use and costs were real-world evidence (e.g. national health services), clinical trials, and studies that evaluated healthcare resource utilisation in patients with SMA. The external validity of these figures for resource use and costs were then ensured through literature reviews and experts' opinions in majority of these studies.

NICE TA588 used Hospital Episode Statistics (HES) in the UK and SMA linked direct expenses in the UK healthcare system to estimate resource use and cost.[2] TA755 adopted the resource uses associated with the health states from NICE TA588,[2] as well as unit costs from the NHS. SMC-OA 2021 obtained costs from the Scottish Health Services Cost,[263] while Wang et al., 2022 used cost estimates from Australian national health services data in cost-effectiveness analysis.[255] As such, these studies undertook an approach where region specific data on cost from the national health services were deemed appropriate. CADTH-Nusinersen, 2019 derived costs from Klug et al,[267] a study of the economic burden of SMA in Germany,[259] while SMC-risdiplam 2022 used data from real-world evidence studies by the respective companies.[265]

The sources of data used for estimating costs in these studies varied based upon the setting of the study, availability of data and study perspective. In the majority of the studies, there has been a conscientious effort to adapt the national health services or local health services data for estimating cost. Where there was a lack of sufficient evidence, the studies relied on published literature, studies from pharmaceutical companies, or expert opinion.

The analysis of cost in the included studies showed variation in terms of the granularity of how costs were broken down. Some studies used detailed cost breakdowns with respect to different components and items, while others reported more aggregated cost estimate. In studies like NICE TA755,[3] costs were applied universally in the BSC arm and a part of the intervention arms, wherever applicable. Across the studies, researchers can understand the existing methodologies and criteria on estimating cost of SMA treatments, through the differences in sources informing the costs, methods of cost estimation in model and cost conversion practices in countries like UK, Australia and Canada.

Similar to studies included in the original SLR, the new study, Khuntha et al. 2025[248] obtained resource use and costs primarily from real-world evidence. Interviews with Thai patients provided information on resource use and costs incurred by patients and carers, while direct medical costs were retrieved from hospital databases and pharmaceutical companies. The lower price of OA used in this study was reported to be like that of a similar study in Brazil, and thus was thought to be a reference price for middle-income country settings. Costs input into the model were reported transparently, broken down by parameter and calculated for each health state in each SMA subtype. The consumer price index was used to adjust all costs to 2023 values and the recommended WTP threshold of 4444 USD per QALY gained was applied, which equated to 160,000 Thai baht per QALY gained using an exchange rate of 1 USD ≈ 36 Thai baht.

14.7 Results of engaging patients and stakeholders

In the original SLR, it was noted that across included studies the methods and extent to which engagement with patients and stakeholders occurred, varied between different locations and the established review systems. The incorporation of patient and stakeholder perspectives highlighted the commitment to include those impacted by SMA in the assessment and reporting process.

While not stated to be involved in the utility value estimations, patient and carer groups were reported to participate and provide their insights during the assessment processes for TA588,[2] TA755,[3] HST15,[43] and HST24.[17] Additionally, in ICER-2019,[249] patients were directly involved in the discussion at early stages of the study. In some evaluations, for example SMC-risdiplam-2022,[265] patient groups and clinicians contributed to assessing the value of risdiplam, while in others like SMC-nusinersen-2018[260] and SMC-OA-2021,[260,263] patient group representatives were engaged in the evaluation of the additional benefits of SMA treatment. Inputs from patients were directly obtained in the CADTH-risdiplam-2021[261] through the standardised CADTH review process,[261] while in CADTH-OA-2021 surveys and semi-structured interviews were employed.[250]

In the cost utility analyses by Khuntha et al. 2025[248] newly identified in this SLR update, the authors conducted interviews with Thai patients and caregivers to collect data on transitional probabilities, non-medical costs and utilities. Additionally, as a form of face validity testing, consultation meetings with stakeholders took place to consider the proposal, model,

conceptualisation, input parameters and preliminary results of the study. Although some outcomes from the meetings were described, a complete account of the meetings, including all attendees, was not provided.

14.8 Results of resource use and costs

In the original SLR, the included studies indicated a range of approaches used for resource use and costs in modelling of the economic burden of SMA, which reflected the study contexts and highlighted the complexities and nuances in treating patients with SMA.

TA588 included the itemisation of cost based on categories such as drugs, medical tests, hospitalisations and social services.[2] The cost analysis in TA755 was adapted from the TA588 real-world evidence study, which provided cost data based up expert opinion of clinicians.[2,3] Both Zuluaga-Sanchez et al. and NCPE-2017 undertook a similar approach by focusing on health-state costs, drug-acquisition and related costs.[256,258] However, some studies like SMC-Risdiplam-2022 and Malone et al. 2019 had their own unique perspective on resource use and subsequent estimation of cost.[264,265] Wang et al. focused on drug-acquisition and monitoring among health states,[255] while Thokala et al. leaned towards resource allocation and treatment costs.[257]

In the review update, Khuntha et al. 2025 calculated lifetime costs for each SMA subgroup (type 1 and types 2/3) from the provider perspective, which included only direct medical costs in current practice such as disease diagnosis, assistive equipment and medication costs during ambulatory care and hospitalisation.[248] Moreover, lifetime costs from the societal perspective were estimated, which in addition to direct medical costs included direct non-medical costs incurred by patients and caregivers, as well as indirect costs including other out-of-pocket charges for informal care and productivity costs from caregivers.

14.9 Results of survival modelling

In the previous SLR, it was noted that the methods used in the included studies for estimating the survival in patients with SMA varied based on the type of SMA and data availability. Furthermore, the range of unique and complex strategies adopted in the survival analysis of patients, reflected the complexity of treatment and dynamic nature of the patient disease conditions that were considered in modelling survival outcomes for patients with SMA.

For example, TA588 adopted different approaches for type 1 SMA and type 2/3 SMA.[2] In type 1 SMA, flexible spline Weibull models were used for extrapolating the overall survival while in type 2/3 SMA, 2 knot spline flexible models were used. This was based on the best fit on the trial data. The end-of-life criteria were applied with an adjustment factor of 0.75. NICE TA755 adopted a similar approach to modelling survival estimates in SMA patients.[3] The latter used two different approaches to model survival of patients with type 1 and type 2/3 SMA. Based on trial data, different models were used on data from the two trial arms (risdiplam and BSC) in type 1 SMA, an exponential model was applied to the risdiplam group and an indirect hazard ratio (HR) comparison for various health conditions was used for the BSC group. For type 2 SMA, parametric models were fitted to pseudo-IPD data, while in type 3 SMA, the mortality rate was considered similar to that of the general population. Furthermore, a HR of 0.75 was applied to the intervention arm of type 2 patients to reflect the likelihood reduction of mortality associated with treatment, which was also adopted in TA588.[2]

The long-term survival estimates for patients with SMA in HST24 involved using the standard methods of fitting parametric models to data from natural history studies and UK National life table data.[17] Additional assumptions from HST15 and clinical expert opinion were also adopted to prevent having clinically implausible survival estimates.[262]

In the cost utility analyses by Khuntha et al. 2025[248] identified in the SLR update, parametric survival curves were modelled to extrapolate lifetime transition probabilities for each health state transitions under SOC based on medical records from one of the largest Faculties of Medicine in Bangkok, Thailand (n=114 patients with SMA from the first diagnosis in 1999 to the current diagnosis in 2021). The Akaike information criterion, the Bayesian information criterion, and a visual inspection of fit were the methods used to select the appropriate distribution. The Weibull and Gompertz distributions for SMA type 1 and types 2–3, respectively, were deemed the most appropriate fits. Calculation of health state transitions and mortality with OA and risdiplam treatment used unpublished and published clinical trial data.

14.10 Assumptions used in studies and reports

In the previous SLR, a range of assumptions based on common themes were identified in the included studies and were centred on the survival of patients, mortality risk, motor milestones and its sustainability, disease progression, treatment effects and discontinuation, patient/caregiver utilities and treatment/monitoring cost. The implementation of these assumptions varied among the SMA models and was based on the study perspective and availability of real-world data. The individual patient-level data on various aspects of SMA treatments are scarce because of the nature of the disease and characteristics of the patient population and, this was a limitation that was observed across the included studies.

In TA588,[2] several assumptions around patients' mortality, trial duration, treatment response, utility estimates, scoliosis surgery and data sources were made. TA755 established assumptions about utility values, carer disutilities, complications and treatment costs.[2] The assumptions made in HST15 were around carer disutilities, milestones and transition of patients among health states;[262] HST24 maintained these assumptions in its cost-effectiveness analysis.[17]

CADTH-Nusinersen, 2019 implemented modelling assumptions regarding the disease progression, treatment discontinuation and the mortality in patients with SMA.[259] The CADTH-Risdiplam, 2021 evaluation made several assumptions regarding the motor milestones in patients, treatment discontinuation, treatment outcomes and mortality risk in patients with SMA, based on the inputs from clinicians and patients.[261] In the evaluation CADTH-OA-2021,[250] assumptions adopted included those regarding motor milestones, risk of mortality, health states associated patient transitions, permanent ventilation as a health state and monitoring costs. In SMC-Nusinersen-2018,[260] treatment discontinuation, treatment effects post discontinuation and mortality were the areas of focus for making assumptions. SMC-OA-2021 incorporated scenarios about age-appropriated motor milestones in presymptomatic and symptomatic SMA patients, treatment efficacy and discontinuation assumptions.[263]

Wang et al. made assumptions about patient transitions among the health states, survival of patients, sustainability of motor milestones, patient utilities and treatment administration duration in SMA.[255] Zuluaga Sanchez et al. 2019[256] integrated assumptions regarding, cost, health state utilities, continuation of treatment effects during follow-ups, mortality rates,

caregivers, health-state costs, motor milestones and its impacts. Thokala et al. 2020 made assumptions about survival, costs, utilities, and whether the motor function milestones were sustained over lifetime, ventilations, patient transitions and disease progressions.[257] In Broekhoff et al 2021,[251] key assumptions were made for health state maintenance and transitions, effect of motor milestones on survival, health-related quality of life and reversibility of health conditions. Malone et al. 2019 made assumptions with respect to the disease progression, milestone, lifelong treatment effects and treatment continuity.[264]

The one study added in the review update, Khuntha et al. 2025[248] used several assumptions around model structure in the cost-effectiveness analysis. For instance, the patients in the SoC arm would either be stable or experience deterioration in their health states. Other assumptions surrounded health state occupancy and transition of patients, mortality rates and that all patients who enter the model have their disease confirmed through genetic testing for SMA.

14.11 Model inputs used across studies

Across the studies included in the previous SLR, it could be inferred that the economic analyses collectively addressed variables and parameters, which are common factors associated with SMA and treatment pathways, across locations and local healthcare systems. The elements driving the model and explored in the cost-effectiveness analysis of SMA treatments included utility values, health state costs and risk of mortality.

For example, in terms of the UK perspective, TA588 and TA755 considered parameters such as health state occupancy and transitions, surgery and age at which surgery occurred, overall survival, utilities of patients and caregivers, cost associated with health states.[2] Malone et al. 2019 used similar model inputs for the cost-utility analysis, except that Malone et al. 2019 was from a US perspective.[264] HST24 undertook a similar approach by modelling parameters like time horizon, health state utilities and costs, mortality risk and mean age of patients.[17] The study by Zuluaga-Sanchez et al. 2019 followed a comparable approach as well, with emphasis on resource use and cost.[256] Thokala et al. 2020 and Meijer et al. 2023 explored health state specific utility values, administration and monthly costs for SMA treatments.[254,257]

Different model inputs included in Khuntha et al. 2025[248] were survival estimates of SMA patients, transition probabilities in the model, treatment effects, mortality risks, utility estimates and resource use and cost estimates (for middle-income countries). The healthcare costs included both direct and indirect medical costs, drug costs and cost of hospitalisation.

14.12 Characterising uncertainty in different studies

In the included studies identified in the original SLR, it was reported that uncertainties were addressed through a range of methods to quantify the effects of various parameters on the cost-effectiveness result. TA588[2] and Zuluaga Sanchez et al.[256] employed probabilistic sensitivity analysis (PSA) and different scenario analyses to characterise the uncertainties in their respective studies. Similarly, HST15,[43] and HST24,[17] CADTH-Nusinersen-2019,[259] as well as CADTH-Risdiplam, 2021,[261] undertook both sensitivity and scenario analyses to address the uncertainty around the results. TA755 and Wang et al. 2022 used both probabilistic sensitivity analysis (PSA) and deterministic sensitivity analysis (DSA) for analysing the uncertainties introduced by the parameters and variable.[3,255] CADTH-OA-2021[250] and SMC-OA-2021[263] utilised numerous scenario analyses while, Thokala et al.[257] and Dean et al.[253] used one-way sensitivity analysis (OWSA) and scenario analysis to study the

variability in clinical benefits of treatment. SMC-Risdiplam-2022[265] focused on different scenario analyses to demonstrate the intervention benefit over other treatments. Broekhoff et al. 2021[251] and Malone et al. 2019[264] used sensitivity and scenario analyses to investigate the impact of parameters in the model outcomes. In conclusion, the studies utilised various sensitivity analyses and multiple scenario analyses to characterise the uncertainties in the cost-effectiveness estimates.

Furthermore in the economic evaluation by Khuntha et al. 2025[248] identified in the SLR update, uncertainty was characterised using multiple sensitivity and scenario analyses. OWSA was used to study the impact of variability of parameters on the ICER while PSA was utilised for assessing the uncertainties of all parameters. The effect of variation in treatment cost on ICER was observed by employing various scenario analysis.

14.13 Limitations identified across studies

Across the economic evaluations of SMA therapies conducted in the studies included the original SLR, several limitations and trends were identified, such as uncertainty in the clinical data available. In TA588[2] and TA755,[3] there was uncertainty around clinical effectiveness of the treatments and evaluation of utility estimates. Similarly, NICE HST-15[262] had limitations around the cost-effectiveness results due to uncertainty in the clinical data. NICE HST-24[17] also presented uncertainties around clinical effectiveness due to a narrow range in age of participants in the clinical trial. SMC-Nusinersen, 2018[260] had no long-term survival data from the trial which created uncertainties in the cost-effectiveness by overestimating the benefits. Thokala et al. 2020[257] had similar limitations due to lack of longer term follow-up data. The previous SLR also noted that bias due to the incomplete follow-up in survival data, presented uncertainty in the cost effectiveness estimates in SMC-Risdiplam, 2022.[265]

Zuluaga Sanchez et al. 2019[256] was limited by a small sample size in the trial impacting the clinical outcome of the treatments, resources and cost data that impacts the cost estimation of SMA therapy. In Wang et al. 2022,[255] there was a similar type of limitation arising due to lack of long-term data, while Dean et al. 2021[253] had incomplete follow-up data resulting in uncertain cost-effectiveness estimates.

CADTH-Nusinersen-2019[259] faced challenges around the uncertainty in utility estimates. Similarly, CADTH-OA-2021[250] had problems with utility values and limited clinical data. For CADTH-Risdiplam-2021,[261] comparative treatment benefits and modelling assumptions were sources of uncertainty. ICER 2019[249] grappled with a lack of robust data which introduced structural uncertainty in the SMA models.

Meijer et al. 2023[254] presented uncertainty in the model generated due to variability in patient characteristics. Moreover, Connock et al. 2020[252] and Malone et al. 2019[264] struggled with limitations in data availability. All the limitations discussed here were stated to reflect the lack of clinical data which underpins the complex methodologies and challenges faced when conducting economic evaluation for SMA treatments.

The major limitation of the Khuntha et al. 2025[248] identified in the SLR update was the small sample size of the study informing real-world clinical data. But this was understandable given the rarity of the disease. The clinical trial included one site, representing 50% of SMA patients in the country, and the results from this study were used to inform national policy on SMA therapy. Hence, there were concerns about the generalisability of the clinical effectiveness

data of SMA treatments. Additionally, the study did not include the various adverse events from treatment, but it was assumed that its effect were captured in the medication costs and health state utility estimates of patients.

14.14 Reporting and methodological quality assessment

14.14.1 Reporting quality assessment

The quality assessment of reporting in the 20 studies in the previous SLR and in this SLR update were conducted using the CHEERS 2022 Checklist[97] and the results are provided in Appendix 8 (Section 19.8).

Most of the studies included in the original SLR were noted to have a clear structure in reporting with title, introduction, methods, results and discussion. Thus, the reporting quality of the studies were considered satisfactory. Many published studies had an abstract which included a summary with excerpts from all the different sections included in the content. While the included reports, most likely as it was not a prerequisite during their preparation, did not include an abstract.[260,263,265] Although, these reports were noted to provide detailed descriptions about the economic analysis conducted, when compared to other published studies. Almost all the studies reported methods used in the economic analysis such as patient characteristics, location and settings, study perspective, comparators, choice of time horizon, measurement and valuation of outcomes.

Some studies did not score particularly well against the CHEERS 2022 checklist,[97] despite having detailed reporting on their methods and results, and was concluded to be because the studies lacked a health economics plan (HEAP), consideration of distributional effects or engagement with a patient population. These items were added as an update in CHEERS 2022[97] appraisal tool from its previous version.

It was also noted that the SMC reports did not provide adequate information on the description and justification for selecting the model, methods of analysis, as well as the statistical methods used for evidence synthesis and for characterising heterogeneity. While other studies did not have clear explanation about parametrisation and accounting for uncertainty introduced in the model.[260,263] Overall, it was therefore reported that the included studies adhered to the CHEERS 2022 criteria[97] to varying degrees with some studies lacking in reporting of items recommended when preparing health economic evaluations.

Khuntha et al. 2025[248] had a clear structure in reporting with title, introduction, methods, results and discussion like the articles in the original SLR. When assessing specific sections, the article did not note that a health economics assessment plan (HEAP) was developed prior to conducting the analysis. It did not provide information about characterisation of distributional effects of individuals on impacts and lacked description about methods used to assess uncertainty introduced by heterogeneity.

14.14.2 Methodological quality assessment

The Philips Checklist[98] was used to assess the methodological quality of the 20 studies included in the original SLR and in the SLR update. The results are reported in Appendix 9 (Section 19.9). The articles, reports and supplementary papers or evidence that are publicly available as electronic evidence were used to apply the qualitative methods of assessment in the Philips Checklist.

From the included studies, those that performed best overall in the assessment were TA588,[2] HST24,[204] and ICER Spinraza and Zolgensma 2019,[253] in terms of quality of methodology and low risk of bias. While SMC Onasemnogene -2021[263] and NCPE-2017[258] performed less well in quality assessment with respect to adopting and justifying the modelling methods used, and lack of clarity about the information on the cost estimation methods used.

The quality of data used in TA588[2] and NICE-Onasemnogene HST24-presymptomatic[17] was highly appraised. Additionally, HST24-presymptomatic[17] and Meijer et al. 2023[254] were noted to maintain consistency in their methods, leading to a robust analysis. Zuluaga-Sanchez et al. 2019[256] and Malone et al. 2019[264] outperformed the other studies in terms of providing structural quality throughout the study and providing description and justification about the modelling methods and assumptions.

In conclusion, the methodological and structural uncertainties were addressed in most of the studies but showed inconsistencies in making assumptions about treatment effects, incorporation of data and addressing the uncertainties created in the analysis. The assessment of these studies was proposed to help improve the methodological quality and robustness of studies in future.

There were uncertainties around the methods used in identification, quality assessment and validation of data used in cost-effectiveness analysis in Khuntha et al. 2025.[248] Another section that was unclear was about the alternative assumption used around treatment effects and the lack of adequate discussion about the rationale of these assumptions in the analysis. In the model, it was unclear whether half-cycle correction was used. These are definite areas of improvement which were also observed in some studies in the original SLR.

14.15 Assessment of cost-effectiveness

14.15.1 Discussion

The original SLR, which included 20 studies, was updated to include the period post January 2024 to March 2025 and the results were updated accordingly. The studies that undertook cost-effectiveness analysis were included for assessing the different aspects of modelling in SMA. One new study was identified as relevant in the SLR update and presented the first economic evaluation of OA and risdiplam from a middle-income country in this SLR.[248]

Across all studies included in the original SLR and update, economic evaluations varied based on the target population considered, interventions and comparators included, outcomes, modelling methods, resource use and costs, health-state utility estimates, time horizons, analyses, assumptions and limitations, and patient and professional groups engagements. All of the studies were limited to patients with SMA types 1, 2 and/or 3, with some studies using subgroup analysis based on age and disease characteristics.[2] The interventions considered were risdiplam, nusinersen and/or onasemnogene abeparvovec, which were compared against the basic SoC available in the region. The cost-effectiveness was assessed using ICER that compared cost against unit of benefits (QALY or LYG) gained in all of these studies. Studies mostly adopted Markov models with health states defined by functional motor milestones and ventilation support, which were used to capture the SMA disease progression. There were marked differences in models in their time horizons, horizons, discount rates used for cost and utility estimates, and sources of utility values. The studies engaged with patients and experts in varying degrees when evaluating the treatments. The SLR thus provided critical

and valuable insights to the different complexities that need to be addressed when considering SMA treatments.

14.15.1.1 *Type of model*s including health states used

All the studies in consideration adopted the Markov models for the cost-effectiveness analysis. But there were some noticeable differences in terms of the included health states, structures, assumptions on disease progression, mortality and treatment efficacy. The definitions of the health states differed in terms of the disease progression and functional motor milestones observed in patients. In HST24,[17] short-term and long-term models to capture different disease phases and milestones by using transitions between sitting, walking, and death. In terms of the models used, TA588[17] used two separate Markov models to differentiate between infantile onset (SMA type 1) and later onset (SMA type2/3) SMA. The elements under consideration among all the studies for modelling SMA treatments were assumptions on disease modification, treatment discontinuation, and survival were common factors influencing health state selection and transitions, when deciding the health states and transitions between different health states. In Broekhoff et al. 2021[251] the progression to specific health states was based on disease severity and treatment outcomes, thus reflecting the survival rates of different SMA types. All the studies had clear differences between health state selection and progression, which would indicate the need for better and transparent methodologies for accurate analysis of SMA treatments.

14.15.1.2 *Modelling* long-term effects

A very important consideration in SMA modelling is the long-term implications of treatments. But there are several limitations across these studies that reiterate the need for long term safety and efficacy data to fully capture the benefits of SMA treatments. Some of the bottle necks when it comes to modelling long-term impacts are treatment sustainability expressed in terms of motor function milestones and HRQoL. When it comes to lifetime projections, different patient characteristics, uncertainty in long-term effects and assumptions and varying definitions of motor milestones among the included studies were some of the factors that prove challenging in SMA analysis. For patients with different types of SMA, tailoring the economic evaluation is crucial in accurately reflecting the outcomes across different population groups with varying disease progression rates. There is an evidence gap around long-term follow-up data and real-world evidence, that could enhance the accuracy of evaluation and improve the decision-making on SMA treatments.

14.15.1.3 Sources of utility estimates

SMA is included in the category of rare diseases and hence it could be challenging to estimate robust utility values. In the absence of long-term data, studies conducted by NICE, ICER and CADTH indicate the complexities and variations in determining utility values for different health states in SMA patients. There is a broad lack of consensus among various studies about the best method to estimate the utility values.

The patient population concerned is paediatric population which makes it difficult to elicit utilities using measurement instruments designed for adults. There is a lack of validation of these values since the population is too young. TA588,[2] the CADTH-Nusinersen[261] and CADTH-OA-2021[250] outlines the challenges with robust utility values, use of generic patient-reported outcome measure to estimate health related quality of life and lack of long-term effectiveness data impacting the economic evaluations. These studies also point out that there

was a lack of validity and reliability when it comes to clinical data. These challenges are compounded by a small sample population and absence of direct treatment comparison data, especially when it comes to nusinersen and risdiplam.

Another source of utility values observed were from clinical expert opinion, which is adopted in SMC studies. The NICE guidelines[42] stipulate that in the absence of reliable sources for measuring HRQoL in patients, the data could be obtained from caregivers rather than clinical experts. The health states in such situations should align closely with public opinion.

There is a need for continued research in exploring methods to collect robust data and transparent methods of reporting to create a consensus in techniques to improve the precision and reliability of treatments in rare diseases like SMA.

14.15.1.4 Sources of resource use and costs

The sources of resource use and cost used differed based on the region of the study. For example, TA588[2] and TA755[3] used data specific to the UK. CADTH-Nusinersen[259] and CADTH-Risdiplam[261] appraisal resource use and costs were obtained from studies undertaken in Germany and Canada, respectively. This would result in variation in the resource use and cost estimation in the model, leading to the results being not fit to be compared.

Another method adopted was introducing age-adjustment in estimating costs, which would give insights about the nuances associated with financial burden of SMA treatments on patients at different stages of their life.

The different assumptions made across various studies did impact the cost estimates. This resulted in discrepancies that reflected in the cost-effectiveness results across various studies. Some of the factors that influenced the cost estimates were assumptions around long-term treatment effects, disease progression, differences in discontinuation rates and assumptions around additional costs incurred to patients.

Another aspect that influenced the resource use and cost estimates were varying definitions of BSC or standard of care. When new treatments options are added to BSC or standard care, it impacts the cost-effectiveness estimation resulting from variation in baseline estimates. (TA588[2] and CADTH-Risdiplam[261])

Additionally, there is lack of clinical data from direct comparison of treatment efficacy between various treatments and standard of care. There are discrepancies in data sources, methodologies and assumptions around estimation of cost and resource use data.

In short, the factors under consideration for estimating resource use and cost in SMA treatments are data sources, age-adjusted cost estimates, assumptions around resource use and treatment modelling, different definitions of BSC or standard of care, and other complexities and heterogeneity around SMA treatment modelling assumptions, that makes the comparison of estimates among different studies difficult.

14.16 Conclusion

All the included studies from the SLR undertook economic evaluation of SMA treatments. The studies varied based on the patient population, interventions and comparators, outcome measures, modelling methods adopted, resource use and costs, health-state utility estimates,

time horizons, analyses, assumptions and limitations, and patient and professional engagements. SMA types 1, 2 and/or 3 were considered in most of the studies, with some using subgroup analysis based on age and disease characteristics.

There was a consensus in the type of model adopted for cost-effectiveness evaluation, with the studies using Markov models for estimating the SMA treatment effectiveness. There was a need for generating robust and reliable data on long-term follow-up and real-world evidence on treatment efficacy that could enhance the accuracy of evaluation and improve the decision-making on SMA treatments. There were significant variations in sources and methods used for utility estimates among different studies, due to a lack of consensus around the best source and methods that could be used to elicit the utility estimates. The resource use quantification and subsequent cost estimation was influenced by variations in data sources, age-adjusted cost estimates, assumptions in treatment modelling, definitions of BSC or standard of care, and other complexities and heterogeneity around SMA treatment modelling assumptions, resulting in the cost-effectiveness results across the studies not fit for comparison. It would be difficult to draw conclusions to inform SMA treatment modelling choices from the results of the SLR. But these studies could be used to analyse the impact of different data sources, methods and assumptions in modelling SMA treatments. The assessment of cost-effectiveness SLR results indicate a need for robust and reliable data on treatment effectiveness, real-world evidence generation of utility estimates and consensus in adopting resource use and estimating costs for SMA treatment evaluation.

15 EAG cost-effectiveness analysis results

This section presents the results from the independent assessment of cost-effectiveness of the disease modifying therapies conducted by the EAG. These results should be read in the context of the qualitative analysis exploring experiences of those living with SMA, their carers and wider network of family and friends, as well as their experiences of treatment. The qualitative analyses related specifically to the cost effectiveness analyses can be found in Section 1.1.

Based on the results from the EAG base-case analyses presented independently for nusinersen and risdiplam based exclusively on patient quality of life, the EAG assessed the eligibility across each patient population to the severity modifier criteria. Table 15.1 reports the most appropriate severity modifier by treatment based on the QALY estimates in each economic model.

Table 15.1: Severity modifier eligibility based on the EAG base-case analyses for the economic models in each company

Population	Expected QALYs	BSC QALYs	Absolute shortfall	Proportional Shortfall	Eligible severity modifier
Biogen - nusinersen					
Presymptomatic	24.89	[redacted]	[redacted]	[redacted]	1.2 [a]
Type 1	24.87	[redacted]	[redacted]	[redacted]	1.7
Type 2&3	24.55	[redacted]	[redacted]	[redacted]	1.2
Roche - risdiplam					
Presymptomatic	24.87	[redacted]	[redacted]	[redacted]	1.7 [b]
Type 1	24.87	[redacted]	[redacted]	[redacted]	1.7
Type 2&3	24.02	[redacted]	[redacted]	[redacted]	1.2

[a] A severity modifier of 1.7 is also explored to maintain consistency across Biogen and Roche presymptomatic population models

[b] A severity modifier of 1.2 is also explored to maintain consistency across Biogen and Roche presymptomatic population models

Abbreviations: QALY = quality adjusted life year; BSC = best supportive care

15.1 Nusinersen – using Biogen model

15.1.1 Presymptomatic

This section presents the EAG results for the presymptomatic population. The EAG's definition of base-case cost-effectiveness analysis for presymptomatic population is presented in Section12.2.1.

15.1.1.1 Deterministic base-case analysis

The EAG's base-case analysis (without incorporating the severity modifier) show that nusinersen would be [redacted] treatment over BSC in presymptomatic population (Table 15.2). Even after applying the severity modifier, nusinersen [redacted] treatment.

Table 15.2: Deterministic base-case results for the presymptomatic population (using nusinersen PAS price)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£/QALY)	ICER (£/QALY)- with severity modifier
Nusinersen	[redacted]	20.65	[redacted]	-	-	-	-	-
BSC	[redacted]	19.84	[redacted]	[redacted]	0.81	[redacted]	[redacted]	[redacted]*

* Nusinersen remained [redacted] with a severity modifier of 1.7 (same as the one used in Roche presymptomatic population models)

Abbreviations: BSC = Best Supportive Care, ICER = Incremental Cost-Effectiveness Ratio, LYG = Life-Year Gained, QALY = Quality Adjusted Life Years, NHB = Net Health Benefits.

15.1.1.2 Probabilistic sensitivity analysis

In the probabilistic sensitivity analysis (PSA), the base-case deterministic results remained mostly stable, where nusinersen was [redacted] intervention over BSC in the treatment of presymptomatic population (Table 15.3). The cost-effectiveness plane shows that a majority of cost-effectiveness simulations run had [redacted] for nusinersen when compared with BSC (Figure 34). The probability of nusinersen being cost-effective over BSC was [redacted] (Figure 35).

Table 15.3: Probabilistic results for the presymptomatic population (using nusinersen PAS price)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£/QALY)
Nusinersen	[redacted]	20.69 (20.34 to 21)	[redacted]	-	-	-	-
BSC	[redacted]	19.85 (19.50 to 20.15)	[redacted]	[redacted]	0.84 (0.58 to 1.10)	[redacted]	[redacted]
Probability cost-effective at a 30k willingness to pay value							[redacted]

Abbreviations: BSC: Best Supportive Care, ICER: Incremental Cost-Effectiveness Ratio, LYG: Life-Year Gained, QALY: Quality Adjusted Life Years, NHB: Net Health Benefits

Figure 34: Cost-effectiveness plot showing cost-effectivenss of nusinersen vs BSC (presymptomatic)



Abbreviations: BSC = best supportive care; GBP = British pounds; QALY = quality-adjusted life year

Figure 35: Cost-effectiveness acceptability curve for nusinersen vs BSC



Abbreviations: BSC = best supportive care; GBP = British pounds; QALY = quality-adjusted life year; WTP = willingness to pay

15.1.1.3 One-way sensitivity analysis

The one-way sensitivity analysis suggested the health state costs (not sitting, sitting without support, permanent ventilation) followed by health state utilities had highest impact on the ICER (Figure 36). However, nusinersen [redacted] in all the 9 parameter changes where impact on ICER was observed.

Figure 36: Deterministic one-way sensitivity analysis for the comparison between nusinersen and BSC (presymptomatic, using the PAS price for nusinersen)



Abbreviations: BSC = best supportive care; PAS = Patient Access Scheme

15.1.1.4 Scenario analyses

The scenario analyses conducted by the EAG, to assess the impact of parameter changes to baseline cost-effectiveness results, are summarised in Table . A subgroup analysis for each of the population with SMN2 and SMN3 copies was also conducted. In addition, the EAG also assessed the cost-effectiveness of nusinersen vs OA (Table 15.4).

With the nusinersen PAS price, the cost-effectiveness results were [redacted] in all the scenarios including the sub-groups of SMN2 and SMN3 populations, except in the scenario when the healthcare resource utilisation costs were sourced from TA588[2]/TA755[3], where the [redacted] the £30,000 willingness to pay threshold set by NICE. Assuming £0 price for nusinersen resulted in [redacted] List price analyses have been included to aid transparency.

In the scenarios, where nusinersen was compared with OA (Table 15.5), the cost-effectiveness results [redacted] when nusinersen PAS price was used. These results were based on list price for OA. However, these results comparing nusinersen against OA needs to be interpreted with caution, because of the assumptions of clinical equivalence (all parameters assumed equal with nusinersen apart from the price of the therapy) or non-equivalence (based on differences in state occupancy informed by poor evidence from an unanchored MAIC from SPR1NT data[33]). In the EAG model, discontinuations from nusinersen (as modelled in the company submission) to BSC were kept unchanged. In contrast, no discontinuations from OA were considered practical. Therefore, driven by these discontinuation assumptions, there remains a QALY difference between nusinersen and OA in the results, even when equivalence in state occupancy is assumed.

Table 15.4: Scenario analyses for cost-effectiveness of nusinersen vs BSC in presymptomatic population

Scenario	Incremental costs (£)	Incremental Life Years	Incremental QALYs	ICER (£/QALY)	NHB at £30,000/QALY
With nusinersen PAS price					
Including carer utilities [73a]	[redacted]	0.81	8.76	[redacted]	[redacted]
Including carer utilities [a1]	[redacted]	0.81	[redacted]	[redacted]	[redacted]
Including carer utilities [b]	[redacted]	0.81	[redacted]	[redacted]	[redacted]
Including carer utilities [b1]	[redacted]	0.81	[redacted]	[redacted]	[redacted]
Utilities sourced from TA755	[redacted]	0.81	[redacted]	[redacted]	[redacted]
Health state costs	[redacted]	0.81	[redacted]	[redacted]	[redacted]

Scenario	Incremental costs (£)	Incremental Life Years	Incremental QALYs	ICER (£/QALY)	NHB at £30,000/QALY
sourced from TA588 and TA755					
Sub-group (2 copies)	[redacted]	1.27	[redacted]	[redacted]	[redacted]
Sub-group (3 copies)	[redacted]	0.38	[redacted]	[redacted]	[redacted]
£0 nusinersen price	[redacted]	0.81	[redacted]	[redacted]	[redacted]
With nusinersen list price					
Base-case	[redacted]	0.81	[redacted]	[redacted]	[redacted]
Including carer utilities [a]	[redacted]	0.81	[redacted]	£199,024	[redacted]
Including carer utilities [a1]	[redacted]	0.81	[redacted]	£152,590	[redacted]
Including carer utilities [b]	[redacted]	0.81	[redacted]	£432,045	[redacted]
Including carer utilities [b1]	[redacted]	0.81	[redacted]	£260,176	[redacted]
Utilities sourced from TA755	[redacted]	0.81	[redacted]	£274,407	[redacted]
Health state costs sourced from TA588 and TA755	[redacted]	0.81	[redacted]	£387,291	[redacted]
Sub-group (2 copies)	[redacted]	1.27	[redacted]	£250,886	[redacted]
Sub-group (3 copies)	[redacted]	0.38	[redacted]	£442,724	[redacted]

[a & a1] Carer QALYs were based on absolute increments from Lo et al. (2022)[73] assuming 1 carer and following average carer characteristics in the study and with severity modifier 1.2 and 1.7 applied to patient QALYs respectively.
[b & b1] Carer utilities based on absolute decrements from Lo et al. (2022)[73] assuming 1 carer and following average carer characteristics in the study and with severity modifier 1.2 and 1.7 applied to patient QALYs respectively.

Abbreviations: BSC: Best Supportive Care, ICER: Incremental Cost-Effectiveness Ratio, LYG: Life-Year Gained, QALY: Quality Adjusted Life Years, NHB: Net Health Benefits.

Table 15.5: Deterministic cost-effectiveness analysis of nusinersen vs OA

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£/ QALY)
Scenario: Nusinersen vs OA (using PAS price for nusinersen)							
Nusinersen	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
OA (equivalence assumed in state occupancy)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
OA (no equivalence assumed in state occupancy)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Scenario: Nusinersen vs OA (using list price for nusinersen)							
Nusinersen	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-
OA (equivalence assumed in state occupancy)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominated
OA (no equivalence assumed in state occupancy)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominated

Dominated: More costly, less effective

Abbreviations: BSC: Best Supportive Care, ICER: Incremental Cost-Effectiveness Ratio, LYG: Life-Year Gained, QALY: Quality Adjusted Life Years, NHB: Net Health Benefits.

15.1.2 Type 1

This section presents the EAG results for the type 1 SMA population. The EAG's definition of base-case cost-effectiveness analysis for type 1 SMA population is presented in Section 8.2.1.

15.1.2.1 Deterministic base-case analysis

The EAG's base-case analysis (without incorporating the severity modifier) findings show that [redacted] than the £30,000 willingness to pay threshold, and nusinersen would [redacted] intervention in the treatment of type1 SMA population (Table 15.6). Applying the severity modifier lowered the ICER [redacted] but it remained [redacted] NICE's willingness to pay threshold, therefore nusinersen was [redacted].

Table 15.6: Deterministic base-case results for the type 1 population (using nusinersen PAS price)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£/QALY)	ICER (£/QALY)- with severity modifier
Nusinersen	[redacted]	6.81	[redacted]	-	-	-	-	-
BSC	[redacted]	2.91	[redacted]	[redacted]	3.90	[redacted]	[redacted]	[redacted]
Abbreviations: BSC: Best Supportive Care, ICER: Incremental Cost-Effectiveness Ratio, LYG: Life-Year Gained, QALY: Quality Adjusted Life Years, NHB: Net Health Benefits.								

15.1.2.2 Probabilistic sensitivity analysis

In the probabilistic sensitivity analysis (PSA), the base-case deterministic results remained mostly stable, where nusinersen was [redacted] compared with BSC (Table 15.7).

The cost-effectiveness plane (Figure 37) shows that a majority of cost-effectiveness simulations run [redacted] QALY gains for nusinersen when compared with BSC. The probability of nusinersen being cost-effective over BSC was [redacted] (Figure 38).

Table 15.7: Probabilistic results for the type 1 population (using nusinersen PAS price)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£/QALY)
Nusinersen	[redacted]	6.87 (5.70 to 8.36)	[redacted]	-	-	-	-
BSC	[redacted]	3.05(1.57 to 5.21)	[redacted]	[redacted]	3.82 (2.72 to 4.82)	[redacted]	[redacted]
Probability cost-effective at a 30k willingness to pay value							[redacted]
Abbreviations: BSC: Best Supportive Care, ICER: Incremental Cost-Effectiveness Ratio, LYG: Life-Year Gained, QALY: Quality Adjusted Life Years, NHB: Net Health Benefits.							

Figure 37: Cost-effectiveness plot showing cost-effectiveness of nusinersen vs BSC (type 1)



Abbreviations: BSC = best supportive care; GBP = British pounds; QALY = quality-adjusted life year

Figure 38: Cost-effectiveness acceptability curve for nusinersen vs BSC (type 1)



Abbreviations: BSC = best supportive care; GBP = British pounds; QALY = quality-adjusted life year; WTP = willingness to pay

15.1.2.3 One-way sensitivity analysis

The EAG one-way sensitivity analyses showed that changing the health state utilities by +-20% had a highest impact on the ICER, followed by health state costs for permanent ventilation, not sitting, and sitting without support respectively (Figure 39). Per-cycle discontinuation rates for standing with support had the least impact followed by standing with support.

Figure 39: Deterministic one-way sensitivity analysis for the comparison between nusinersen and BSC (type 1, using the PAS price for nusinersen)



Abbreviations: BSC = best supportive care; ICER = incremental cost-effectiveness ratio; PAS = Patient Access Scheme; QALY = quality-adjusted life year

15.1.2.4 Scenario analyses

The scenario analyses conducted by the EAG, to assess the impact of parameter changes to baseline cost-effectiveness results, are summarised in Table 15.8. In addition, the EAG also assessed the cost-effectiveness of nusinersen vs OA (Table 15.9).

With the nusinersen [redacted] the cost-effectiveness results were not in favour of nusinersen in all the scenarios because the ICER was well above the £30,000 willingness to pay threshold set by NICE. In addition, [redacted].

In the scenarios, where nusinersen was compared with OA (Table), the cost-effectiveness results were not in favour of nusinersen with nusinersen being less costly and less effective when either of the nusinersen PAS price or list price was used. However, these results comparing nusinersen against OA need to be interpreted with caution, because of the assumptions of clinical equivalence (all parameters assumed equal with nusinersen apart from the price of the therapy) or non-equivalence (based on differences in state occupancy informed by poor evidence from an unanchored MAIC from STR1VE data[33]). In the EAG model, discontinuations from nusinersen (as modelled in the company submission) to BSC were kept unchanged. In contrast, no discontinuations from OA were considered practical. Therefore, driven by these discontinuation assumptions, there remains a QALY difference between nusinersen and OA in the results, even when equivalence in state occupancy is assumed.

Table 15.8: Scenario analyses for cost-effectiveness of nusinersen vs BSC in type 1 population

Scenario	Incremental costs (£)	Incremental Life Years	Incremental QALYs	ICER (£/QALY)	NHB at £30,000/ QALY
With nusinersen PAS price					
Including carer utilities[a] [73]	[redacted]	3.90	[redacted]	[redacted]	[redacted]
Including carer utilities[b]	[redacted]	3.90	[redacted]	[redacted]	[redacted]
Utilities sourced from TA755	[redacted]	3.90	[redacted]	[redacted]	[redacted]
Health state costs sourced from TA588 and TA755	[redacted]	3.90	[redacted]	[redacted]	[redacted]
£0 nusinersen price	[redacted]	3.90	[redacted]	[redacted]	[redacted]
With nusinersen list price					
Base-case	[redacted]	3.90	[redacted]	£534,405	[redacted]

Scenario	Incremental costs (£)	Incremental Life Years	Incremental QALYs	ICER (£/QALY)	NHB at £30,000/ QALY
Including carer utilities [a]	[redacted]	3.90	[redacted]	£310,121	[redacted]
Including carer utilities [b]	[redacted]	3.90	[redacted]	£318,708	[redacted]
Utilities sourced from TA755	[redacted]	3.90	[redacted]	£879,292	[redacted]
Health state costs sourced from TA588 and TA755	[redacted]	3.90	[redacted]	£564,976	[redacted]

[a] Carer QALYs were based on absolute increments from Lo et al. (2022)[73] assuming 1 carer and following average carer characteristics in the study, with severity modifier 1.7 applied to patient QALYs

[b] Carer QALYs based on absolute decrements from Lo et al. (2022)[73] assuming 1 carer and following average carer characteristics in the study, with severity modifier 1.7 applied to patient QALYs

Abbreviations: BSC: Best Supportive Care, ICER: Incremental Cost-Effectiveness Ratio, LYG: Life-Year Gained, QALY: Quality Adjusted Life Years, NHB: Net Health Benefits.

Table 15.9: Deterministic cost-effectiveness analysis of nusinersen vs OA

Technologies	Total costs (£)	Total LYG	Total QALYs	Inc. costs (£)	Inc. LYG	Inc. QALYs	ICER (£/QALY)
Scenario: Nusinersen vs OA (with PAS price for nusinersen)							
Nusinersen	[redacted]	6.81	[redacted]	-	-	-	-
OA (equivalence assumed in state occupancy)	[redacted]	15.68	[redacted]	[redacted]	-8.87	[redacted]	[redacted]
OA (no equivalence assumed in state occupancy)	[redacted]	15.68	[redacted]	[redacted]	-8.87	[redacted]	[redacted]
Scenario: Nusinersen vs OA (with list price for nusinersen)							
Nusinersen	[redacted]	6.81	[redacted]	-	-	-	-
OA (equivalence assumed in state occupancy)	[redacted]	15.68	[redacted]	[redacted]	-8.87	[redacted]	Less costly, less effective (ICER for OA vs Nusinersen= £307,697)
OA (no equivalence	[redacted]	15.68	[redacted]	[redacted]	-8.87	[redacted]	Less costly, less effective

Technologies	Total costs (£)	Total LYG	Total QALYs	Inc. costs (£)	Inc. LYG	Inc. QALYs	ICER (£/QALY)
assumed in state occupancy)							(ICER for OA vs Nusinersen= £305,312)
Abbreviations: BSC: Best Supportive Care, ICER: Incremental Cost-Effectiveness Ratio, LYG: Life-Year Gained, QALY: Quality Adjusted Life Years, NHB: Net Health Benefits.							

15.1.3 Type 2/3

This section presents the EAG results for type 2/3 SMA. The EAG's definition of base-case cost-effectiveness analysis for type 2/3 SMA population is presented in Section 12.2.1.3.

15.1.3.1 Deterministic base-case analysis

The EAG's base-case analysis (without incorporating the severity modifier) findings show that ICER [redacted] than the £30,000 willingness to pay threshold, and nusinersen [redacted] intervention in the treatment of type 2/3 SMA population (Table 15.10). Applying the severity modifier lowered the ICER [redacted] but it remained [redacted] NICE's willingness to pay threshold, therefore nusinersen was [redacted].

Table 15.10: Deterministic base-case results for the type 2/3 population (using nusinersen PAS price)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£/QALY)	ICER (£/QALY)- with severity modifier
Nusinersen	[redacted]	23.08	[redacted]	-	-	-	-	-
BSC	[redacted]	22.85	[redacted]	[redacted]	0.23	[redacted]	[redacted]	[redacted]
Abbreviations: BSC: Best Supportive Care, ICER: Incremental Cost-Effectiveness Ratio, LYG: Life-Year Gained, QALY: Quality Adjusted Life Years, NHB: Net Health Benefits; PAS = Patient Access Scheme								

15.1.3.2 Probabilistic sensitivity analysis

In the probabilistic sensitivity analysis (PSA), the base-case deterministic results remained mostly stable, where [redacted] compared with BSC (Table 15.11). The cost-effectiveness plane (Figure 40) shows that all of the cost-effectiveness simulations run [redacted] for nusinersen when compared with BSC. The probability that nusinersen being cost-effective over BSC was [redacted](Figure 41).

Table 15.11: Probabilistic results for the type 2/3 population (using nusinersen PAS price)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£/QALY)
Nusinersen	[redacted]	23.08	[redacted]	-	-	-	-

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£/QALY)
		(23.03 to 23.14)					
BSC	[redacted]	22.85 (22.80 to 22.90)	[redacted]	[redacted]	0.23 (0.19 to 0.28)	[redacted]	[redacted]
Probability cost-effective at a 30k willingness to pay value							[redacted]

Abbreviations: BSC: Best Supportive Care, ICER: Incremental Cost-Effectiveness Ratio, LYG: Life-Year Gained, QALY: Quality Adjusted Life Years, NHB: Net Health Benefits.

Figure 40: Cost-effectiveness plot showing cost-effectiveness of nusinersen vs BSC (type 2/3)

[redacted]

Abbreviations: BSC = best supportive care; GBP = British pounds; QALY = quality-adjusted life year

Figure 41: Cost-effectiveness acceptability curve for nusinersen vs BSC (type 2/3)



Abbreviations: BSC = best supportive care; GBP = British pounds; QALY = quality-adjusted life year; WTP = willingness to pay

15.1.3.3 One-way sensitivity analysis

The EAG's one-way sensitivity analyses (Figure 42) showed that changing health state costs for "sitting without support", followed by changes in annual state utilities, and health state costs for "not sitting" and "sitting without support" had the highest impact on the base case results. Per cycle discontinuation in "not sitting" had the least impact, followed by health state costs of walking independently.

Figure 42: Deterministic one-way sensitivity analysis for the comparison between nusinersen and BSC (type 2/3, using the PAS price for nusinersen)



Abbreviations: BSC = best supportive care; GBP = British pounds; ICER = incremental cost-effectiveness ratio; PAS = Patient Access Scheme; QALY = quality-adjusted life year

15.1.3.4 Scenario analyses

The scenario analyses conducted by the EAG, to assess the impact of parameter changes to baseline cost-effectiveness results, is summarised in (Table 15.12). With the nusinersen [redacted] in all the scenarios because the ICER was [redacted] willingness to pay threshold set by NICE. However, [redacted]

Table 15.12: Scenario analyses for cost-effectiveness of nusinersen vs BSC in type 2/3 population

Scenario	Incremental costs (£)	Incremental Life Years	Incremental QALYs	ICER (£/QALY)	NHB at £30,000/QALY
With nusinersen PAS price					
Including carer utilities [a] [73]	[redacted]	0.23	[redacted]	[redacted]	[redacted]
Including carer utilities [b]	[redacted]	0.23	[redacted]	[redacted]	[redacted]
Utilities sourced from TA755	[redacted]	0.23	[redacted]	[redacted]	[redacted]
Health state costs sourced from TA588 and TA755	[redacted]	0.23	[redacted]	[redacted]	[redacted]
Utilities sourced from Roche base-case i.e. from Lloyd 2019	[redacted]	0.23	[redacted]	[redacted]	[redacted]
Utilities sourced from Roche SUNFISH trial	[redacted]	0.23	[redacted]	[redacted]	[redacted]
With additional impact of bulbar dysfunction	[redacted]	0.23	[redacted]	[redacted]	[redacted]
Subgroup (type 2 SMA)	[redacted]	0.14	[redacted]	[redacted]	[redacted]
Subgroup (type 3 SMA)	[redacted]	0.13	[redacted]	[redacted]	[redacted]

Scenario	Incremental costs (£)	Incremental Life Years	Incremental QALYs	ICER (£/QALY)	NHB at £30,000/QALY
£0 nusinersen price	[redacted]	0.23	[redacted]	[redacted]	[redacted]
With nusinersen list price					
Base-case	[redacted]	0.23	[redacted]	£781,225	[redacted]
Including carer utilities [a]	[redacted]	0.23	[redacted]	£487,647	[redacted]
Including carer utilities [b].	[redacted]	0.23	[redacted]	£979,015	[redacted]
Utilities sourced from TA755	[redacted]	0.23	[redacted]	£581,533	[redacted]
Health state costs sourced from TA588 and TA755	[redacted]	0.23	[redacted]	£824,916	[redacted]
Utilities sourced from Roche base-case i.e. from Lloyd 2019	[redacted]	0.23	[redacted]	£651,232	[redacted]
Utilities sourced from Roche SUNFISH trial	[redacted]	0.23	[redacted]	£1,330,593	[redacted]
With additional impact of bulbar dysfunction	[redacted]	0.23	[redacted]	£782,332	[redacted]
Subgroup (type 2 SMA)	[redacted]	0.14	[redacted]	£1,365,398	[redacted]
Subgroup (type 3 SMA)	[redacted]	0.13	[redacted]	£1,232,287	[redacted]

[a] Carer QALYs were based on absolute increments from Lo et al. (2022)[73] assuming 1 carer and following average carer characteristics in the study, and severity modifier of 1.2 applied to patient QALYs

[b] Carer QALYs were based on absolute decrements from Lo et al. (2022)[73] assuming 1 carer and following average carer characteristics in the study, and severity modifier of 1.2 applied to patient QALYs

Scenario	Incremental costs (£)	Incremental Life Years	Incremental QALYs	ICER (£/QALY)	NHB at £30,000/QALY
Abbreviations: BSC: Best Supportive Care, ICER: Incremental Cost-Effectiveness Ratio, LYG: Life-Year Gained, PAS = Patient Access Scheme; QALY: Quality Adjusted Life Years, NHB: Net Health Benefits.					

15.2 Risdiplam - using Roche model

15.2.1 Presymptomatic

15.2.1.1 Deterministic base-case analysis

The base-case analysis for the presymptomatic population comparing risdiplam with BSC, focusing on patient HRQoL, including the PAS discount for risdiplam, showed that risdiplam [redacted] NICE's £20,000/QALY willingness to pay threshold. Applying a severity modifier of 1.7 led to a reduction of the risdiplam ICER to [redacted]QALY. When a severity modifier of 1.2 (consistent with the Biogen model) was applied, the risdiplam ICER increased to [redacted]/QALY.

Probabilistic results showed that risdiplam was [redacted]) and [redacted]) with an ICER of [redacted]. Applying a severity modifier of 1.7 led to an ICER of [redacted]. This showed a substantial uncertainty in the incremental costs of risdiplam compared to BSC. Table 15.14 reports deterministic and probabilistic results (Table 15.13 reports results based on risdiplam list price), while Figure 43 shows the cost-effectiveness plane. The probabilistic analysis in the Roche model relied on extended dominance between all the DMTs and BSC, therefore the probability of cost-effectiveness between risdiplam and BSC only could not be extracted.

Table 15.13: Cost effectiveness results for risdiplam versus BSC in the EAG base-case (list prices)

Technologies	Total costs (£)	Total LYs	Total QALYs	Inc. costs (£)	Inc. LYs	Inc. QALYs	ICER (£/QALY)	Severity modifier
Deterministic								
Risdiplam	[redacted]	25.96	[redacted]					
BSC	[redacted]	12.91	[redacted]	[redacted]	13.05	[redacted]	£227,628	£133,899
Abbreviations: BSC = best supportive care; ICER = incremental cost-effectiveness ratio; LY = life year; QALY = quality-adjusted life year								

Table 15.14: Cost effectiveness results for risdiplam versus BSC in the EAG base-case (using risdiplam PAS price)

Technologies	Total costs (£)	Total LYs	Total QALYs	Inc. costs (£)	Inc. LYs	Inc. QALYs	ICER (£/QALY)	Severity modifier
Deterministic								
Risdiplam	[redacted]	25.96	[redacted]					
BSC	[redacted]	12.91	[redacted]	[redacted]	13.05	[redacted]	[redacted]	[redacted]
Probabilistic								
Risdiplam	[redacted]		[redacted]					
BSC	[redacted]		[redacted]	[redacted]		[redacted]	[redacted]	[redacted]
Probability cost-effective							NA	
* Risdiplam had an ICER of [redacted] with a severity modifier of 1.2 (same as the one used in Biogen presymptomatic population models) Abbreviations: BSC = best supportive care; ICER = incremental cost-effectiveness ratio; LY = life year; QALY = quality-adjusted life year								

Figure 43: Cost-effectiveness plane for the EAG base-case analysis (presymptomatic)

Abbreviations: BSC = best supportive care; QALY = quality-adjusted life year; WTP = willingness to pay

15.2.1.2 One-way sensitivity analysis

Parameters with the biggest impact on the ICER compared to BSC were the drug price of risdiplam, disease related costs for children at the “not sitting” and “sitting” health-states, the risk of permanent ventilation and disease related costs for adults at “not sitting” and “walking” health states. (Figure 44)

Parameters with the biggest impacts on costs were the drug price of risdiplam, disease-related costs at “not sitting” and “sitting”, and the risk of permanent ventilation.(Figure 45) Parameters with the biggest impact on quality of life were patient utilities at “walking” and “standing”, the treatment benefit of receiving risdiplam, and the risks of long-term motor decline for risdiplam. (Figure 46)

Figure 44: One-way sensitivity analysis on the ICER between risdiplam and BSC for the EAG base-case (presymptomatic)



Abbreviations: BSC = best supportive care; HSUV = health state utility value; ICER = incremental cost-effectiveness ratio; PV = permanent ventilation; QALY = quality-adjusted life year

Figure 45: One-way sensitivity analysis on incremental costs between risdiplam and BSC for the EAG base-case (presymptomatic)



Abbreviations: BSC = best supportive care; PV = permanent ventilation

Figure 46: One-way sensitivity analysis on incremental QALYs between risdiplam and BSC for the EAG base-case (presymptomatic)



Abbreviations: BSC = best supportive care; HSUV = health state utility value; PV = permanent ventilation; QALY = quality-adjusted life year

15.2.1.3 Scenario analyses

Base-case scenarios: risdiplam vs BSC

The scenario analysis between risdiplam and BSC showed that scenarios with the biggest impact on the ICER were the choice of time horizon being less than lifetime, the patient health-state related costs, and pooling the impact on carers and patients together (Table 15.15).

Table 15.15: Scenario analysis for risdiplam versus BSC in the EAG base-case (using risdiplam PAS price) (presymptomatic)

Technologies	Inc. costs (£)	Inc. LYs	Inc. QALYs	ICER (£/QALY)	% change
Base-case					
Risdiplam	[redacted]	13.05	[redacted]	[redacted]	-
Scenarios					
Patient and carer utilities[a]	[redacted]	13.05	[redacted]	[redacted]	-59.6%
Patient and carer utilities [b]	[redacted]	13.05	[redacted]	[redacted]	-53.5%
Utilities from Roche base-case[c]	[redacted]	13.05	[redacted]	[redacted]	-1%
Costs from Roche base-case	[redacted]	13.05	[redacted]	[redacted]	137%
Time horizon of 10 years	[redacted]	1.00	[redacted]	[redacted]	-
Time horizon of 30 years	[redacted]	6.07	[redacted]	[redacted]	-
Assuming price of risdiplam = £0	[redacted]	13.05	[redacted]	[redacted]	-

[a] Carer utilities were based on absolute decrements from Lo et al. (2022)[73] assuming 1 carer and following average carer characteristics in the study, patient utilities had a severity modifier of x1.7.
[b] Carer utilities were based on absolute increments from Lo et al. (2022)[73] assuming 1 carer and following average carer characteristics in the study, patient utilities had a severity modifier of x1.7.
[c] Negative utilities assumed equal to 0
Abbreviations: BSC = best supportive care; ICER = incremental cost-effectiveness ratio; LY = life year; QALY = quality-adjusted life year

Risdiplam compared to nusinersen (equivalent effectiveness)

The scenario analysis for the presymptomatic population comparing risdiplam with nusinersen, focusing on patient HRQoL, including the PAS discount for risdiplam, showed that nusinersen was equally effective and [redacted], [redacted]. Table reports the results of all scenarios comparing risdiplam with nusinersen and OA; please note that these were based on list prices for nusinersen or OA.

Risdiplam compared to nusinersen (naïve comparison)

The scenario for the presymptomatic population comparing risdiplam with nusinersen, focusing on patient HRQoL, including the PAS discount for risdiplam, showed that risdiplam was [redacted].

Risdiplam compared to OA (equivalent effectiveness)

The scenario analysis for the presymptomatic population comparing risdiplam with OA, focusing on patient HRQoL, including the PAS discount for risdiplam, showed that OA was [redacted], [redacted].

Table 15.16: Scenario analysis for risdiplam versus nusinersen and OA using the EAG approach (presymptomatic)

Technologies	Total costs (£)	Total LYs	Total QALYs	Inc. costs (£)	Inc. LYs	Inc. QALYs	ICER (£/QALY)	Severity modifier
Deterministic: risdiplam vs nusinersen (equivalent effectiveness)								
Risdiplam	[redacted]	25.96	[redacted]	[redacted]				
Nusinersen	[redacted]	25.96	[redacted]	[redacted]	0	0	[redacted]	-
Deterministic: risdiplam vs nusinersen (naïve comparison)								
Risdiplam	[redacted]	25.96	[redacted]					
Nusinersen	[redacted]	25.95	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-
Deterministic: risdiplam vs OA (equivalent effectiveness)								
Risdiplam	[redacted]	25.96	[redacted]					
OA	[redacted]	25.96	[redacted]	[redacted]	0	0	[redacted]	-
Probabilistic: risdiplam vs nusiNersen (naïve comparison)								
Risdiplam	[redacted]		[redacted]					
Nusinersen	[redacted]		[redacted]	[redacted]		[redacted]	[redacted]	-
Probability cost effective							NA	
Probabilistic: risdiplam vs OA (equivalent effectiveness)								
Risdiplam	[redacted]		[redacted]					
OA	[redacted]		[redacted]	[redacted]		[redacted]	[redacted]	-
Probability cost effective							NA	

Abbreviations: BSC = best supportive care ICER = incremental cost-effectiveness ratio; LY = life year; QALY = quality-adjusted life year

15.2.1.4 One-way sensitivity analyses for the scenario with disease modifying therapies

Risdiplam versus nusinersen (naïve comparison)

Parameters with the biggest impacts on costs were the drug price of nusinersen, the drug price of risdiplam, the relative effectiveness for moving from “sitting” to “standing” (Figure 47). Parameters with the biggest impacts on utilities were the relative effectiveness of moving from “sitting” to “standing” and the effectiveness of moving from “not sitting” to “sitting” (Figure 48).

Figure 47: One-way sensitivity analysis on incremental costs between risdiplam and nusinersen for the EAG approach (presymptomatic)



Abbreviations: OR = odds ratio

Figure 48: One-way sensitivity analysis on incremental QALYs between risdiplam and nusinersen for the EAG approach (presymptomatic)



Abbreviations: HSUV = health state utility value; OR = odds ratio; QALY = quality-adjusted life year

Risdiplam versus OA (equivalent effectiveness)

Parameters with the largest impacts on costs were the drug prices of risdiplam and OA, respectively (see Figure 49). Parameters with the largest impacts on utilities were relative effectiveness for moving from “not sitting” to “sitting” and “sitting” to “standing” (see Figure 50).

Figure 49: One-way sensitivity analysis on incremental costs between risdiplam and OA (presymptomatic)



Abbreviations: OA = onasemnogene abeparvovec; OR = odds ratio; p.a. = per annum; RDI = relative dose intensity

Figure 50: One-way sensitivity analysis on incremental QALYs between risdiplam and OA (presymptomatic)



Abbreviations: kg = kilogram; OA = onasemnogene abeparvovec; OR = odds ratio; p.a = per annum; QALY = quality-adjusted life year

15.2.2 Type 1

15.2.2.1 Deterministic base-case analysis

The base-case analysis for the type 1 population comparing risdiplam with BSC, focusing on patient HRQoL, including the PAS discount for risdiplam, showed that risdiplam effective and more costly than BSC at a [redacted] above NICE's £20,000/QALY willingness to pay threshold. Applying a severity modifier of 1.7 led to a reduction of the risdiplam ICER to [redacted] QALY.

Probabilistic results showed that risdiplam was more costly [redacted]) and more effective [redacted]) with an ICER of [redacted] QALY. Applying a severity modifier of 1.7 led to an ICER of [redacted] QALY. Table 15.18 reports deterministic and probabilistic results (Table 15.17 reports the results based on risdiplam list price), and Figure 51 shows the cost-effectiveness plane.

Table 15.17: Cost effectiveness results for risdiplam versus BSC in the EAG base-case (list prices – type 1)

Technologies	Total costs (£)	Total LYs	Total QALYs	Inc. costs (£)	Inc. LYs	Inc. QALYs	ICER (£/QALY)	Severity modifier
Deterministic								
Risdiplam	[redacted]	19.05	[redacted]					
BSC	[redacted]	3.98	[redacted]	[redacted]	15.06	[redacted]	£370,959	£218,211
Abbreviations: BSC = best supportive care; ICER = incremental cost-effectiveness ratio; LY = life year; QALY = quality-adjusted life year								

Table 15.18: Cost effectiveness results for risdiplam versus BSC in the EAG base-case (type 1)

Technologies	Total costs (£)	Total LYs	Total QALYs	Inc. costs (£)	Inc. LYs	Inc. QALYs	ICER (£/QALY)	Severity modifier
Deterministic								
Risdiplam	[redacted]	19.05	[redacted]	-	-	-	-	-
BSC	[redacted]	3.98	[redacted]	[redacted]	15.06	[redacted]	[redacted]	[redacted]
Probabilistic								
Risdiplam	[redacted]	-	[redacted]	-	-	-	-	-
BSC	[redacted]	-	[redacted]	[redacted]	-	[redacted]	[redacted]	[redacted]
Probability cost-effective							NA	
Abbreviations: BSC = best supportive care; ICER = incremental cost-effectiveness ratio; LY = life year; QALY = quality-adjusted life year								

Figure 51: Cost-effectiveness plane for the EAG base-case analysis (type 1)



Abbreviations: QALY = quality-adjusted life-year; WTP = willingness to pay

15.2.2.2 One-way sensitivity analysis

Parameters with the biggest impact on the ICER compared to BSC were the overall survival benefit of risdiplam, the drug cost of risdiplam, disease-related costs at “sitting”, and the differences in permanent ventilation risks. (Figure 52)

Parameters with the biggest impacts on costs were difference in overall survival risk, the drug cost of risdiplam, disease-related costs for children and adults at “sitting”, and the risk and cost of permanent ventilation (Figure 53). Parameters with the largest impact on patient quality of life were utilities at “sitting”, the treatment benefit of risdiplam, treatment utilities at “standing” and “walking”, and the risk of permanent ventilation (Figure 54).

Figure 52: One-way sensitivity analysis on the ICER between risdiplam and BSC for the EAG base-case (type 1)



Abbreviations: HR = hazard ratio; HSUV = health state utility value; ICER = incremental cost-effectiveness ratio; OS = overall survival; QALY = quality-adjusted life year

Figure 53: One-way sensitivity analysis on incremental costs between risdiplam and BSC for the EAG base-case (type 1)



Abbreviations: EFS = event-free survival; HR = hazard ratio; OS = overall survival

Figure 54: One-way sensitivity analysis on incremental QALYs between risdiplam and BSC for the EAG base-case (type 1)



Abbreviations: BSC = best supportive care; EFS = event-free survival; HR = hazard ratio; HSUV = health state utility value; OS = overall survival; QALY = quality-adjusted life year

15.2.2.3 Scenario analyses

Base-case scenarios: risdiplam vs BSC

The scenario analysis between risdiplam and BSC showed that scenarios with the biggest impact on the ICER were using the utilities from the base-case analysis in the Roche submission, changing the length of the time horizon, and pooling patient and carer utilities. Table 15.19 shows the results.

Table 15.19: Scenario analysis for risdiplam versus BSC in the EAG base-case (type 1)

Technologies	Inc. costs (£)	Inc. LYs	Inc. QALYs	ICER (£/QALY)	% change
Base-case					
Risdiplam	[redacted]	15.06	[redacted]	[redacted]	-
Scenarios					
Company relative effectiveness estimates	[redacted]	15.06	[redacted]	[redacted]	-0.3%
Patient and carer utilities [a]	[redacted]	15.06	[redacted]	[redacted]	-62.2%
Patient and carer utilities [b]	[redacted]	15.06	[redacted]	[redacted]	-50.8%
Utilities from Roche base-case*	[redacted]	15.06	[redacted]	[redacted]	82.0%
Costs from Roche base-case	[redacted]	15.06	[redacted]	[redacted]	-13.2%
Time horizon of 10 years	[redacted]	4.14	[redacted]	[redacted]	-61.3%
Time horizon of 30 years	[redacted]	11.13	[redacted]	[redacted]	-11.7%
Assuming risdiplam cost = £0	[redacted]	15.06	[redacted]	[redacted]	-

*Negative utilities assumed equal to 0

[a] Carer utilities were based on absolute decrements from Lo et al. (2022)[73] assuming 1 carer and following average carer characteristics in the study.

[b] Carer utilities based on absolute increments from Lo et al. (2022)[73] assuming 1 carer and following average carer characteristics in the study.

Abbreviations: ICER = incremental cost-effectiveness ratio; LY = life year; QALY = quality-adjusted life year

Risdiplam compared to nusinersen

The base-case analysis for the type 1 population comparing risdiplam with nusinersen, focusing on patient HRQoL, including the PAS discount for risdiplam, showed that risdiplam [redacted] than nusinersen, [redacted]. Table shows the results comparing risdiplam with nusinersen and with OA. Please note that PAS discounts were not included for nusinersen or OA, only list prices were used.

Risdiplam compared to OA

The base-case analysis for the type 1 population comparing risdiplam with OA, focusing on patient HRQoL, including the PAS discount for risdiplam, showed that risdiplam [redacted] OA, [redacted].

Table 15.20: Scenario analysis for risdiplam versus nusinersen and OA using the EAG approach (type 1)

Technologies	Total costs (£)	Total LYs	Total QALYs	Inc. costs (£)	Inc. LYs	Inc. QALYs	ICER (£/QALY)
Deterministic: Risdiplam vs nusinersen							
Risdiplam	[redacted]	19.05	[redacted]				
Nusinersen	[redacted]	11.66	[redacted]	[redacted]	7.38	[redacted]	[redacted]
Deterministic: Risdiplam vs OA							
Risdiplam	[redacted]	19.05	[redacted]				
OA	[redacted]	18.82	[redacted]	[redacted]	0.23	[redacted]	[redacted]
Probabilistic: Risdiplam vs nusinersen							
Risdiplam	[redacted]		[redacted]				
Nusinersen	[redacted]		[redacted]	[redacted]		[redacted]	[redacted]
Probability cost effective						NA	
Probabilistic: Risdiplam vs OA							
Risdiplam	[redacted]		[redacted]				
OA	[redacted]		[redacted]	[redacted]		[redacted]	[redacted]
Probability cost effective						NA	

Abbreviations: BSC = best supportive care; ICER = incremental cost-effectiveness ratio; LY = life year; QALY = quality-adjusted life year

15.2.2.4 One-way sensitivity analyses for the scenario with disease modifying therapies

Risdiplam versus nusinersen

Parameters with the biggest impacts on costs were the overall survival hazard ratio between risdiplam and nusinersen, the cost of nusinersen, the hazard ratio in permanent ventilation, and the odds ratio of “sitting” to “standing” (Figure 55). Parameters with the biggest impacts on quality of life were the hazard ratio in overall survival, the odds ratio from “sitting” to “standing”, and the hazard ratio in the risk of permanent ventilation (Figure 56).

Figure 55: One-way sensitivity analysis on incremental costs between risdiplam and nusinersen (type 1)



Abbreviations: EFS = event-free survival; HR = hazard ratio; OR = odds ratio; OS = overall survival

Figure 56: One-way sensitivity analysis on incremental QALYs between risdiplam and nusinersen (type 1)



Abbreviations: DMT = disease-modifying therapy; EFS = event-free survival; HR = hazard ratio; HSUV = health state utility value; OR = odds ratio; OS = overall survival

Risdiplam versus OA

Parameters with the biggest impacts on costs between risdiplam and OA were the drug cost of OA, the drug cost of risdiplam, the odds ratio of “not sitting” to “sitting”, the odds ratios in overall survival, and disease-related costs at sitting (see Figure 57). Parameters with the biggest impacts on quality of life were the risk of permanent ventilation, the odds ratio from “not sitting” to “sitting”, and the hazard ratio in overall survival (see Figure 58).

Figure 57: One-way sensitivity analysis on incremental costs between risdiplam and OA (type 1)



Abbreviations: BSC = best supportive care; HR = hazard ratio; OA = onasemnogene abeparvovec; OR = odds ratio

Figure 58: One-way sensitivity analysis on incremental QALYs between risdiplam and OA (type 1)



Abbreviations: DMT = disease-modifying therapy; EFS = event-free survival; HR = hazard ratio; HSUV = health state utility value; OR = odds ratio; OS = overall survival; QALY = quality-adjusted life year

15.2.3 Type 2/3

15.2.3.1 Deterministic base-case analysis

The base-case analysis for the type 2/3 population comparing risdiplam with BSC, focusing on patient HRQoL, including the PAS discount for risdiplam, showed that risdiplam [redacted] NICE's £20,000/QALY willingness to pay threshold. Applying a severity modifier of 1.2 led to a reduction of the risdiplam ICER to [redacted]QALY.

Probabilistic results showed that risdiplam was [redacted]) and [redacted]) with an ICER of [redacted]/QALY. Applying a severity modifier of 1.2 led to an ICER of [redacted]QALY. Table 15.22 reports deterministic and probabilistic results (Table 15.21 reports the results based on risdiplam list price), Figure 59 shows the cost-effectiveness plane.

Table 15.21: Cost effectiveness results for risdiplam versus BSC in the EAG base-case (type 2/3, list prices)

Technologies	Total costs (£)	Total LYs	Total QALYs	Inc. costs (£)	Inc. LYs	Inc. QALYs	ICER (£/QALY)	Severity modifier
Deterministic								
Risdiplam	[redacted]	24.47	[redacted]					
BSC	[redacted]	22.03	[redacted]	[redacted]	2.44	[redacted]	£793,780	£661,382
Abbreviations: BSC = best supportive care; ICER = incremental cost-effectiveness ratio; LY = life year; QALY = quality-adjusted life year								

Table 15.22: Cost effectiveness results for risdiplam versus BSC in the EAG base-case (type 2/3)

Technology	Total costs (£)	Total LYs	Total QALYs	Inc. costs (£)	Inc. LYs	Inc. QALYs	ICER (£/ QALY)	Severity modifier
Deterministic								
Risdiplam	[redacted]	24.47	[redacted]					
BSC	[redacted]	22.03	[redacted]	[redacted]	2.44	[redacted]	[redacted]	[redacted]
Probabilistic								
Risdiplam	[redacted]		[redacted]					
BSC	[redacted]		[redacted]	[redacted]		[redacted]	[redacted]	[redacted]
Probability cost-effective							NA	
Abbreviations: BSC = best supportive care; ICER = incremental cost-effectiveness ratio; LY = life year; QALY = quality-adjusted life year								

Figure 59: Cost-effectiveness plane for the EAG base-case analysis (type 2/3)



Abbreviations: BSC = best supportive care; QALY = quality-adjusted life year

15.2.3.2 One-way sensitivity analysis

Parameters with the biggest impact on the ICER were the drug cost of risdiplam, disease-related costs at “not sitting” for adults, utilities for “sitting without support”, and disease-related costs at “sitting without support” for adults (Figure 60).

Parameters with the biggest impact on costs were the drug cost of risdiplam, disease-related costs at “not sitting” and “sitting without support” for adults, and disease-related costs at “not sitting” for children (Figure 61). Parameters with the biggest impact on quality of life were utilities for “sitting without support” and “not sitting”, the treatment benefit of risdiplam, and utility at “sitting with support” (Figure 62).

Figure 60: One-way sensitivity analysis on the ICER between risdiplam and BSC for the EAG base-case (type 2/3)



Abbreviations: BSC = best supportive care; HSUV = health state utility value; ICER = incremental cost-effectiveness ratio; QALY = quality-adjusted life year

Figure 61: One-way sensitivity analysis on incremental costs between risdiplam and BSC for the EAG base-case (type 2/3)



Abbreviations: BSC = best supportive care; DMT = disease-modifying therapy

Figure 62: One-way sensitivity analysis on incremental QALYs between risdiplam and BSC for the EAG base-case (type 2/3)



Abbreviations: BSC = best supportive care; DMT = disease-modifying therapy; HSUV = health state utility value; QALY = quality-adjusted life year

15.2.3.3 Scenario analyses

Base-case scenarios: risdiplam vs BSC

The scenario analysis between risdiplam and BSC showed that scenarios with the biggest impact on the ICER were using utilities from the SUNFISH trial, using utilities from the base-case in the Roche submission, shortening the time horizon to 10 years. Table 15.23 shows the results.

Table 15.23: Scenario analysis for risdiplam versus BSC in the EAG base-case (type 2/3)

Technologies	Inc. costs (£)	Inc. LYs	Inc. QALYs	ICER (£/QALY)	% change
Base-case					
Risdiplam	[redacted]	2.44	[redacted]	[redacted]	-
Scenarios					
ITT SUNFISH incl. Asia	[redacted]	2.41	[redacted]	[redacted]	[redacted]
Patient and carer utilities [a]	[redacted]	2.44	[redacted]	[redacted]	[redacted]
Patient and carer utilities [b]	[redacted]	2.44	[redacted]	[redacted]	[redacted]
Utilities from Roche base-case*	[redacted]	2.44	[redacted]	[redacted]	[redacted]
Utilities from the SUNFISH trial[46]	[redacted]	2.44	[redacted]	[redacted]	[redacted]
Including the impact of bulbar dysfunction from Roche base-case	[redacted]	2.44	[redacted]	[redacted]	[redacted]
Including the impact of bulbar dysfunction from the van der Heul et al. 2019[75]	[redacted]	2.44	[redacted]	[redacted]	[redacted]
Costs from Roche base-case	[redacted]	2.44	[redacted]	[redacted]	[redacted]
Time horizon of 10 years	[redacted]	2.44	[redacted]	[redacted]	[redacted]
Time horizon of 30 years	[redacted]	2.44	[redacted]	[redacted]	[redacted]
Assuming risdiplam cost = £0	[redacted]	2.44	[redacted]	[redacted]	[redacted]

*Negative utilities assumed equal to 0

[a] Carer utilities were based on absolute decrements from Lo et al. (2022)[73] assuming 1 carer and following average carer characteristics in the study.

[b] Carer utilities based on absolute increments from Lo et al. (2022)[73] assuming 1 carer and following average carer characteristics in the study.

Abbreviations: BSC = best supportive care; ICER = incremental cost-effectiveness ratio; ITT = intention to treat; LY = life year; QALY = quality-adjusted life year

Risdiplam compared to nusinersen

The base-case analysis for the type 2 and 3 population comparing risdiplam with nusinersen, focusing on patient HRQoL, including the PAS discount for risdiplam, showed that risdiplam [redacted] than nusinersen, [redacted]. Table 15.24 presents the results. Please note, these do not include PAS discounts for nusinersen, only the list price was used.

Table 15.24: Scenario analysis for risdiplam versus nusinersen using the EAG approach (type 2/3)

Technologies	Total costs (£)	Total LYs	Total QALYs	Inc. costs (£)	Inc. LYs	Inc. QALYs	ICER (£/QALY)
Deterministic							
Risdiplam	[redacted]	24.47	[redacted]	-	-	-	-
Nusinersen	[redacted]	23.52	[redacted]	[redacted]	0.95	[redacted]	[redacted]
Probabilistic							
Risdiplam	[redacted]		[redacted]				
Nusinersen	[redacted]		[redacted]	[redacted]		[redacted]	[redacted]
Probability cost-effective						N/A	
Abbreviations: BSC = best supportive care; ICER = incremental cost-effectiveness ratio; LY = life year; QALY = quality-adjusted life year							

15.2.3.4 One-way sensitivity analyses for the scenario with disease modifying therapies
Risdiplam versus nusinersen

Parameters with the biggest impact on costs were the drug cost of nusinersen, the drug cost of risdiplam, disease-related costs for adults at “not sitting” and “sitting without support” (Figure 63). Parameters with the biggest impact on patient quality-of-life were the odds ratio for responding to treatment, the utility at “sitting without support”, the treatment benefit of risdiplam and nusinersen respectively, and utility at “not sitting” (Figure 64).

Figure 63: One-way sensitivity analysis on incremental costs between risdiplam and nusinersen (type 2/3)



Abbreviations: DMT = disease-modifying therapy; RULM = Revised Upper Limb Module

Figure 64: One-way sensitivity analysis on incremental QALYs between risdiplam and nusinersen (type 2/3)



Abbreviations: DMT = disease-modifying therapy; HSUV = health state utility value; QALY = quality-adjusted life year; RULM = Revised Upper Limb Module

15.3 Qualitative analyses surrounding economic impact and finances

This section considers the results of the qualitative framework analysis described in Section 9 specifically in relation to the economic impacts of SMA and treatment. Qualitative results surrounding clinical effectiveness outcomes is presented in Section 13.5.

The financial burden on patients and families of managing SMA and the overall cost to the health service were frequently mentioned within the submissions and case studies. Some of the submissions from patient experts and organisations highlighted the need to use a wide range of health services to both monitor and manage SMA. This included: physiotherapy; hydrotherapy; hippotherapy; hospitalisations because of falls; dieticians; speech and language therapy; BiPAP ventilation where required; gastrostomy if needed; surgery (e.g. for scoliosis); and occupational therapy. Potential inequalities in the availability of NHS services amongst different populations and across the UK was highlighted within submissions. A submission from a professional organisation highlighted differences in availability of health services between adults with SMA and children with SMA, as well as by a professional expert submission.

“Before the MAA there were no defined pathways for adults with SMA. There was significant local variation in care (e.g. frequency of follow-up in neurology clinic, respiratory monitoring and access with physio) depending on the local interests of the neurologist and availability of neuromuscular specialist neurologists” – Association of British Neurologists submission

“Orthotics provision is fragmented nationally as well as management of orthopaedic problems.” – Professional expert submission

A similar disparity across the UK in the ability to access Continuing Care funding was also highlighted by one patient expert submission. Not being able to access to some services through the NHS could also lead to families paying for private treatment.

“Unfortunately, physio comes in blocks on the NHS so it is not continuous throughout the year. These voids are filled with paid, private physio.” – Patient expert submission 2 (carer for a child with SMA)

[redacted]

As well as the potential of paying for services beyond the NHS, submissions and case studies also often mentioned the need for families and carers to buy their own specialist equipment to help facilitate activities of daily living and maintain a level of independence. Equipment and devices mentioned included: equipment needed for physiotherapy; wheelchairs with modifications not covered by standard healthcare services; accessible vehicles; and hot tubs for hydrotherapy. The cost of accessing these services and equipment was noted to be substantial and individuals, carers and wider families noted that they had to fundraise to be

able to afford these pieces of equipment, highlighting the wider impact of SMA on carers and families.

“Fundraising has been necessary to ensure our child gets the correct care to provide things like orthotics and private physiotherapy and other equipment that the nhs have been unable to provide” – Quotation from SMA UK/ MD UK/ Treat SMA joint organisation submission; carer of child with SMA

“[…] the financial implications this all had, especially when trying to source vital equipment that the NHS would not supply. I had to fundraise as this was my only option to purchase this equipment, which was another thing I had to take ownership of.” – Patient expert submission 2 (carer for child with SMA)

Despite the significant costs to individuals and families associated with managing SMA, the difficulty of capturing the costs associated with using private services or purchasing equipment within metrics such as QALYs was highlighted by a professional expert submission.

In terms of services associated with administering nusinersen and risdiplam, some patient expert submissions noted that there is a higher cost associated with nusinersen treatment due to the need for lumbar punctures every four months. They highlighted the need for facilities to be able to conduct the procedure, including radiology or CT scans were needed. By contrast, one patient expert submission (adult with SMA) noted that risdiplam would have less impact on the NHS because it is administered at home. However, a professional group submission also noted that specialist pharmacy knowledge and dispensing was required when prescribing risdiplam, implying a greater level of training needed to dispense the treatment. Members of patient groups who spoke with the EAG noted that, despite the costs associated with nusinersen compared with risdiplam, it was important to consider patient choice and the accessibility of both treatment options. As previously noted, a professional expert submission also highlighted that adverse events or no perceived benefits may be reasons for people to switch treatments. Furthermore, Association of British Neurologists noted that if both treatments were available outside of the current MAA, the need for monitoring in the adult population could be reduced from every 6 to every 12 months, given that motor function appears to stabilise and “no blood abnormalities have been detected”.

15.4 Summary of cost-effectiveness results

The EAG assessed the cost-effectiveness of nusinersen and risdiplam in the treatment of people with presymptomatic SMA, type 1 SMA and types 2/3 SMA. The differences in patient characteristics for nusinersen and risdiplam meant that cost-effectiveness of these DMTs were assessed by making changes to Biogen’s and Roche’s base-case models, respectively (see Section 12.2). The cost-effectiveness results should also be read in the context of the qualitative analyses (see Section 13.5), as well as specific qualitative analyses surrounding economic considerations (see Section 15.3).

15.4.1 Presymptomatic population

The EAG’s base-case analysis for nusinersen compared to BSC using the economic evidence provided by Biogen showed that [redacted]

[redacted]compared to BSC. Both the deterministic and probabilistic results were consistent, where nusinersen had a [redacted]probability of being cost-effective. Results closely aligned with Biogen's base-case economic analysis. Disease-related costs of "not sitting", "sitting without support" and "permanent ventilation" had the largest impact on the results. Scenarios with the most impact were using health-state costs from TA588[2] and TA755[3]. The scenario analysis comparing nusinersen with OA showed that [redacted].

The EAG's base-case analysis for risdiplam compared to BSC using the economic evidence provided by Roche showed that risdiplam was [redacted]and [redacted]. Parameters with the biggest impact on the ICER compared to BSC were the drug price of risdiplam, disease related costs for children at the "not sitting" and "sitting" health-states, the risk of permanent ventilation and disease-related costs for adults at "not sitting" and "walking" health states. Scenarios with the biggest impact on the ICER were the choice of time horizon, using health-state costs from TA588[2] and TA755[3], and adding carer utilities.

The scenario analysis comparing risdiplam with nusinersen, assuming equivalent effectiveness, showed [redacted]. Comparing risdiplam with nusinersen using the naïve comparison showed [redacted]. The scenario analysis comparing risdiplam with OA assuming equivalent effectiveness showed [redacted].

15.4.2 Type 1 SMA

The EAG's base-case analysis for nusinersen compared to BSC using the economic evidence provided by Biogen showed that [redacted]. The probabilistic analysis showed similar results to the base-case, indicating [redacted] probability of nusinersen being cost-effective compared with BSC. Parameters with the biggest impact on the ICER were health-state utilities and health-state costs for "permanent ventilation", "not sitting" and "sitting without support," respectively. Scenarios with the largest impact were using health-state utilities from TA755[3] and using health-state related costs from TA588[2] and TA755[3].[redacted][268][redacted] The scenario comparing nusinersen with OA showed [redacted].

The EAG's base-case analysis for risdiplam compared to BSC using the economic evidence provided by Roche showed that risdiplam was [redacted]. Parameters with the biggest impact on the ICER compared to BSC were the overall survival benefit of risdiplam, the drug cost of risdiplam, patient disease-related

costs and disease-related utilities at "sitting", as well as the benefit surrounding risk of permanent ventilation. The scenario analysis between risdiplam and BSC showed that scenarios with the biggest impact on the ICER were using the utilities from the Roche base-case analysis (based on TA755[3]), changing the length of the time horizon, and pooling patient and carer utilities. [redacted].

The scenario comparing risdiplam with nusinersen in type 1 patients showed [redacted]. The scenario comparing risdiplam with OA showed [redacted].

15.4.3 Type 2/3 SMA

The EAG's base-case analysis for nusinersen compared to BSC using the economic evidence provided by Biogen showed that [redacted]. The probabilistic analysis showed similar results to the base-case, [redacted]. Parameters with the biggest impact on the ICER compared to BSC were disease-related health-state costs for "sitting without support" and "not sitting", as well as disease-related health-state utilities. Scenarios with the largest impact on the ICER were including carer utilities, using patient utility estimates from TA755[3], using patient utility estimates from the SUNFISH trial, and using health-state costs from TA755[3] and TA588[2]. Subgroup analyses for type 2 and type 3, run separately, led to [redacted]. Assuming a £0 price for nusinersen would make nusinersen [redacted] for the type 2/3 SMA population.

The EAG's base-case analysis for risdiplam compared to BSC using the economic evidence provided by Roche showed [redacted]. Parameters with the biggest impact on the ICER compared to BSC were the drug cost of risdiplam, disease-related costs at "not sitting" and "sitting without support" for adults, and utilities for "sitting without support". Scenarios with the largest impact on the ICER were using patient disease-related health-state utilities from the Roche base-case (sourced from Lloyd et al[69]) or from the SUNFISH[49] trial, shortening the time horizon, using patient and carer utilities, and using disease-related health-state costs from the Roche base-case.

The scenario comparing risdiplam with nusinersen in type 2 and 3 patients showed that risdiplam was [redacted] than nusinersen, [redacted].

15.5 Decision modifiers

An online meeting was held between NICE, the EAG, and the manufacturers (Biogen and Roche) to discuss alternative approaches to caregiver quality of life and the severity modifiers. At this meeting, the EAG clarified that there were significant clinical differences in the data

used to populate each respective model, which led to different predictions of long-term prognosis under BSC despite the EAG's attempt to use a consistent approach to assumptions modelling long-term prognosis. As the severity modifier criteria is based on long-term prognosis, differences in modelled prognosis in the EAG's base-case (due to differences in the underlying data) led to differences in the EAG's suggested severity modifier weight for the presymptomatic population. Differences between the approaches to the severity modifier between the manufacturers and the EAG are reported in Table 15.25. [269]

Table 15.25: Differences between the manufacturer and the EAG's approach to severity modifiers for each economic model

SMA subpopulation	Biogen model		Roche model	
	Biogen's base-case	EAG's base-case	Roche's base-case	EAG's base-case
Presymptomatic	x1.2/x1.7	x1.2	*	x1.7
Type 1	x1.7	x1.7	x1.7	x1.7
Type 2/3	x1.2	x1.2	x1.7	x1.2

*Roche's base-case analysis presented a cost-comparison across DMTs, therefore the severity modifier does not alter the company's results
Abbreviations: SMA = spinal muscular atrophy; EAG = evidence assessment group

15.6 Key issues in the models and cost-effectiveness results

The EAG note that there were several key issues surrounding the modelling of cost-effectiveness for nusinersen and risdiplam. Firstly, the effectiveness data (e.g. transitions, relative effect, decline in health states) used in the cost-effectiveness models largely come from single arm trials in the absence of RCTs. Whilst it may not be always feasible or ethical to conduct a RCT for treatments in rare diseases like 5q SMA, therefore making it necessary to use the effectiveness data derived from single arm trials. However, using evidence from single arm trials where principles of randomisation and blinding cannot be applied, may introduce bias into the results, often in favour of the treatments under evaluation. [269]

The motor milestone scores used in defining the disease progression in terms of model health states are derived from different tools which vary in their scoring system. The EAG notes that assuming equivalence between health states defined by these differing tools may introduce uncertainties around motor functions, patient health states and, ultimately, in the cost-effectiveness results.

The utility scores used for each model's health states may not adequately capture the nuanced motor improvements from treatments that are meaningful to SMA patients, as well as their families and carers (e.g. lifting the head, holding objects, or sitting independently for a few seconds). These smaller but important improvements in fine motor functions highlighted in the qualitative analyses from discussions between the EAG and professional and patient organisations. To reflect these benefits, a utility increment of 0.1 was assumed and incorporated into the economic models. However, the EAG cautions that this utility increment may not fully or accurately represent the true value of these additional improvements.

The EAG's base-case models did not explicitly incorporate the utility and costs impacts of bulbar function, non-ventilatory respiratory support and scoliosis separately. These impacts were assumed to be captured within the HSUVs and associated resource utilisation costs.

The EAG was concerned that including these elements separately could result in double counting of their impact on cost-effectiveness. However, based on input from the clinical experts and patient organisations, the EAG recognises the particular importance of maintaining or improving bulbar function for people with SMA (see Section 13.5.11). In response, the EAG conducted a scenario analysis within type 2/3 model, incorporating both utility decrement and additional healthcare costs associated with bulbar function. Due to a lack of relevant data, it was not possible to model the impact of bulbar function for presymptomatic or type 1 populations. Even within the type 2/3 model, the data used to inform the bulbar dysfunction were limited and several assumptions were required. Therefore, the results of this scenario analysis should be interpreted with caution.

Carer utility increments were not incorporated in the EAG's base-case models because of concerns regarding the methodological approaches used and the robustness of the underlying evidence. There are a significant number of issues to appropriately incorporate carer utilities into the analysis requiring lots of assumptions which introduce uncertainty. Some of these assumptions include whether carer utilities vary according to the age of the person cared for, whether they vary according to the functional state in addition to the SMA type the person cared for is in, what the characteristics of the carer are (i.e starting age, sex, impact on their health and life-expectancy) in order to estimate utility scores, how long the carer can provide care for and what would happen if they were no longer able to provide care. This clearly needs significant thought and data collection to capture and incorporate in a meaningful manner. Nonetheless, qualitative discussions with patient organisations highlighted the significant financial, physical, psychological and social burdens experienced by those caring for individuals with SMA, and should not be undermined (see Sections 13.5 and 15.3). While the exclusion of carer utility gains from the EAG's base-case analysis may have understated the full value of treatments, the impact of incorporating, in a limited manner, carer utility in the cost-effectiveness results was explored through the scenario analyses to show the potential impact.

Discontinuations from treatments were informed by the MAA data but was incorporated only into the nusinersen model. Roche did not include treatment discontinuations in their model, reasoning that discontinuation from risdiplam was unlikely or impractical - however this assumption may have favoured risdiplam as the EAG's discussions with clinical experts suggested that people may discontinue or switch from risdiplam due to known adverse events, such as potential effects on fertility. The EAG also notes that the discontinuation data used in the models were based on short-term MAA follow-up, which may have overestimated the sustained benefits from treatments over the patient's lifetime. In addition, discontinuations from nusinersen incorporated into the Biogen model assume that patients discontinuing treatments would go onto receive BSC, accruing the costs and outcomes of BSC after discontinuation. However, in clinical practice, those discontinuing may switch to alternative DMTs rather than BSC alone. Due to the lack of robust evidence, the potential impact of treatment switching could not be modelled. The EAG therefore, cautions that assumptions surrounding treatment discontinuations may introduce additional uncertainty into the cost-effectiveness results.

Furthermore, in the scenario analysis comparing nusinersen with OA using the presymptomatic and type 1 models, the EAG assumed equal effectiveness between the two treatments. This assumption may be inaccurate and could potentially favour one treatment over the other. To address this, a scenario analysis was conducted assuming non-

equivalence, based on state occupancy data derived using the unanchored MAIC. However, due to the limited robustness of the unanchored MAIC data, any conclusions drawn from this analysis should be interpreted with caution.

Overall, the cost-effectiveness results are largely based on limited evidence and should be interpreted with caution. In the absence of robust comparative data, the EAG concludes that there is insufficient evidence to accurately estimate the relative net health benefits of risdiplam or nusinersen in patients with SMA.

16 Discussion

16.1 Statement of principle findings

16.1.1 Qualitative

Overall, the qualitative framework analysis highlighted the great impacts of living with SMA, not just on individuals' functional status (e.g. motor function) but also on their ability to socialise and interact with others, activities of daily living (e.g. being able to eat, wash and clothe themselves independently), and overall quality of life. The analysis also highlighted the personal financial implications of SMA on patients and their families and carers, such as the need to buy specialist equipment to facilitate daily living. Although motor function was often mentioned by people within the qualitative analyses, the data also suggested that treatments for SMA can improve bulbar and respiratory function, which in turn improves overall quality of life and people's ability to perform daily activities. Potential adverse events of either nusinersen or risdiplam were less frequently mentioned within the qualitative data.

In discussion with the EAG, it was also stated by professionals and representatives of patient organisations that outcomes such as bulbar function and stamina or fatigue were highly important to people with SMA but that data on these outcomes were less frequently captured and reported within the current evidence base; this was true of the current updated SLR. Furthermore, the qualitative analysis highlighted that the current tools used to measure motor function, of which the bulk of the quantitative analysis in the SLR focuses, are not sensitive enough to capture important maintenance and improvements in fine motor skills (e.g. being able to independently use cutlery or a wheelchair).

16.1.2 Clinical effectiveness

Motor function: In the controlled and uncontrolled evidence for both nusinersen and risdiplam, maintenance or improvement in assessed motor functions were generally reported. This was coupled with little evidence of deterioration. This is true for all types of SMA included in the report (presymptomatic, type 1, type 2/3).

Bulbar function: For nusinersen, the evidence across the SMA types suggested there was a reduction in the need for nutritional support. This was demonstrated by improvement or stability in ability to swallow, maintenance of eating function and a reduced need for gastrostomy or nasogastric tube feeding indicating overall enhancement in bulbar functions. However, there is evidence for increased need for nasogastric tube feeding in a few studies, especially those with multiple and unreported type SMA. Additionally, treated patients maintained their swallowing functions, most notably amongst SMA type 1 patients. Furthermore, there was consistent evidence of reduced need for speech therapy among participants receiving nusinersen treatment, particularly those who adhered closely to the regimen. Importantly, there was no evidence for deterioration in cry function among the patients. For risdiplam, there was similar evidence for presymptomatic and type 1 patients, with both either maintaining or improving their bulbar function. In type 1 patients there were observed increases in the number of patients able to feed orally.

Hospitalisation: Data was limited for both treatments. Risdiplam was shown, in a single study, to reduce hospitalisation rates per person year to 0.7, compared to a natural history range of 4.2 and 7.6 every year, in type 1 patients. Nusinersen reportedly had rates of 4.5 per patient year, which was higher than OA treated type 1 patients. Although hospitalisation data

for nusinersen were limited, lower SAE rates in treatment groups suggest a stabilising effect on disease progression, with potential implications for reduced hospital-based care.

Respiratory function: For risdiplam there was a general maintenance of respiratory functions among patients especially in FVC maintenance and a phase reduction in respiratory plethysmography. Additionally, no patients required ventilatory support across all SMA types. There was evidence for improved or preserved respiratory functions in most assessments across all SMA types. Notably, nusinersen-treated patients demonstrated preserved respiratory function, with no progression to permanent ventilation reported across multiple cohorts.

Complications: While complications in later-onset SMA—such as respiratory infections and scoliosis—were reported, they were generally manageable and not directly attributed to the drugs. In some cases, these complications may reflect disease progression or, to a lesser extent, the method of treatment administration, underscoring the importance of integrated, multidisciplinary long-term care, including orthopaedic and rehabilitative support.

Fatigue and stamina: With regards to patient reported fatigue and stamina, the evidence for nusinersen was mixed. Two studies among mixed type SMA reported improvement in fatigue, whilst one noted increased fatigue. There was no available patient reported evidence for this outcome assessing risdiplam treatment. For clinical measures of fatigue and stamina (i.e. 6MWT), nusinersen consistently showed improvements across different SMA types. While risdiplam had evidence from one study showing improvements in ambulant patients.

Mortality: For both drugs mortality was generally low. Both drugs were particularly impactful for type 1 patients, where natural history median life expectancy is 10 months; however 75% of patients were still alive on nusinersen after three years and 91% of patients on risdiplam after five years. Most deaths were attributed to SMA-related complications. Findings support a durable survival benefit across both infantile- and later-onset SMA, particularly with early initiation.

Adverse events: Across SMA types, both nusinersen and risdiplam demonstrated favourable long-term safety profiles, with most AEs reported as mild to moderate in severity and declining in frequency over time. SAEs were more frequently observed in control groups, and treatment discontinuation remained rare for both therapies. Long-term data consistently reinforced the tolerability and durability of clinical benefit, with no new safety signals emerging across trials.

PROMs and QoL: For nusinersen and risdiplam limited evidence was found by the SLR regarding PROMs and QoL outcomes, which were highlighted as key outcomes by the patient and professional groups. Further work is necessary here to understand the impact on patients' and carers' QoL following treatment.

Nusinersen and risdiplam (comparative evidence): A single study directly compared the efficacy of nusinersen and risdiplam in a prospective cohort. This study further highlighted the differences in populations for the two treatments, with statistically significant differences for baseline characteristics including motor function outcomes, therefore supporting the view that ITC is likely inappropriate. Both nusinersen and risdiplam showed statistically significant improvements in motor function from baseline to 6 months. However, no statistically significant difference was observed between the two treatments. Another study was identified but the

results were reported as a combination of disease modifying treatments (OA, nusinersen, and risdiplam); inferences for the individual treatments were therefore not possible.

MAA: The MAA data showed evidence of maintenance or improvement mostly for motor outcomes, across all types, for both nusinersen and risdiplam. For the paediatric registry, nusinersen had a longer follow-up data available than risdiplam (~4+ years vs ~1.5+ years, respectively) for motor outcomes. While the adult registry for risdiplam did extend to ~4 years, the patient numbers were smaller at this point than those in the nusinersen MAA. This is to be expected given the timelines of when each drug was made available, with nusinersen being made available first. The PROMS outcomes lack data, with some varying results but maintenance or improvement was reported for some scales. Similarly, the QoL results are lacking in data but do show some improvement. Importantly, mortality rates in the MAA were generally low for both treatments, and deaths that did occur appeared to not be related to treatments.

Overall, these findings support the ongoing use of both agents as safe, well-tolerated, and clinically effective options in the long-term management of SMA. However, while clinical effectiveness is evident—particularly in comparison to control groups—cost-effectiveness assessments may be less favourable, especially when compared with single-dose gene therapies. This highlights the need for continued economic evaluation and prioritisation within healthcare decision-making frameworks.

16.1.3 Cost-effectiveness

Differences in the eligible populations for nusinersen and risdiplam, reflected in the very limited comparative data and the robustness of indirect treatment comparisons and the associated MAICs, meant that the EAG did not consider it appropriate to combine the assessment of the two therapies in a single model. The EAG's base-case analysis therefore focused on evaluating nusinersen and risdiplam independently. Each treatment was compared separately against best supportive care (BSC), rather than directly against one another or against OA.

16.1.3.1 Cost-effectiveness analysis for nusinersen

Presymptomatic

Biogen compared nusinersen only with BSC for the presymptomatic population justifying this approach on the basis that there was insufficient evidence to support a reliable comparison between nusinersen and risdiplam or OA. The economic model structure in the Biogen submission focused on a set of motor-milestone gains and loses defined by the WHO-MM instrument and categorised as "not sitting", "sitting without support", "standing with support", "walking independently". The presymptomatic and type 1 models also included the risk of moving from "not sitting" to "permanent ventilation". While this focus on a defined set of motor milestones was a pragmatic approach given the available evidence, patients and clinical expert raised concerns that some of the instruments used may not capture all relevant aspects of the disease progression or treatment benefit, particularly more subtle changes in mobility.

For the presymptomatic population, Biogen used data from the NURTURE,[31,36] a single-arm study and conducted a naïve comparison against BSC using data from the control arms in ENDEAR[28] and CHERISH[29] for motor milestones. Due to a lack of events, survival assumptions in this model were informed by the most recent NICE appraisal in this area (HST24[17]).

[redacted]

Patient health-related quality of life (HRQoL) data were not collected from NURTURE nor ENDEAR, instead, the model adopted the approach to patient HRQoL from HST24[17] and applied it to the presymptomatic, type 1, and type 2 and 3 population models. The EAG noted there were large uncertainties in the utility estimates used to calculate patient HRQoL, particularly around the most severe health-states of "permanent ventilation" and "not sitting" given the methodological difficulties of measuring HRQoL on children, the severity, and the rarity of the condition.

The base-case analysis from Biogen pooled together the HRQoL of informal carers and patients using estimates from the literature and the approach from TA755[3]. As the base-case approach combined patient and carer HRQoL, a severity modifier was not applied to the results. The EAG raises concern that carer HRQoL data were not collected from the clinical studies but instead were derived from a previous NICE appraisal. Additionally, the EAG highlights there was a lack of standardisation in the methods for including informal carer HRQoL. The EAG recognises that the perspective from informal carers is relevant and an important dimension in SMA and NICE methods guidelines supports its inclusion; therefore the EAG conducted a scenario analysis pooling patient and carer HRQoL, assuming on average a single carer per patient and using more recent HRQoL estimates from Lo et al.[73] Considering the limitations in the evidence, the EAG considered it more appropriate to focus the base-case analysis on patient HRQoL alone as a better reflection of disease severity, moreover this approach also aligns with previous appraisals on this area.[250,259]

The Biogen model applied health care cost estimates from the recent NICE appraisal in this area (HST24[17]) across presymptomatic, type 1, and type 2/3 models. The EAG noted large variation in disease-related costs estimates across previous NICE appraisals (HST24[17] TA755[3]). While the EAG considers the estimates from the latest appraisal to be appropriate, it also acknowledges uncertainties around costs for "permanent ventilation", "not sitting", and "sitting without support" which can substantially influence the cost-effectiveness results.

The approach to modelling the disease included a long-term risk of motor-milestone decline beginning after [redacted] for patients receiving nusinersen, and 15 months for BSC based on the evidence available from the clinical trials and the literature. Additionally, patients receiving nusinersen were also at risk of discontinuing after which they moved to BSC, an assumption based on discontinuation observed in the trials.

Cost-effectiveness results from Biogen showed [redacted]. Parameters with the largest impact on cost-effectiveness as expected were disease-related costs estimates at "sitting without support", "not sitting", and "permanent ventilation".

The EAG analysis updated costs and mortality estimates to the most recent values, assumed a 10% increase in patient utility from treatment, and focused on patient HRQoL and meeting the criteria for the severity modifiers. The EAG also explored a scenario comparing nusinersen with OA using the evidence provided by Biogen. The EAG's base-case analysis comparing

nusinersen to BSC resulted in nusinersen being [redacted] and had [redacted] probability of being cost-effective. Uncertainty around estimates of disease-related costs above also impacted the EAG's results. The scenario analysis comparing nusinersen with OA showed that nusinersen was [redacted] and [redacted] than OA, [redacted].

Type 1

For type 1, Biogen compared nusinersen only with BSC, justifying that it was not appropriate to assess the relative effectiveness of nusinersen against risdiplam or OA, given the gaps in the relative effectiveness evidence available. The economic model structure in the Biogen submission followed the same structure as the presymptomatic population.

For the type 1 population, Biogen used data from the ENDEAR[28]-SHINE[37] controlled trial and its extension, which informed transitions in motor-milestones, risk of death and risk of permanent ventilation for both nusinersen and BSC. [redacted]

The approach to incorporate patient and informal health-related quality of life (HRQoL) in the type 1 model followed the same assumptions used in the presymptomatic model, therefore the same critiques apply to type 1 population. The approach to include disease-related health care costs in type 1 model was same as that of the presymptomatic model, however the EAG considers the concerns around the lack of robust evidence for costs in severe disease health states to be even more critical for type 1 population.

The approach to modelling the disease included a long-term risk of motor-milestone decline after [redacted] for nusinersen, and 15 months for BSC based on the evidence available from ENDEAR[28] and the literature. Patients receiving nusinersen were also at risk of discontinuing and moving to BSC based on evidence from the trials.

Cost-effectiveness results from Biogen showed that nusinersen compared to BSC [redacted]. Parameters with the largest impact the company base-case were disease-related patient utility values (although the model could not present the impact of utility values for each health-state), and the costs at "permanent ventilation", "sitting without support" and "not sitting". [redacted]

The EAG analysis updated costs and mortality estimates to the most recent values, assumed a 10% increase in patient utility from treatment, and focused on patient HRQoL and meeting the criteria for the severity modifiers. The EAG also explored a scenario comparing nusinersen with OA using the evidence provided by Biogen. The EAG's base-case analysis comparing nusinersen to BSC showed that [redacted]

[redacted]. The scenario comparing nusinersen with OA showed [redacted].

Type 2/3

For type 2/3, Biogen compared nusinersen only with BSC justifying that it was not appropriate to assess the relative effectiveness of nusinersen against risdiplam, given the gaps in the relative effectiveness evidence available. The economic model structure in the Biogen submission[33] included the same motor-milestone health states as those used in the presymptomatic and type 1 models. However, unlike the previous models type 2/3 model did not include a transition from "not sitting" to "permanent ventilation" reflecting the disease progression for type 2/3 population.

For the type 2/3 population, data were drawn from the CHERISH[29]-SHINE[37] controlled trial and extension study to inform motor milestone transitions for both nusinersen and BSC. Due to a lack of events, survival assumptions in this model were informed by the approach in the previous NICE submission HST24[17], and general UK population survival. [redacted]

The approach to include patient and informal health-related quality of life (HRQoL) followed the same assumptions as the presymptomatic and type 1 models, therefore the same critiques apply. The approach to include disease-related health care costs from the presymptomatic model was also followed for the type 1, and type 2/3 models with the same concerns regarding the high variance and lack of evidence supporting estimates of disease-related costs. After consultations with patients and clinical experts, bulbar function was featured as a key concern for patients for which there was little evidence of treatment effect from the clinical studies. The EAG included a scenario analysis explicitly modelling the impact of bulbar dysfunction as a reduction in patient HRQoL, but due to the paucity of evidence we could not inform the base-case analysis. The evidence considered to explore the impact of bulbar dysfunctions was drawn from the Roche submission[46] and involved applying disutilities and additional costs on an assumed proportion of patients in each health state (excluding death). Nevertheless, the EAG cautions that these data may not accurately reflect the characteristics of patients treated with nusinersen.

The approach to modelling the disease included a long-term risk of motor-milestone decline after [redacted] for nusinersen, and 15 months for BSC based on the evidence available from CHERISH[29] and the literature. Patients receiving nusinersen were also at risk of discontinuing and moving to BSC based on evidence from the trials.

Cost-effectiveness results from Biogen showed that [redacted].
Parameters with the largest impact on results were the carer and patient utility values, and disease-related costs at "sitting without support" and "not sitting".

The EAG analysis updated costs and mortality estimates to the most recent values, assumed a 10% increase in patient utility from treatment, and focused on patient HRQoL and meeting the criteria for the severity modifiers. The EAG also presented alternative scenarios using

patient HRQoL from the Roche submission, patient HRQoL from the SUNFISH[49] trial, and the inclusion of bulbar function based on data from the Roche type 2/3 submission[46]. The EAG's base-case analysis for nusinersen compared to BSC showed [redacted]. Scenarios with the largest impact on results were including the impact on carer HRQoL, changing the patient utility estimates to those in the Roche type 2/3 model, or using utility estimates from the SUNFISH[49] trial, [redacted].

16.1.3.2 Cost-effectiveness analysis for risdiplam

Presymptomatic

For the presymptomatic population, Roche compared risdiplam with nusinersen and OA. BSC was considered inappropriate comparator in this population, as it is rarely used in clinical practice for presymptomatic patients. The economic model structure used in the Roche submission was based on TA755[3] and defined health states focused on a set of motor milestone gains and loses measured by the HINE-2 instrument. These health states were categorised as "not sitting", "sitting with or without support", "standing with or without support", and "walking with or without support". The presymptomatic and type 1 models also included the risk of moving from "not sitting" to "permanent ventilation". While focusing on this set of motor milestones was a pragmatic approach aligned with the available the trial evidence, the patients and clinical experts raised concerns that some of the instruments used may place too much emphasis on certain aspects of disease, and they may overlook other meaningful changes in mobility and other broader treatment benefits.

For the presymptomatic population, Roche used data from the RAINBOWFISH[59] single-arm study and assumed equivalent effectiveness across risdiplam, nusinersen and OA, based on result of a naïve comparison with NURTURE[31] and SPR1NT studies.[46] Although the model included data for BSC derived from an internal, unpublished natural history study, Roche did not consider the BSC to be a relevant comparator in the decision problem as it would be quite rare in clinical for presymptomatic population not to be treated. [redacted] While the EAG acknowledges that BSC does not represent current clinical practice in the presymptomatic population; it also highlights important gaps in the relative effectiveness evidence between risdiplam and other disease modifying therapies. Therefore, from an analytical perspective, the EAG opted to include a comparison of the cost-effectiveness of risdiplam relative to the absence of risdiplam in BSC, assuming the natural history of disease progression provided by Roche for the presymptomatic model.

The Roche model assumed long-term maintenance or improvement of motor milestones after 120 months for risdiplam, nusinersen, and OA, with no risk of treatment discontinuation for patients receiving risdiplam. However, the EAG considered that this assumption may overestimate long-term benefits of risdiplam, especially given the lack of long-term follow-up data from clinical trials. Therefore, in order to improve consistency between the economic models submitted for this appraisal the EAG adopted the approach used in Biogen model and assumed a long-term risk of either maintaining or losing motor milestones after 72 months for risdiplam and 12 months for BSC, based on available trial evidence and supporting literature. The EAG acknowledges this may be a conservative assumption, particularly if further evidence

demonstrates sustained motor milestones with the disease modifying therapy. Nevertheless, the EAG considers this approach of assuming long-term risk of maintaining or losing motor milestones more appropriate given the uncertainty around long-term data.

In the absence of an appropriate estimate for treatment related discontinuation with risdiplam, the EAG retained the assumption of no discontinuations for risdiplam (and for nusinersen in the scenario analysis) in the Roche model. However, the EAG acknowledges that this is a favourable assumption for the disease modifying therapy as it may overestimate the long-term treatment benefits, particularly given the clinical expert opinion that some patients may discontinue because of adverse events or issues related to fertility.

Patient health-related quality of life (HRQoL) data was not collected from either RAINBOWFISH[59] or FIREFISH. [58] Instead, the model adopted the approach to patient HRQoL from TA755[3] and applied it through the presymptomatic and type 1 population models. The EAG noted there were large uncertainties in the utility estimates used to calculate patient HRQoL, particularly around the most severe health-states of permanent ventilation and “not sitting”, given the methodological difficulties of measuring HRQoL on children, the severity, and the rarity of the condition.

The EAG also noted the presence of negative utility values at the permanent ventilation state in the Roche base-case approach. There was a general concern about utility at this stage as utility values were anchored at death equivalent to 0, therefore gains in survival at the permanent ventilation state would count against any intervention. We consulted a clinician who showed further concern for this assumption around negative utilities at permanent ventilation. The approach adopted by the EAG based on HST24[17] assumed a utility of 0 at permanent ventilation, which is still a cause of concern but does not punish improvements in survival at this health-state. While the EAG also explored alternative scenarios with different patient utility values, any negative utilities were always assumed to be equal to 0 in our analyses.

The Roche model added separately the impact and costs of bulbar dysfunction, severe scoliosis, and non-permanent respiratory support on BSC using estimates from an internal, unpublished, natural history of disease study. The EAG was concerned this approach resulted in double-counting the disease-related burden in patient HRQoL in BSC, as the impact of disease-related events is likely to be included in HRQoL estimates of the disease. Moreover, there was a lack of evidence from the clinical studies around the impact of risdiplam on these disease-related events relative to BSC. Therefore, the EAG opted to exclude the added impact on these disease-related events in the base-case analysis.

The base-case analysis pooled together patient and informal care HRQoL based on an approach used in TA755.[3] As the base-case approach combined patient and carer HRQoL, a severity modifier should not have been applied to the results. The EAG express concern that evidence on informal carers came from a previous NICE appraisal rather than being collected in the clinical studies; at the same time there was a lack of standardisation in the methods for including informal carer HRQoL, with important differences in the approaches employed by Biogen and Roche regarding numbers of carers and the conceptualisation of the carer burden.

The EAG acknowledges that the perspective of informal carers is an important consideration in SMA and, given that the NICE methods guidelines support the inclusion of the carer HRQoL, the EAG conducted a scenario analysis that pooled together the patient and carer HRQoL,

assuming on average, a one informal carer per patient and using HRQoL estimates from a more recent study by Lo et al.[73] However, given the limitations in the evidence available, the EAG opted to focus the base-case analysis on patient HRQoL alone as a more appropriate approach to represent the severity of the disease, moreover this approach aligns with that taken in previous appraisals on this area.[250,261]

Roche's submission used an expert elicitation exercise conducted by the company to inform NHS-related and personal social services costs across patients with type 1, type 2, and type 3 SMA. Costs for presymptomatic patients were assumed to be equivalent to type 1 patients. The EAG noted considerable variation in disease-related costs estimates used in the Roche model and those from previous NICE appraisals (e.g. HST24[17] and TA755[3]), and the EAG considered estimates from the recent NICE appraisal (HST24[17]) were appropriate. However, there significant uncertainties remain around costs for "permanent ventilation", "not sitting", and "sitting with or without support", all of which have a substantial impact on the cost-effectiveness of the treatment.

Cost-effectiveness results from Roche showed that including carer and patient HRQoL risdiplam [redacted] For the comparison between risdiplam and BSC parameters with the biggest impacts on results were drug related costs for risdiplam, disease-related costs for children at "sitting" and "not sitting" health states, and patient and carer utilities at "walking".

The EAG changed the time horizon from [redacted] in the Roche base-case to 100 years, as risk improvements in survival from treatment beyond the initial time horizon would not be accounted for as well as treatment-related resource use. Only a small proportion of patients are expected to reach the end of our time-horizon, making sure that we captured all relevant health benefits and costs.

The EAG analysis incorporated updated costs and mortality estimates to the most recent data, assumed a 10% increase in patient utility from treatment, and focused on patient HRQoL and ensuring alignment with the criteria for the severity modifier. Our base-case analysis focused on risdiplam and BSC, with scenario analyses comparing risdiplam and nusinersen, and risdiplam and OA using the available evidence provided by Roche. Due to the lack of survival data in the trial, survival assumptions followed the approach from HST24.[17]

The EAG's base-case results showed that risdiplam compared to BSC [redacted]. Results were highly sensitive to the drug price of risdiplam, disease-related costs for children at the "not sitting" and "sitting" health-states, the risk of permanent ventilation and disease-related costs for adults at "not sitting" and "walking" health states. The scenario analysis comparing risdiplam with nusinersen, assuming equivalent effectiveness [redacted]. Comparing risdiplam with nusinersen using the naïve comparison showed [redacted]. The scenario analysis comparing risdiplam with OA assuming equivalent effectiveness [redacted].

Type 1

For type 1, risdiplam was compared with nusinersen, OA, and BSC. The economic model structure in the Biogen submission followed the same structure as the presymptomatic population.

For the type 1 population, Roche used data from the FIREFISH[58] trial, a single-arm trial for risdiplam, and applied the estimates from the unanchored MAIC with ENDEAR[28] to estimate the relative effectiveness of nusinersen and BSC, as well as STR1VE-EU[67] for OA. These data informed model transitions for motor milestones, overall survival, and the risk of death or permanent ventilation (from EFS data). [redacted]. In line with our concerns with the quality around the relative efficacy data available, the EAG's base-case analysis focused on comparing risdiplam with BSC, but this meant using the unanchored MAIC results between FIREFISH[58] and ENDEAR[28] as the best available evidence. The EAG also presented scenario analyses using the evidence from Roche to compare risdiplam and nusinersen, and risdiplam and OA.

The Roche model assumed long-term maintenance or improvement of motor milestones after 66 months for risdiplam, nusinersen, and OA, with no risk of treatment discontinuation for patients receiving risdiplam. The EAG challenged this assumption in the presymptomatic model and adopted the approach to modelling long-term risk of decline from the Biogen submission using estimates from the published MAIC results in Ribero et al. 2022.[66] This approach assumed that risk of maintenance of decline starts after 60 months for risdiplam and 12 months for BSC. The assumption of no discontinuation for risdiplam and nusinersen was maintained in the type 1 model, the concerns of favouring these disease-modifying therapies presented for the presymptomatic model also applied here.

Patient HRQoL data was not collected from either RAINBOWFISH[59] or FIREFISH. [58] Instead, the model adopted the approach to patient HRQoL from TA755[3] and applied it through the presymptomatic and type 1 population models. For consistency, patient utilities from HST24[17] were applied across the presymptomatic, type 1, and type 2/3 models. Our concerns around negative utilities from the presymptomatic model still applied here.

The Roche model added separately the impact and costs of bulbar dysfunction, severe scoliosis, and non-permanent respiratory support on risdiplam and BSC using estimates from the literature. The EAG was concerned about the appropriateness of this approach given the risk of double-counting the impact of disease-related events, and the gap in the evidence regarding the impact of disease-modifying therapies in this area, therefore these were excluded from the base-case analysis. The approach to incorporate carer utilities was the same for presymptomatic, type 1, and type 2/3 patients, therefore our concerns still applied here. The approach to include disease-related health care costs in type 1 model was same as that of the presymptomatic model, however the EAG considers the concerns around the lack of robust evidence for costs in severe disease health states to be even more critical for type 1 population.

Cost-effectiveness results from Roche showed that including carer and patient HRQoL risdiplam compared to BSC [redacted]. Results were sensitive to estimated overall survival improvements, estimated permanent ventilation risk improvements, and the cost of risdiplam.

The EAG analysis incorporated updated costs and mortality estimates to the most recent data, assumed a 10% increase in patient utility from treatment, and focused on patient HRQoL and ensuring alignment with the criteria for the severity modifier. The EAG also changed the time horizon from [redacted] in the Roche base-case to 100 years, as risk improvements in survival from treatment beyond the initial time horizon would not be accounted for as well as treatment-related resource use. Only a small proportion of patients are expected to reach the end of our time-horizon, making sure that we captured all relevant health benefits and costs. Our base-case analysis focused on risdiplam and BSC, with scenario analyses comparing risdiplam and nusinersen, and risdiplam and OA using published evidence from Ribero et al. 2022.[66]

The EAG's base-case analysis for risdiplam compared to BSC [redacted]. Results were sensitive to the overall survival benefit of risdiplam, the drug cost of risdiplam, patient disease-related costs and disease-related utilities at "sitting with or without support", as well as the risk of permanent ventilation. Assuming a drug price of £0 for risdiplam still led to risdiplam being above the £30,000/QALY threshold, showing there is a potential that, due to the high costs between "not sitting" and "sitting with or without support", risdiplam as a therapy was not cost-effective at £0.[268] The scenario analysis comparing risdiplam with nusinersen showed that risdiplam was [redacted] than nusinersen, [redacted]. The scenario analysis comparing risdiplam with OA showed that showed that risdiplam was more effective and less costly than OA, [redacted].

Type 2/3

For the type 2/3 model in the Roche submission, risdiplam was compared with nusinersen and with BSC. The economic model structure used in the Roche submission was based on TA755[3] and defined health states focused on a set of motor milestone gains and loses measured by the MFM-32 and the HFMSE instruments. These health states were categorised as "not sitting", "sitting with support", "sitting without support", "standing (with or without support)", and "walking (with or without support)".

Data was sourced from the SUNFISH[55] study, a controlled trial informing transitions between motor milestones for nusinersen and BSC. Due to a lack of events, survival assumptions were informed by pooled survival data from published studies identified in the literature review for type 2 patients, and general population survival for type 3 patents, and an assumption of lower overall survival for BSC. [redacted][55] [redacted]. Given the absence in survival evidence and for consistency with the previous economic models the EAG followed the survival assumptions from HST24[17], where survival gains are a result of improvements in mobility and not a directly influenced by treatment in the type 2 and 3 population.

The Roche model assumed long-term maintenance or improvement of motor milestones after 60 months for risdiplam and nusinersen, with no risk of treatment discontinuation for patients receiving risdiplam or nusinersen. The EAG challenged this assumption in the presymptomatic model and adopted the approach to modelling long-term risk of decline from the Biogen submission using published estimates from SUNFISH in Oskuoi et al. 2023.[53] This approach assumed that risk of maintenance of decline starts after 96 months for risdiplam and 12 months for BSC. The assumption of no discontinuation for risdiplam and nusinersen was maintained in the type 2/3 model, the concerns of favouring these disease-modifying therapies presented for the presymptomatic model also applied here.

Patient EQ-5D data was collected from SUNFISH[55], but the estimates were not validated by experts. Instead, the model adopted the approach to patient HRQoL from Lloyd et al. 2019[69] and applied it to the type 2 and 3. For consistency, the EAG applied patient utilities from HST24[17] across the presymptomatic, type 1, and type 2 and 3 models. Our concerns around negative utilities from the presymptomatic model still applied here. The EAG also explored a scenario using patient utilities from SUNFISH.[55]

The Roche model added separately the impact and costs of bulbar dysfunction, severe scoliosis, and non-permanent respiratory support on risdiplam and BSC using estimates from an internal, unpublished, natural history study. The EAG was concerned about the appropriateness of this approach given the risk of double-counting the impact of disease-related events, and the gap in the evidence regarding the impact of disease-modifying therapies in this area, therefore these were excluded from the base-case analysis. The EAG explored the impact of bulbar dysfunction in as a scenario to highlight the importance patients put on the impact of bulbar dysfunction.

The approach to incorporate carer utilities was the same for presymptomatic, type 1, and type 2/3 patients, therefore our concerns still applied here. The approach to include disease-related health care costs in type 2/3 model were sourced from an expert elicitation exercise conducted by Roche. For consistency in our approach, the EAG used health care costs from HST24[17] but noted the large differences in disease-related costs in both approaches, and the lack of data in this area.

Cost-effectiveness results from Roche showed that including carer and patient HRQoL risdiplam compared to BSC showed that risdiplam was [redacted]. Results were sensitive to carer utilities at “sitting without support” and “not sitting”, the cost of risdiplam, and risdiplam treatment benefits at “sitting without support”.

The EAG analysis incorporated updated costs and mortality estimates to the most recent data, assumed a 10% increase in patient utility from treatment, and focused on patient HRQoL and ensuring alignment with the criteria for the severity modifier. The EAG also changed the time horizon from [redacted] in the Roche base-case to 90 years, although this was not expected to significantly alter the results. Our base-case analysis focused on risdiplam and BSC, with scenario analyses comparing risdiplam and nusinersen, using published evidence from Ribero et al. 2022.[66]

The EAG’s base-case analysis for risdiplam compared to BSC showed [redacted]. Results were sensitive to the drug cost of risdiplam, disease-related costs at “not sitting”

for adults, utilities for “sitting without support”, and disease-related costs at “sitting without support” for adults. Using utility values from the Roche base-case or the SUNFISH trial, including carer utilities and changing the costs to the Roche base-case had a large impact on results [redacted]. The scenario comparing risdiplam to nusinersen showed that risdiplam was [redacted] than nusinersen, [redacted].

Overall, our conclusions on cost-effectiveness of nusinersen and risdiplam are broadly consistent with those reported by Biogen[33] and Roche[46],and other HTA bodies such as CADTH (Canada)[259;250] and ICER (US),[77] despite the differences in the model assumptions and input parameters.

However, these results are largely based on limited evidence and should be interpreted with caution. In the absence of robust comparative data, there remains insufficient evidence to reliably estimate the relative net health benefits of risdiplam, nusinersen or OA in patients with SMA. Therefore, there is a clear and continued need for further evidence to minimise the uncertainty in the cost-effectiveness analysis of these treatments for SMA.

16.2 Strengths and limitations of the assessment

16.2.1 Strengths

The EAG conducted a comprehensive assessment of the company submissions. These submissions were reviewed and critiqued in terms of the clinical evidence and economic models used to assess the effectiveness and cost-effectiveness of nusinersen and risdiplam. The EAG adhered to established NICE methods and best practices in health technology assessments to ensure a fair critique and assessment. The EAG conducted a thorough update of the previously conducted systematic review of the available literature assessing nusinersen and risdiplam, using standard systematic review methods.

Furthermore, the EAG also actively engaged with the clinical experts, and patient and professional organisations, to ensure the assessment accurately reflected the clinical practice and where possible, patients’ voices were heard. The inclusion of the qualitative framework analysis meant that the clinical- and cost-effectiveness results were contextualised by the experiences of people with SMA, their families and caregivers. This included their experiences of both nusinersen and risdiplam treatment, highlighting individuals’ perspectives on the treatments and what effects they may have had on their condition. The EAG conducted the framework analysis according to principles of CLIP-Q,[78] while coding and narratives surrounding the qualitative data were checked by independent researchers to ensure the analysis was adequately contextualised and no major subthemes were erroneously missed.

16.2.2 Limitations

The analysis was constrained by the lack of robust comparative data between treatments. The economic assessment had to rely on assumptions in the absence of long-term effectiveness data and discontinuations from treatment. Health state utility values incorporated into the model had significant impact on the cost-effectiveness of the treatments, however these values relied on previously collected data, mostly not representative of the trial population receiving these treatments. Moreover, results were often sensitive to the estimates of disease-related resource use, yet there was a lot of variation and uncertainty around these estimates.

In updating the clinical effectiveness SLR the EAG were unable to fully integrate the findings of the update with those of the previous SLR. In particular, the incorporation of additional outcomes identified as important by patients and professional groups was limited to the newly identified studies, in which reported data were limited for these outcomes.

The qualitative analysis was limited by several factors; these have been described in depth in Section 10.6. In brief, these limitations included: conducting a framework analysis instead of a thematic analysis; a lack of demographic information about the people included; some lack of clarity surrounding what treatment those included in the analyses were undertaking; the primary caregiver not being the respondent on behalf of children in the paediatric registry free-text data. These factors made it challenging to fully contextualise the qualitative data and, occasionally, to provide specific information surrounding peoples' experiences of nusinersen and risdiplam. It also limited the extent to which these data could be fully integrated with the other elements of the appraisal.

17 Conclusions

The previously completed technology assessments highlighted a lack of longitudinal and comparative data for nusinersen (TA588) and risdiplam (TA755). This has been addressed by longer follow-up periods of the clinical trials (~8 years for nusinersen and 5 years for risdiplam) and the use of an MAA to provide further data. For both nusinersen and risdiplam, there is evidence of maintenance or improvement of motor functions. Maintenance should be considered extremely beneficial in this patient population, as emphasised by both patients and professionals. Both drugs had an impact on mortality: for type 1 patients, compared to natural history median of 10 months life expectancy, 75% of patients were still alive on nusinersen after three years and 91% of patients on risdiplam after five years. There were no deaths in the presymptomatic group in any of the included studies. Patients with types 2 and 3 have substantially greater life expectancy and an impact of treatment would likely require much longer follow-up to be evidenced. Other evidence, such as quality of life and other patient reported outcomes, show mixed results for both nusinersen and risdiplam. There is a lack of direct comparative evidence between the two treatments and the available gene therapy. The original technology assessment for risdiplam noted that there was a lack of comparative evidence to usual care for type 1 patients. There is still no clinical trial comparing type 1 patients receiving risdiplam to treatment-naïve patients. However, the differences in eligible populations for each of the treatments means direct comparisons are difficult. There is also a lack of data for some outcomes deemed important by patients, carers, and professionals, such as bulbar function and stamina and fatigue, which conclusions difficult to make.

The cost-effectiveness studies included in the original SLR and the SLR update varied based on the target population considered, interventions and comparators included, outcomes, modelling methods, resource use and costs, health-state utility estimates, time horizons, analyses, assumptions and limitations, and patient and professional groups engagements. There was a consensus about the type of models adopted for SMA cost-effectiveness evaluation being Markov models. But the results of the SLR indicate a need for robust and reliable data on treatment effectiveness, real-world evidence generation of utility estimates and consensus in adopting resource use and estimating costs for SMA treatment evaluation.

Cost-effectiveness results by the EAG for the presymptomatic population suggested that both risdiplam and nusinersen have the potential to be [redacted] compared against BSC without a disease-modifying therapy, caveating that the evidence base in this area is still weak and relies on single-arm studies. Due to gaps in the evidence, it was challenging to compare across DMTs.

Cost-effectiveness results by the EAG for the type 1 population showed that both risdiplam and nusinersen were [redacted] when compared against BSC without a disease-modifying therapy. Further analysis showed that across both drugs it was plausible that they would not be considered cost-effective against no treatment even assuming zero drug costs. This counter-intuitive result arises from the high health-care resource use associated with patients whose mobility is below the level of being able to stand- exceeding what the health-care system is typically willing to pay. However, meaningful comparison across disease modifying therapies remains challenging because of significant evidence gaps.

Cost-effectiveness results by the EAG for the type 2 and 3 population showed that both risdiplam and nusinersen were [redacted] interventions when compared against BSC without a disease-modifying therapy. Relative to the more severe disease types above in this

patient population the benefits of both drugs were less clear-cut, with therapies helping patients maintain the motor milestones gained.

The cost-effectiveness results are largely based on limited evidence and should be interpreted with caution. In the absence of comparative data, the EAG concludes that there is insufficient evidence to estimate the relative net health benefits of comparing risdiplam to nusinersen for patients with SMA. Therefore, there is a clear and continued need for further evidence to minimise the uncertainty in the cost-effectiveness analysis of these treatments for SMA.

17.1 Suggested research priorities

There is a lack of evidence comparing nusinersen to risdiplam and either or both treatments to OA. While the eligibility criteria means there are currently differences in the populations being treated by the respective treatments, future research could aim to conduct a randomised controlled trial for DMTs. Additionally, trials assessing the safety, efficacy and cost-effectiveness of combined treatments (i.e. nusinersen, risdiplam, and OA) would provide evidence of any incremental benefits that may be available. However, the EAG acknowledges that there could be challenges in conducting RCTs for treatments of rare diseases like SMA.

Risdiplam still requires evidence for type 1 patients compared to a control (usual care) group. The clinical trial for type 1 (FIREFISH) is a single arm trial. Risdiplam should therefore be assessed in a comparative clinical trial for type 1 SMA patients.

A consistent issue highlighted throughout the review process, especially within the qualitative data, is the lack of sensitivity of motor function assessment tools. There is a focus on gross motor skills, such as sitting, rather than fine motor skills (e.g. wheelchair control) that are likely to be important for quality of life; indeed, these were highlighted in the qualitative analyses as being important functions. Further work should look to ascertain what changes in motor function are important to patients, carers, and professionals and ultimately to incorporate these into future assessments.

While the MAA has generated some real-world data, alongside other observational studies identified in the literature, there is still a lack of long-term evidence for some outcomes. For example, HRQoL and other PROMs are generally lacking. It will be important to continue to capture such outcomes, as there is currently a sparsity of data, and this leads to uncertainty about the impact of treatments. Future research should look to further capture important QoL measures over an extended period.

The cost-effectiveness results for the presymptomatic population showed the sooner patients are treated the better value for money disease-modifying therapies represent, which leads to questions around the value of testing to maximise the value of these therapies. The economic analysis for the symptomatic populations with types 1, 2 and 3 further showed the importance of exploring the disease-related resource use for the NHS and for carers and similarly the disease-related quality of life for patients and carers.

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19 Appendices

19.1 Appendix 1: Search critique and MEDLINE strategy for EAG systematic review

The previous review conducted combined clinical effectiveness and economic website searches on 25/01/24, the main clinical effectiveness database searches on 29/01/24, The main economic database searches on 30/01/24 and 31/01/24. The previous review reports the use of economic design filters. Conference abstracts were sought on all databases as part of the search. The previous review states that date and language limitations were imposed on the searches, dates aligning with the last company submissions for single technology appraisal. A summary of the search-related information is provided in the table below.

The search strategy encompassed concepts from the population, combined with the intervention, and date limitation concepts of the decision problem.

The EAG appraised the searches using the PRESS checklist and the latest NICE methods manual[42]. The number of records retrieved per search line was shown and the methods and terms used to search the conference abstracts were presented as might be expected when using the PRISMA-S reporting guidance.

EAG comments:

- All relevant studies were attained by the searches.
- Multidisciplinary electronic databases were searched and described in full, including platform, date of search, search terms, retrieved numbers, and date of coverage.
- Relevant search terms were used and combined appropriately. However, we query the use of [(spinal muscul* atroph* or SMA)] search terms, and whether this should have been an adjacency search to ensure coverage of spinal and bulbar muscular atrophy and spinal progressive muscular atrophy.
- Search terms were based on a search strategy from a previous Cochrane review. This was reported but no justification was given for adaption of the search strategy (for example the removal of terms that did not meet the population outlined in the decision problem). An economic study design filter was used and appropriately referenced/reported. No alterations were made to the filter.
- Searches excluded animal study terms, as standard practice.
- Date limitations were applied with justification. However, justification for English language limitations was not given.
- No individual conferences were searched; however, conference abstracts were included in the search strategy.
- Clinical trial databases were searched for ongoing/unpublished trials.

Search strategies	Details
Clinical effectiveness database searches	29/01/24

Search strategies	Details
	Data limitations specific to interventions Nusinersen – 01/01/2017 onwards Risdiplam – 01/01/2020 onwards Limited to English language
Economic database searches	30/01/24 or 31/01/24 Data limitations specific to interventions Nusinersen – 01/01/2017 onwards Risdiplam – 01/01/2020 onwards Limited to English language
Combined clinical effectiveness and economic website searches	25/01/24 Limitations applied where feasible Data limitations specific to interventions Nusinersen – 01/01/2017 onwards Risdiplam – 01/01/2020 onwards Limited to English language

Database(s): Ovid MEDLINE(R) and Epub Ahead of Print, In-Process, In-Data-Review & Other Non-Indexed Citations, Daily and Versions 1946 to March 10, 2025

#	Searches	Results
1	exp Muscular Atrophy, Spinal/	7026
2	(spinal muscul* atroph* or SMA).mp.	36085
3	(Werdnig adj Hoffman*).mp.	404
4	(Kugelberg adj Welander*).mp.	214
5	1 or 2 or 3 or 4	37966
6	(Nusinersen or spinraza* or isis smn* or isis 396443).mp.	961
7	(Risdiplam or evrysdi* or RG 7916 or RG7916).mp.	258
8	5 and 6	913
9	5 and 7	238
10	(201710* or 201711* or 201712* or 2018* or 2019* or 2020* or 2021* or 2022* or 2023* or 2024* or 2025*).dt,ez,da,cb.	11727236
11	8 and 10	902
12	limit 8 to yr="2017 -Current"	905
13	11 or 12	907
14	(2020* or 2021* or 2022* or 2023* or 2024* or 2025*).dt,ez,da,cb.	8802194
15	9 and 14	230
16	limit 9 to yr="2020 -Current"	230
17	15 or 16	230

#	Searches	Results
18	(exp Animals/ or exp Animal Experimentation/) not (Humans/ or exp Human Experimentation/)	5315416
19	Editorial.pt.	722508
20	13 or 17	972
21	20 not (18 or 19)	933
22	limit 21 to english language	894

19.2 Appendix 2: Domains and sub-domains included in the data extraction spreadsheet for each drug

Admin

- Reviewer
- Checker

Study characteristics

- First author surname
- Year
- Trial name
- Title
- Publication type
- Linked records
- Primary reference? (yes/no)
- NCT number
- Countries
- Funding sources
- COIs
- Design
- Aims
- Setting / data source
- Inclusion criteria
- Exclusion criteria

Intervention details

- Treatment name
- Method of administration
- Dose
- Frequency
- Treatment duration
- Switch between treatments?(yes/no with details)
- Treatment fidelity

Intervention group patient characteristics

- SMA sub-type
- Number of SMN2 copies
- Age
- Sex
- Comorbidities
- Prior treatments
- Sample size (enrolled)
- Sample size (analysed)
- N and reasons for withdrawal

Comparator group 1 (for between group studies)

- Treatment name
- Method of administration
- Dose
- Frequency
- Treatment duration
- Switch between treatments? (yes/no with details)

Comparator group 1 (for between group studies) patient characteristics

- SMA sub-type
- Number of SMN2 copies
- Age
- Sex
- Comorbidities
- Prior treatments
- Sample size (enrolled)
- Sample size (analysed)
- N and reasons for withdrawal

Data analysis

- Statistical method
- Sub-group analyses

Conclusions

- Author conclusions
- Reviewer conclusions

Admin

- Reviewer
- Checker

Reference

- First author surname
- Year
- Title

Motor function

- Measurement tool
- Follow-up time
- Results

Adverse effects of treatment

- Measurement tool
- Follow-up time
- Results

Bulbar function

- Measurement tool
- Follow-up time
- Results

Hospitalisation

- Measurement tool
- Follow-up time
- Results

Respiratory function

- Measurement tool
- Follow-up time
- Results

Complications of SMA

- Measurement tool
- Follow-up time
- Results

Need for ventilation

- Measurement tool
- Follow-up time
- Results

Stamina and fatigue

- Measurement tool
- Follow-up time
- Results

Mortality

- Measurement tool
- Follow-up time
- Results

Health-related quality of life (patients and carers)

- Measurement tool
- Follow-up time
- Results

ADLs

- Measurement tool
- Follow-up time
- Results

Ability to socialise

- Measurement tool
- Follow-up time
- Results

Emotional impact

- Measurement tool
- Follow-up time
- Results

Independence

- Measurement tool
- Follow-up time
- Results

Impact on education

- Measurement tool
- Follow-up time
- Results

Impact on ability to work

- Measurement tool
- Follow-up time
- Results

Impact on family and carers

- Measurement tool
- Follow-up time
- Results

Looking to the future (e.g., anticipatory grief, hope for the future)

- Measurement tool
- Follow-up time
- Results

Maintenance and stabilisation of condition

- Measurement tool
- Follow-up time
- Results

Patient choice

- Measurement tool
- Follow-up time
- Results

Spectrum of SMA

- Measurement tool
- Follow-up time
- Results

19.3 Appendix 3: Data extraction sheet (economic evaluation review)

Table 19.1: Completed data extraction sheet of an economic analysis in the economic evaluation systematic review update

Study details	
Study title	Onasemnogene Abeparvovec Gene Therapy and Risdiplam for the Treatment of Spinal Muscular Atrophy in Thailand: A Cost-Utility Analysis
First author	Khuntha
Co-authors	Prawjaeng, J., Ponragdee, K., Sanmaneechai, O., Srinonprasert, and Leelahavarong, P.
Source of publication Journal yy;vol(issue):pp	Applied Health Economics and Health Policy 2025;23:277-290
Publication link	https://doi.org/10.1007/s40258-024-00915-y
Language	English
Publication type	Journal article
Inclusion criteria/study eligibility/PICOS	
Population	Patients with symptomatic SMA patients (SMA type 1 age onset at 3 months, SMA type 2 age onset at 12 months, and SMA type 3 age onset at 18 months)
Intervention(s)	•Patients with SMA type 1: risdiplam plus diagnosis and SOC, or onasemnogene abeparvovec plus diagnosis and SOC •Patients with SMA type 2-3: risdiplam plus diagnosis and SOC
Comparator(s)	Disease diagnosis and SOC
Outcome(s)	Life-years (LYs), and quality-adjusted life-years (QALYs)
Study design	Economic Evaluation (cost-utility analyses)
Methods	
Target population and subgroups	SMA type 1 age onset at 3 months, SMA type 2 age onset at 12 months, and SMA type 3 age onset at 18 months, based on disease severity and treatment indications
Setting and location	Thailand

Approach to engagement with patients and others affected by the study	Interviews with patients and caregivers provided data on non-medical costs and utilities.
Study perspective	Thai health care system
Comparators	Standard of care (comprehensive approach encompassing various domains: (1) rehabilitation and bone management; (2) nutrition and swallowing care; (3) respiratory care; (4) care for other bodily systems; (5) ethical and palliative care; (6) attention to educational, emotional, and socioeconomic aspects; (7) utilization of traditional medicines; and (8) the facilitation of assistive devices essential for the patient's daily activities)
Time horizon	Time horizon: •SMA types 1-3: Lifetime horizon Cycle length: •Under the SOC, patients may experience a deteriorating health state or remain stable, while in the onasemnogene and risdiplam group, patient outcomes may improve or worsen depending on the treatment responses. These transitions occur within a 6-month cycle length according to the natural history of the disease as defined in the CHOP INTEND outcome measure.
Discount rate	3% annual discount rate
Outcome(s)	Life-years (LYs), and quality-adjusted life-years (QALYs)
Measurement of effectiveness	The Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorder (CHOP INTEND)
Measurement and valuation of preference-based outcomes	The EQ-5D-Y questionnaire (a youth version of the EuroQol measure) translated into Thai was used to interview patients and caregivers. In the absence of an EQ-5D-Y valuation study for Thailand, the published tariff from Japan (Shiroiwa et al., 2021; doi:10.1177/0272989X211001859), viewed as a prototypical country in Asia, was obtained to calculate utility values. Because of the limited number of patients, only the (A) BRND, (C) sitting, and (E) PAV health states were observed. Consequently, values for the other health states were deduced using a percentage of the difference between each health state from a study in China (Hu et al., 2022; doi.org/10.3389/fpubh.2022.1054931) that collected utility values for SMA patients from the Chinese EQ-5D-Y using data from the Chinese EQ-5D-3L valuation study as a proxy.
Methods for identifying resource use	•Hospital data bases and pharmaceutical companies •Patient and caregiver interviews

Resource use and costs	•Direct medical costs for the current practice include disease diagnosis, assistive equipment such as wheelchairs, ventilator and maintenance costs, body support, and medication costs during ambulatory care and hospitalization. •Direct non-medical costs including accommodation, transportation, meals, and indirect costs including other out-of-pocket charges for informal care, and productivity costs from caregivers.
Data source of resource use	•The costs of medical devices or equipment were retrieved from the hospital. Likewise, charges for the 114 SMA patients incurred from both out- and in-patient care were collected from the hospital database between January 2016 and December 2021, and these charges were adjusted to costs using the hospital-based ratio of charge-to-cost. The costs were calculated for each health state in each SMA subtype. •For the costs of the new treatments, pharmaceutical companies submitted drug prices for assessment in this study only. •Direct non-medical costs and productivity costs from caregivers were collected from patient and caregiver interviews during hospital visits. The interview was conducted between June 2022 and February 2023; of 114 cases, patients from 3 cases for SMA type 1 and 12 cases for SMA types 2–3 had hospital visits and were able to interview
Currency, price date and conversion	All costs were adjusted to 2023 values using the consumer price index (CPI) and the recommended WTP threshold of 4444 US dollars (USD) per QALY gained (i.e., 160,000 Thai baht per QALY gained using an exchange rate of 1 USD ≈ 36 THB)
Analytic approach and model type (if applicable)	Model: •A Markov model was constructed to simulate the progression of disease on the basis of the CHOP INTEND outcome measure. The model's population consisted of symptomatic SMA patients categorized into two groups: SMA type 1 age onset at 3 months, SMA type 2 age onset at 12 months, and SMA type 3 age onset at 18 months, based on disease severity and treatment indications. The SMA type 1 group received either onasemnogene or risdiplam, where the comparative choices included (i) onasemnogene plus diagnosis and SOC and (ii) risdiplam plus diagnosis and SOC, compared with (iii) disease diagnosis and SOC alone. The SMA types 2–3 group received risdiplam, where the comparative options included (i) risdiplam plus diagnosis and SOC and (ii) disease diagnosis and SOC alone. These decision-analytic alternatives are mutually exclusive, where the probability of each option is separate, resulting in the adoption of one of the interventions. Drug administrations for SMA type 1 and 2–3 were based on their age and weight. States: (A) a broad range of normal development (BRND; defined as able to walk independently); (B) walking with support or equivalent to SMA type 3; (C) sitting (defined as able to sit without support, stand alone, or stand with assistance) or equivalent to SMA type 2; (D) not sitting but living ventilation-free (defined as lacking head

	control, voluntary grasping, voluntary kicking or rolling over completely, and not requiring permanent ventilation) or equivalent to SMA type 1; (E) permanent assisted ventilation (PAV; defined as 16 or more hours per day of breathing support) or equivalent to SMA type 1; and 'Death'. Other points: •The Assessment of the Validation Status of Health-Economic decision models (AdViSHE) tool was used to evaluate four aspects of validation: (1) validation of the conceptual model; (2) input data validation; (3) validation of the computerized model; and (4) operational validation Transitional probabilities •Under the SOC, the 6-month transitional probabilities were analysed for SMA patients at one of the largest Faculties of Medicine in Bangkok, Thailand, from the first diagnosis in 1999 to the current diagnosis in 2021, which included 114 patients. •Onasemnogene effectiveness, derived from clinical trials [NCT02122952, NCT03306277, NCT03461289] and unpublished data, was provided by the pharmaceutical company to calculate health state transitions. Two probabilities were observed from the data, namely (D) not sitting to (C) sitting and (C) sitting to (B) walking transitions. •Deaths, as reported from the clinical trials [NCT02122952, NCT03306277, NCT03461289], were compared with the SOC in Thailand. •For risdiplam, unpublished data from clinical trials were provided by the pharmaceutical company for the calculation of health state transitions and mortality for both SMA type 1 [NCT03306277, NCT03461289] and types 2–3 [NCT02391831, NCT02908685].
Assumptions	•Patients entering the model were confirmed SMA by genetic testing. The population in this study was confirmed to be SMA as symptomatic patients who passed genetic testing. So, the related costs were included. •Patients entering the model can start at any health state by adjusting the proportion from data of Thai patients. Once patients are diagnosed, they have different disease severity according to the age of onset and the number of SMN2 copies. So, patients can start in the model at any health state to be consistent with the nature of the disease. •Patients have a chance to move to any health state. In this study, a 6-month cycle length was used. So, patients can improve or worsen their health states according to clinical evidence and the experts •The effect of onasemnogene was assumed to prolong the lifetime of patients despite it being administered once. According to the indication of onasemnogene, it is administered once in the early stage of a patient's life. Moreover, it is a gene replacement that would yield a normal gene once it is fixed. Although the follow-up periods after treatment in the clinical studies were not long enough to capture a lifetime, the effects will be extrapolated based on the longest follow-up time (i.e., 12-24 months). •The mortality rate from other causes of death will be applied to death

	in the general population in Thailand. In this model, all patients have a chance of death from other causes in addition to disease-related mortality. So, the life table of death in the general population will be used to inform this value.
Results	
Study parameters	Characteristics of patients included in the study, transitional probability in the SOC, mortality rate in the SOC, probability of death in the general population in Thailand, treatment effects of onasemnogene and risdiplam, drug administration and unit costs of onasemnogene and risdiplam, risdiplam price per age and body weight in the Thai population, direct medical costs in the current practice, direct non-medical and indirect costs, disutility
Total QALYs	SMA type 1: •Onasemnogene: 11.66 •Risdiplam: 6.56 •SOC: 1.82 SMA type 2-3: •Risdiplam: 15.83 •SOC: 10.71
Total LYs	SMA type 1: •Onasemnogene:16.09 •Risdiplam: 12.51 •SOC: 3.07 SMA type 2-3: •Risdiplam: 22.01 •SOC: 16.00
Total Costs	SMA type 1: •Onasemnogene: 1900000 •Risdiplam: 1045000 •SOC: 294000 SMA type 2-3: •Risdiplam: 2753000 •SOC: 211000
ICER/QALY:	USD/QALY gained: •SMA type 1: Onasemnogene vs SOC: 163102 •SMA type 1: Risdiplam vs SOC: 158357 •SMA type 2-3: Risdiplam vs SOC: 496704
Characterising uncertainty	•Sensitivity analysis was used to examine the effects of uncertainties on the model's input parameters. One-way sensitivity analysis (OWSA) was used to assess each parameter's impact on the ICER by varying its lower bound and upper bound values while holding all other parameters constant. •Probabilistic sensitivity analysis was used to assess the uncertainties of all parameters at once using a Monte Carlo simulation with 1000 iterations •Scenario analysis was used to calculate ICER values at different percentages of reduction in treatment costs

Discussion	
Study findings	•For SMA type 1, given a WTP threshold of 4444 USD per QALY gained, the SOC has a 99% chance of being cost effective. If the WTP threshold were increased to 153,000 USD per QALY gained, both onasemnogene and the SOC would share similar probabilities (36%). If the WTP were to reach 278,000 USD per QALY gained, onasemnogene would have a 76% chance of being cost-effective. •For SMA types 2–3, given the current WTP threshold, the SOC is the 100% cost-effective option. Risdiplam and the SOC would have similar probabilities of being cost-effective (i.e., 54% versus 46%) were the WTP threshold to approach 500,000 USD per QALY gained. Likewise, risdiplam would have a 99% chance of being a favourable treatment were the WTP value to soar past 556,000 USD per QALY gained
Limitations	•Adverse events from treatments were excluded because of the nature of the disease and its numerous complications, although the costs and ebbing quality of life resulting from adverse events were implicitly included in medication costs and utilities per each health state. •While this study optimized the benefits of using real-world data from Thai patients to calculate transitional probabilities in the SOC, rather than data using derived from clinical trials, only rare cases were available, thus the data could only be analysed for the transition from health states (D) not sitting to (E) PAV in SMA type 1. •Because the clinical trials encountered a limited number of patients, with rare cases and characteristics, there was concern over the applicability of the effectiveness data. The clinical trials were single-arm, open-label, nonrandomized, and non-blinded, with a historical cohort as a control. Due to a limited number of treatment options for a well-characterized and life-threatening disease, conducting a placebo-controlled study was considered unethical, making it one of the few data sets available for this study •In addition, the patient data in this study relied on a single site, albeit one that represented 50% of all patients in the country, the consideration of this finding for the national policy should be made cautiously. Given the rare cases, only the (D) not sitting to (E) PAV health state transition could be analysed for SMA type 1. Besides that, the mortality data for SMA types 1 and 2–3 were aggregated because there was inadequate data to analyse each health state on its own. Some medical costs in SMA type 1 were also borrowed from SMA types 2–3, in the case of health states (A) BRND, (B) walking, and (C) sitting. •For the utility values, 15 cases represented only health states (C) sitting and (E) PAV. Hence, a study from a similar setting in China was obtained to inform any proportional adjustments to the other health states.
Generalisability	See limitations above.
Other	

Source of funding	Open access funding provided by Mahidol University. This study was supported by the Siriraj Research Developmental Fund, Faculty of Medicine Siriraj Hospital, Mahidol University [grant no. (IO) R016532007]
Conflicts of interest	The authors declare that they have no conflicts of interest
Comments	Even though risdiplam and onasemnogene are available in Thailand, these treatments are not yet included on the reimbursement list for the Thai universal health coverage (UHC) plan. In early 2023, the Rare Disease Care Working Group under the National Health Security Office (NHSO) Subcommittee for Scopes and Types of Health Services, which oversees the Thai UHC reimbursement list, together with the Subcommittee for the National List of Essential Medicines (NLEM), which administers the Thai pharmaceutical reimbursement list, required supporting evidence before determining whether the novel therapies should be included in the reimbursement lists. Therefore, this study aimed to evaluate the cost-utility of the existing Thai FDA-approved treatments (namely risdiplam and onasemnogene) in addition to the current healthcare services for SMA including disease diagnosis and SOC.
Authors conclusion	While onasemnogene and risdiplam exceeded the value-for-money threshold of the Thai healthcare system, they yielded the highest QALY gains among all approved medications. Policymakers should incorporate various pieces of evidence alongside the cost-effectiveness results for rare diseases with costly drugs. Additionally, cost-effectiveness findings are useful for price negotiations and alternative financial funding, which allows policymakers to seek solutions to ensure patient access, aligning with universal health coverage principles in Thailand.
Reviewer's conclusion	From a Thai context neither onasemnogene nor risdiplam were shown to be cost-effective for SMA type 1. In addition, risdiplam was not cost-effectiveness for SMA types 2-3. Discount rates for both costs and outcomes were the most influential parameters to the calculated mean ICER values. In a scenario analysis, despite drug price reductions of up to 75% neither treatment option achieved cost-effectiveness in the Thai context. Although there were limitations within this study, it is reported to be one of the first studies to investigate the cost-utility of onasemnogene and risdiplam in symptomatic SMA types 1, 2, and 3 patients in the LMIC context. While highlighting the ICERs of these treatments are high, this study provides evidence on the economic and health consequences of these high-cost treatments for policy consideration in other LMIC settings.

19.4 Appendix 4: Table of included studies for nusinersen

Study name	Country	Data source	Study design	Population	Comparator	Outcomes	Subgroups analysed	Follow-up
AlRuthia 2021[164]	Saudi Arabia	Parents/ carers interviewed	Cross sectional	n = 36 parents/carers Patients: Nusinersen: Type 1 (54%), other types NR	Standard care: Type 1 (25%), type 2 (53%), type 3 (22%)	HRQoL	NA	NR
AlTawari 2024[270]	Kuwait	Treatment centres	Retrospective Case series	n = 38 Paediatric: n = 20 Type 1 (40%), type 2 (40%), type 3 (20%) Adult: n = 18 Type 2 (11%), type 3 (89%)	NA	Motor function Adverse effects	NA	80 months
Aragon-Gawinska 2020[132]	France, Belgium	Registry data	Retrospective Before after	n = 53 Type 1 Mean age = 22 months	NA	Motor function Mortality Adverse effects	Sitter, non-sitter	14 months
Arslan 2023[220]	Turkey	Treatment centre	Prospective Before after	n = 32 Type 2 (19%), type 3 sitters (50%), type 3 walkers (31%) Median age = 33.5 years	NA	Motor function Adverse effects ADL	NA	23 months
Audic 2020[186]	France	Treatment centres	Retrospective Before after	n = 123 Type 1 (28%), type 2 (72%)	NA	Motor function Nutrition support Ventilation Adverse effects	<2 years, >2 years	1 year
Audic 2024[183]	France	Treatment centres	Retrospective Before after	n = 57 Type 1 (56%) , type 2 (44%)	NA	Motor Nutrition support Ventilation	NA	36 months

Study name	Country	Data source	Study design	Population	Comparator	Outcomes	Subgroups analysed	Follow-up
				Median age = 16 months		Complication Socialisation		
Axente 2022[191]	Romania	Treatment centre	Retrospective Before after	n = 34 Type 1 (32%), type 2 (47%), type 3 (21%)	NA	Motor function	NA	26 months
Bahadir Senol 2025[101]	Turkey	Hospital files	Retrospective Before after	n = 33 Type 1 (45%), type 2 (41%), type 3 (12%)	NA	Motor function Adverse effects	NA	NR
Barp 2023[102]	Italy	Treatment centre	Prospective controlled	n = 37 Nusinersen: n = 17 Type 2 (57%), type 3 (43%) Healthy control: n = 20	Healthy controls	Motor function	NA	NR
Belancic 2023[195]	Croatia	Treatment centres	Retrospective	n = 52 Type 1 (35%), type 2 (12%), type 3 (54%) Median age = 13.4 years	NA	Motor function Feeding support Respiratory function Treatment switch	NA	NR
Berti 2022[133]	Italy	Treatment centre	Prospective Before after	n = 20 Type 1 Mean age = 6.5 months	NA	Oral and swallowing	Normal swallowing Tube feeding + by mouth Tube feeding no tracheostomy Tracheostomy + tube feeding	62 months
Bjelica 2023[229]	Germany	Treatment centre	Prospective Before after	n = 38 Type 1 (3%), type 2 (37%), type 3 (55%), type 4 (5%) Mean age = 38.4 years	NA	Motor function Respiratory function Fatigue QoL	SMA types SMN2 copy number Baseline HFMSE score	30 months

Study name	Country	Data source	Study design	Population	Comparator	Outcomes	Subgroups analysed	Follow-up
							Previous spinal infusion Use of NIV Use of PEG	
Bonanno 2020 (child)[103]	Italy	Treatment centre	Prospective Before after	n = 21 Type 2 (76%), type 3 (24%)	NA	Motor function	NA	6 months
Bonanno 2022 (adult)[104]	Italy	Multiple treatment centres	Retrospective Before after	n = 78 Type 2 (9%), type 3 (88%), type 4 (3%)	NA	Motor function Fatigue HRQoL	Sex SMN2 copies Disease duration	14 months
Brakemeier 2021[217]	Germany	Treatment centre	Prospective Before after	n = 57 Type 2 (55%), type 3 (45%) Mean age = 38.5 years	NA	Motor function Bulbar function	SMA type	14 months
Cavaloiu 2024a[271]	Romania	Treatment centres	Prospective Before after	n = 37 Type 2 (62%), type 3 (38%) Median age = 29 years	NA	Motor function	NA	54 months
Cavaloiu 2024b[272]	Romania	Treatment centres	Prospective	n = 43 Type 1 (12%), type 2 (60%), type 3 (28%) Median age = 20 years	NA	HRQoL	NA	6 months
Chacko 2022[196]	Australia	Treatment centre	Prospective Before after	n = 28 Type 1 (25%), type 2 (43%), type 3 (32%)	NA	Motor function	NA	12 months
Chen 2024[273]	China	Treatment centre	Retrospective Before after	n = 52 Type 1 (10%), type 2 (77%), type 3 (13%) Median age = 44.5 months	NA	Motor function	NA	14 months
CHERISH[29]	International	Treatment centres	Prospective RCT	Nusinersen: n = 84 Type 2 and 3	Sham injection	Motor function	NA	15 months

Study name	Country	Data source	Study design	Population	Comparator	Outcomes	Subgroups analysed	Follow-up
				Sham: n = 42 Type 2 and 3				
Chiriboga 2016[167]	USA	Treatment centres	Prospective Before after	NR	Nusinersen at different doses	Safety Tolerability Motor function Quality of life	NA	9-14 months
Cho 2023[202]	South Korea	Dataset 1: Reimbursement data Dataset 2: Treatment centres	Retrospective Before after	n = 137 Type 1 (15%), type 2 (75%), type 3 (9%)	NA	Motor function	NA	1, 2 and 3 years
Coratti 2021[144]	Italy, USA, UK	Specialised neuromuscular sites	Prospective Before after	n = 77 Type 2 Mean age = 7.47 years	NA	Motor function	Age	12 months
Coratti 2024[143]	Italy	iSMAc consortium	Retrospective Before after	n = 130 Type 2	NA	Motor function	Age	12 months
CS2/CS12[222]	USA	Treatment centres	Prospective	n = 47 Type 2 (39%), type 3 (61%) Mean age = 8 years	NA	Motor function Adverse effects	NA	6 months post-treatment
D'Amico 2019[105]	Italy	EAP (Italy), 1 hospital	Prospective Before after	n = 57 Type 1 (66%), types 2 and 3 (33%)	NA	Motor function Bulbar function Respiratory function Adverse events QoL	NA	NR
de la Banda 2021[168]	France	Treatment centres	Prospective Before after	n = 54 Type 1 and 2 Mean age = 8.2 years	Untreated controls	Motor function	NA	6 months
De Wel 2021[211]	Belgium	Treatment centre	Prospective/ Retrospective	n = 64 Types 3 and 4 Mean age = 6.5 years	NA	Motor function	NA	14 months
Duan 2022[124]	China	Beijing Meier Advocacy &	Prospective Non-	Nusinersen: n = 51	Treatment naïve	HRQoL	NA	Three surveys

Study name	Country	Data source	Study design	Population	Comparator	Outcomes	Subgroups analysed	Follow-up
		Support Center for SMA (Meier)	randomised trial	Type 1 (27%), type 2 (59%), type 3 (14%) Non-medication: n = 281 Type 1: (16%), type 2 (59%), type 3 (25%)				conducted: December 2019, April 2020 and September 2020
Duong 2021[225]	USA	NR	Prospective Before after	n = 42 Type 2 (43%), type 3 (57%) Mean age = 34 years	NA	Motor function Respiratory function	SMA type SMN2 copies Functional status History of spinal surgery	24 months
EAP (multiple)[112]	International	EAP (multiple locations), Treatment centre	Prospective Cohort study	n = 33 Type 1 Median age = 21.3 months	NA	Motor function Respiratory function	SMN2 copies	6 months
Edel 2021[131]	UK	EAP (UK)	Prospective Before after	n = 20 Type 1 Median age = 9.5 months	NA	Respiratory function	NA	18 months
EMBRACE[30]	US/Germany	Treatment centres	Prospective RCT	Nusinersen: n = 14 Multiple types, patients who are ineligible for ENDEAR and CHERISH Sham: n = 7 Multiple types, Multiple types, patients who are ineligible for ENDEAR and CHERISH	Sham injection	Adverse effects		14 months
ENDEAR[28]	International	Treatment centres	Prospective RCT	Nusinersen: n = 80 Type 1	Sham injection	Motor function Time to death or		13 months

Study name	Country	Data source	Study design	Population	Comparator	Outcomes	Subgroups analysed	Follow-up
				Sham: n = 41 Type 1		permanent ventilation Survival		
Erdem 2024[216]	Turkey	Treatment centre	Retrospective Before after	n = 31 Type 2 (6%), type 3 (94%) Mean age = 36 years	NA	Motor function QoL	NA	15 months
Fainmesser 2022[205]	Israel	Treatment centre	Prospective Before after	n = 37 Type 2 (41%), type 3 (59%) Mean age = 38 years	NA	Motor function Respiratory function	NA	Baseline, 6 months, then every 4 months up to 30 months
Finkel 2021[134]	USA/Canada	Treatment centres	Prospective Before after	n = 23 Type 1 Mean age = 141 days	NA	Motor function Event-free survival Adverse events	SMN2 copies	3.7 years
Freigang 2021a[274]	Germany	Nine neurological specialist care centres	Retrospective Before after	n = 234 Type 2 (34%), type 3 (66%) Mean age = 36.2 years	NA	Motor outcomes	NA	18 months
Freigang 2021b[129]	Germany	4 motor neuron disease specialist centres	Prospective Controlled	Nusinersen: n = 79 Type 1, 2 and 3 Mean age = 31 years Healthy controls: n = 30	Controls matched by age and sex; not administered nusinersen	Motor	SMA type SMN2 copies	14 months
Freigang 2023[228]	Germany	Neurology department of one hospital	Prospective Before after	n = 24 Type 2 (42%), type 3 (58%)	NA	Respiratory function	NA	Follow-up visit 1: n=22, 15.5 months Follow-up visit 2: n=19, 26.6 months Follow-up visit 3: n=9, 38.3 months

Study name	Country	Data source	Study design	Population	Comparator	Outcomes	Subgroups analysed	Follow-up
Gaboli 2024[275]	Spain	EAP (Spain); Hospital	Prospective Before after	n = 28 Type 1 (39%), type 2 (43%), type 3 (19%)	NA	Bulbar function Respiratory function	NA	24 months
Gauthier 2021[107]	USA	Dataverse claims database (US)	Retrospective Before after	Mean age and SD (median in brackets) Type 1 discontinuation (n=11): 0.82 ± 0.75 (1.00) Type 1 non-discontinuation (n=12): 0.67 ± 0.49 (1.00) Type 2 discontinuation (n=24): 2.92 ± 1.61 (3.00) Type 2 non-discontinuation (n=17): 2.76 ± 1.03 (3.00) Type 3 discontinuation (n=146): 12.49 ± 8.53 (10.00) Type 3 non-discontinuation (n=114): 17.53 ± 11.44 (14.50)	NA	Speech therapy Need for nutritional support - gastrostomy Nasogastric tube	Discontinuation versus no discontinuation Adherent versus non-adherent	NR
Goedeker 2024[151]	USA	Local tertiary care centres	Retrospective Before after	n = 29 Mean age at last follow-up: 8.5 months	NA	Adverse events ventilation motor functions mortality	NA	N/A - retrospective, reviewed laboratory reports
Gonski 2023[180]	Australia	Two tertiary treatment sites	Retrospective Before after	n = 48 Type 1 (21%), type 2 (48%), type 3 (31%) Mean age = 6.98 years	NA	Motor function Hospitalisations Respiratory function Ventilation	NA	2 years before and 2 years after treatment started

Study name	Country	Data source	Study design	Population	Comparator	Outcomes	Subgroups analysed	Follow-up
Govoni 2024[145]	Italy	Multiple treatment centres	Retrospective Before after	Type 3 Mean age = 39.7 years	NA	Motor function Fatiguability	NA	14 months
Gunther 2024[214]	Germany, Austria and Switzerland	SMArtCare platform	Prospective Before after	n = 237 Type 1: 14 months: 5/237 (2%), 26 months: 3/171 (2%), 38 months: 2/120 (2%) Type 2: 14 months: 67/237 (28%), 26 months: 44/171 (26%), 38 months: 33/120 (27%) Type 3: 14 months: 156/237 (66%), 26 months: 117/171 (68%), 38 months: 83/120 (69%0 Type 4: 14 months: 9/237 (4%), 26 months: 7/171 (4%), 38 months: 2/120 (2%)	NA	Motor function	NA	171 patients with a treatment period of 26 months, and 120 patients with a treatment period of 38 months
Hagenacker 2020[215]	Germany	Multiple treatment centres	Prospective Before after	n = 173 6-month analysis Type 1 (2%), type 2 (36%), type 3 (62%) Mean age = 36 years 10-month analysis Type 1 (1%), type 2 (33%), type 3 (65%), type 4 (1%) Mean age = 37 years 14-month analysis Type 2 (35%), type 3	NA	Motor function	NA	Minimum treatment time of 6 months to a follow-up of up to 14 months

Study name	Country	Data source	Study design	Population	Comparator	Outcomes	Subgroups analysed	Follow-up
				(65%) Mean age = 33 years				
Hodgkinson 2021[128]	Canada	National registry	Retrospective Controlled	n = 146	Treatment naïve	Motor function	NR	
Huang 2025[276]	China	Hospital	Prospective Before after	n = 49 Type 2 (67%), type 3 (33%)	NA	Motor function HRQoL Independence	Disease duration	18 months
Ip 2024[185]	Hong Kong	EAP (Hong Kong); Multiple treatment centres	Prospective Before after	n = 23 Type 1 (35%), type 2 (30%), type 3 (35%) Median age = 5.8 years	NA	Motor function	NA	Median follow-up of 3.4 years
Jiang 2024[277]	China	Multiple treatment centres	Retrospective Before after	n = 50 Type 1 (20%), types 2/3 (80%) Median age = 4.6 years	NA	Adverse events Motor function	Age	2 years
Kariyawasam 2021[192]	Australia	Treatment centre	Prospective Before after	n = 20 Type 1 (30%), type 2 (50%), type 3 (20%) Median age = 12 months	NA	Motor function	NA	Median 13.8 months (4–33.5)
Kolbel 2022[278]	Germany	NR	Prospective Before after	n = 45 Type 1 or 2	Watchful waiting	Carer QoL	NA	NR
Konersman 2020[199]	USA	Treatment centre	Retrospective Before after	n = 35 Type1 (11%), type 2 (40%), type 3 (37%)	NA	Motor function	NA	22 months
Kotulska 2022[194]	Poland	16 paediatric sites	Prospective Before after	Presymptomatic (1.4%) Type 1 (44%), type 2 (23%), type 3 (32%) Mean age = 6.9 years	NA	Motor function	Outcome measure CHOP-INTEND, HFMSE	1 year
Kroksmark 2023[169]	Sweden	Treatment centre	Prospective Before after	N = 20 Type 2 (55%), type 3 (45%)	No formal comparator, but when	Motor function Bone mineral density Biochemical	NA	2 years

Study name	Country	Data source	Study design	Population	Comparator	Outcomes	Subgroups analysed	Follow-up
					nusinersen was approved, the patients were started on treatment, from youngest first. At baseline, none of the patients were treated with nusinersen, By follow-up, 10 had started treatment	assessments Nutritional status		
Krupa 2023[279]	Poland	Polish healthcare system	Retrospective Before after	n = 875 Presymptomatic (2%) Type 1 (25%), type 2 (24%), type 3 (49%)	NA	Time to death Ventilation	Later vs earlier treatment	2014-2022, 2019-2022. Assessments taken every year (2019, 2020, 2021, first five months of 2022)
Lavie 2021[135]	Israel	SMA specialised referral centre	Retrospective Before after	n=20 Type 1	NA	Bulbar function Spinal deformities	NA	3 years
Le Goff 2023[108]	France	Multiple treatment centres	Retrospective Before after	n = 41 Type 1 (54%), type 2 (46%) Age = 2.81 ± 0.82 years (type 1), 3.53 ± 0.73 years (type 2)	NA	Motor function	SMA type	Mean 17 months
Lee 2024[238]	South Korea	Treatment centres	Prospective Before after	n = 24 Type 2 (79%), type 3 (21%)	NA	Motor function Ventilation Feeding support Adverse effects Complications	Sex Ventilator support Scoliosis	26 months

Study name	Country	Data source	Study design	Population	Comparator	Outcomes	Subgroups analysed	Follow-up
						HRQoL ADL Caregiver burden	Contracture SMA type	
Lemska 2024[280]	Poland	Treatment centre	Prospective Before after	n=23 Type 1 (70%), type 2 (31%), type 3 (13%) Mean age = 31.09 months	NR	Motor function	NR	22 months
Li 2024a[127]	China	Treatment centre	Retrospective Case control	n=42 Type 2 (76%), type 3 (24%) Mean age = 57 months	n = 42 healthy controls	Motor function	NR	6 months, 14 months
Li 2024b[281]	China	Treatment centres	Retrospective Before after	n = 84 Type 1 (11%), type 2 (68%), type 3 (21%) Mean age = 6.47 years	NA	Motor function	NA	14 months
Li 2024c[282]	International	FAERS database	Retrospective Before after	n=4807	NR	Adverse events	NR	NR
Li 2025[109]	China	Hospital	Retrospective Before after	n = 42 Type 1 (29%), type 2 (62%), type 3 (9%)	NA	Motor function Adverse effects	Age	24 months
Lilien 2024[283]	International	Multiple treatment centres	Prospective Before after	n=99 Type 1, 2, 3 Median age = 11.2 years	NR	HRQoL	Non-responder Responder non-clinically significant Responder clinically significant	15 months
Lusakowska 2023[188]	Poland	Treatment centres	Prospective Before after	n=20 Type 1 (10%), type 2 (16%), type 3 (74%)	NA	Motor function Adverse events	NR	30 months
Maggi 2020[208]	Italy	18 secondary or tertiary care centres	Retrospective Before after	n=116 Type 2 (11%), type 3	NA	Motor function Respiratory function Adverse events	SMA type	6 and 14 months

Study name	Country	Data source	Study design	Population	Comparator	Outcomes	Subgroups analysed	Follow-up
				"sitters" (44%), type 3 "walkers" (45%)				
Mendonca 2021a (Clinical)[136]	Brazil	Treatment centre	Prospective Before after	n = 21 Type 1	NA	Motor functions Nutritional support Respiratory support	NA	6-24 months
Mendonca 2021b (RWD)[237]	Brazil	Treatment centre	Retrospective Before after	Nusinersen: Type 2 (47%), Type 3: (53%)	Control group Type 2 (44%), type 3 (46%)	Motor functions Hospitalisation	NA	12 and 24 months
Meyer 2021[235]	Germany	Treatment centres	Prospective Before after	n = 151 Type 1 (6%), type 2 (34%), type 3 (60%)	NA	Motor function Respiratory function ADLs	NA	No follow-up
Modrzejewska 2021[184]	Poland	Treatment centres	Prospective Before after	n = 26 Type 1 Median age = 23 months	NA	Motor function	NA	18-26 months
Moshe-Lilie 2020[218]	NR	Chart review	Retrospective Before after	n = 22 Type 2 (41%), type 3 (59%) Median age = 36 years	NA	Motor function	NA	24 months
NICE 2020[146]	UK	European registries	Prospective Before after	n = 168 Type 3 (non-ambulant) Adults and children	NA	Motor function	NA	NR
NICE-SMA study[125]	India	Treatment centre	Prospective Controlled before-after	SMA: n = 16 (nusinersen) n = 26 (standard of care) Type 2 (40%), type 3 (60%)	Natural history cohort: n = 72	Motor function QoL Adverse effects	NA	12 months
NURTURE[31,231]	International	Treatment centres	Prospective Before after	n=25 Presymptomatic Mean age = 20.5 days	NA	Motor function Respiratory function Adverse events	NA	5 years
Okamoto 2020[189]	Japan	Treatment centres	Retrospective Before after	n=21 Type 1 (43%), type 2 (24%), type 3 (24%),	NA	Motor function	NA	NR

Study name	Country	Data source	Study design	Population	Comparator	Outcomes	Subgroups analysed	Follow-up
				type 4 (5%), unidentified (5%) Adults and children				
Osmanovic 2021a[234]	Germany	Treatment centre	Prospective Before after	n= 28 Type 2 (46%), type 3 (50%), type 4 (4%) Median age = 36 years	NA	Motor function Treatment wearing	NA	34 months
Osmanovic 2021b[213]	Germany	Neuromuscular centres	Prospective Before after	n=31 Type 2 (36%), type 3 (59%), type 4 (5%) Mean age = 35.4 years	NA	Motor function Patient satisfaction	NA	2 months
Osredkar 2021[175]	Slovenia/ Czech Republic	Treatment centres	Prospective Before after	Median age (range in years), 8.6 (0.2e18.8) Type 1 (26%), type 2 (52%), type 3 (21%)	NA	Motor functions	SMA type	14 months
Pane 2019[137]	Italy	EAP (Italy)	Retrospective Before after	n=85 Type 1 2 months to 15 years	NA	Motor functions	NA	12 months
Pane 2021[138]	Italy	EAP (Italy)	Prospective Before after	n = 122 Type 1 Mean age = 3.96 years	NA	Motor functions	Non-sitter Sitter	2 years
Pane 2022(iSMAc)[171]	Italy	Registry	Retrospective Before after	n=111 Type 2 (41%), type 3 (59%) Mean age = 12.51 years	Compared to untreated group but no information provided about characteristics of comparator	Motor functions	NA	24 months
Pane 2023[139]	Italy	EAP (Italy)	Prospective Before after	n=48 Type 1 Mean age = 3.3 years	NA	Motor functions	NA	4 years (results from 2 years previously reported)
Pane 2024[284]	Italy	National registry	Prospective Before after	n = 75 Type 1	NA	Motor function Tube feeding	NA	12 months

Study name	Country	Data source	Study design	Population	Comparator	Outcomes	Subgroups analysed	Follow-up
				Nusinersen (n = 69) Switched to OA (n = 18) Switched to risdiplam (n = 5)				
Pechmann 2022[181]	Germany/ Austria/ Switzerland	SMArtCare registry	Prospective Before after	n=256 Type 2 (85%), type 3 (15%) Mean age: Younger sitters: 30.8 months Older sitters: 120.9 months Lost sitters: 98.5 months Lost walkers: 134.7 month	NA	Motor functions Need for ventilator support Need for tube feeding Mortality Adverse events	Sitter types Number of copies	Maximum follow-up period of 38 months
Pechmann 2023a[140]	Germany/Austria/ Switzerland	SMArtCare registry	Prospective Before after	n = 88 (cohort 1) SMA type not reported Mean age = 8.4 months	n = 55 (cohort 2) Mean age = 89.8 months	Motor functions Need for ventilator support Need for tube feeding Mortality Adverse events	Sitter types Number of copies	Maximum follow-up period of 38 months
Pechmann 2023b[212]	Germany/ Austria/ Switzerland	SMArtCare registry	Prospective Before after	n = 231 Mean age: Pediatric walker: 103.3 months Adult walker: 443.5 months SMA type: Any type- Did not include type 3 who had lost ambulation	NA	Motor function Need for ventilator support Need for tube feeding Mortality Adverse events	Paediatric walkers Adult walkers	Up to 38 months follow-up

Study name	Country	Data source	Study design	Population	Comparator	Outcomes	Subgroups analysed	Follow-up
Peng 2025[285]	China	Hospital	Prospective Before after	n = 41 (with ≥6 months treatment) Type 1 (10%), Type 2 (73%), Type 3 (17%) Median age at treatment = 4.2 years	NA	Motor function Adverse effects	SMA types 1–3; Physical therapy vs no physical therapy	Baseline, 6, 10, and 14 months
Pera 2021 (iSMAc)[206]	Italy	Registry	Prospective Before after	n = 144 Type 3A (n = 74), Type 3B (n = 70) Age range = 30 months–68.27 years	NA	Motor function	Pediatric vs adult Sitters vs walkers Type 3A vs 3B	Mean follow-up = 1.83 years
Pinar 2024[286]	Turkey	Treatment centre	Prospective Before after	n = 37 Type 1 (41%), Type 2 (27%), Type 3 (32%) Median age = 72 months (range 48–132)	NA	HFMSE, CHOP-INTEND; nutritional outcomes (HFA, BMI); malnutrition screening scores (PYMS, STAMP)	SMA types 1, 2, 3	Before and after study period (2022–2023)
RESPOND[110,232]	NR	Treatment centre	Prospective Before after	n = 29	NA	Motor function Adverse effects	SMN2 copies	NR
Rich 2022[147]	USA	Treatment centre	Retrospective Before after	n = 33 Type NR, adult SMA with 3+ SMN2 copies Mean age = 38.5 years	Control group (n = 6; limited data reported)	Serum and CSF NfL & pNfH; correlation with functional measures (RULM, HFMSE, SMAFRS, 6MWT)	Ambulatory (n = 13) vs non-ambulatory (n = 20)	Baseline, day 180, day 420
Sansone 2020[141]	Italy	EAP (Italy)	Retrospective Before after	n = 118 Type 1 Median age = 42.8 months	NA	Respiratory function Carer perception of change	Age	6 months, 10 months
Sarikaya Uzan 2022[197]	Turkey	Treatment centre	Retrospective Before after	n = 27 Type 1 (48.1%), Type 2 & 3 (51.8%) Median age = Type 1: 9.5 months, Type 2 & 3: 72 months	NA	CHOP-INTEND (Type 1), HFMSE (Type 2 & 3)	Type 1 vs Type 2 & 3	Up to 6 doses Two groups were followed up between

Study name	Country	Data source	Study design	Population	Comparator	Outcomes	Subgroups analysed	Follow-up
								September 2017 and June 2021
Scheijmans 2022[187]	Netherlands	Treatment centre	Retrospective Before after	n = 71 Presymptomatic (3%), type 1 (32%), type 2 (42%), type 3 (23%) Median age = 54 months	NA	Motor function (CHOP-INTEND, HFMSE, HINE-2), respiratory and bulbar function, adverse events	Types 1b, 1c, 2a, 2b, 3a Presymptomatic subgroup	Median follow-up: 38 months (range 5–52 months) By type: Type 1b: 41 months, Type 1c: 45.5months, Type 2a: 34.5months, Type 2b: 36months, Type 3a: 33.5months
Schneider 2021[148]	Germany	Treatment centre	Prospective Before after	n = 15 Type 3 (100%) Median age = 36 years	Healthy controls (n = 15), ALS patients (n = 9)	RULM, HFMSE, Motor Unit Number (MScanFit), CMAP amplitude, D50 value	Walkers vs wheelchair users	4–8 months
Scoto 2018a[111]	UK	EAP (UK); single centre	Prospective Before after	n= 24 age range 3 months-9 years Type 1	NA	Motor function Adverse events	NA	NR
Scoto 2018b[112]	UK	EAP (UK); 17 centres	Prospective Before after	Type 1	NA	Motor function Need for ventilation	NR	Follow-up up to 5th injection
Shin 2023[113]	South Korea	Hospital	Retrospective Before after	N = 30 Age: 24.85 ± 8.59 (7.48–41.23) Age at first symptom onset: 1.16 ± 0.61 (0.5–	NA	Motor function Adverse events	Some demographic details reported by SMA type	6, 14, 22 and 26 months

Study name	Country	Data source	Study design	Population	Comparator	Outcomes	Subgroups analysed	Follow-up
				3) Age at treatment: 22.90 ± 8.84 (4.98–39.5) Type 2and 3 Type 2: 27/30 (90%) Type 3: 3/30 (10%)			Complications sub grouped by sex (male versus female) and SMA type (2 versus 3)	
SHINE[37,123]	SHINE		Prospective Before after	n=207 Examining infantile and later-onset patients Median age 4.0 range 0.6 to 19.3 years Type 1 (expanded access programs had a common inclusion criterion of diagnosis of SMA type I) SHINE included people with type 2 or type 3 SMA	All received nusinersen in SHINE- previously some participants had received sham procedure in ENDEAR and CHERISH studies	Motor functions Ventilation outcomes Hospitalisation HRQoL Adverse events		30 months
Simek 2024[114]	Turkey	Hospital	Prospective Before after	n=31 Range: 19 to 69 years Types 2-4	NA	Motor functions HRQoL Respiratory function	NA	1.5 years
Simic 2024[176]	Croatia		Prospective Before after	n = 30 Type 1 (43%), Type 2 (13%), Type 3 (30%) Median age = range 1 month–17 years	NA	CHOP INTEND and HFMSE scores CSF protein levels: t-tau, NfL, S100B	SMA types 1, 2, 3 and number of nusinersen doses	75–1275 days (average 675 days) Also reported as 18–24 months in some outcome analyses

Study name	Country	Data source	Study design	Population	Comparator	Outcomes	Subgroups analysed	Follow-up
Szabo 2020[198]	Hungary		Retrospective Before after	n = 57; Type 1 (n = 13), Type 2 (n = 21), Type 3 (n = 23); mean age = 6.3 years (±5.4)	NA	Motor function, adverse events	SMA type, SMN2 copies, age at treatment	440 days (408 median)
Tachibana 2024[287]	Japan	Multiple treatment centres	Prospective Before after	n = 401; SMA ..... SMA type: Infantile-onset: 126/401 (31.4%) Later-onset: 275/401 Type 2: 165/401 (41.1%) Type 3: 105/401 (26.2%) Type 4: 5/401 (1.2%); ..... Age at first nusinersen treatment > 0 - <3 months, n = 7 (1.7%) >3 - <6 months = 12 (3.0%) >6 - <12 months = 8 (2.0%) >12 - <24 months = 21	NA	AEs, Clinical Global Impressions of Improvement (CGI-I) for effectiveness, HINE, 6MWT, HFMSE	SMA type	In patients with infantile-onset SMA, the mean duration of treatment was 383 days (SD 237 days) and the median duration of treatment was 421 days (range 1–814 days). In patients with later-onset SMA, the mean duration of treatment was 297 days (SD 197 days) and the median duration of

Study name	Country	Data source	Study design	Population	Comparator	Outcomes	Subgroups analysed	Follow-up
				(5.2%) >2 - <15 years = 197 (49.1%) >15 < 65 years = 142 (35.4%) >65 years = 13 (3.2%)				treatment was 288 days (range 1–823 days).
Trancho 2024[149]	NR		Prospective Before after	n = 35; SMA group (n = 19), control group (n = 16); mean age SMA = 32.9 years	Age-matched control group	Bone mineral density, motor function, physical activity	Group (SMA vs control)	1.0 ± 0.3 years
Trucco 2023[165]	Italy	Multiple treatment centres	Prospective Before after	n = 45 children n = 22 adults (treated) n = 11 adults (untreated) Types 2 and 3	NA	Bulbar function	Sitter/walker Children/adults Treated/untreated	2 years
Trucco 2024[126]	Italy	Italian SMA network, US PNCR network, SMA REACH UK	Retrospective Controlled	n = 69 Type 2 (77%), type 3 (23%) Mean age = 9.1 (type 2), 9.9 (type 3)	n = 103 natural history control Mean age = 9.3 (type 2), 11.7 (type 3)	Motor function Respiratory function Comorbidities Anthropometric	NA	5 years
Trucco 2022[115]	Italy	Italian SMA network, US PNCR, UK SMA REACH	Retrospective Before after	n = 100 Type 2 (81%), type 3 (19%) Mean age = 8 years (type 2), 9.4 years (type 3)	NA	Respiratory	Age	5 years
Tscherter 2022[193]	Switzerland		Prospective Before after	n = 44; Type 1 (n = 11), Type 2 (n = 21), Type 3 (n = 12);	NA	Motor function, feeding, ventilation, speech	SMA type, age at treatment, SMN2 copies	42 months

Study name	Country	Data source	Study design	Population	Comparator	Outcomes	Subgroups analysed	Follow-up
				median age = varies by type (0.2–18.5 yrs)				
Tulinius 2020[116]	Sweden	Hospital	Retrospective Before after	n = 70	NA	Motor function	NA	NR
Unver 2024[117]	Turkey	Multiple treatment centres	Prospective Before after	n = 44 Presymptomatic	NA	Motor function Bulbar function	NA	NR
van der Heul 2020[75]	Netherlands		Prospective Before after	n = 16; Type 1; palliative (n = 11), nusinersen (n = 5); median age = 52–63 days	Palliative care vs nusinersen	Feeding, swallowing, motor function	Treatment group	NR
Van der Woude 2024[288]	Netherlands	Hospital	Prospective Before after	n = 46; Type 2a (n = 23), 2b (n = 9), 3a (n = 14); median age = 5.2 years	NA	Motor function (HFMSE item-level changes)	SMA subtype, motor function category	20 months
Vázquez-Costa 2022[172]	Spain		Prospective Before after	n = 79; Type 2a (n = 22), Type 2b (n = 8), Type 3a (n = 23), Type 3b (n = 23), Type 4 (n = 3); mean age = 30.3 (non-treated), 33.4 years (treated)	Nusinersen vs untreated	Motor function, respiratory, activities of daily living, adverse events	SMA type, motor function level, SMN2 copies	16 months
Vidovic 2023[209]	Germany		Prospective Before after	n = 23; Type 2 (n = 9), Type 3 (n = 14); mean age = 38.1 years	NA	Motor function, cognitive outcomes	SMA type	14 months
Vill 2021[200]	Germany		Prospective Before after	n = 43; SMN2 copies: 2 (n = 17), 3 (n = 10), 4 (n = 14), 5 (n = 2); age = 0–24 months	NA	Motor function, electrophysiological outcomes	SMN2 copy number, treatment status	13 months

Study name	Country	Data source	Study design	Population	Comparator	Outcomes	Subgroups analysed	Follow-up
Wang 2024[289]	China	Multiple treatment centres	Retrospective Before after	n = 54; Type 2 (n = 9), Type 3 (n = 43), Type 4 (n = 2); mean age = 27.0 years	NA	Motor function, respiratory, electrophysiological outcomes, adverse events	SMA type, function level (sitters/walkers), SMN2 copies	10 months
Weaver 2021[173]	USA		Retrospective Before after	n = 35; Type 1 (n = 15), Type 2 (n = 14), Type 3 (n = 6); mean age not reported (children only)	NA	HRQoL, family impact, communication, daily activities	SMA type, nusinersen treatment stage	24 months
Weber 2024[219]	Germany		Prospective Before after	n = 39; Adults (n = 23), Children (n = 16); Type 2 (n = 22), Type 3 (n = 17); median age adults = 38.4 years, children = 10.0 years	NA	Grip strength, motor function	SMA type, age group, SMN2 copies	12 months
Weststrate 2021[118]	UK	Hospital	Retrospective Controlled	n = 28 Type 1	n = 38 treatment naïve Type 1	Bulbar function Ventilation Mortality	NA	NR
Weststrate 2022[130]	UK		Retrospective Before after	n = 24; Type 1a (n = 3), Type 1b (n = 9), Type 1c (n = 12); median age = 11 months	NA	Bulbar function, motor function, respiratory, feeding	SMA subtype, age at treatment initiation, SMN2 copies	24 months
Wohnrade 2023[236]	Germany		Prospective Before after	n = 39; Type 2 (n = 13), Type 3/4 (n = 26); median age = 36 years (range 19–65)	NA	Motor function, HRQoL, activities of daily living, depression/anxiety, caregiver burden	SMA type, SMN2 copy number, mobility status	16 months
Wurster 2024[119]	Germany	Hospital	Prospective Before after	n = 42 Type 1 (5%), type 2 (36%), type 3 (57%), type 4 (2%)	NA	Respiratory function	SMA type Smokers vs non-smokers	Median 22.1 months

Study name	Country	Data source	Study design	Population	Comparator	Outcomes	Subgroups analysed	Follow-up
Yang 2023[120]	China	2 hospitals	Retrospective Observational cohort	n = 46 Type 1 (17%), type 2 (67%), type 3 (15%)	NA	Motor function Adverse effects	SMA type	NR
Yao 2024[290]	China	Pediatric SMA China Registry	Retrospective Before after	n = 385 Type 1 (11%), type 2 (56%), type 3 (33%) Median age: 42 months (type 1), 62.5 months (type 2), 20 months (type 3)	NA	Motor function Adverse effects	NA	14 months
Yasar 2024[142]	Turkey	Turkish E-Nabiz patient database	Retrospective Before after	n = 29 Type 1 Mean age = 3.7 years	NA	Motor function Bulbar function Scoliosis Radiological assessments	NA	Mean 3.3 years (range 2 to 6 years)
Yildiz 2023[121]	Turkey	Hospital	Retrospective Before after	n = 46 Type 1 (39%), type 2 (33%), type 3 (28%)	NA	Motor function Bulbar function Adverse effects Ventilation Complications	SMA type Age	NR
Zaidman 2023[122]	USA	Unclear	Prospective Before after	n = 43 Types 2 and 3 Mean age = 37.1 years	NA	Motor function Respiratory function Adverse effects	NA	NR
Zhang 2024[150]	International	FAERS database	Retrospective Before after	n = 12,124,854 reports (FAERS); type not reported; majority children (37.3%); mean/median age not reported	NA	Adverse events (safety)	Age (children vs adults)	88 months

19.5 Appendix 5: Table of included studies for risdiplam

Study name	Country	Data source	Study design	Population	Comparator	Outcomes	Follow-up time
Brakemeier 2024[156]	Germany	Treatment centre	Prospective Before after	n = 29 Type 2 (96%), type 3 (4%) Eligible: type 2 or 3 on risdiplam for 4+ months Mean age = 34.32 years	NA	Motor function Bulbar function	12 months
Cornell 2024[159]	UK	SMA REACH	Retrospective Before after	n = 92 Type 1 (78%), type 2 (22%) Eligible: 2 months to <18 years Median age = 12 years Previously treated with nusinersen, risdiplam (trial), or olesoxime (trial)	NA	Adverse events Discontinuation	Median treatment duration 11 months
EAP (US)[155]	USA	Treatment centres	Prospective Before after	n = 155 Type 1 (47%), type 2 (53%) Eligible: >2 months Median age = 11 years Previously treated with nusinersen, OA, or both	NA	Adverse effects Discontinuation	Median treatment duration 4.8 months
FIREFISH[56-58]	International	Treatment centres	Prospective Phase 2 Single arm Open label	n = 41 Type 1 Eligible: 1 month to 7 months Median age = 5.3 months	NA	Motor function Feeding Respiratory function Mortality Ventilation	60 months
Goedeker 2024[151]	USA	Chart review at 3 centres	Retrospective Observational	n = 29 Type NR Eligible: Newborn screen or prenatal test Mean age = 8.5 months	NA	Motor function Feeding support Mortality Ventilation Adverse effects	NR
Hahn 2022[157]	Germany	Treatment centres	Retrospective Single arm	n = 134 Type 1 (28%), type 2 (72%) Eligible: >2 months	NA	Adverse effects Discontinuation	Mean treatment duration (type 1) 5 months Mean treatment

Study name	Country	Data source	Study design	Population	Comparator	Outcomes	Follow-up time
				Mean age (type 1) = 13.5 years Mean age (type 2) = 29 years Previously received nusinersen or nothing			duration (type 2) 3.4 months
JEWELFISH[63,64,291,292]	International	Treatment centres	Prospective Phase 2 Single arm Open label	n = 173 Type 1 (9%), type 2 (62%), type 3 (29%) Eligible: 6 months to 60 years Median age = 14 years Previously enrolled in MOONFISH or received nusinersen or olesoxime or AVXS-101	NA	Adverse effects Discontinuation	24 months
Nascimento 2024[152]	Spain	Treatment centres	Retrospective Before after	n = 25 Type 2 Eligible: any with type 2 Mean age = 14.1 years	NA	Motor function Adverse effects	8 months
RAINBOWFISH[59,60,62]	International	Treatment centres	Prospective Phase 2 Single arm Open label	n = Presymptomatic 1 day to 6 weeks Median age = 26.5 days	NA	Motor function Mortality Ventilation Adverse effects	2 years
Sitas 2024[158]	Croatia	Treatment centre	Prospective Before after	n = 31 Type 2 (48%), type 3 (52%) Eligible: treatment naïve adults Median age = 30 years	NA	Motor function Bulbar function Adverse effects HRQoL	Type 2 median duration 16 months (n = 3) and 30 months (n = 12) Type 3 median duration 16 months (n = 16)
SUNFISH[49,51-55]	International	Treatment centres	Prospective Phase 3 RCT	n = 176 Type 2 (73%), type 3 (27%) Eligible: 2 – 25 years Mean age = 9.9 years	Placebo	Motor function Bulbar function Hospitalisation Respiratory function	5 years

Study name	Country	Data source	Study design	Population	Comparator	Outcomes	Follow-up time
				(risdiplam) Mean age = 10.3 years (placebo) Non-ambulant		Mortality Adverse effects Independence	
Weng 2024[153]	China	Treatment centre	Prospective Before after	n = 20 Type 1 (10%), type 2 (90%) Eligible: type 1 and 2 Median age = 20.7 years	NA	Motor function Adverse effects Independence	3 years
Yu 2024[154]	International	FAERS database	Retrospective Before after	n = 1588 Type NR Eligible: patient reports linked to risdiplam	NA	Adverse effects	NA

19.6 Appendix 6: Table of included studies for mixed drugs

Study name	Country	Data source	Study design	Population	Comparator	Outcomes	Follow-up time
Ashrafi 2024[160]	Iran	Treatment centres	Prospective Controlled	Risdiplam (n = 73) Type 2 (73%), type 3 (27%)	Nusinersen (n = 52) Type 2 (66%), type 3 (34%)	Motor function Adverse effects Mortality	6 months
Dabbous 2022[161]	USA	Chart review	Retrospective Chart review	n = 30 Type 1 Nusinersen (n =11) OA (n = 8) Nusinersen to OS (n = 5)	NA	Motor function Bulbar function	NR
Lee 2022[163]	USA	Treatment centre	Retrospective Before after	OA (n = 23) Nusinersen (n = 1) Risdiplam (n = 1) Nusinersen to OA (n = 5) OA to risdiplam (n = 2) Prenatally identified	NA	Motor function Respiratory function Bulbar function	3 years
Mirea 2022[162]	Romania	Treatment centre	Retrospective Before after	Age: 0-17 years Type 1: 20 Type 2: 26 Type 3: 9	As not all patients could attend daily PT- due to location, sample was split into two groups: Nusinersen and PT (PT-N) compared to Nusinersen only (N group) Nusinersen administered the same in both groups- addition of PT in PT-N group	Motor function	12 months

19.7 Appendix 7: Summary of included cost-effectiveness analysis studies

Table 19.2: Summary of the economic analyses included in the original systematic review and updated review

Study, year	Target population and subgroup(s)	Intervention(s), Comparator(s) Outcome(s), Study perspective, Location & Setting	Model structure and health states	Time horizon, cycle length and discount rate	Source of utility values used	Sources of Health state costs, currency and conversion
Original systematic review (up to January 2024)						
NICE-Nusinersen TA588, 2019[2]	**Target population:** Paediatric patients with 5q SMA (Types 1,2 and 3) **Subgroups:** 1- infantile Infantile-onset (type 1) • ≤12 weeks disease duration • >12 weeks disease duration 2- Later-onset ((types II and III) SMA.) • <25 months disease duration • ≥25 months disease duration	**Intervention:** Nusinersen **Comparator:** BSC **Outcomes:** LYG, QALYs **Study perspective:** NHS and PSS of UK **Location (Setting):** UK (relevant settings (e.g. inpatient, outpatient/clinic))	**Two Markov models:** • Infantile onset (type 1) • Later-onset (type 2/3) **Health states:** Type 1: Eight health states based on HINE-2 including: No milestone achieved, mild milestones, moderate milestones, sits without support, stands with assistance, walks with assistance, stands/walks unaided and dead. Type 2/3: Seven states based on	**Time horizon:** • Type 1: 60 years • Type 2/3: 80 years **Cycle length:** • Type 1: new cycle after 2, 6, 10, 13 and 14 months and every 4 months thereafter • Type 2/3: new cycle after 3, 6, 9, 12 and 15 months and every 4 months thereafter **Discount rate:** • 3.5% per year for both costs and benefits	Patients: Patients (type 1 and type 2/3) had utility values determined by manufacturer experts. Caregiver: Caregiver disutilities were based on Spanish caregiver data and UK population EQ-5D scores. It was assumed that type 1 patients had 3 caregivers, while type 2/3 patients had 2 caregivers, with 3 for those unable to sit.	**Sources of costs:** • Real-World Evidence (RWE) survey to validate the direct expenses linked to SMA within the UK healthcare system (2017 RWE survey involving pediatric neurological consultants from nine UK centers). • Analyzed data from the Hospital Episode Statistics (HES) in the UK **Currency and conversion:** UK pound (£)

Study, year	Target population and subgroup(s)	Intervention(s), Comparator(s) Outcome(s), Study perspective, Location & Setting	Model structure and health states	Time horizon, cycle length and discount rate	Source of utility values used	Sources of Health state costs, currency and conversion
			HMFSE and WHO including: Sits without support but does not roll, sits and rolls independently, sits and crawls with hands and knees, stands/walks with assistance, stands unaided, walks unaided and dead.			
NICE-Risdiplam TA755, 2021[3]	**Target population:** • Paediatric patients with 5q SMA (Types 1,2 and 3) **Subgroups:** • Type 2/3: included both ambulant and non-ambulant patients aged 2–25 years at the time of enrolment with type 2 and 3 SMA. • Type 1: included infants with symptomatic type 1 SMA aged 1–7 months at the time of enrolment.	**Intervention:** Risdiplam **Comparator:** BSC **Outcomes:** LYG, QALYs **Study perspective:** NHS and PSS of UK **Location (Setting):** UK (relevant settings (e.g. inpatient, outpatient/clinic))	Two Markov models: • Type 2/3 model • Type 1 model **Health states:** Type 2/3: Six states based on MFM-32 and HMFSE ('not sitting', 'sitting with support', 'sitting unsupported', 'standing (with or without support)' and 'walking (with or without support)' and 'death'.	**Time horizon:** • Type 1and Type 2/3: 90 years **Cycle length:** • Type 1and Type 2/3: one month. **Discount rate:** • 3.5% per year for both costs and benefits	Patients: Utility values same as NICE-nusinersen TA588.[2] Caregiver (type 1): Adjusted disutility assumption with no QALY losses post 10.23 years. Bereavement considered after 30.58 years. Assumed 2.2 caregivers per patient. Caregiver (type 2/3): Disutility linked to patient health states, caregiver utility returns to normal	**Sources of costs:** • Health state resource use for NICE-nusinersen TA588.[2] • Costs for permanent ventilation are 175% higher than non-sitting health states. • SMA complication costs apply universally in BSC and half in risdiplam groups in severe health states. • The costs per unit and occurrence rates for each complication

Study, year	Target population and subgroup(s)	Intervention(s), Comparator(s) Outcome(s), Study perspective, Location & Setting	Model structure and health states	Time horizon, cycle length and discount rate	Source of utility values used	Sources of Health state costs, currency and conversion
			(Plateau at 26 months) Type 1: Six states based on HINE-2 ('not sitting', 'sitting', 'standing', 'walking') and 'permanent ventilation' and 'death'. (Plateau at 66 months)		after patient death. Disutility of -0.04 applied for 20 years (scenario 1) and 90 years (scenario 2) after patient's death.	were obtained from the NHS Reference Costs of 2019/20. **Currency and conversion:** UK pound (£)
NICE-OA HST15-type1, 2021[262]	patients with 5q SMA- Infantile-onset (type 1)	**Intervention:** Onasemnogene abeparvovec **Comparator:** BSC **Outcomes:** LYG, QALYs **Study perspective:** NHS and PSS of UK **Location (Setting):** UK (relevant settings (e.g. inpatient, outpatient/clinic))	**One Markov model** **Health states:** Six states: not sitting, permanent assisted ventilation, sits unassisted, walks unassisted, within a broad range of normal development and dead.	**Time horizon:** 100 years **Cycle length:** 6-month cycles for first 3 years, 12-month cycles for remainder of model Discount rate: • 3.5% per year for both costs and benefits	PAV: Assumption based on the ERG interim report Not sitting – BSC and onasemnogene abeparvovec: Thompson et al. 2017[293] Sits unassisted – BSC and onasemnogene abeparvovec: TA588[2] Walks unassisted and Broad range of normal development:	**Sources of costs:** Inpatient and outpatient costs: NHS pharmacological therapy resources: PCA **Currency and conversion:** pound (£)-2019

Study, year	Target population and subgroup(s)	Intervention(s), Comparator(s) Outcome(s), Study perspective, Location & Setting	Model structure and health states	Time horizon, cycle length and discount rate	Source of utility values used	Sources of Health state costs, currency and conversion
					Ara and Brazier 2010[294]	
NICE-OA HST24-presymptomatic, 2023[17]	Newborn infants with genetically confirmed, presymptomatic SMA with two or three copies of the *SMN2* gene who were age ≤6 weeks (≤42 days) at time of treatment.	**Intervention:** Onasemnogene abeparvovec **Comparator:** BSC **Outcomes:** LYG, QALYs **Study perspective:** NHS and PSS of UK **Location (Setting):** UK (relevant settings (e.g. inpatient, outpatient/clinic))	**Two Markov model:** • Short-term model • Long-term extrapolation model **Health states:** Short-term: Six states including: 'Sitting and walking independently', 'non-sitter, no PAV', 'non-sitter, PAV'' , 'sitter', 'delayed walker', 'death' Long-term: Seven states including six states from short term and 'experiences later onset SMA'	**Time horizon:** 100 years **Cycle length:** One month **Discount rate:** • 3.5% per year for both costs and benefits	PAV: Assumption based on the ERG interim report Not sitting and Patients in the walking & experiencing later onset SMA state who lase the ability to walk: Thompson et al. 2017[293] Sitting: EAG's clinical experts in TA588[2] Walking and broad range of normal development: Ara and Brazier 2010[294]	**Sources of costs:** Costs sourced from NHS 2019/20, the NHS Business Services Authority prescription cost analysis 2021/22, and the literature. **Currency and conversion:** UK pound (£) inflated to 2021
ICER-Nusinersen & OA, 2019[249]	SMA patients of all ages and types including:	**Intervention:** Nusinersen and onasemnogene abeparvovec	Three de novo Markov models in accordance with target population.	**Time horizon:** Lifetime **Cycle length:**	PAV for both arms, Not sitting for BSC arm: Thompson et al. 2017[293]	**Sources of costs:** Nusinersen:

Study, year	Target population and subgroup(s)	Intervention(s), Comparator(s) Outcome(s), Study perspective, Location & Setting	Model structure and health states	Time horizon, cycle length and discount rate	Source of utility values used	Sources of Health state costs, currency and conversion
	• symptomatic patients with infantile-onset (Type I) SMA • symptomatic patients with later-onset (Type II/III) SMA • presymptomatic SMA patients	**Comparator:** BSC **Outcomes**: LYG, QALYs **Study perspective:** USA health care sector **Location (Setting):** USA (inpatient, outpatient/clinic, office, and home settings)	**Health states:** • Type I and Presymptomatic models: 'Not sitting', 'PV', 'sitting', 'walking', 'death' • Type II/III: 'sitting', 'walking', 'death' Absorbing states For long-term extrapolation model: Type I: 'PV' and 'death' Type II/III: 'death'	One month **Discount rate:** 3.0% for costs and benefits	Not sitting for treatment arm: Assumption Sitting for BSC arm: TA588[2] Sitting for treatment arm: Assumption Walking for both arms: General population utility	Drug: Redbook 2018[295], Magellan 2016[296] Inpatient Cost: Nationwide Children's Hospital Price Information List 2018 Onasemnogene abeparvovec Drug cost: Market analyst Estimate[297] Administration costs for both arms: Physician fee schedule 2018[298]; Facility price Redbook 2018[295] **Currency and conversion**: $**US** inflated to 2017
CADTH-Nusinersen, 2019[259]	Patients with SMA (type 1, 2 and 3)	**Intervention:** Nusinersen **Comparator:** RWC	**Three Markov models:** type I, type II, and type III **Health states:**	**Time horizon:** • type 1: 25 years • type 2: 50 years • type 3: 80 years	Patient: Types 1 and 3 SMA: unpublished utility value analyses by five experts in SMA	**Sources of costs:** Health costs appear to be derived from a study of SMA costs in Germany (Klug et al., 2016)[267].

Study, year	Target population and subgroup(s)	Intervention(s), Comparator(s) Outcome(s), Study perspective, Location & Setting	Model structure and health states	Time horizon, cycle length and discount rate	Source of utility values used	Sources of Health state costs, currency and conversion
		Outcomes: LYG, QALYs Study perspective: Canadian public health care system **Location (Setting):** Canada	• Type I: 'baseline'; 'improved baseline', 'worsened baseline', 'no improvement'; 'sits without support', 'stands with assistance', 'walks with assistance', **'**stand/walks unaided', 'loss of type II/III motor function', and 'death'. • Type II: 'baseline', 'worsened , 'no', 'mild' and 'moderate' improvement, 'stand/walk with assistance', 'stand unaided', 'walks unaided', 'loss of ambulation with/without assistance' and 'death'. • Type III: 'baseline', 'non-ambulatory**'**,	**Cycle length:** • type 1: At 2, 6, 10, 13, and 14 months. Subsequent cycles were every four months. • type 2: three months (For the first 15 months). Subsequent cycles were every four months. • type 3: three months (for the first 27 months), subsequent cycles every 4 months. **Discount rate**: 1.5% costs and benefits per annum	Type 2 SMA: QoL data from CHERISH mapped to EQ-5D	**Currency and conversion**: Canadian dollars for 2017

Study, year	Target population and subgroup(s)	Intervention(s), Comparator(s) Outcome(s), Study perspective, Location & Setting	Model structure and health states	Time horizon, cycle length and discount rate	Source of utility values used	Sources of Health state costs, currency and conversion
			‘ambulatory’, and ‘death’.			
CADTH-risdiplam , 2021[261]	population was divided into two subgroups evaluated separately: • patients with SMA type I • patients with SMA type II or SMA type III	**Intervention:** Risdiplam **Comparator:** BSC **Outcomes**: QALYs **Study perspective:** Canadian publicly funded health care payer **Location (Setting):** Canada	**Two Markov models in accordance with target population.** **Health states:** • **Type I:** six states including ‘not sitting’, ‘sitting,’ ‘standing’, ‘walking,’ ‘permanent ventilation’, and ‘death’ • **Type II/III:** ‘not sitting’, ‘supported sitting’, ‘unsupported sitting’, ‘standing’, ‘walking’, and ‘death’	**Time horizon:** • Type I: 25 years • Type II/III: 80 years **Cycle length:** For both models one month **Discount rate**: 1.5% costs and benefits per annum.	Health state utility values were obtained from a sponsor-commissioned Canadian burden-of-illness survey. (included a EuroQol 5-Dimensions 5-Levels health utility questionnaire). In the absence of available data for the “PV” and “not sitting” states, the value identified in the survey for sitting supported was applied to both health states.	**Sources of costs:** Outpatient, hospitalizations, Medical equipment and medications identified from a Canadian burden-of-illness study. Health care resource utilization come from the Alberta Hospital, the Ontario Ministry of Health 2020. End-of-life costs were obtained from Widger et al.[299] and Seow et al.[300] **Currency and conversion:** Canadian dollars
CADTH-OA, 2021[250]	Patients with SMA type 1 with an onset of symptoms at ≤ 6 months of age, and with 2 copies of the SMN2 gene.	**Intervention:** Onasemnogene abeparvovec **Comparator:** BSC and Nusinersen	**One Markov model** **Health states:** **six states including:** ‘within	**Time horizon:** 60 years **Cycle length:** Six 6 months in the early phase	Utility for the ‘unable to sit unassisted’ and ‘sitting unassisted‘ health states was identified from the literature (TA588)[2]	**Sources of costs:** • Administration costs: Ontario Schedule of Benefits for physician services.

Study, year	Target population and subgroup(s)	Intervention(s), Comparator(s) Outcome(s), Study perspective, Location & Setting	Model structure and health states	Time horizon, cycle length and discount rate	Source of utility values used	Sources of Health state costs, currency and conversion
		Outcomes: QALYs **Study perspective:** Canadian publicly funded health care payer **Location (Setting):** Canada	a broad range of normal development', 'walking unassisted', 'sitting unassisted', 'unable to sit unassisted', 'PAV' and 'death'	and yearly in the extrapolation phase. **Discount rate**: 1.5% costs and benefits per annum.	utility of the general population for the 'walking unassisted' and 'within broad range of normal development' health states were derived from (Ara et al, 2010)[294]	• Screening costs: expert opinion. • Health state costs: unpublished health care resource utilization study conducted by the sponsor. **Currency and conversion:** Canadian dollars
Meijer et al., 2023[254]	Patients with SMA Type I, SMN1 mutation, 2 SMN2 copies, treated before 6 months	**Intervention:** Onasemnogene abeparvovec **Comparator:** BSC **Outcomes**: QALY **Study perspective:** Societal perspective **Location (Setting):** Netherlands	**One Markov model** **Health states:** five health states including: 'not sitting and 'PAV free', 'PAV', 'sitting independently', 'walking independently', and 'dead'.	**Time horizon:** 36 months for short-term and 99 years for long-term **Cycle length:** monthly **Discount rate**: 4% for costs and 1.5% for benefits	Literatures (mainly ZIN report of nusinersen and the comments provided in the ZIN report of Onasemnogene abeparvovec)	**Sources of costs:** Literature (study conducted by Klug et al. in Germany in 2016)[267] **Currency and conversion:** € and adjusted for 2022
Broekhoff et al., 2021[251]	Infants born with SMA I- Mean age (months) = 3.4	**Intervention:** OA **Comparator:** BSC and nusinersen	**One** Markov model **Health states:**	**Time horizon: 100 years**	The base-case model utilized health state utilities sourced from the Dutch	**Sources of costs:** published literature (the ZIN report, which uses cost

Study, year	Target population and subgroup(s)	Intervention(s), Comparator(s) Outcome(s), Study perspective, Location & Setting	Model structure and health states	Time horizon, cycle length and discount rate	Source of utility values used	Sources of Health state costs, currency and conversion
		Outcomes: QALYs **Study perspective:** societal perspective **Location (Setting):** Netherlands	five health states: three states corresponding to SMA types (SMA I-III), one for PV, and one for death.	**Cycle length: one month.** **Discount rate**: 4% for Costs and 1.5% for benefits	National Health Care Institute (ZIN) model, while a scenario analysis incorporated utilities from the Institute for Clinical and Economic Review (ICER Institute).	calculations by Klug et al.)[267] **Currency and conversion:** Euro € and were inflated to 2019
SMC Nusinersen, 2018[260]	patients with symptomatic type 1 SMA	**Intervention:** Nusinersen with BSC **Comparator:** BSC **Outcomes**: QALY, YLG **Study perspective:** NHS Scotland and social work **Location (Setting):** Scotland	**Two Markov models (**type I SMA and type II or III SMA) **Health states:** A 10-state Markov model tracks infant patients' health progression through worsening, stabilizing, improving states, and functional milestones like 'sitting without support' or 'standing without assistance.' The model for later-onset SMA patients mirrors	**Time horizon: 80 years** **Cycle length: Unclear** **Discount rate**: Unclear- it seems %3 for cost and outcome	Health state utilities in the later-onset model were derived by converting PedsQL data from the CHERISH study to EQ-5D. Infantile model values were adjusted from later-onset utilities to reflect infant-specific characteristics.	**Sources of costs:** Unclear **Currency and conversion: £2018**

Study, year	Target population and subgroup(s)	Intervention(s), Comparator(s) Outcome(s), Study perspective, Location & Setting	Model structure and health states	Time horizon, cycle length and discount rate	Source of utility values used	Sources of Health state costs, currency and conversion
			the infant model but includes state adjustments tailored to type II and III SMA.			
SMC OA , 2021[263]	patients with SMA with a bi-allelic mutation in the SMN1 gene (or up to 3 copies of the SMN2 gene) and a clinical diagnosis of SMA type 1.	**Intervention:** Onasemnogene abeparvovec **Comparator:** Nusinersen **Outcomes**: QALY, LYG **Study perspective:** health and social care **Location (Setting):** Scotland	**One Markov models** **Health states:** Six states including 'normal development' , 'unassisted walking' , 'unassisted sitting' , 'inability to sit' , 'reliance on assisted ventilation' , and 'death'	**Time horizon:** lifetime **Cycle length:** six months for the first three years and annually thereafter **Discount rate**: Unclear- it seems 3% for cost and outcome	utility values were sourced from the literature using proxy parental or carer values and/or clinical advice.	**Sources of costs:** Scottish Health Service Costs where available **Currency and conversion:** pound and for 2020
SMC Risdiplam, 2022[265]	Infants with symptomatic type 1 SMA aged 2–7 months were used in the type 1 model, while the type 2/3 model included ambulant and non-	**Intervention:** Risdiplam with BSC **Comparator:** Nusinersen with BSC **Outcomes**: QALY	**Two Markov models:** (type I SMA and type II or III SMA) **Health states:** Both models utilized a six-state	**Time horizon:** lifetime **Cycle length:** one month **Discount rate**: Unclear	Patient and caregiver utility data for motor milestone health states in Type 1 and Type 2/3 models were sourced from literature or NICE submission TA588[2].	**Sources of costs:** Costs for drug acquisition, administration, and resource use of risdiplam and nusinersen were factored in from real-world studies by their

Study, year	Target population and subgroup(s)	Intervention(s), Comparator(s) Outcome(s), Study perspective, Location & Setting	Model structure and health states	Time horizon, cycle length and discount rate	Source of utility values used	Sources of Health state costs, currency and conversion
	ambulant patients aged 2–25 years.	**Study perspective:** Unclear (maybe payer and social perspective) **Setting:** Unclear **Location:** Scotland	Markov model with common motor milestone states: not sitting, sitting, standing, and walking. The type 2/3 model distinguished the 'sitting' state into 'with' and 'without support'. Type 1 model included a 'permanent ventilation (PV)' state. Death was the absorbing state in both models.			respective companies.
Connock et al., 2020[252]	Patients with SMA Type 1	**Intervention:** Onasemnogene abeparvovec **Comparator:** BSC and nusinersen **Outcomes**: QALY **Study perspective:** UK NHS perspective	**One Markov model** **Health states:** Unclear	**Time horizon:** Lifetime **Cycle length:** Unclear **Discount rate**: Maybe 3.5% for both costs and benefits	Total lifetime QALYs for nusinersen, onasemnogene abeparvovec come from Table 8 Malone et al. 2019[264] Total lifetime QALYs for BSC and nusinersen come from Biogen submission to NICE (2018)[33]	**Sources of costs:** Total lifetime costs for nusinersen and onasemnogene abeparvovec come from Malone et al. 2019[264] Total lifetime costs for BSC and nusinersen come from Biogen submission to NICE (2018)[33]

Study, year	Target population and subgroup(s)	Intervention(s), Comparator(s) Outcome(s), Study perspective, Location & Setting	Model structure and health states	Time horizon, cycle length and discount rate	Source of utility values used	Sources of Health state costs, currency and conversion
		Location (Setting): UK				**Currency and conversion:** £UK using 2018 PP exchange rate
Dean et al. , 2021[253]	Symptomatic SMA type 1 patients	**Intervention:** Onasemnogene abeparvovec **Comparator:** Nusinersen, BSC **Outcomes**: QALY **Study perspective:** Commercial payer OF USA **Location (Setting):** USA	**ONE Markov model** **Health states:** The states of the model are like the "ICER - nusinersen & OA 2019" study[249]Markov model for Type I SMA.	**Time horizon:** Lifetime **Cycle length:** 6-monthly for first 3 years then annually **Discount rate**: 3% for both costs and benefits	Equivalent to weightings used in the ICER analysis[249]	**Sources of costs:** Price of onasemnogene abeparvovec $2.125 M one-time dose, other costs were equal to costs used in the ICER analysis (2019)[249], cost of ventilator estimated from a UK study(Noyes et al. 2006)[301] **Currency and conversion:** $US inflated to 2017
Malone et al., 2019[264]	Paediatric with genetically confirmed SMA1 and two copies of SMN2, diagnosed before six months of age, and receiving either the recommended therapeutic amount	**Intervention:** Onasemnogene abeparvovec **Comparator:** Nusinersen **Outcomes**: QALY, LYG	**ONE Markov model** **Health States:** 'Within a broad range of normal development', 'Walking functionally	**Time horizon:** 100 years **Cycle length:** six months for the first three years, and then 12 months for all cycles thereafter	The model incorporated utility values derived from the CHERISH (PedsQL data) clinical trial of nusinersen for later-onset SMA (NCT02292537), which were	**Sources of costs:** SMA patient costs in USA: commercial plans by age at first claim.[302] Nusinersen product cost: based on manufacturer[33]

Study, year	Target population and subgroup(s)	Intervention(s), Comparator(s) Outcome(s), Study perspective, Location & Setting	Model structure and health states	Time horizon, cycle length and discount rate	Source of utility values used	Sources of Health state costs, currency and conversion
	of onasemnogene abeparvovec or nusinersen, along with BSC	**Study perspective:** Commercial insurer in the U.S. **Location (Setting):** USA	equivalent to SMA Type III' , 'Sitting functionally equivalent to SMA Type II' , 'Not sitting and living ventilation-free' , 'Not sitting and requiring permanent assisted ventilation' , and 'Death'	**Discount rate**: 3% for both costs and benefits	transformed to the EQ-5D youth version through a documented algorithm.[293]	nusinersen administration cost: Micro-costed. Hospital mark-up component and Durable medical equipment: expert opinion Hospital stays for anesthesia-related complications: Graham et al.[303] **Currency and conversion:** $US, price year is unclear
Wang et al. 2022[255]	infants born with SMA Type I as the recruited patients in the clinical trials of nusinersen and onasemnogene abeparvovec	**Intervention:** Onasemnogene abeparvovec **Comparator:** SOC and nusinersen **Outcomes**: QALY	**ONE** Markov model **Health states:** Five health states in including: 'not sitting and PAV free', 'sitting independently', and 'walking	**Time horizon:** 100 years **Cycle length:** Monthly **Discount rate**: 5% annually for both costs and benefits	Utility values come from Chambers et al.2020[304]	**Sources of costs:** Treatment costs of nusinersen: PBS[305] Treatment costs of onasemnogene abeparvovec: Market price Administration and monitoring costs of nusinersen and onasemnogene

Study, year	Target population and subgroup(s)	Intervention(s), Comparator(s) Outcome(s), Study perspective, Location & Setting	Model structure and health states	Time horizon, cycle length and discount rate	Source of utility values used	Sources of Health state costs, currency and conversion
		Study perspective: healthcare system in the Australian context **Location (Setting):** Australian	independently' and 'dead'			abeparvovec: PBS[305], MBS[306], NHCDC[307] Health state costs: Recently published study in Australia[304] AND ICER[249] **Currency and conversion: $** Australian were converted to 2020
Zuluaga et al. 2019[256]	Patients with infantile-onset and later-onset SMA	**Intervention:** Nusinersen and SoC **Comparator:** SoC **Outcomes**: QALY **Study perspective:** societal **Location (Setting):** Sweden	**Two Markov model** (infantile-onset SMA and later-onset SMA) Health states: infantile-onset: ten states including: 'baseline' , 'Worsened', 'stabilisation of baseline' and 'Improved' , 'Stands/walks Unaided' , 'Sits Unaided' , 'Stands aided' , 'Walks aided' , 'Loss of	**Time horizon:** 40 years for infantile-onset and 80 years for later-onset **Cycle length: In** trial follow-ups for ENDEAR: days 1, 64, 183, 302 and 394; CHERISH: days 1, 92, 169, 274, 365 and 456; after follow-ups: four months **Discount rate**: 3.0% for both costs and benefits	Health-state utility values come from Lloyd et al. 2017[308] The EQ-5D (youth version) was scored using the EQ-5D-3L UK preference weights.	**Sources of costs:** German study (Klug et al. 2016)[267] and a Spanish study (López-Bastida et al. 2017)[68] Country-specific unit costs were mainly collected from hospital price lists. **Currency and conversion:** SEK (Swedish krona)-inflated to the year 2018

Study, year	Target population and subgroup(s)	Intervention(s), Comparator(s) Outcome(s), Study perspective, Location & Setting	Model structure and health states	Time horizon, cycle length and discount rate	Source of utility values used	Sources of Health state costs, currency and conversion
			later-onset motor function' , 'Death' Later-Onset: 'baseline' , 'Worsened' , 'Stabilised' , 'Mildly improved' , 'Moderately improved' , 'Stands unaided' , 'Walks unaided' , 'Stands/walks with assistance' , 'Loss of ambulation with/without assistance' , 'Death'			
Thokala et al. 2020[257]	patients with infantile-onset SMA (type 1)	**Intervention:** Nusinersen **Comparator:** BSC **Outcomes**: LYG, QALY **Study perspective:** US health care sector	**One Markov model** The model contained two parts: (1) a short-term phase concordant with clinical study data, and (2) a long-term extrapolation model. **Health states:**	**Time horizon:** lifetime **Cycle length:** monthly **Discount rate**: 3% per annum for both costs and benefits	Permanent ventilation for both arms: Thompson et al., 2017[293] (EQ-5D) Not sitting in BSC arm Same as "permanent ventilation" and for Nusinersen based on assumption Sitting for BSC based on TA588[2] and for Nusinersen based on assumption	**Sources of costs:** Nusinersen treatment cost: Magellan 2016[296], Redbook 2018[295] Administration cost: Physician fee schedule 2018[298]; Nationwide Children's Hospital The health care utilization costs: Shieh et al. 2017[302]

Study, year	Target population and subgroup(s)	Intervention(s), Comparator(s) Outcome(s), Study perspective, Location & Setting	Model structure and health states	Time horizon, cycle length and discount rate	Source of utility values used	Sources of Health state costs, currency and conversion
		Location (Setting): US	'permanent ventilation', 'not sitting', 'sitting', 'walking', and 'death'.			**Currency and conversion:** $US-inflated to 2017
NCPE-2017[258]	infantile and later onset SMA	**Intervention:** Nusinersen **Comparator:** SOC **Outcomes**: QALY, LYG **Study perspective:** Health Service Executive **Location (Setting):** Ireland	**Two Markov models** (infantile and later onset SMA) **Health states:** Unclear	**Time horizon:** Lifetime **Cycle length:** determined by motor assessments timing and maintenance dose administration. **Discount rate**: % for costs and benefits	PedsQL data from CHERISH trial determined later-onset SMA utilities, impacting infantile SMA model. Data mapped to EQ5D scale for utility derivation.	**Sources of costs:** Unclear **Currency and conversion:** Euro(€)
Systematic review update						
Khuntha et al, 2025[248]	Infantile, SMA type 1, 2 and 3	**Intervention:** Onasemnogene Abeparvovec, Risdiplam **Comparator:** SOC **Outcomes**: QALY, LYG	**One Markov models:** (SMA type 1, 2 & 3)	**Time horizon:** Lifetime **Cycle length:** 6 months	"The EuroQol Five-dimension Youth (EQ-5D-Y) which used the published tariff from Japan (Shiroiwa et al., 2021 for health states BRND, sitting and PAV. Other health state utility	**Sources of costs:** Hospital, Pharmaceutical drug assessment submissions and direct interviews of patients and caregivers.

Study, year	Target population and subgroup(s)	Intervention(s), Comparator(s) Outcome(s), Study perspective, Location & Setting	Model structure and health states	Time horizon, cycle length and discount rate	Source of utility values used	Sources of Health state costs, currency and conversion
		Study perspective: Thai health care system **Location (Setting):** Thailand		**Discount rate**: 3.0% for both costs and benefits	values from a percentage of the difference between each health state from Hu et al., 2022 - the Chinese EQ-5D-Y using data from the Chinese EQ-5D-3L valuation study as a proxy.	
Abbreviations: BSC = best supportive care; LYG = life-year gained; PSS = personal social service; QALY = quality adjusted life-year; RWE = real-world evidence; SMA = spinal muscular atrophy; OA = Onasemnogene abeparvovec; PCA = pharmacological therapy resources; PAV = permanent assisted ventilation; PPP = purchasing power parity; SOC = Standard Of Care; PBS = Pharmaceutical Benefits Scheme; MBS = Medicare Benefits Schedule; NHCDC = National Hospital Cost Data Collection						

19.8 Appendix 8: Reporting quality assessment of economic studies

The reporting quality of studies assessed in the original systematic review are provided in Table 19.3 and Table 19.4. Additionally, assessment of the reporting quality of the one study included in this review update is provided in Table 19.5.

Table 19.3: Reporting quality of the economic evaluations in the original systematic review using the CHEERS checklist (Part I)

CHEERS criteria	Study and location where item is reported (page for location refer to PDF page)									
	NICE-Nusinersen TA588	NICE-Risdiplam TA755	NICE-Onasemnogene HST15-type1	NICE-Onasemnogene HST24-presymptomatic	ICER Spinraza and Zolgensma 2019	CADTH Nusinersen-2019	CADTH Risdiplam 2021	CADTH Onasemnogene -2021	Meijer 2023	Broekhoff-2021
Title										
Identify the study as an economic evaluation and specify the interventions being compared	Yes	Yes	Yes	Yes	Yes P:1	Yes P:1	Yes P:1	Yes P:1	Yes P:1	Yes P:1
Abstract										
Provide a structured summary that highlights context, key methods, results, and alternative analyses.	No	No	No	No	Yes P:8	Yes P:6-7	Yes P:168-169	Yes P:7-9	Yes P:3	Yes P:1
Introduction										
Give the context for the study, the study question, and its practical relevance for decision making in policy or practice.	No	Yes	Yes	Yes	Yes P:49-61	Yes P:8-10	Yes P:25-30, 44-47	No	Yes P:8-13	Yes P:1-2
Methods										
Health economic analysis plan: Indicate whether a health economic analysis plan was developed and where available.	No	No	No	No	No	No	No	No	No	No
Study population: Describe characteristics of the study population (such as age range, demographics,	Yes	Yes	Yes	Yes	Yes P:101	Yes P:12	Yes P:168	Yes P:11	Yes P:14	Yes P:4

CHEERS criteria	Study and location where item is reported (page for location refer to PDF page)									
	NICE-Nusinersen TA588	NICE-Risdiplam TA755	NICE-Onasemnogene HST15-type1	NICE-Onasemnogene HST24-presymptomatic	ICER Spinraza and Zolgensma 2019	CADTH Nusinersen-2019	CADTH Risdiplam 2021	CADTH Onasemnogene -2021	Meijer 2023	Broekhoff-2021
socioeconomic, or clinical characteristics).										
Setting and Location: Provide relevant contextual information that may influence findings.	Yes	Yes	Yes	Yes	Yes P:57	Yes P:2	Yes P:2	Yes P:2	Yes P:14	Yes P:4
Comparators: Describe the interventions or strategies being compared and why chosen.	Yes	Yes	Yes	Yes	Yes P:55	Yes P:9	Yes P:168	Yes P:7	Yes P:14	Yes P:4
Perspective: State the perspective(s) adopted by the study and why chosen.	Yes	Yes	Yes	Yes	Yes P:27	Yes P:12	Yes P:172	Yes P:7	Yes P:14	Yes P:4
Time Horizon: State the time horizon for the study and why appropriate.	Yes	Yes	Yes	Yes	Yes P:29	Yes P:12	Yes P:168	Yes P:7	Yes P:15	Yes P:4
Discount Rate: Report the discount rate(s) and reason chosen.	Yes	Yes	Yes	Yes	Yes P:27	Yes P:12	Yes P:172	Yes P:11	Yes P:15	Yes P:4
Selection of outcomes: Describe what outcomes were used as the measure(s) of benefit(s) and harm(s).	Yes	Yes	Yes	Yes	Yes P:56	Yes P:12	Yes P:168	Yes P:7	Yes P:15	Yes P:4-5
Measurement of outcomes: Describe how outcomes used to capture benefit(s) and harm(s) were measured.	Yes	Yes	Yes	Yes	Yes P:11	Yes P:15-16	Yes P:174-175	Yes P:13	Yes P:22-23	No
Valuation of outcomes: Describe the population and methods used to measure and value outcomes.	Yes	Yes	Yes	Yes	Yes P: 11	Yes P:15-16	Yes P:174	Yes P:13	Yes P:22-23	Yes P:4-5
Measurement and valuation of resources and costs:	Yes	Yes	Yes	Yes	Yes P: 111-115	Yes P:13	Yes P:174-175	Yes P:13	Yes P:23-25	Yes P:5

CHEERS criteria	Study and location where item is reported (page for location refer to PDF page)									
	NICE-Nusinersen TA588	NICE-Risdiplam TA755	NICE-Onasemnogene HST15-type1	NICE-Onasemnogene HST24-presymptomatic	ICER Spinraza and Zolgensma 2019	CADTH Nusinersen-2019	CADTH Risdiplam 2021	CADTH Onasemnogene -2021	Meijer 2023	Broekhoff-2021
Describe how costs were valued.										
Currency, price date, and conversion: Report the dates of the estimated resource quantities and unit costs, plus the currency and year of conversion.	Yes	No	Yes	Yes	Yes P:11-115	Yes P:14	No	No	Yes P:23	Yes P:5
Rationale and description of model: If modelling is used, describe in detail, and why used. Report if the model is publicly available and where it can be accessed.	yes	yes	Yes	Yes	Yes P:99-101	No	Yes P:171	Yes P:11	Yes P:15-16	No
Analytics and assumptions: Describe any methods for analysing or statistically transforming data, any extrapolation methods, and approaches for validating any model used.	Yes	Yes	Yes	Yes	Yes P:102-103	No	Yes P:171-174	Yes P:20	Yes P:36-37	Yes P:5
Characterizing heterogeneity: Describe any methods used for estimating how the results of the study vary for subgroups.	Yes	Yes	Yes	Yes	Yes P:106-109	Yes 30-31	Yes P:171	Yes P:11	Yes P:12-13	No
Characterizing distributional effects: Describe how impacts are distributed across different individuals or adjustments made to reflect priority populations.	Yes	Yes	Yes	Yes	Yes P:106-109	Yes P:14	Yes P:171	No	No	No
Characterizing uncertainty: Describe methods to	Yes	Yes	Yes	Yes	Yes P:115	No	Yes P:176-181	Yes P:14	Yes P:24-26	Yes P:5-6

CHEERS criteria	Study and location where item is reported (page for location refer to PDF page)									
	NICE-Nusinersen TA588	NICE-Risdiplam TA755	NICE-Onasemnogene HST15-type1	NICE-Onasemnogene HST24-presymptomatic	ICER Spinraza and Zolgensma 2019	CADTH Nusinersen-2019	CADTH Risdiplam 2021	CADTH Onasemnogene -2021	Meijer 2023	Broekhoff-2021
characterise any sources of uncertainty in the analysis.										
Approach to engagement with patients and others affected by the study: Describe any approaches to engage patients or service recipients, the general public, communities, or stakeholders (such as clinicians or payers) in the design of the study.	Yes	Yes	Yes	Yes	Yes P:31	No	Yes P:30-34	Yes P:10	No	No
Results										
Study parameters: Report all analytic inputs (such as values, ranges, references) including uncertainty or distributional assumptions.	Yes	Yes	Yes	Yes	Yes P: 117-136	No	No	Yes P:38	Yes P:25	Yes P:7
Summary of main results: Report the mean values for the main categories of costs and outcomes of interest and summarise them in the most appropriate overall measure.	Yes	No	Yes	No	Yes P:141-143	Yes P:14, 20	Yes P:182	Yes P:7, 24	Yes P:29	Yes P:5
Effect of uncertainty: Describe how uncertainty about analytic judgments, inputs, or projections affect findings. Report the effect of choice of discount rate and time horizon, if applicable.	Yes	Yes	Yes	Yes	Yes P: 117-136	No	Yes P:176-181	Yes P:25-26	Yes P:29-32	Yes P:6-7
Effect of engagement with patients and others affected	Yes	Yes	Yes	Yes	No	No	No	No	No	No

CHEERS criteria	Study and location where item is reported (page for location refer to PDF page)									
	NICE-Nusinersen TA588	**NICE-Risdiplam TA755**	**NICE-Onasemnogene HST15-type1**	**NICE-Onasemnogene HST24-presymptomatic**	**ICER Spinraza and Zolgensma 2019**	**CADTH Nusinersen-2019**	**CADTH Risdiplam 2021**	**CADTH Onasemnogene -2021**	**Meijer 2023**	**Broekhoff-2021**
by the study: Report on any difference patient/service recipient, general public, community, or stakeholder involvement made to the approach or findings of the study										
Discussion										
Study findings, limitations, generalizability, and current knowledge: Report key findings, limitations, ethical or equity considerations not captured, and how these could affect patients, policy, or practice.	Yes	Yes	Yes	Yes	Yes P:139-141	Yes P: 6, 15-19	Yes P: 169	Yes P:15-19, 26	Yes P:35-36	Yes P:9-10
Other										
Source of Funding: Describe how the study was funded and any role of the funder in the identification, design, conduct, and reporting of the analysis	No	No	No	No	Yes P:3	Yes P: 2	Yes P: 2	Yes P: 2	No	Yes P:10
Conflicts of Interest: Report authors conflicts of interest according to journal or International Committee of Medical Journal Editors requirements.	Yes	Yes	Yes	Yes	Yes P:270-272	Yes P: 2	Yes P: 2	Yes P: 2	No	Yes P:10

Table 19.4: Reporting quality of the economic evaluations in the original systematic review using the CHEERS checklist (Part II)

CHEERS criteria	Study and location where item is reported (page for location refer to PDF page)									
	SMC Nusinersen-2018	SMC Onasemnogene - 2021	SMC Risdiplam-2022	Connock et al., 2020	Dean et al. 2021	Malone et al. 2019	Wang et al. 2022	Zuluaga-Sanchez et al. 2019	Thokala et al. 2020	NCPE-2017
Title										
Identify the study as an economic evaluation and specify the interventions being compared	No	No	No	Yes P:1	Yes P:1	Yes P:1	Yes P:1	Yes P:1	Yes P:1	Yes P:1
Abstract										
Provide a structured summary that highlights context, key methods, results, and alternative analyses.	No	No	No	Yes P:2	Yes P:1	Yes P:1	Yes P:1	Yes P:1	Yes P:1	No
Introduction										
Give the context for the study, the study question, and its practical relevance for decision making in policy or practice.	Yes P:3-9	Yes P:2-8	Yes P:2-9	Yes P:2-3	Yes P:1-3	Yes P:1-2	Yes P:1-3	Yes P:1-3	Yes P:1-2	No
Methods										
Health economic analysis plan: Indicate whether a health economic analysis plan was developed and where available.	No	No	No	No	No	No	No	No	No	No
Study population: Describe characteristics of the study population (such as age range,	Yes P:11	Yes P:9	Yes P:10	Yes P:3	Yes P:1	Yes P:2	Yes P:2	Yes P:5	Yes P:2	No

CHEERS criteria	Study and location where item is reported (page for location refer to PDF page)									
	SMC Nusinersen-2018	**SMC Onasemnogene - 2021**	**SMC Risdiplam-2022**	**Connock et al., 2020**	**Dean et al. 2021**	**Malone et al. 2019**	**Wang et al. 2022**	**Zuluaga-Sanchez et al. 2019**	**Thokala et al. 2020**	**NCPE-2017**
demographics, socioeconomic, or clinical characteristics).										
Setting and Location: Provide relevant contextual information that may influence findings.	Yes P:1	Yes P:1	Yes P:1	Yes P:3	Yes P:1	Yes P:2	Yes P:2	Yes P:5	Yes P:2	Yes P:2
Comparators: Describe the interventions or strategies being compared and why chosen.	Yes P:11	Yes P:9	Yes P:10	Yes P:3	Yes P:3	Yes P:2	Yes P:3	Yes P:5	Yes P:2	Yes P:6
Perspective: State the perspective(s) adopted by the study and why chosen.	Yes P:11	Yes P:10	No	Yes P:3	Yes P:1	Yes P:2	Yes P:3	Yes P:5	Yes P:2	**Yes P:5**
Time Horizon: State the time horizon for the study and why appropriate.	Yes P:11	Yes P:10	Yes P:10	Yes P:3	Yes P:7	Yes P:2	Yes P:3	Yes P:5	Yes P:2	**Yes P:5**
Discount Rate: Report the discount rate(s) and reason chosen.	No	No	No	No	Yes P:7	Yes P:3	Yes P:3	Yes P:5	Yes P:2	**Yes P:6**
Selection of outcomes: Describe what outcomes were used as the measure(s) of benefit(s) and harm(s).	Yes P:11	Yes P:11	Yes P:13	Yes P:3	Yes P:1	Yes P:2-3	Yes P:6	Yes P:5	Yes P:2	**Yes P:1**
Measurement of outcomes: Describe	Yes P:12	Yes P:10	Yes P:11	Yes P:3	Yes P:3	Yes P:6-7	Yes P:3	Yes P:13-14	Yes P:5-6	**Yes P:5**

CHEERS criteria	Study and location where item is reported (page for location refer to PDF page)									
	SMC Nusinersen-2018	**SMC Onasemnogene - 2021**	**SMC Risdiplam-2022**	**Connock et al., 2020**	**Dean et al. 2021**	**Malone et al. 2019**	**Wang et al. 2022**	**Zuluaga-Sanchez et al. 2019**	**Thokala et al. 2020**	**NCPE-2017**
how outcomes used to capture benefit(s) and harm(s) were measured.										
Valuation of outcomes: Describe the population and methods used to measure and value outcomes.	Yes P:12	Yes P:10-11	Yes P:11	Yes P:3	Yes P:3-4	Yes P:6-7	Yes P:3	Yes P:13-14	Yes P:5-6	**Yes** **P:5**
Measurement and valuation of resources and costs: Describe how costs were valued.	No	Yes P:11	Yes P:11	Yes P:3	Yes P:3-4	Yes P:6	Yes P:3-4	Yes P:12-13	Yes P:6	**No**
Currency, price date, and conversion: Report the dates of the estimated resource quantities and unit costs, plus the currency and year of conversion.	Yes P:16	Yes P:16	Yes P:16	Yes P:3	Yes P:5	No	Yes P:4	Yes P:12	Yes P:6	**No**
Rationale and description of model: If modelling is used, describe in detail, and why used. Report if the model is publicly available and where it can be accessed.	No	No	No	No	No	Yes P:2-4	No	No	No	No
Analytics and assumptions: Describe any methods for analysing or	No	No	No	No	No	Yes P:3	Yes P:3	Yes P:5	Yes P:2	No

CHEERS criteria	Study and location where item is reported (page for location refer to PDF page)									
	SMC Nusinersen-2018	SMC Onasemnogene - 2021	SMC Risdiplam-2022	Connock et al., 2020	Dean et al. 2021	Malone et al. 2019	Wang et al. 2022	Zuluaga-Sanchez et al. 2019	Thokala et al. 2020	NCPE-2017
statistically transforming data, any extrapolation methods, and approaches for validating any model used.										
Characterizing heterogeneity: Describe any methods used for estimating how the results of the study vary for subgroups.	Yes	No	No	No	No	No	No	No	Yes P:7	No
Characterizing distributional effects: Describe how impacts are distributed across different individuals or adjustments made to reflect priority populations.	No	No	No	No	No	No	No	No	No	No
Characterizing uncertainty: Describe methods to characterise any sources of uncertainty in the analysis.	No	No	No	No	No	Yes P:7	Yes P:5-6	Yes P:14	Yes P:7	Yes P:6
Approach to engagement with patients and others affected by the study: Describe any approaches to engage patients or	Yes P:10	Yes P:8-9	Yes P:9-10	No	No	No	No	No	No	No

CHEERS criteria	Study and location where item is reported (page for location refer to PDF page)									
	SMC Nusinersen-2018	**SMC Onasemnogene - 2021**	**SMC Risdiplam-2022**	**Connock et al., 2020**	**Dean et al. 2021**	**Malone et al. 2019**	**Wang et al. 2022**	**Zuluaga-Sanchez et al. 2019**	**Thokala et al. 2020**	**NCPE-2017**
service recipients, the general public, communities, or stakeholders (such as clinicians or payers) in the design of the study.										
Results										
Study parameters: Report all analytic inputs (such as values, ranges, references) including uncertainty or distributional assumptions.	No	No	No	No	No	No	Yes P:4	Yes P:4-10	No	No
Summary of main results: Report the mean values for the main categories of costs and outcomes of interest and summarise them in the most appropriate overall measure.	Yes P:12-13	Yes P:11	Yes P:12	Yes P:2	Yes P:7	Yes P:9	Yes P:6	Yes P:15	Yes P:7	Yes P:6
Effect of uncertainty: Describe how uncertainty about analytic judgments, inputs, or projections affect findings. Report the effect of choice of discount rate and time horizon, if applicable.	Yes P:12-13	Yes P:12	Yes P:12	Yes P:4	Yes P:8	Yes P:10-11	Yes P:6-7	Yes P:14-17	Yes P:8-9	Yes P:6

CHEERS criteria	Study and location where item is reported (page for location refer to PDF page)									
	SMC Nusinersen-2018	**SMC Onasemnogene - 2021**	**SMC Risdiplam-2022**	**Connock et al., 2020**	**Dean et al. 2021**	**Malone et al. 2019**	**Wang et al. 2022**	**Zuluaga-Sanchez et al. 2019**	**Thokala et al. 2020**	**NCPE-2017**
Effect of engagement with patients and others affected by the study: Report on any difference patient/service recipient, general public, community, or stakeholder involvement made to the approach or findings of the study	No	No	No	No	No	No	No	No	No	No
Discussion										
Study findings, limitations, generalizability, and current knowledge: Report key findings, limitations, ethical or equity considerations not captured, and how these could affect patients, policy, or practice.	Yes P:12-13	Yes P:13	Yes P:12-13	Yes P:4-5	Yes P:9-11	Yes P:11-12	Yes P:6, 8-9	Yes P:15-18	Yes P:9-10	No
Other										
Source of Funding: Describe how the study was funded and any role of the funder in the identification, design, conduct, and reporting of the analysis	No	No	No	Yes P:5	Yes P:11	Yes P:13	Yes P:9	Yes P:18	Yes P:11	No
Conflicts of Interest: Report authors	No	No	No	Yes P:5	Yes P:11	Yes P:12-13	Yes P:9	Yes P:18	Yes P:11	No

CHEERS criteria	Study and location where item is reported (page for location refer to PDF page)									
	SMC Nusinersen-2018	SMC Onasemnogene - 2021	SMC Risdiplam-2022	Connock et al., 2020	Dean et al. 2021	Malone et al. 2019	Wang et al. 2022	Zuluaga-Sanchez et al. 2019	Thokala et al. 2020	NCPE-2017
conflicts of interest according to journal or International Committee of Medical Journal Editors requirements.										

Table 19.5: Reporting quality of the economic evaluation in the systematic review update using the CHEERS checklist

CHEERS criteria	Location where item is reported (page for location refer to PDF page)
Title	
Identify the study as an economic evaluation and specify the interventions being compared	Yes P.1-2
Abstract	
Provide a structured summary that highlights context, key methods, results, and alternative analyses.	Yes p.1
Introduction	
Give the context for the study, the study question, and its practical relevance for decision making in policy or practice.	Yes p.1-2
Methods	
Health economic analysis plan: Indicate whether a health economic analysis plan was developed and where available.	No
Study population: Describe characteristics of the study population (such as age range, demographics, socioeconomic, or clinical characteristics).	Yes p.2-3; appendix 2 p5
Setting and Location: Provide relevant contextual information that may influence findings.	Yes p.3-4
Comparators: Describe the interventions or strategies being compared and why chosen.	Yes p.1-3
Perspective: State the perspective(s) adopted by the study and why chosen.	Yes p.3
Time Horizon: State the time horizon for the study and why appropriate.	Yes p.3
Discount Rate: Report the discount rate(s) and reason chosen.	Yes p.3
Selection of outcomes: Describe what outcomes were used as the measure(s) of benefit(s) and harm(s).	Yes p.5
Measurement of outcomes: Describe how outcomes used to capture benefit(s) and harm(s) were measured.	Yes p.5
Valuation of outcomes: Describe the population and methods used to measure and value outcomes.	Yes p.4-5
Measurement and valuation of resources and costs: Describe how costs were valued.	Yes p.4; Appendix 2, Table 6–9

Currency, price date, and conversion: Report the dates of the estimated resource quantities and unit costs, plus the currency and year of conversion.	Yes p.3
Rationale and description of model: If modelling is used, describe in detail, and why used. Report if the model is publicly available and where it can be accessed.	Yes p.2-3; appendix 1
Analytics and assumptions: Describe any methods for analysing or statistically transforming data, any extrapolation methods, and approaches for validating any model used.	Yes p4-5; appendix 3
Characterizing heterogeneity: Describe any methods used for estimating how the results of the study vary for subgroups.	No
Characterizing distributional effects: Describe how impacts are distributed across different individuals or adjustments made to reflect priority populations.	No
Characterizing uncertainty: Describe methods to characterise any sources of uncertainty in the analysis.	Yes p.5; appendix 3
Approach to engagement with patients and others affected by the study: Describe any approaches to engage patients or service recipients, the general public, communities, or stakeholders (such as clinicians or payers) in the design of the study.	Yes appendix 3
Results	
Study parameters: Report all analytic inputs (such as values, ranges, references) including uncertainty or distributional assumptions.	Yes p5-4; appendix 2
Summary of main results: Report the mean values for the main categories of costs and outcomes of interest and summarise them in the most appropriate overall measure.	Yes p5-8
Effect of uncertainty: Describe how uncertainty about analytic judgments, inputs, or projections affect findings. Report the effect of choice of discount rate and time horizon, if applicable.	Yes p6-9
Effect of engagement with patients and others affected by the study: Report on any difference patient/service recipient, general public, community, or stakeholder involvement made to the approach or findings of the study	Yes p9
Discussion	
Study findings, limitations, generalizability, and current knowledge: Report key findings, limitations, ethical or equity considerations not captured, and how these could affect patients, policy, or practice.	Yes p.8-10
Other	
Source of Funding: Describe how the study was funded and any role of the funder in the identification, design, conduct, and reporting of the analysis	Yes P.11
Conflicts of Interest: Report authors conflicts of interest according to journal or International Committee of Medical Journal Editors requirements.	Yes P.11

19.9 Appendix 9: Methodological quality assessment of economic studies

The quality assessment of the economic evaluations included in the original systematic review are provided in Table 19.6 and Table 19.7. Additionally, the quality assessment of the study included in the systematic review update is provided in Table 19.8.

Table 19.6: Critical appraisal of the economic models in the original systematic review using an adapted Philips checklist (Part I)

Philips criteria		NICE-TA588	NICE-TA755	NICE-HST15-type1	NICE-HST24-presymptomatic	ICER Spinraza and Zolgensma 2019	CADTH Nusinersen-2019	CADTH Risdiplam-2021	CADTH Onasemnogene - 2021	Meijer et al., 2023	Broekhoff et al., 2021
Structure											
1	Is there a clear statement of the decision problem?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
2	Is the objective of the model specified and consistent with the stated decision problem?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
3	Is the primary decision maker specified?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Unclear	Unclear
4	Is the perspective of the model stated clearly?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
5	Are the model inputs consistent with the stated perspective?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
6	Has the scope of the model been stated and justified?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Unclear	Unclear
7	Are the outcomes of the model consistent with the perspective, scope and overall	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes

Philips criteria		NICE-TA588	NICE-TA755	NICE-HST15-type1	NICE-HST24-presymptomatic	ICER Spinraza and Zolgensma 2019	CADTH Nusinersen-2019	CADTH Risdiplam-2021	CADTH Onasemnogene - 2021	Meijer et al., 2023	Broekhoff et al., 2021
	objective of the model?										
8	Is the structure of the model consistent with a coherent theory of the health condition under evaluation?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No
9	Are the sources of the data used to develop the structure of the model specified?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
10	Are the causal relationships described by the model structure justified appropriately?	Yes	Yes	Yes	Yes	Yes	Unclear	Yes	Yes	Yes	Yes
11	Are the structural assumptions transparent and justified?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
12	Are the structural assumptions reasonable given the overall objective, perspective and scope of the model?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
13	Is there a clear definition of the options under evaluation?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes

Philips criteria		NICE-TA588	NICE-TA755	NICE-HST15-type1	NICE-HST24-presymptomatic	ICER Spinraza and Zolgensma 2019	CADTH Nusinersen-2019	CADTH Risdiplam-2021	CADTH Onasemnogene - 2021	Meijer et al., 2023	Broekhoff et al., 2021
14	Have all feasible and practical options been evaluated?	No	No	No	No	No	No	No	No	No	No
15	Is there justification for the exclusion of feasible options?	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear
16	Is the chosen model type appropriate given the decision problem and specified casual relationships within the model?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No
17	Is the time horizon of the model sufficient to reflect all important differences between the options?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
18	Are the time horizon of the model, the duration of treatment and the duration of treatment described and justified?	Yes	Yes	Yes	Yes	Yes	Yes	Unclear	Yes	No	Yes
19	Do the disease states (state transition model) or the pathways (decision tree model) reflect the underlying biological process of the disease in question	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No

Philips criteria		NICE-TA588	NICE-TA755	NICE-HST15-type1	NICE-HST24-presymptomatic	ICER Spinraza and Zolgensma 2019	CADTH Nusinersen-2019	CADTH Risdiplam-2021	CADTH Onasemnogene - 2021	Meijer et al., 2023	Broekhoff et al., 2021
	and the impact of interventions?										
20	Is the cycle length defined and justified in terms of the natural history of disease?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Data											
21	Are the data identification methods transparent and appropriate given the objectives of the model?	Yes	Unclear	Yes	Yes	Unclear	Unclear	Unclear	Unclear	Yes	Unclear
22	Where choices have been made between data sources are these justified appropriately?	Yes	Yes	Yes	Yes	Yes	Unclear	Yes	Yes	Yes	Yes
23	Has particular attention been paid to identifying data for the important parameters of the model?	Yes	Yes	Yes	Yes	Yes	Unclear	Yes	Yes	Yes	Yes
24	Has the quality of the data been assessed appropriately?	Yes	Yes	Yes	Yes	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear
25	Where expert opinion has been used are the methods	Yes	Yes	Unclear	Unclear	Yes	Yes	Unclear	Unclear	No	No

Philips criteria		NICE-TA588	NICE-TA755	NICE-HST15-type1	NICE-HST24-presymptomatic	ICER Spinraza and Zolgensma 2019	CADTH Nusinersen-2019	CADTH Risdiplam-2021	CADTH Onasemnogene - 2021	Meijer et al., 2023	Broekhoff et al., 2021
	described and justified?										
26	Is the data modelling methodology based on justifiable statistical and epidemiological techniques?	Yes	Yes	Yes	Yes	Yes	Unclear	Yes	Yes	No	Unclear
27	Is the choice of baseline data described and justified?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
28	Are transition probabilities calculated appropriately?	Yes	Yes	Yes	Yes	Yes	Unclear	Yes	Yes	No	Yes
29	Has a half-cycle correction been applied to both costs and outcomes?	Yes	Yes	Yes	Yes	Yes	Unclear	Unclear	Unclear	Yes	Unclear
30	If not, has the omission been justified?	-	-	-	-	-	Unclear	Unclear	Unclear	-	Unclear
31	If relative treatment effects have been derived from trial data, have they been synthesised using appropriate techniques?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Unclear	Unclear	Unclear
32	Have the methods and assumptions	Yes	Yes	Yes	Yes	Yes	Unclear	Yes	Yes	Yes	Yes

Philips criteria		NICE-TA588	NICE-TA755	NICE-HST15-type1	NICE-HST24-presymptomatic	ICER Spinraza and Zolgensma 2019	CADTH Nusinersen-2019	CADTH Risdiplam-2021	CADTH Onasemnogene - 2021	Meijer et al., 2023	Broekhoff et al., 2021
	used to extrapolate short-term results to final outcomes been documented and justified?										
33	Have alternative extrapolation assumptions been explored through sensitivity analysis?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
34	Have assumptions regarding the continuing effect of treatment once treatment is complete been documented and justified?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
35	Have alternative assumptions regarding the continuing effect of treatment been explored through sensitivity analysis	No	No	No	No	No	No	No	No	No	Yes
36	Are the costs incorporated into the model justified?	Yes	Unclear	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
37	Has the source for all costs been described?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
38	Have discount rates been described and	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes

Philips criteria		NICE-TA588	NICE-TA755	NICE-HST15-type1	NICE-HST24-presymptomatic	ICER Spinraza and Zolgensma 2019	CADTH Nusinersen-2019	CADTH Risdiplam-2021	CADTH Onasemnogene - 2021	Meijer et al., 2023	Broekhoff et al., 2021
	justified given the target decision maker?										
39	Are the utilities incorporated into the model appropriate?	Yes	Yes	Yes	Yes	Yes	Unclear	Yes	Yes	Yes	Yes
40	Is the source of utility weights referenced?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
41	Are the methods of derivation for the utility weights justified?	Yes	Yes	Yes	Yes	Unclear	Yes	Yes	Yes	Yes	Yes
42	Have all data incorporated into the model been described and referenced in sufficient detail?	Yes	Yes	Yes	Yes	Yes	Unclear	Unclear	Unclear	Unclear	Unclear
43	Has the use of mutually inconsistent data been justified (i.e. are assumptions and choices appropriate?)	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Unclear	Unclear
44	Is the process of data incorporation transparent?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
45	If data have been incorporated as distributions, has the choice of distributions for each parameter	Yes	Unclear	Yes	Yes	Yes	Unclear	Unclear	Unclear	Yes	Yes

Philips criteria		NICE-TA588	NICE-TA755	NICE-HST15-type1	NICE-HST24-presymptomatic	ICER Spinraza and Zolgensma 2019	CADTH Nusinersen-2019	CADTH Risdiplam-2021	CADTH Onasemnogene - 2021	Meijer et al., 2023	Broekhoff et al., 2021
	been described and justified?										
46	If data have been incorporated as distributions, is it clear that second order uncertainty is reflected?	Yes	Unclear	Yes	Yes	Yes	Unclear	Unclear	Unclear	Yes	Yes
47	Have the four principal types of uncertainty been addressed?	Yes	Yes	Yes	Yes	Yes	No	No	No	No	No
48	If not, has the omission of particular forms of uncertainty been justified?	-	-	-	-	-	No	No	No	No	No
49	Have methodological uncertainties been addressed by running alternative versions of the model with different methodological assumptions?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
50	Is there evidence that structural uncertainties have been addressed via sensitivity analysis?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
51	Has heterogeneity been dealt with by running the model	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No

Philips criteria		NICE-TA588	NICE-TA755	NICE-HST15-type1	NICE-HST24-presymptomatic	ICER Spinraza and Zolgensma 2019	CADTH Nusinersen-2019	CADTH Risdiplam-2021	CADTH Onasemnogene - 2021	Meijer et al., 2023	Broekhoff et al., 2021
	separately for different sub-groups?										
52	Are the methods of assessment of parameter uncertainty appropriate?	Yes	Yes	Yes	Yes	Yes	Unclear	Yes	Yes	Yes	Yes
53	If data are incorporated as point estimates, are the ranges used for sensitivity analysis stated clearly and justified?	Yes	Yes	Yes	Yes	Yes	No	No	No	Yes	Yes
54	Is there evidence that the mathematical logic of the model has been tested thoroughly before use?	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear
55	Are any counterintuitive results from the model explained and justified?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
56	If the model has been calibrated against independent data, have any differences been explained and justified?	Unclear	Unclear	Unclear	-	-	-	-	-	-	-
57	Have the results been compared with those	Yes	Yes	Yes	Yes	Unclear	No	No	No	Yes	Yes

Philips criteria		NICE-TA588	NICE-TA755	NICE-HST15-type1	NICE-HST24-presymptomatic	ICER Spinraza and Zolgensma 2019	CADTH Nusinersen-2019	CADTH Risdiplam-2021	CADTH Onasemnogene - 2021	Meijer et al., 2023	Broekhoff et al., 2021
	of previous models and any differences in results explained?										
N- No; N/A- Not Applicable; Y- Yes; UNC-Unclear											

Table 19.7: Critical appraisal of the economic models in the original systematic review using an adapted Philips checklist (Part II)

Philips criteria		SMC Nusinersen - 2018	SMC Onasemnogene - 2021	SMC Risdiplam-2022	Connock et al., 2020	Dean et al. 2021	Malone et al. 2019	Wang et al. 2022	Zuluaga-Sanchez et al. 2019	Thokala et al. 2020	NCPE-2017
Structure											
1	Is there a clear statement of the decision problem?	Unclear	Unclear	Unclear	Yes	Yes	Yes	Yes	Yes	Yes	Yes
2	Is the objective of the model specified and consistent with the stated decision problem?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
3	Is the primary decision maker specified?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
4	Is the perspective of the model stated clearly?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
5	Are the model inputs consistent with the stated perspective?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
6	Has the scope of the model been stated and justified?	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear

Philips criteria		SMC Nusinersen - 2018	SMC Onasemnogene - 2021	SMC Risdiplam-2022	Connock et al., 2020	Dean et al. 2021	Malone et al. 2019	Wang et al. 2022	Zuluaga-Sanchez et al. 2019	Thokala et al. 2020	NCPE-2017
7	Are the outcomes of the model consistent with the perspective, scope and overall objective of the model?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
8	Is the structure of the model consistent with a coherent theory of the health condition under evaluation?	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Unclear
9	Are the sources of the data used to develop the structure of the model specified?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
10	Are the causal relationships described by the model structure justified appropriately?	Yes	Yes	Yes	Unclear	Yes	Yes	Yes	Yes	Yes	Unclear
11	Are the structural assumptions transparent and justified?	No	No	No	Unclear	Yes	Yes	Yes	Yes	Yes	Unclear
12	Are the structural assumptions reasonable given the overall objective, perspective and scope of the model?	No	No	No	Unclear	Unclear	Yes	Yes	Yes	Yes	Unclear
13	Is there a clear definition of the options under evaluation?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
14	Have all feasible and practical options been evaluated?	Yes	No	No	Yes	Yes	Yes	No	Yes	No	Yes

Philips criteria		SMC Nusinersen - 2018	SMC Onasemnogene - 2021	SMC Risdiplam-2022	Connock et al., 2020	Dean et al. 2021	Malone et al. 2019	Wang et al. 2022	Zuluaga-Sanchez et al. 2019	Thokala et al. 2020	NCPE-2017
15	Is there justification for the exclusion of feasible options?	-	Unclear	Unclear	-	-	-	Unclear	-	Unclear	-
16	Is the chosen model type appropriate given the decision problem and specified casual relationships within the model?	Yes	Yes	Yes	Unclear	Yes	Yes	Yes	Yes	Yes	Unclear
17	Is the time horizon of the model sufficient to reflect all important differences between the options?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
18	Are the time horizon of the model, the duration of treatment and the duration of treatment described and justified?	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Unclear
19	Do the disease states (state transition model) or the pathways (decision tree model) reflect the underlying biological process of the disease in question and the impact of interventions?	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Unclear
20	Is the cycle length defined and justified in terms of the natural history of disease?	Unclear	Yes	Yes	No	Unclear	Yes	Yes	Yes	Yes	Yes
Data											

Philips criteria		SMC Nusinersen - 2018	SMC Onasemnogene - 2021	SMC Risdiplam-2022	Connock et al., 2020	Dean et al. 2021	Malone et al. 2019	Wang et al. 2022	Zuluaga-Sanchez et al. 2019	Thokala et al. 2020	NCPE-2017
21	Are the data identification methods transparent and appropriate given the objectives of the model?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Unclear
22	Where choices have been made between data sources are these justified appropriately?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Unclear
23	Has particular attention been paid to identifying data for the important parameters of the model?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Unclear
24	Has the quality of the data been assessed appropriately?	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear
25	Where expert opinion has been used are the methods described and justified?	Unclear	Unclear	Unclear	Unclear	-	-	-	Unclear	-	-
26	Is the data modelling methodology based on justifiable statistical and epidemiological techniques?	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear
27	Is the choice of baseline data described and justified?	Unclear	Unclear	Unclear	Yes	Unclear	Yes	Yes	Yes	Yes	Unclear
28	Are transition probabilities calculated appropriately?	Unclear	Unclear	Yes	Unclear	Unclear	Yes	Yes	Yes	Yes	Unclear
29	Has a half-cycle correction been applied to	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Yes	Yes	Unclear	Unclear

Philips criteria		SMC Nusinersen - 2018	SMC Onasemnogene - 2021	SMC Risdiplam-2022	Connock et al., 2020	Dean et al. 2021	Malone et al. 2019	Wang et al. 2022	Zuluaga-Sanchez et al. 2019	Thokala et al. 2020	NCPE-2017
	both costs and outcomes?										
30	If not, has the omission been justified?	-	-	-	-	-	-	-	-	-	-
31	If relative treatment effects have been derived from trial data, have they been synthesised using appropriate techniques?	Unclear	Unclear	Yes	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear
32	Have the methods and assumptions used to extrapolate short-term results to final outcomes been documented and justified?	Unclear	Unclear	Unclear	Unclear	Yes	Yes	Yes	Yes	Yes	Unclear
33	Have alternative extrapolation assumptions been explored through sensitivity analysis?	Unclear	Unclear	Unclear	No	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear
34	Have assumptions regarding the continuing effect of treatment once treatment is complete been documented and justified?	Yes	Yes	Yes	Unclear	Unclear	Yes	Unclear	Yes	Unclear	Unclear
35	Have alternative assumptions regarding the continuing effect of treatment been explored through sensitivity analysis	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear

Philips criteria		SMC Nusinersen - 2018	SMC Onasemnogene - 2021	SMC Risdiplam-2022	Connock et al., 2020	Dean et al. 2021	Malone et al. 2019	Wang et al. 2022	Zuluaga-Sanchez et al. 2019	Thokala et al. 2020	NCPE-2017
36	Are the costs incorporated into the model justified?	Unclear	Yes	Unclear	Yes	Yes	Yes	Yes	Yes	Yes	Unclear
37	Has the source for all costs been described?	Unclear	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Unclear
38	Have discount rates been described and justified given the target decision maker?	Unclear	Unclear	Unclear	Unclear	Yes	Yes	Yes	Yes	Yes	Yes
39	Are the utilities incorporated into the model appropriate?	Yes	No	No	Yes	Yes	Yes	Yes	Yes	Yes	Unclear
40	Is the source of utility weights referenced?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
41	Are the methods of derivation for the utility weights justified?	Unclear	Unclear	Unclear	Unclear	Yes	Yes	Unclear	Yes	Yes	Yes
42	Have all data incorporated into the model been described and referenced in sufficient detail?	No	No	No	Unclear	Unclear	Yes	Yes	Yes	Yes	Unclear
43	Has the use of mutually inconsistent data been justified (i.e. are assumptions and choices appropriate?)	No	No	No	Yes	No	No	No	No	No	Unclear
44	Is the process of data incorporation transparent?	Unclear	Unclear	Unclear	Yes	Unclear	Yes	Yes	Yes	Yes	Unclear
45	If data have been incorporated as	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Yes	Yes	Unclear	Unclear

Philips criteria		SMC Nusinersen - 2018	SMC Onasemnogene - 2021	SMC Risdiplam-2022	Connock et al., 2020	Dean et al. 2021	Malone et al. 2019	Wang et al. 2022	Zuluaga-Sanchez et al. 2019	Thokala et al. 2020	NCPE-2017
	distributions, has the choice of distributions for each parameter been described and justified?										
46	If data have been incorporated as distributions, is it clear that second order uncertainty is reflected?	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Yes	Unclear	Unclear
47	Have the four principal types of uncertainty been addressed?	Unclear	Unclear	Unclear	No	No	Yes	Yes	Yes	Yes	Unclear
48	If not, has the omission of particular forms of uncertainty been justified?	-	-	-	Unclear	No	-	-	-	-	Unclear
49	Have methodological uncertainties been addressed by running alternative versions of the model with different methodological assumptions?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
50	Is there evidence that structural uncertainties have been addressed via sensitivity analysis?	Unclear	Unclear	Unclear	Yes	Yes	Unclear	Unclear	Unclear	Unclear	Unclear
51	Has heterogeneity been dealt with by running the model separately for different sub-groups?	Unclear	Unclear	Unclear	No	No	No	No	Yes	No	Unclear

Philips criteria		SMC Nusinersen - 2018	SMC Onasemnogene - 2021	SMC Risdiplam-2022	Connock et al., 2020	Dean et al. 2021	Malone et al. 2019	Wang et al. 2022	Zuluaga-Sanchez et al. 2019	Thokala et al. 2020	NCPE-2017
52	Are the methods of assessment of parameter uncertainty appropriate?	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Unclear
53	If data are incorporated as point estimates, are the ranges used for sensitivity analysis stated clearly and justified?	Unclear	Unclear	Unclear	Unclear	No	No	Yes	Yes	Yes	Unclear
54	Is there evidence that the mathematical logic of the model has been tested thoroughly before use?	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear
55	Are any counterintuitive results from the model explained and justified?	No	No	No	Yes	Yes	Yes	Yes	Yes	Yes	No
56	If the model has been calibrated against independent data, have any differences been explained and justified?	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear
57	Have the results been compared with those of previous models and any differences in results explained?	No	No	No	Yes	Yes	Yes	Yes	Yes	Yes	No
N- No; N/A- Not Applicable; Y- Yes; UNC-Unclear											

Table 19.8: Critical appraisal of the economic model included in the systematic review update using an adapted Philips checklist

Structure		**Khuntha et al. 2024**
1	Is there a clear statement of the decision problem?	Yes
2	Is the objective of the model specified and consistent with the stated decision problem?	Yes
3	Is the primary decision maker specified?	Yes
4	Is the perspective of the model stated clearly?	Yes
5	Are the model inputs consistent with the stated perspective?	Yes
6	Has the scope of the model been stated and justified?	Yes
7	Are the outcomes of the model consistent with the perspective, scope and overall objective of the model?	Yes
8	Is the structure of the model consistent with a coherent theory of the health condition under evaluation?	Yes
9	Are the sources of the data used to develop the structure of the model specified?	Yes
10	Are the causal relationships described by the model structure justified appropriately?	Yes
11	Are the structural assumptions transparent and justified?	Yes
12	Are the structural assumptions reasonable given the overall objective, perspective and scope of the model?	Yes
13	Is there a clear definition of the options under evaluation?	Yes
14	Have all feasible and practical options been evaluated?	Yes
15	Is there justification for the exclusion of feasible options?	Yes
16	Is the chosen model type appropriate given the decision problem and specified casual relationships within the model?	Yes
17	Is the time horizon of the model sufficient to reflect all important differences between the options?	Yes
18	Are the time horizon of the model, the duration of treatment and the duration of treatment described and justified?	Yes

19	Do the disease states (state transition model) or the pathways (decision tree model) reflect the underlying biological process of the disease in question and the impact of interventions?	Yes
20	Is the cycle length defined and justified in terms of the natural history of disease?	Yes
Data		
21	Are the data identification methods transparent and appropriate given the objectives of the model?	Unclear
22	Where choices have been made between data sources are these justified appropriately?	Yes
23	Has particular attention been paid to identifying data for the important parameters of the model?	Yes
24	Has the quality of the data been assessed appropriately?	Unclear
25	Where expert opinion has been used are the methods described and justified?	Yes
26	Is the data modelling methodology based on justifiable statistical and epidemiological techniques?	Yes
27	Is the choice of baseline data described and justified?	Yes
28	Are transition probabilities calculated appropriately?	Yes
29	Has a half-cycle correction been applied to both costs and outcomes?	Unclear
30	If not, has the omission been justified?	Unclear
31	If relative treatment effects have been derived from trial data, have they been synthesised using appropriate techniques?	Yes
32	Have the methods and assumptions used to extrapolate short-term results to final outcomes been documented and justified?	Yes
33	Have alternative extrapolation assumptions been explored through sensitivity analysis?	Unclear
34	Have assumptions regarding the continuing effect of treatment once treatment is complete been documented and justified?	NA
35	Have alternative assumptions regarding the continuing effect of treatment been explored through sensitivity analysis	NA
36	Are the costs incorporated into the model justified?	Yes

37	Has the source for all costs been described?	Yes
38	Have discount rates been described and justified given the target decision maker?	Yes
39	Are the utilities incorporated into the model appropriate?	Yes
40	Is the source of utility weights referenced?	Yes
41	Are the methods of derivation for the utility weights justified?	Yes
42	Have all data incorporated into the model been described and referenced in sufficient detail?	Yes
43	Has the use of mutually inconsistent data been justified (i.e. are assumptions and choices appropriate?)	No
44	Is the process of data incorporation transparent?	Yes
45	If data have been incorporated as distributions, has the choice of distributions for each parameter been described and justified?	Yes
46	If data have been incorporated as distributions, is it clear that second order uncertainty is reflected?	Yes
47	Have the four principal types of uncertainty been addressed?	Yes
48	If not, has the omission of particular forms of uncertainty been justified?	NA
49	Have methodological uncertainties been addressed by running alternative versions of the model with different methodological assumptions?	Yes
50	Is there evidence that structural uncertainties have been addressed via sensitivity analysis?	Yes
51	Has heterogeneity been dealt with by running the model separately for different sub-groups?	No
52	Are the methods of assessment of parameter uncertainty appropriate?	Yes
53	If data are incorporated as point estimates, are the ranges used for sensitivity analysis stated clearly and justified?	NA
54	Is there evidence that the mathematical logic of the model has been tested thoroughly before use?	Yes
55	Are any counterintuitive results from the model explained and justified?	Yes

56	If the model has been calibrated against independent data, have any differences been explained and justified?	Unclear
57	Have the results been compared with those of previous models and any differences in results explained?	Yes
N/A- Not Applicable		

SMA EAG addendum of economics results post consultation [ID6195]

Confidential appendix (Results based on additional information after the consultation process)

Produced by	Newcastle University
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Date completed	02/10/2025

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Confidential comparator prices are highlighted in green throughout the report.

Any de-personalised data are highlighted in pink throughout the report.

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1. Background

Following the initial submission of the EAG assessment report, an online meeting was held on 20th August 2025 between NICE, the EAG, and the manufacturers (Biogen and Roche) to discuss the application of the severity modifier and caregiver QALYs in ID6195. In the meeting NICE requested the manufacturers Biogen and Roche to update the severity calculations in their base-case analysis, and to provide scenario analyses using an incremental and a decremental QALY approach to caregiver QALYs. NICE also requested the EAG to update its carer QALY calculations where relevant, and to provide scenarios using different severity weights for the presymptomatic population (due to differences between the severity modifier obtained in the Biogen model compared to the Roche model).

Decision modifiers:

In accordance with NICE guidance,{University of Sheffield, #5871} the severity modifiers were corrected to ensure consistency between the Biogen and Roche models. They were applied only to patient QALYs, and carer QALYs were added to patient QALYs (without the severity increment) to generate total QALYs.{University of Sheffield, #5871} Summary tables of these results from each company are presented in this addendum.

Approach to caregiver QALYs:

The approach to modelling caregiver QALYs varied in each of the two company submissions: Biogen used an incremental approach in incorporating carer QALYs focusing on QALY gains, whereas Roche applied a more commonly used decremental approach focused on QALY losses prevented. During the consultation process, NICE requested both companies to present results for their own base-case models using both the incremental and decremental approach to carer QALYs.

EAG's own analysis:

In addition, as the severity modifier calculated for the EAG's base-case analysis for the presymptomatic population differed between the Biogen model (x1.2) and the Roche model (x1.7), NICE requested the EAG to provide a scenario using a severity modifier of x1.2 and x1.7 on QALY increments across both economic models. NICE also requested the EAG to calculate additional scenarios using the incremental and decremental approach to carer QALYs on its base-case analyses.

After the consultation responses the EAG updated the economic models for any errors found and used it to build the additional scenarios proposed by NICE. Section 2 of this document presents the results submitted by Biogen, Section 3 presents the results submitted by Roche,

and Section 4 presents the additional analyses performed by the EAG, finally Section 5 reports the differences the EAG found after correcting the economic models following the consultation.

Overall, the EAG's base-case conclusions remained robust across all scenarios: for the Biogen model, [redacted].

For the Roche model, [redacted].

2. Biogen submitted cost-effectiveness results

Biogen's results were based on the EAG versions of the three cost-effectiveness models that were originally submitted by Biogen and subsequently amended by the EAG. For the utility increment approach, Biogen assumed one caregiver across all health states. In the utility decrement approach, they assumed a differential number of caregivers, one for 'walking independently' and 'standing with assistance' and two caregivers for all remaining health states. No bereavement disutility was implemented.

Scenario 1: utility increments (Originally Biogen approach)

Table 1 Incremental carer utilities: Presymptomatic Biogen company base-case analysis, deterministic, pairwise, x1.2 severity modifier for incremental patient QALYs for BSC

Technologies	Total costs (£)	Total LYG	Total QALYs	Incr. costs (£)	Incr. LYG	Incr. QALYs	ICER (£/QALY)
Nusinersen	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
BSC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Onasemnogene abeparvovec	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Dominant means less costly and more effective
Abbreviations: BSC = best supportive care; ICER = incremental cost-effectiveness ratio; LY = life year; QALY = quality-adjusted life year

Table 2 Incremental carer utilities: Presymptomatic Biogen company base-case analysis, deterministic, pairwise, x1.7 severity modifier for incremental patient QALYs for BSC

Technologies	Total costs (£)	Total LYG	Total QALYs	Incr. costs (£)	Incr. LYG	Incr. QALYs	ICER (£/QALY)
Nusinersen	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
BSC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Onasemnogene abeparvovec	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Dominant means less costly and more effective
Abbreviations: BSC = best supportive care; ICER = incremental cost-effectiveness ratio; LY = life year; QALY = quality-adjusted life year

Table 3 Incremental carer utilities: Type 1 Biogen company base-case analysis, deterministic, pairwise, x1.7 severity modifier for incremental patient QALYs for BSC

Technologies	Total costs (£)	Total LYG	Total QALYs	Incr. costs (£)	Incr. LYG	Incr. QALYs	ICER (£/QALY)
Nusinersen	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
BSC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Onasemnogene abeparvovec	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Abbreviations: BSC = best supportive care; ICER = incremental cost-effectiveness ratio; LY = life year; QALY = quality-adjusted life year							

Table 4 Incremental carer utilities: Type 2/3 Biogen company base-case analysis, deterministic, x1.2 severity modifier for incremental patient QALYs for BSC

Technologies	Total costs (£)	Total LYG	Total QALYs	Incr. costs (£)	Incr. LYG	Incr. QALYs	ICER (£/QALY)
Nusinersen	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
BSC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Abbreviations: BSC = best supportive care; ICER = incremental cost-effectiveness ratio; LY = life year; QALY = quality-adjusted life year							

Scenario 2: utility decrements (Original Roche approach)

Table 5 Decremental carer utilities: Presymptomatic Biogen company base-case analysis, deterministic, pairwise, x1.2 severity modifier for incremental patient QALYs for BSC

Technologies	Total costs (£)	Total LYG	Total QALYs	Incr. costs (£)	Incr. LYG	Incr. QALYs	ICER (£/QALY)
Nusinersen	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
BSC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Onasemnogene abeparvovec	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Dominant means less costly and more effective Abbreviations: BSC = best supportive care; ICER = incremental cost-effectiveness ratio; LY = life year; QALY = quality-adjusted life year							

Table 6 Decremental carer utilities: Presymptomatic Biogen company base-case analysis, deterministic, pairwise, x1.7 severity modifier for incremental patient QALYs for BSC

Technologies	Total costs (£)	Total LYG	Total QALYs	Incr. costs (£)	Incr. LYG	Incr. QALYs	ICER (£/QALY)
Nusinersen	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
BSC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Onasemnogene abeparvovec	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Dominant means less costly and more effective							

Abbreviations: BSC = best supportive care; ICER = incremental cost-effectiveness ratio; LY = life year; QALY = quality-adjusted life year

Table 7 Decremental carer utilities: Type 1 Biogen company base-case analysis, deterministic, pairwise, x1.7 severity modifier for incremental patient QALYs for BSC

Technologies	Total costs (£)	Total LYG	Total QALYs	Incr. costs (£)	Incr. LYG	Incr. QALYs	ICER (£/QALY)
Nusinersen	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
BSC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Onasemnogene abeparvovec	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Abbreviations: BSC = best supportive care; ICER = incremental cost-effectiveness ratio; LY = life year; QALY = quality-adjusted life year							

Table 8 Decremental carer utilities: Type 2/3 Biogen company base-case analysis, deterministic, pairwise, x1.2 severity modifier for incremental patient QALYs for BSC

Technologies	Total costs (£)	Total LYG	Total QALYs	Incr. costs (£)	Incr. LYG	Incr. QALYs	ICER (£/QALY)
Nusinersen	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
BSC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Abbreviations: BSC = best supportive care; ICER = incremental cost-effectiveness ratio; LY = life year; QALY = quality-adjusted life year							

3. Roche submitted cost-effectiveness results

After the consultation Roche did not provide an update to the base-case analysis in the company submission. Instead, the company revised and submitted the EAG's base-case analysis, based on the corrections agreed on the 20th August 2025 meeting. The following Section presents Roche's base-case estimates using the approach to the severity modifier suggested by NICE, and the analyses requested by NICE in the EAG's model.

Roche's base-case based on the company submission

Table 9 Presymptomatic Roche company base-case analysis, deterministic, pairwise, x1.2/x1.7 severity modifier for incremental patient QALYs for BSC, carer utilities excluded

Technologies	Total costs (£)	Total LYG	Total QALYs	Incr. costs (£)	Incr. LYG	Incr. QALYs	ICER (£/QALY)	Severity modifier
Risdiplam	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Nusinersen	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Onasemnogene abeparvovec	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
BSC (x1.2)[a]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
BSC (x1.7)[b]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

[a]EAG base-case for the Biogen model
[b]EAG base-case for the Roche model
Dominant means less costly and more effective
Abbreviations: BSC = best supportive care; ICER = incremental cost-effectiveness ratio; LY = life year; QALY = quality-adjusted life year

Table 10 Type 1 Roche company base-case analysis, deterministic, pairwise, x1.7 severity modifier for incremental patient QALYs for BSC, carer utilities excluded

Technologies	Total costs (£)	Total LYG	Total QALYs	Incr. costs (£)	Incr. LYG	Incr. QALYs	ICER (£/QALY)	Severity modifier
Risdiplam	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Nusinersen	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Onasemnogene abeparvovec	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
BSC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Dominant means less costly and more effective
Abbreviations: BSC = best supportive care; ICER = incremental cost-effectiveness ratio; LY = life year; QALY = quality-adjusted life year

Table 11 Type 2/3 Roche company base-case analysis, deterministic, pairwise, x1.2 severity modifier for incremental patient QALYs for BSC, carer utilities excluded

Technologies	Total costs (£)	Total LYG	Total QALYs	Incr. costs (£)	Incr. LYG	Incr. QALYs	ICER (£/QALY)	Severity modifier
Risdiplam	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Nusinersen	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
BSC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Dominant means less costly and more effective Abbreviations: BSC = best supportive care; ICER = incremental cost-effectiveness ratio; LY = life year; QALY = quality-adjusted life year								

Scenario 1: decremental carer QALY (Original Roche approach) based on the models submitted by Roche for the consultation responses

Table 12 Decremental carer utilities: Presymptomatic Roche company base-case analysis, deterministic, pairwise, x1.2/x1.7 severity modifier for incremental patient QALYs for BSC

Technologies	Total costs (£)	Total LYG	Total QALYs	Incr. costs (£)	Incr. LYG	Incr. QALYs	ICER (£/QALY)
Risdiplam	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Nusinersen	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Onasemnogene abeparvovec	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
BSC (x1.2)[a]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
BSC (x1.7)[b]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

[a]EAG base-case for the Biogen model
[b]EAG base-case for the Roche model
Dominant means less costly and more effective
Abbreviations: BSC = best supportive care; ICER = incremental cost-effectiveness ratio; LY = life year; QALY = quality-adjusted life year

Table 13 Decremental carer utilities: Type 1 Roche company base-case analysis, deterministic, pairwise, x1.7 severity modifier for incremental patient QALYs for BSC

Technologies	Total costs (£)	Total LYG	Total QALYs	Incr. costs (£)	Incr. LYG	Incr. QALYs	ICER (£/QALY)
Risdiplam	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Nusinersen	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Onasemnogene abeparvovec	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
BSC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Dominant means less costly and more effective
Abbreviations: BSC = best supportive care; ICER = incremental cost-effectiveness ratio; LY = life year; QALY = quality-adjusted life year

Table 14 Decremental carer utilities: Type 2/3 Roche company base-case analysis, deterministic, pairwise, x1.2 severity modifier for incremental patient QALYs for BSC

Technologies	Total costs (£)	Total LYG	Total QALYs	Incr. costs (£)	Incr. LYG	Incr. QALYs	ICER (£/QALY)
Risdiplam	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Nusinersen	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
BSC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Dominant means less costly and more effective
Abbreviations: BSC = best supportive care; ICER = incremental cost-effectiveness ratio; LY = life year; QALY = quality-adjusted life year

Scenario 2: incremental carer QALY (Original Biogen approach) based on the models submitted by Roche for the consultation responses

Table 15 Incremental carer utilities: Presymptomatic Roche company base-case analysis, deterministic, pairwise, x1.2/x1.7 severity modifier for incremental patient QALYs for BSC

Technologies	Total costs (£)	Total LYG	Total QALYs	Incr. costs (£)	Incr. LYG	Incr. QALYs	ICER (£/QALY)
Risdiplam	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Nusinersen	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Onasemnogene abeparvovec	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
BSC (x1.2)[a]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
BSC (x1.7)[b]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

[a]EAG base-case for the Biogen model
[b]EAG base-case for the Roche model
Dominant means less costly and more effective
Abbreviations: BSC = best supportive care; ICER = incremental cost-effectiveness ratio; LY = life year; QALY = quality-adjusted life year

Table 16 **Incremental carer utilities: Type 1 Roche company base-case analysis, deterministic, pairwise, x1.7 severity modifier for incremental patient QALYs for BSC**

Technologies	Total costs (£)	Total LYG	Total QALYs	Incr. costs (£)	Incr. LYG	Incr. QALYs	ICER (£/QALY)
Risdiplam	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Nusinersen	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Onasemnogene abeparvovec	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
BSC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Dominant means less costly and more effective
Abbreviations: BSC = best supportive care; ICER = incremental cost-effectiveness ratio; LY = life year; QALY = quality-adjusted life year

Table 17 **Incremental carer utilities: Type 2/3 Roche company base-case analysis, deterministic, pairwise, x1.2 severity modifier for incremental patient QALYs for BSC**

Technologies	Total costs (£)	Total LYG	Total QALYs	Incr. costs (£)	Incr. LYG	Incr. QALYs	ICER (£/QALY)
Risdiplam	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Nusinersen	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
BSC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Dominant means less costly and more effective
Abbreviations: BSC = best supportive care; ICER = incremental cost-effectiveness ratio; LY = life year; QALY = quality-adjusted life year

4. EAG's analyses after the consultation responses

Biogen model: EAG's base-case of nusinersen compared to BSC

Presymptomatic population

Table 18 Presymptomatic EAG analysis, deterministic, severity modifier for incremental patient QALYs for BSC

Scenario	Total costs	Total LYs	Total QALYs	Incremental costs (£)	Incremental Life Years	Incremental QALYs	ICER (£/QALY)
EAG Base-case for Biogen (x1.2 modifier)							
Nusinersen	[redacted]	[redacted]	[redacted]	-	-	[redacted]	[redacted]
BSC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Alternative x1.7 severity modifier							
Nusinersen	[redacted]	[redacted]	[redacted]	-	-	[redacted]	[redacted]
BSC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Incremental carer utilities (x1.2 modifier)							
Nusinersen	[redacted]	[redacted]	[redacted]	-	-	[redacted]	[redacted]
BSC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Incremental carer utilities (x1.7 modifier)							
Nusinersen	[redacted]	[redacted]	[redacted]	-	-	[redacted]	[redacted]
BSC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Decremental carer utilities (x1.2 modifier)							
Nusinersen	[redacted]	[redacted]	[redacted]	-	-	[redacted]	[redacted]
BSC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Decremental carer utilities (x1.7 modifier)							
Nusinersen	[redacted]	[redacted]	[redacted]	-	-	[redacted]	[redacted]
BSC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Dominant means less costly and less effective
Abbreviations: BSC = best supportive care; ICER = incremental cost-effectiveness ratio; LY = life year; QALY = quality-adjusted life year

Type 1 population

Table 19 Type 1 Biogen EAG analysis, deterministic, severity modifier for incremental patient QALYs for BSC

Scenario	Total Costs	Total LYs	Total QALYs	Incremental costs (£)	Incremental Life Years	Incremental QALYs	ICER (£/QALY)
EAG Base-case (x1.7 modifier)							
Nusinersen	[redacted]	[redacted]	[redacted]	[redacted]	-	[redacted]	[redacted]
BSC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Incremental carer QALYs (x 1.7 modifier)							

Nusinersen	[redacted]	[redacted]	[redacted]	[redacted]	-	[redacted]	[redacted]
BSC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Decremental carer QALYs (x 1.7 modifier)							
Nusinersen	[redacted]	[redacted]	[redacted]	[redacted]	-	[redacted]	[redacted]
BSC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Abbreviations: BSC = best supportive care; ICER = incremental cost-effectiveness ratio; LY = life year; QALY = quality-adjusted life year							

Type 2/3 population

Table 20 Type 2/3 EAG analysis, deterministic, severity modifier for incremental patient QALYs for BSC

Scenario	Total Costs	Total LYs	Total QALYs	Incremental costs (£)	Incremental Life Years	Incremental QALYs	ICER (£/QALY)
EAG Base-case (x1.2 modifier)							
Nusinersen	[redacted]	[redacted]	[redacted]	[redacted]	-	[redacted]	[redacted]
BSC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Incremental carer QALYs (x 1.2 modifier)							
Nusinersen	[redacted]	[redacted]	[redacted]	[redacted]	-	[redacted]	[redacted]
BSC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Decremental carer QALYs (x 1.2 modifier)							
Nusinersen	[redacted]	[redacted]	[redacted]	[redacted]	-	[redacted]	[redacted]
BSC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Abbreviations: BSC = best supportive care; ICER = incremental cost-effectiveness ratio; LY = life year; QALY = quality-adjusted life year							

Roche model: EAG's base-case of risdiplam compared to BSC

Presymptomatic population

Table 21 Presymptomatic EAG analysis, deterministic, severity modifier for incremental patient QALYs for BSC

Technologies	Total costs (£)	Total LYG	Total QALYs	Incr. costs (£)	Incr. LYG	Incr. QALYs	ICER (£/QALY)
EAG base-case for Roche (x1.7 modifier)							
Risdiplam	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
BSC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Alternative x1.2 severity modifier							
Risdiplam	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
BSC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Incremental carer utilities (x1.7 modifier)							
Risdiplam	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
BSC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Decremental carer utilities (x1.7 modifier)							
Risdiplam	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
BSC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Incremental carer utilities (x1.2 modifier)							
Risdiplam	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
BSC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Decremental carer utilities (x1.2 modifier)							
Risdiplam	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
BSC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Dominant means less costly and more effective
Abbreviations: BSC = best supportive care; ICER = incremental cost-effectiveness ratio; LY = life year; QALY = quality-adjusted life year

Type 1 population

Table 22 Type 1 EAG analysis, deterministic, severity modifier for incremental patient QALYs for BSC

Technologies	Total costs (£)	Total LYG	Total QALYs	Incr. costs (£)	Incr. LYG	Incr. QALYs	ICER (£/QALY)
EAG base-case (x1.7 modifier)							
Risdiplam	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
BSC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Incremental carer utilities (x1.7 modifier)							
Risdiplam	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
BSC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Decremental carer utilities (x1.7 modifier)							
Risdiplam	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
BSC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: BSC = best supportive care; ICER = incremental cost-effectiveness ratio; LY = life year; QALY = quality-adjusted life year

Type 2/3 population

Table 23 Type 2/3 EAG analysis, deterministic, severity modifier for incremental patient QALYs for BSC

Technologies	Total costs (£)	Total LYG	Total QALYs	Incr. costs (£)	Incr. LYG	Incr. QALYs	ICER (£/QALY)
EAG base-case (x1.2 modifier)							
Risdiplam	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
BSC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Incremental carer utilities (x1.2 modifier)							
Risdiplam	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
BSC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Decremental carer utilities (x1.2 modifier)							
Risdiplam	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
BSC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Abbreviations: BSC = best supportive care; ICER = incremental cost-effectiveness ratio; LY = life year; QALY = quality-adjusted life year							

5. Corrections to the EAG's analysis using the Roche model

After the response to the consultation Roche highlighted an error that affected both the Presymptomatic and Type 2/3 economic models. The EAG has used the corrected models for the analyses presented in this addendum. These corrections had a small impact on the cost-effectiveness estimates but did not change the EAG's conclusions.

Correcting errors in the Type 2/3 Roche model

Table 24 Before corrections: Type 2/3 EAG analysis, deterministic, x1.2 severity modifier for incremental patient QALYs for BSC, carer utilities excluded

Technology	Total costs (£)	Total LYs	Total QALYs	Inc. costs (£)	Inc. LYs	Inc. QALYs	ICER (£/ QALY)	Severity modifier
Risdiplam	[redacted]	[redacted]	[redacted]	-	-	-	-	-
BSC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: BSC = best supportive care; ICER = incremental cost-effectiveness ratio; LY = life year; QALY = quality-adjusted life year

Table 25 After correction: Type 2/3 EAG analysis, deterministic, x1.2 severity modifier for incremental patient QALYs for BSC, carer utilities excluded

Technology	Total costs (£)	Total LYs	Total QALYs	Inc. costs (£)	Inc. LYs	Inc. QALYs	ICER (£/ QALY)	Severity modifier
Risdiplam	[redacted]	[redacted]	[redacted]	-	-	-	-	-
BSC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: BSC = best supportive care; ICER = incremental cost-effectiveness ratio; LY = life year; QALY = quality-adjusted life year

Correcting errors in the Presymptomatic Roche model

Table 26 Before corrections: Presymptomatic EAG analysis, deterministic, x1.7 severity modifier for incremental patient QALYs for BSC, carer utilities excluded

Technology	Total costs (£)	Total LYs	Total QALYs	Inc. costs (£)	Inc. LYs	Inc. QALYs	ICER (£/ QALY)	Severity modifier
Risdiplam	[redacted]	[redacted]	[redacted]	-	-	-	-	-
BSC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: BSC = best supportive care; ICER = incremental cost-effectiveness ratio; LY = life year; QALY = quality-adjusted life year

Table 27 After corrections: Presymptomatic EAG analysis, deterministic, x1.7 severity modifier for incremental patient QALYs for BSC, carer utilities excluded

Technology	Total costs (£)	Total LYs	Total QALYs	Inc. costs (£)	Inc. LYs	Inc. QALYs	ICER (£/ QALY)	Severity modifier
Risdiplam	[redacted]	[redacted]	[redacted]	-	-	-	-	-
BSC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: BSC = best supportive care; ICER = incremental cost-effectiveness ratio; LY = life year; QALY = quality-adjusted life year

NICE National Institute for Health and Care Excellence

Multiple Technology Appraisal

Nusinersen and risdiplam for treating spinal muscular atrophy (MA review of TA588 and TA755) [ID6195]

External Assessment Group Report consultation response form

As a stakeholder you have been invited to comment on the External Assessment Group (EAG) Report for this appraisal.

Please do not embed documents (such as PDFs or tables) because this may lead to the information being mislaid or make the response unreadable. Please type information directly into the form.

Do not include medical information about yourself or another person that could identify you or the other person.

We are committed to meeting the requirements of copyright legislation. If you want to include journal articles in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs. For copyright reasons, we will have to return forms that have attachments without reading them. You can resubmit your form without attachments, but it must be sent by the deadline.

Combine all comments from your organisation (if applicable) into 1 response. We cannot accept more than 1 set of comments from each organisation.

Please underline all confidential information, and separately highlight information that is submitted under 'commercial in confidence' in turquoise and all information submitted under 'depersonalised data' in pink. If confidential information is submitted, please also send a second version of your comments with that information redacted. See the NICE health technology evaluation guidance development manual (sections 5.4.1 to 5.4.10) for more information.

The deadline for comments is **5pm** on **Wednesday 10 September 2025**. Please log in to your NICE Docs account to upload your completed form, as a Word document (not a PDF). Thank you for your time.

NICE National Institute for Health and Care Excellence

About you

Your name	[redacted]
Organisation name: stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder, please leave blank)	Biogen Idec Ltd
Disclosure Please disclose any funding received from the company bringing the treatment to NICE for evaluation or from any of the comparator treatment companies in the last 12 months [Relevant companies are listed in the appraisal stakeholder list.] Please state: • the name of the company • the amount • the purpose of funding including whether it related to a product mentioned in the stakeholder list • whether it is ongoing or has ceased.	**N/A**
Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry	**N/A**

NICE National Institute for Health and Care Excellence

Comments on the External Assessment Report

General Comments
Biogen appreciate the efforts from NICE and the EAG since re-commissioning a new report to engage with the SMA community including SMA patient organisations, SMA REACH, individual clinicians, and the manufacturers. This has contributed to a report which more appropriately contextualises SMA and the available treatments.
Biogen agree with the EAG's assessment of the clinical effectiveness and safety data for nusinersen. We also agree with the EAG's critique of both manufacturers ITCs and the data limitations that inhibit a robust comparison of the interventions. We agree that comparisons against BSC are not ideal and do not reflect current UK clinical practice (either as first line or assuming BSC use when discontinuation of a DMT occurs), however such comparisons are a more appropriate use of the available data without introducing further complexity, assumption, and uncertainty.
Biogen acknowledge the limited data available for nusinersen use in type 4 SMA patients is insufficient for health technology appraisal, however excluding type 4 patients from a recommendation may widen health inequality for SMA patients.
Biogen agree with EAG base case and adaptations made to the Biogen economic models, except for excluding caregiver health-related quality of life. We acknowledge that different methods and data sources have been used across manufacturer submissions and that no NICE guidance exists for how this should be approached. Following a request from NICE, we have submitted an addendum which covers this topic in more detail and assesses the impact of the different manufacturer approaches on model outcomes.
Biogen request the EAG include further narrative and critique of the different model health state definitions (with clinical expert input) including how well the data available to populate the models align with these definitions. The Biogen models use narrow definitions for motor milestones with clearer distinction between health states e.g. sitting without support, standing with assistance, and walking independently, whereas the Roche models use broad definitions e.g. sitting (with or without support), standing (with or without assistance) and walking (cruising or independently). We would therefore query how clinically distinct the health state definitions are in the Roche model (e.g. is there sufficient distinction between a patient who can stand unaided and those who can cruise), when each health state could include patients with a broad range of abilities and how well the associated costs and utilities reflect the potentially diverse populations within these health states.
Biogen acknowledge the efforts of the EAG to make the models as consistent as possible despite the different structures, however we request further narrative to be included in the report to explain the differences in model outcomes (note, only total life years and some QALY data are unredacted). For example in the EAG adapted presymptomatic models, the estimates for BSC are 19.84 and 12.91 years in the Biogen and Roche models, respectively. We presume this is predominantly driven by differences in the natural history data underpinning outcomes for BSC in addition to differences in the distribution of SMN2 copy numbers. Furthermore, the report would benefit from further investigation into discontinuations and specifically the assumption of no discontinuation for any DMT in the Roche models. Although short-term, data exists from the nusinersen MAA which highlights that discontinuation does occur, mainly due to scoliosis and the inability to continue to safely give nusinersen via intrathecal administration given current levels of service provision in UK clinical practice and the availability of alternative DMTs. However, the assumption of no discontinuation also means that patients receive the benefit of the 'on treatment' utility increment for the entire lifetime of the model (particularly in the case of OA in the Biogen economic models) which may overestimate the benefit of treatment.
Biogen agree with the EAG that the symptomatic populations treated with nusinersen and risdiplam are clinically different, however we do not support the application of different severity modifiers. In table 106 of the EAG report, the severity modifiers are the same for type 1 and type 2/3, however the modifiers are different for the presymptomatic population (1.2 in the Biogen models vs 1.7 in the Roche models). Our understanding is that this is a consequence of

different underlying natural history for the BSC arm as opposed to differences in the presymptomatic populations and therefore a consistent severity modifier should be applicable. At the request of NICE, Biogen have provided further detail on this issue in a separate addendum.		
Biogen would like to re-emphasise that we still do not have access to sufficient data (despite requests to NICE and Roche) to understand the clinical and cost-effectiveness of nusinersen is being assessed using the Roche models due to the level of redaction. This therefore limits our ability to scrutinise data and assumptions for appropriateness. Should the Roche models be used to inform decision making for nusinersen without further information being provided to Biogen, we deem this procedurally unfair.		
Text clarifications		
Page/ Paragraph	**Text/ Issue**	**Comment**
P6, para 1	"A single study directly comparing nusinersen and risdiplam suggested no statistically significant differences between treatments but baseline imbalances in prognostic factors limit data comparability. "	Add SMA type and follow-up period: type 2/3 patients and 6 months.
P8, para 3 (also applies to p55, para 1)	"The intrathecal injection (12 mg/5 mL) requires an initial loading phase of four doses, with the first three doses taken at 14-day intervals and the fourth dose 30 days after the third dose."	Typographical error, the 4th doses is given 35 days after the third dose, as per the license." Spinraza treatment should be initiated as early as possible after diagnosis with 4 loading doses on Days 0, 14, 28 and 63."
P14, para 3	"While the adult registry for risdiplam extended to ~4 years, the patient numbers were smaller"	Clarify that patient numbers at 4 years were smaller, rather than patient numbers in the adult registry being overall smaller for risdiplam than for nusinersen.
P17, para 3	"What is the issue: The EAG did not identify any evidence surrounding the effectiveness or cost-effectiveness of nusinersen or risdiplam in patients with SMA types 0 and 4. Why this is considered important: Patients with either type 0 or type 4 SMA are not represented within the clinical and cost-effectiveness sections of this report due to the lack of data. Representatives of patient organisations highlighted to the EAG that the lack of access to the MAA for adults with type 4 SMA is a potential equality issue. "	Biogen did submit available evidence for type 4 SMA patients from the SMARTCARE registry; however we acknowledge data are limited and likely insufficient for HTA purposes. Due to the mechanism of action of nusinersen increasing the levels of functional SMN protein, it is expected to have a treatment effect in type 4 SMA, however the magnitude is uncertain due to higher SMN2 copy numbers and unknown extent of neuronal changes prior to treatment initiation. However, excluding type 4 patients from any recommendation may increase health inequality among SMA patients.
P18, para 2	"What is the issue: There are no controlled studies that include any therapy for presymptomatic patients. Risdiplam also lacked controlled studies for type 1 patients. Why this is considered important: The lack of data means that the evidence for this population is more uncertain.	Whilst factually accurate, conducting placebo/sham-controlled studies in presymptomatic SMA is considered unethical. Furthermore without treatment of presymptomatic patients, symptomatic SMA would be a certain eventuality for patients and the natural history of symptomatic forms are well characterised.

P19, para 3	"What is the issue: The effectiveness data (e.g. transitions, relative effect, decline in health states) used in the cost-effectiveness models largely come from single arm trials in the absence of RCTs. Why this is considered important: Whilst it may not always be feasible or ethical to conduct a RCT for treatments in rare diseases like 5q SMA, it therefore becomes necessary to use the effectiveness data coming from single arm trials. Using evidence from single arm trials may introduce bias in favour of the treatments under evaluation"	Additional context should be added that the pivotal studies across the symptomatic SMA types for nusinersen were sham-controlled studies (ENDEAR and CHERISH).
P19, para 4	"What is the issue: The motor milestone scores used in defining disease progression in terms of model health states are derived from different tools which vary in their scoring system. Why this is considered important: The EAG note that assuming equivalence of health states defined by tools varying in their scoring system may add further uncertainty in motor functions, patient health states, and ultimately in the cost-effectiveness outcomes due to the sensitivity in how well the tools capture the true impact of the disease as valued by patients and carers. "	Additional context should be added that often the transition between tools is driven by age and functional status as per section 4.4. With regards to nusinersen, the transition from HINE-2 to the WHO motor milestones occurs in the type 1 model providing a patient could sit without support and was >2 years of age. The WHO motor milestones are potentially more permissive focusing on whether a child can demonstrate the skill e.g. for sitting without support, the Infant sits upright with head erect ≥10 seconds, without using arms/hands for support whereas in the HINE -2, the infant would be required to show stability and progression from prop (sitting with support) to stable/ pivot (sitting without support).
P20, para 2	"What is the issue: Discontinuation from treatments were informed by the MAA data but were only incorporated into the Biogen model for nusinersen. Roche did not account for treatment discontinuation in their economic model, reasoning that discontinuation from risdiplam was unlikely in clinical practice - a justification based on the trial data, REACH data, and clinical expert feedback. Why this is considered important: Not incorporating treatment discontinuation in the Roche models may favour risdiplam as the EAG's discussions with clinical experts suggested that people may discontinue or switch from	MAA data reflect real world data collected in UK clinical practice and should inform the cost-effectiveness models. The majority of patients who discontinued nusinersen during the MAA period did so due to scoliosis and the inability to safely administer intrathecally, part of which is linked to variable service provision across the UK for intrathecal administration for more complex cases. Biogen do not support the assumption of zero discontinuations in the Roche models and we agree this may overestimate the sustained benefits of treatment which is linked to an 'on treatment' utility benefit.

	risdiplam due to known adverse events, such as potential effects on fertility. The EAG also notes that the discontinuation data used in the models were based on short-term MAA follow-up, which may overestimate the sustained benefits from treatment over the patient's lifetime. In addition, discontinuation from nusinersen incorporated into the Biogen (nusinersen) model assume that patients discontinuing treatments would go on to receive BSC, accruing the costs and outcomes of BSC after discontinuation. However, in clinical practice, those discontinuing may switch to alternative DMTs rather than BSC alone. Due to the lack of robust evidence, the potential impact of treatment switching could not be modelled. Therefore, the EAG caution that assumptions surrounding treatment discontinuations may introduce additional uncertainty into the cost-effectiveness results. "	Biogen agree that a patient discontinuing treatment would switch to an alternative DMT (if eligible) as opposed to BSC. Whilst trials are ongoing to assess the efficacy and safety of DMTs when used in sequence, there is currently limited data for use in economic models which would require further assumption and lead to more uncertainty. Furthermore, due to nusinersen being available earlier than both OA and risdiplam, treatment switches were often away from nusinersen and switching back to nusinersen requires input from the NHSE clinical panel, making this more challenging.
P43, para 1	"Type 1 SMA is the most common type of disease, occurring in 60% of cases."	Clarify that type 1 SMA occurs in 60% of diagnosed cases, it does not represent the most comment type in the prevalent population due to high mortality rates in the absence of DMTs.
P45, table 2	Eligibility criteria This table states the different start criteria for the nusinersen and risdiplam MAA.	Aside from criteria regarding intrathecal administration, the eligibility criteria are identical despite not being written the same.
P55, para 1	"The committee noted that there may be a delayed response to nusinersen for some people (for at least 2 years). "	Please clarify what is meant by "some people." Whilst motor improvements may continue to accrue beyond the completion of loading doses and across 12-24 months in older children and those with more advanced disease, this does not reflect a delayed response to treatment. Also, as noted in the EAG report, stabilisation of disease progression should be seen as a positive outcome when compared to natural history.
P63, para 8	"The restriction to studies that included at least 100 participants meant that a number of eligible smaller studies were omitted, but no controlled studies."	Biogen acknowledge this may have led to the omission of some studies, however as stated in the company submission, this was done for pragmatic reasons given the volume of literature identified.

P77, para 1	"It should be noted, then, that the CHERISH trial is not generalisable to UK clinical practice because participants did not receive the relevant dose, and because of restrictions in eligibility around age, complications and ventilation requirements. "	Outside of age restrictions, participants do reflect the UK population treated with nusinersen (e.g. without severe scoliosis and contractures). It should be noted that the dose used in CHERISH is less than the licensed dose (3 loading doses and maintenance every 6 months vs 4 loading doses over 2 months and maintenance dosing every 4 months thereafter). Based on dose response relationships demonstrated in early phase studies, a greater treatment effect may be expected with use of the licensed dosing regimen. A protocol amendment was made in SHINE so that all patients received the licensed 4 monthly maintenance dose.
P75,2	"The company reported that none of the presymptomatic patients had died or required permanent ventilation by a median age of 4.9 years (range 3.8 to 5.5 years), compared to an estimated average age of mortality from natural history of 19.2 months (SD 10.1 months).20 Children with three SMN2 copies were walking independently within normal developmental timeframes; 13 of the 15 children with two SMN2 copies achieved the WHO motor milestone of standing alone and walking alone, whilst 14 achieved hands and knees crawling and walking with assistance, and all achieved sitting without support and standing with assistance. A total of 88% of children achieved the maximum CHOP-INTEND score, and mean HFMSE scores showed continuous improvement. "	Updated end of study results are available for NURTURE and have been provided to NICE. Biogen acknowledge the timing of study completion and CSR availability meant this data could not be incorporated into the current report but should be included in future updates.
P81, para 1	"Patients receiving nusinersen were assumed to have no risk of progression to 'permanent ventilation' based on results from NURTURE. "	This is factually accurate for the first 72 months i.e. the period of NURTURE only, in the long-term if a patient enters the non-sitting state depending on the rate of decline, they have a risk of entering the permanent ventilation state.
P82, para 4	"The HINE-2 outcome measure was collected in the NURTURE trial informing clinical effectiveness of nusinersen treatment and is considered more comprehensive than the WHO MM for its inclusion of voluntary grasp and head control"	Voluntary grasp and head control are not modelled health states. The attainment of milestones used to define health states should be considered similar across the WHO and HINE-2, although the former maybe more permissive.

P82, para 5	"The EAG understands there is a lack of data on patients with presymptomatic SMA receiving BSC however, cautions that adjustments to the state occupancy for patients receiving BSC in the presymptomatic model"	The adjustments made to the BSC arm were to avoid patients achieving milestones earlier than WHO developmental norms given the differences in the age for patients in ENDEAR/ CHERISH and the start age in the presymptomatic model.
P83, para 7	"Based on both the clinical context and the evidence available, the EAG cautions against the use of BSC as an appropriate comparator in the presymptomatic SMA population"	We agree the DMTs would be given to presymptomatic patients in addition to BSC, as opposed to BSC alone, however the choice for not including DMTs was based on data limitations and issues around comparability of populations and outcomes as highlighted in the ITCs.
P83, para 7	"EAG notes that the company model relied on strong assumptions of outcomes under BSC"	These assumptions reflect the sham-control arms in ENDEAR and CHERISH where relevant, reflecting symptomatic forms of SMA which, without treatment, would be the certain outcome for patients not treated presymptomatically.
P88, para 3	"However, it is likely that those discontinuing nusinersen may not transition to receive BSC alone, but instead may receive alternative disease modifying treatments. This would have implications for both the costs and outcomes, which are not fully captured in the current models. "	Biogen agree that a patient discontinuing treatment would switch to an alternative DMT (if eligible) as opposed to BSC. Whilst trials are ongoing to assess the efficacy and safety of DMTs when used in sequence, there is currently limited data for use in economic models which would require further assumption and lead to more uncertainty.
P109, para 2	"A hazard ratio was applied to these survival data to reflect those with England and Wales setting."	For clarity, the HR to reflect the England and Wales setting was not applied by Biogen. The survival curves were taken directly from HST24 which already included this adjustment (the HR is not reported within HST24 papers) as per p112: "For survival in this health state, data for patient cohorts (with SMA types 2a and 2b) are pooled from a recent natural history study based on a Dutch cohort (in which more recent clinical practice is reflected (3)). Due to few deaths in the type 2a population and zero events in the type 2b population, parametric curves fitted to the extracted data resulted in unrealistic flat curves and thus are not used directly in this model. Instead, parametric curves were fitted to the pooled data and then compared with the general population curve for the Netherlands. A constant hazard ratio was calculated relative to general

		population and applied to the UK general population life tables."
P121, para 1	“For risdiplam compared to nusinersen, unanchored MAICs suggested a statistically significant difference between the treatments for CHOP-INTEND, HINE-2, adverse events and survival (see Table). The ESS for these analyses is >35, which suggest the potential for less bias and uncertainty in these results. “	It should be also noted that there are important differences in exclusion criteria between trials regarding pulmonary events and pulmonary function, which are key factors influencing outcomes such as permanent ventilation and overall survival. FIREFISH included more restrictive exclusion criteria than ENDEAR (e.g., excluded patients with hospitalisation for pulmonary event within the last 2 months; with invasive ventilation or tracheostomy; requiring non-invasive ventilation or hypoxemia with or without ventilator support; and history of respiratory failure or severe pneumonia and had not fully recovered their pulmonary function at time of screening vs. excluded patients with hypoxemia at screening). Incomparable exclusion criteria used in FIREFISH and ENDEAR may have enriched for a population in FIREFISH with less pulmonary burden compared to patients in ENDEAR that cannot be resolved through MAIC weighting. In addition, only three baseline variables were considered for weighting (age at first dose, disease duration at baseline and CHOP-INTEND score). The exclusion of important variables e.g. body weight and nutritional support may have introduced bias into the analysis. Furthermore post weighting, there were imbalances in baseline variables (e.g. sex and age at symptom onset). Lastly, there are differences in the schedule of assessments for motor endpoints which may have introduced further bias. Motor milestones were assessed at 12 months in FIREFISH whereas ENDEAR ended early with an average of 9 months follow-up (based on a positive benefit risk assessment of a prespecified interim analysis). However no additional follow-up data from SHINE was used to bridge this gap. Differences in the timing of assessment can have a meaningful impact as the

		attainment of motor milestones (e.g. sitting without support) are time dependent.
P137, para 4	"For risdiplam treatment effectiveness was assumed to last 72 months by the EAG, similar to the available follow-up data for nusinersen,30- which is a favourable assumption to risdiplam, given that the follow-up from RAINBOWFISH was only 12 months."	We agree this is a strong assumption and should be validated against later data cuts for risdiplam.
P143, Table 49 (also applicable to p181, table 68)	Cost per cycle from TA588	Could the EAG clarify these are 4 monthly cycle costs as opposed to monthly cycle costs in the Roche model or whether they have been adjusted for comparability.
P179, para 2	"An unanchored MAIC was used to compare RULM scores for risdiplam from the SUNFISH trial with RULM score for nusinersen from the CHERISH trial and present them as odds ratios (ORs). Although the company reported high uncertainties around the estimated results from the MAIC, these were used to estimate the relative effectiveness between risdiplam and nusinersen in the economic model. The economic model assumes a monthly relative risk of nusinersen versus risdiplam for improving to a higher motor milestone"	Biogen cannot see the data for nusinersen and it is unclear what the RULM scores relate to (change from baseline or > 2 points) and how well improvements in RULM scores correlate to moving between gross motor milestones.
p 213 table 79	In the exploratory analysis, it was considered inappropriate to have discontinuation from OA, as it is a one-off treatment.	Whilst we agree it is inappropriate to assume discontinuation from OA, consideration should be given to the on-utility treatment increment, as this would be assumed for the entire model horizon, potentially overestimating treatment effect and cost-effectiveness.
P 277 para8	"Three randomised controlled trials (RCTs) were assessed using the Cochrane risk of bias tool (ROB 2.0): CHERISH, ENDEAR, and EMBRACE. All three trials were judged overall to have some concerns."	This contradicts the ratings given in table 86 p 229 which are noted as "serious".
P238, para 3	"The clinical trials reporting data for the effects of nusinersen on motor function were SM201 and NURTURE for patients with presymptomatic SMA"	NURTURE and SM201 are the same study.
P238, para 3	"Another study reported significant increases in type 1 and 2 patients but not type 3 patients."	Consideration should be given to the baseline score and possible ceiling effects. Furthermore the CHOP-INTEND is unlikely to be administered to a type 3 patients.

P239, para 1	"New final analysis data from NURTURE further supports the long-term benefit of nusinersen in presymptomatic patients."	This is not the final analysis of NURTURE, the final end of study data contains up to 8 years of data and has been provided to NICE, however Biogen acknowledge this was not available within the period needed for inclusion in this report.
P239, para 2	"No studies reported WHO motor milestones in type 1 patients"	WHO motor milestones for type 1 patients were reported in SHINE, however we acknowledge this falls under "mixed SMA types" in the report.
P 241, Table 89	Type 1 EAP	context for type 1 EAP patients – please add a footnote or text to acknowledge that the data presented represents outcomes from entry into the MAA and not since the initiation of treatment. A further footnote should be added to highlight that type 2/3 walkers cannot attain motor milestone beyond walking.
P 246	"reported data from the RESPOND trial, showing that, at day 183 following nusinersen treatment, there were mean changes (SD) in CHOP INTEND scores of +6.7 ± 6.76 for people aged ≤ 9 months with 2 copies of SMN2 and +0.6 ± 5.50 for patients aged > 9 months with 2 SMN2 copies. Among non-sitters, the mean changes were +6.7 ± 6.76 for people aged ≤ 9 months with 2 copies of SMN2 and+3.6 ± 3.91 for those aged > 9 months with 2 copies of SMN2"	For context, it should be noted RESPOND is post OA use.
P357, table 106	Difference in severity modifiers	Whilst the treated populations are different, SMA is a severe and debilitating disease across the spectrum – we do not see why presymptomatic treatment should have different severity modifiers and this calculation likely reflects differences in the model structure and underlying BSC disease progression rates which should be explored further. We have provided an appendix on this issue as requested by NICE.

NICE National Institute for Health and Care Excellence

Multiple Technology Appraisal

Nusinersen and risdiplam for treating spinal muscular atrophy (MA review of TA588 and TA755) [ID6195]

External Assessment Group Report consultation response form

As a stakeholder you have been invited to comment on the External Assessment Group (EAG) Report for this appraisal.

Please do not embed documents (such as PDFs or tables) because this may lead to the information being mislaid or make the response unreadable. Please type information directly into the form.

Do not include medical information about yourself or another person that could identify you or the other person.

We are committed to meeting the requirements of copyright legislation. If you want to include journal articles in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs. For copyright reasons, we will have to return forms that have attachments without reading them. You can resubmit your form without attachments, but it must be sent by the deadline.

Combine all comments from your organisation (if applicable) into 1 response. We cannot accept more than 1 set of comments from each organisation.

Please underline all confidential information, and separately highlight information that is submitted under [redacted] and all information submitted under [redacted]. If confidential information is submitted, please also send a second version of your comments with that information redacted. See the NICE health technology evaluation guidance development manual (sections 5.4.1 to 5.4.10) for more information.

The deadline for comments is **5pm** on **Wednesday 10 September 2025**. Please log in to your NICE Docs account to upload your completed form, as a Word document (not a PDF). Thank you for your time.

NICE National Institute for Health and Care Excellence

About you

Your name	[redacted]
Organisation name: stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder, please leave blank)	Roche Products Ltd.
Disclosure Please disclose any funding received from the company bringing the treatment to NICE for evaluation or from any of the comparator treatment companies in the last 12 months [Relevant companies are listed in the appraisal stakeholder list.] Please state: • the name of the company • the amount • the purpose of funding including whether it related to a product mentioned in the stakeholder list • whether it is ongoing or has ceased.	**N/A**
Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry	**N/A**

NICE National Institute for Health and Care Excellence

Comments on the External Assessment Report

Clinical and economic comments	
Clinical effectiveness	
1	Patient heterogeneity - the spectrum of SMA The EAG have reported on the spectrum of outcomes in individuals with SMA, which was highlighted by patient organisations and clinical experts and recognised by Roche. Timing of treatment initiation is another variable which has a significant impact on the outcomes of individuals with SMA. The awareness of SMA has increased in the UK, thanks to collaborative efforts of patient advocacy groups and clinical teams working with their community colleagues to educate on the early symptoms of the condition. There are anecdotal cases in neuromuscular centres of children being referred earlier than they would have been in previous years, however there are still sadly too many children who are diagnosed after symptoms have been present for weeks or even months. Between Jan 1, 2019, and Nov 1, 2024, 507 individuals with SMA were registered in the SMA REACH UK database. The mean age at diagnosis was 0·5 years (SD 0·4) for those with SMA type 1, 1·6 years (SD 0·8) for those with SMA type 2, and 2·9 years (SD 1·7) for those with SMA type 3 (1). The effectiveness of newborn screening and impact of earlier treatment for infants with SMA in the real-world setting has been reported in a nonrandomised controlled trial in Germany, Austria and Switzerland (2). Patients born in two federal states in Germany underwent screening in a newborn screening pilot project (n=44 (18.8%)). All other patients were diagnosed after clinical symptom onset (n=190 children (81.2%)). All patients received standard care within the same health care system. Functional outcomes and thus the response to treatment were significantly better in the newborn screening cohort compared to the unscreened clinical symptom onset group. The mean (SD) age at start of treatment with 1 of the approved disease-modifying drugs was 1.3 (2.2) months in the newborn screening cohort and 10.7 (9.1) months in the clinical symptom onset cohort. In the newborn screening cohort, 40 of 44 children (90.9%) gained the ability to sit independently vs 141 of 190 (74.2%) in the clinical symptom onset cohort. For independent ambulation, the ratio was 28 of 40 (63.6%) vs 28 of 190 (14.7%). A UK government funded In-Service Evaluation of newborn screening for SMA has been announced, and supporters anticipate that this will lead to newborn screening being implemented across England and Wales in the coming years. As reported in the European nonrandomised controlled trial (2), treatment with a disease modifying therapy earlier in individuals with SMA will result in improved outcomes, which will have a

positive effect on the individuals and families as well as reducing the cost and burden on the NHS and society (3).

Patient heterogeneity - comparability of individuals receiving risdiplam or nusinersen in the real-world and in trials

The EAG has accurately reflected that the initial cohort of risdiplam treated individuals enrolled on the pre-licence Early Access to Medicines Scheme (EAMS) and NHS patients treated with risdiplam were more progressed compared to the nusinersen treated population. This is a direct result of the treatment landscape at the point at which risdiplam became available for use. As nusinersen was made routinely available in the UK before risdiplam and onasemnogene abeparvovec, any patients who were eligible for treatment were largely initiated on nusinersen. Historically (pre-licence), patients receiving risdiplam as part of the EAMS were ineligible for alternative licensed treatments, and inherently were either more progressed in their condition and couldn't receive nusinersen due to scoliosis or spinal surgery precluding intrathecal administration or had other clinical justification for not being able to receive nusinersen.

The timing of availability of risdiplam compared with nusinersen has had an impact on the extent of the follow-up data available within the Managed Access Agreement data collection. The EAG stated that “From the paediatric registry, nusinersen had longer follow-up data available than risdiplam for motor outcomes (~4+ years vs ~1.5+ years, respectively).” Roche would like to confirm that longer term data has been reported in the SMA REACH paediatric report to NICE MAOG/EAG dated April 2025. The SMA REACH paediatric registry included 164 MAA cohort patients, and the most recent data cut taken in February 2025 included 3-year data for 17 individuals with SMA. Of these, n=3 were type 1, n=2 SMA types 2/3 non-sitters and n=12 type 2/3 sitters/walkers. The three-year available data set had been reduced from the numbers available at 30 months (n=50 all SMA types, with n=6 type 1 SMA, n=14 type 2/3 SMA non sitters and n=30 type 2/3 sitters/walkers).

Furthermore, the Managed Access Agreement heavily restricted patients (and their HCP) from switching therapies unless there was a strong clinical need to do so which means that the treatment landscape has been more static than other countries. As with the pivotal clinical trial data, the real-world evidence captured within the SMA REACH registry will have the initial cohort of risdiplam treated individuals representing a more progressed condition than those receiving nusinersen.

In the current UK commissioning/ treatment landscape, patient selection for a DMT treatment is not driven by the status of a patient's condition (except in the case of scoliosis precluding IT access). Excluding SMA Types 0 and 4, the licensed indications and clinical eligibility criteria for nusinersen and risdiplam are identical, hence a new SMA type 1, 2 or 3 patient today would have the option for treatment with either DMT (with the further option of onasemnogene abeparvovec for Type 1 patients).

Regarding the clinical development programmes for nusinersen and risdiplam, there were differences in the eligibility criteria for each of the studies that have been documented in the inclusion and exclusion criteria differences Tables 1, 2, and 3 in the April 2025 additional clarification questions submission document (4). The risdiplam clinical development programme enrolled a more heterogeneous, older population with more severe disability (scoliosis and contractures) compared to the clinical development programme for nusinersen, which makes comparison

	between the two treatments challenging, however an ITC of the two treatments is considered an appropriate and relevant methodological approach to assessing cost effectiveness - please refer to Company Comment 8. The EAG identified a single comparative study (5) and stated that the baseline imbalances in prognostic factors limited comparability. Roche would like to highlight that this study should be identified as investigating SMA Types 2 and 3. The children in the nusinersen group were on average 12 months younger at the start of treatment, far fewer had scoliosis, and scored about 10 points better in HFSME and RULM. The difference in RULM and HFMSE score after 3 and 6 months of treatment compared to the baseline showed significant changes in both groups (P-value <0.001). According to the results of the linear regression model, after adjusting for the baseline value of the HMFSE and RULM scores, no significant difference was observed between the two types of drugs used after three and six months in this study. When age of treatment, age of diagnosis, the number of *SMN2* gene copies, and disease type was controlled, there was no significant difference in HMFSE and RULM scores between the two groups at 3 and 6 months (P-value >0.05). The differences in the populations on each treatment in the Ashrafi study reflects the real-world experience in the UK, with historically more severely affected individuals receiving treatment with risdiplam compared to those treated with nusinersen due to the eligibility criteria for the risdiplam Early Access to Medicines Scheme and the fact that nusinersen was the first disease modifying therapy available to people with SMA.
2	<u>Availability of data - lack of controlled trials for presymptomatic and type 1 SMA patients</u> Roche acknowledge that these were not placebo controlled trials as it was not considered appropriate or ethical to include a control arm within the RAINBOWFISH or FIREFISH studies due to the severity of the natural history of the condition, particularly as this natural history is very well established (6). The randomised, sham-controlled trial of nusinersen in infants with type 1 SMA (ENDEAR) was terminated early after a positive interim analysis to allow for participants to enroll into an open label study (7). Subsequent disease modifying therapy trials have not used a placebo arm. Survival data up to 60 months from the FIREFISH study has been shared with the EAG in the addendum dated July 2024 and the 24-month RAINBOWFISH data was submitted in the Clarification Questions response B1 in March 2025. Please see Company Comment 1 regarding a nonrandomised controlled trial investigating the effectiveness of newborn screening for infants with SMA in the real-world setting (2). Functional outcomes and thus the response to treatment were significantly better in the newborn screening cohort compared to the unscreened clinical symptom onset group, with 40 of 44 children (90.9%) sitting independently vs 141 of 190 (74.2%) respectively, and 28 of 40 (63.6%) children identified by newborn screening walking independently vs 28 of 190 (14.7%) in those identified by clinical symptoms. Please see Company Comment 8 for the company position on ITCs.

	In addition, Roche does not think the statement "*Using evidence from single arm trials may introduce bias in favour of the treatments under evaluation*." is appropriate. It is uncertain if using evidence from single arm trials may bias in favour of the treatments under evaluation. The EAG's statement unnecessarily frames the evidence base as favouring risdiplam and nusinersen. The single arm studies may introduce uncertainty, but it is unclear whether using the evidence biases in favour or against the treatments and it is unfair for the EAG to conclude one way or another. Roche would also like to highlight that single arm evidence is appropriate in rare diseases where it would be unethical to withhold highly effective treatment to allow for a randomised controlled trial. Availability of data - lack of data in type 0 and type 4 SMA The licence/marketing authorisation for risdiplam is for the treatment of 5q SMA in patients with a clinical diagnosis of SMA Type 1, Type 2 or Type 3 or with one to four *SMN2* copies. The risdiplam clinical trials included individuals with SMA types 1, 2 or 3 and presymptomatically those infants who had a genetic diagnosis of 5q-autosomal recessive SMA, including confirmation of homozygous deletion or compound heterozygosity predictive of loss of function of the *SMN1* gene - in the RAINBOWFISH study there was no maximum number of *SMN2* copies, though only 5/26 (19%) of the babies enrolled had 4 or more copies of the *SMN2* gene (and potentially could go on to develop SMA type 4) and no infant enrolled with fewer than 2 *SMN2* copies. Roche accept that there is no evidence from pivotal clinical trials that demonstrates efficacy of risdiplam in individuals with SMA type 0 or type 4 - this is reflected in the marketing authorisation.
3	Outcomes - lack of data considered important by individuals affected by SMA With the evolving phenotype of SMA associated with DMT use, clinical and scientific understanding of outcomes and ability to capture data is also evolving. It is understandable that there is a relative paucity of evidence available on elements such as activities of daily living, ability to socialise, the impact on education or work engagement as well as the impact on carers and families, given the focus initially would have been demonstration of clinical efficacy and safety. Qualitative analysis of PROMs and the integration of PROM reporting within the MAA has meant that a narrative of these outcomes is included. The EAG highlight that "it was often not clear what treatments the people in the analyses were taking, making it challenging to find out more about what effect each of the treatments separately had on the lives of people with SMA and their carers" (Results; key findings, Qualitative analysis, pages 13-14). Roche appreciate that some of the verbatim submissions from the patient community may be challenging to attribute; there were attributable statements in the Patient Registry submission that clearly define the individual thoughts on risdiplam treatment, but the company does appreciate that it is not possible to draw conclusions from the limited data available. The paucity of data means that the holistic benefits of treatment are not possible to ascertain. The systematic literature review conducted by Warwick Evidence (MTA final protocol ID6195) incorporated exclusion criteria for published literature with a population who had received spinal fusion surgery following a diagnosis of scoliosis (due to its preclusion for safe administration of nusinersen), and history of surgery for scoliosis or hip fixation which may have led to exclusion of risdiplam publications. Evidence on

risdiplam outcomes may have been missed for this reason.

The paediatric SMA REACH April 2025 report (page 13) states: "... the initial treated cohort was mainly older and more chronic than more recently treated patients, they had more 'difficult' spines which prevented nusinersen treatment. Once the risdiplam drug approval was implemented and extended to babies younger than 6 weeks, the cohort of treated patients changed, becoming younger and therefore expected to have a better outcome."

The nature of publication timelines may reflect this earlier cohort, potentiated by the global access to nusinersen prior to risdiplam authorisation; subsequently there may be a more balanced cohort of real-world outcomes available.

Due to the evolving phenotype and increased scientific and clinical knowledge of SMA, there are evidence gaps around outcomes such as bulbar function, cognition, fatigability and patient reported outcomes within the registrational trials. These are particularly pertinent in the Type 1 patients who had historically passed away before these challenges became apparent. As we learn more about these outcomes, they may become a differentiating factor for treatment choice across the breadth of SMA types. However, there is no standardisation of bulbar functional tools that are assessed in clinical practice and hence real-world evidence publications report on different assessments in this domain. The trajectory of bulbar function deterioration is heterogeneous and disease modifying treatment intervention after SMA symptom onset has variable results in terms of bulbar function outcomes.

Respiratory function

Evidence from the Clinical effectiveness SLR stated for nusinersen that "Stability or maintenance in respiratory function was generally suggested", (Results, key findings, page 12) is less definitive than the statement regarding respiratory function in the abstract ("Evidence also suggested that nusinersen provided stability for respiratory function"). For risdiplam, (Results, key findings, page 13) states "Evidence suggested maintenance of small increases or decreases in respiratory function, although evidence was sparse." Orthopaedic deformity progresses in children and adults with SMA, and respiratory impairment is a consequence of this as the thoracic cage is impacted as growth occurs. It could be postulated that the real-world evidence available in the literature reflects the use of risdiplam in those individuals who have spinal deformity and scoliosis and are unable to receive intrathecal administration of nusinersen.

Roche would like to advocate for access to DMTs to be available for people who are on permanent ventilation or who have a tracheostomy. This was raised by a professional expert in the statement "Operating on the principle that those who are long term ventilated unnecessarily have a less good quality of life is an equality issue" (Page 327, section 13.5.6: Equality considerations). People with SMA types 1 and 2 who were on permanent ventilation or had a tracheostomy were eligible for enrollment in the risdiplam Early Access to Medicines Scheme (EAMS) - this was advocated for by the clinical and patient advocacy community when the EAMS was being set up in 2020. Twelve people (n=6 paediatric and n=6 adults) who were receiving ventilation support for more than 16 hours per day ('permanent ventilation') or had a tracheostomy ('SMA-PV')

	were enrolled in the risdiplam EAMS and have been receiving risdiplam through a compassionate supply scheme for almost five years. Ongoing supply has been reliant on the prescriber confirming that the individual has been obtaining clinical benefit from risdiplam treatment. SMA-PV was an exclusion criteria for pivotal clinical trials with DMTs due to permanent ventilation being an event to demonstrate disease progression. However, permanent ventilation or tracheostomy are not contraindications for risdiplam treatment. Motor function assessments mandated during the MAA have excluded individuals who were not able to perform the necessary movements, and permanent ventilation could be considered a proxy for severe disability associated with SMA and other neuromuscular conditions. There is paucity of published evidence of DMTs in SMA-PV. Roche Products Ltd. supported a Delphi consensus process with a panel of neurologists, respiratory consultants and physiotherapists with experience in managing individuals with SMA or SMA-PV. Statements that outline the clinical benefits associated with DMT use in people with SMA-PV and best practice recommendations regarding DMT use were developed through an evidence-based consensus process. Complete endorsement of the statement “PV alone should not preclude the use of DMTs in patients with SMA-PV” was achieved in the first voting round. Clinical benefits achieved from risdiplam treatment in SMA-PV includes stabilisation of motor function, and particularly upper limb function that has such an important role in maintaining a degree of independence. Examples within the Delphi consensus process included individuals who worked full time. Control of power chairs, computer mouses and communication technologies was called out as functions that have a disproportionate impact on severely disabled individuals' wellbeing. Stronger coughs, reduced salivary secretion and reduced suction requirements were also commented on, and this was postulated as a reason for fewer respiratory infections and associated hospitalisations. There are also reports of reduced fatigue and increased and clearer vocalisation. ATEND and the EK motor function scores were proposed as more appropriate assessment tools for individuals unable to perform RULM, CHOP-INTEND, or the RHS. It is important to remember that SMA is a progressive condition, whatever the baseline an individual is at when initiating a DMT, and without active treatment an individual will deteriorate and lose functions that are important to them. Stabilisation, or slowing down the deterioration, is valuable for the individual and access to DMTs should be based on a holistic appraisal and not just the requirement (or not) of permanent ventilation/tracheostomy (8). <u>Fatigue and stamina</u> The EAG stated (Section 16.1.2: Clinical effectiveness - Fatigue and stamina) that “There was no available evidence for this outcome assessing risdiplam treatment.”

	Roche would like to highlight evidence available. In the JEWELFISH study, at 24 months an increase in the total distance walked in the six minute walk test (6MWT) was observed in ambulant patients. A decrease in fatigue was also observed (measured by change from baseline in the distance walked from the first to sixth minute of the 6MWT) (9). Impact on models Please see Company Comment 4. Roche is disappointed that the EAG has excluded methods used by the company to account for disease-related complications, such as scoliosis, respiratory support and bulbar function. Roche appreciates that data for these complications is limited but feel that the EAG approach moves the analysis further away from capturing the full scale of SMA and the true value of DMTs. Roche has heard passionately from the SMA community of the importance that these disease impacts have on patient and carer quality-of-life (also see CS Document B, Section 3.13 (10)), and that there may be a general lack of understanding of the nuances of SMA. We have heard how loss or lack of mobility does not constitute the totality of the condition, and whether considering quality-of-life stratified by motor function only is appropriate. For example, the ability to breathe efficiently and swallow effectively are more likely to have a positive impact on the majority of people with SMA than the ability to walk or stand unaided, and impacts to bulbar and respiratory function are likely to have a substantial negative effect on patient quality-of-life and carer burden. During the managed access period, Roche made extensive efforts to generate additional informative data and improve the modelling of SMA as accurately as possible. This included conducting a utility study in people with SMA and their caregivers, but ultimately, due to data limitations, it was only possible to adopt a simplistic approach to modelling these benefits. Roche considers it inappropriate for the impact of these disease effects to not be considered in the EAG's model in any capacity. In line with the EAG, the company has removed these model features from the base case. However, the company emphasises that the economic results should be interpreted in the context of a rare disease, where the disease burden is significant and may not be fully reflected by the CEM. This is evident from the exclusion of factors such as bulbar function, respiratory support, and scoliosis from the model. So, the committee should consider the results alongside potential benefits that may extend beyond those explicitly captured in the model. While Roche recognises the limited data available specifically for these disease complications, we call for the EAG to acknowledge that the models, and the cost-effectiveness results, do not capture the full benefits associated with DMTs. Therefore any cost-effectiveness outcomes could be considered conservative. Additionally, it is unclear to the company why the EAG conducted a scenario analysis within the Type 2/3 models incorporating both utility decrement and additional healthcare costs associated with bulbar function only. Roche advocates for a model scenario to be conducted in all models to consider the impacts of all disease complications. It is important for the committee to consider the potential benefits that may extend beyond those explicitly captured in the model.
4	Outcomes - insensitivity of tools to assess motor function to capture improvements considered important by patients, families and their carers

	Roche agree with the EAG that the motor function assessments used within the MAA and clinical trials do not fully demonstrate the benefits that DMTs can bring to individuals with SMA due to the sensitivity of the scales used. We agree that the inclusion of the 0.1 utility increment may not adequately capture benefits for individuals with severe disability, and would like to emphasise the disproportionate impact of stabilisation/maintenance of small motor movements such as fingertip control have on independence in individuals who have very limited motor function. Similarly, the impact of improved secretion management on respiratory exacerbations is more significant in those severely affected individuals. Roche understand why the EAG attempted to use a pragmatic approach to capture the effect on patient health-related quality of life and agree with the 0.1 increment used to account for nuanced motor improvements. These nuances are described to great detail in the qualitative assessment in correspondence with patients, carers and clinical experts. This qualitative assessment is a real strength of the Newcastle EAG report. However, Roche is disappointed that the EAG has excluded methods used by the company to account for disease-related complications, such as scoliosis, respiratory support and bulbar function. Roche appreciates that data for these complications is limited, but feel that the EAG approach moves the analysis further away from capturing the full scale of SMA and the true value of DMTs. Roche has heard passionately from the SMA community of the importance that these disease impacts have on patient and carer quality-of-life (also see CS Document B, Section 3.13 (10)), and that there may be a general lack of understanding of the nuances of SMA. We have heard how loss or lack of mobility does not constitute the totality of the condition, and whether considering quality-of-life stratified by motor function only is appropriate. For example, the ability to breathe efficiently and swallow effectively are more likely to have a positive impact on the majority of people with SMA than the ability to walk or stand unaided, and impacts to bulbar and respiratory function are likely to have a substantial negative effect on patient quality-of-life and carer burden. During the managed access period, Roche made extensive efforts to generate additional informative data and improve the modelling of SMA as accurately as possible. This included conducting a utility study in people with SMA and their caregivers, but ultimately, due to data limitations, it was only possible to adopt a simplistic approach to modelling these benefits. Roche considers it inappropriate for the impact of these disease effects to not be considered in the EAG's model in any capacity. So, while Roche agree with the 0.1 utility increment to account for nuanced motor movements, Roche believe that the EAG should have included this in addition to capturing motor function health state utilities **and** impacts of disease-related complications or alternatively included a greater increment to account for the nuanced motor movements **and** impacts of disease-related complications that the EAG acknowledge are uncaptured as well.
5	<u>Outcomes - heterogeneity in the motor milestones used to define disease progression in the model</u> Recommendations (11) made in the 2018 update on standards of care for SMA state that clinical assessments in SMA should focus on the

	musculoskeletal system and related functional impairments, assessing strength and range of joint motion, relevant motor functional scales and timed tests to monitor aspects of function that reflect activities of daily living. The choice of scale should be based on the patient's age, SMA type and neurological status and should objectively assess the individual's functional status. It has been highlighted by clinical experts and patient advocacy groups that SMA manifests as a spectrum, with individual variation around outcomes within definitions of the types of SMA. The motor function assessment conducted for each individual should be chosen depending on age and functional ability; there are acknowledged and reported advantages and disadvantages of each scoring system, such as behavioural states and compliance being taken into account, sensitivity, and which muscle groups are assessed and there is some overlap between the motor function assessments that may be used. However, each scale rates individuals' in a different way, and it is not possible to directly translate scores from one scale to another (12). Roche has acknowledged this challenge (see Roche clarification responses March 2025, B1 (13)) - Roche advocated that clinical expert advice was sought to assess the appropriateness of comparing BSID-III or HINE-2 milestones with WHO milestones in the study cohort. Outcomes in the RAINBOWFISH study (published in the NEJM since our previous submission (14)), in which the Bayley Scales of Infant and Toddler Development (third edition, BSID-III) were used as the primary outcome measure; these were compared to the WHO windows for healthy children. Hammersmith Infant Neurological Examination, Module 2 (HINE-2) scoring of motor milestones was assessed as a secondary outcome in the RAINBOWFISH study. While HINE-2 milestone attainment could plausibly align with WHO motor milestones in the presymptomatic cohort, equivalence between the two scales has not been explored. Extreme caution should be taken in extrapolating the same connection for any symptomatic cohorts. The natural history of individuals with SMA type 2 and 3 suggests that they would experience declines in both RULM and MFM32 scores and appreciate the EAG highlighting that WHO motor milestones are insensitive to small changes (15, 16).
6	<u>Costs associated with administration of risdiplam</u> The EAG included comments regarding the administration and dispensing of risdiplam (Page 414, Section 15.3 Qualitative analyses surrounding economic impact and finances). "One patient expert submission (adult with SMA) noted that risdiplam would have less impact on the NHS because it is administered at home. However, a professional group submission also noted that specialist pharmacy knowledge and dispensing was required when prescribing risdiplam, implying a greater level of training needed to dispense the treatment." The risdiplam licence states that "Treatment with Evrysdi should be initiated by a physician with experience in the management of SMA." Risdiplam is prescribed in neuromuscular specialist centres as required by the High Cost Drugs route via Blueteq, and the prescribing consultants manage the patients routinely with no onerous monitoring necessary. The vast majority of risdiplam (around 99%) is dispensed by a

	Roche funded homecare vendor who manage prescriptions, reconstitution and deliveries direct to patients homes through cold chain delivery. Home delivery/dispensing in the community addresses one of the key drivers in the NHS 10 year plan of more care being available on people's doorsteps, and also VAT savings are realised when risdiplam is not dispensed by hospital pharmacies. Risdiplam's oral route of administration offers patients convenience and avoids the need to travel (in some cases long distances, and often utilising NHS transport services due to the disabling nature of SMA and incurring significant personal costs when hotel accommodation and equipment hire is necessary) to a specialist neuromuscular centre to receive treatment. In addition, risdiplam's at home administration does not require any additional NHS capacity or resource to deliver, hence it does not have a treatment administration tariff. In the small number of cases where risdiplam is dispensed by the hospital pharmacy, reconstitution is required which takes a few minutes without specialist equipment being required. Instructions for reconstitution are clearly described in the Summary of Product Characteristics.
Economic	
7	<u>Summary of Roche position on economic models</u> Roche understands that, as part of a multiple technology appraisal (MTA), a single analysis considering both treatments is required using one trusted and executable cost-effectiveness model. Roche is pleased to read that the EAG considers the Roche models were logical and appropriate. However, it is clear that facilitating an open and transparent appraisal of limited evidence in rare conditions is not without considerable challenges. For this iteration of EAG assessment, Newcastle have decided that the most appropriate mechanism to assess the cost-effectiveness of risdiplam and nusinersen for SMA is to consider the value of each treatment versus BSC in standalone models. As explained in Comment 8 and Comment 9, Roche has issues basing the whole cost-effectiveness value on obsolete and irrelevant BSC comparisons. However, Roche also considers the approach to consider cost-effectiveness of multiple treatments in separate models at odds with the reasoning, spirit and technical rigour expected in a multiple technology appraisal. A key challenge with the new EAG modelling approach is that, due to the range of alternative analyses in the various populations and the need now for the EAG to perform these in two separate confidential models, it is increasingly difficult to understand the real implications of alternative EAG assumptions. These results will be considered in committee decision making and the current approach means that Roche and other stakeholders will be entering the committee meeting without a full picture and little indication of the cost-effectiveness of risdiplam and other treatments for SMA and key drivers of model results.

	Roche is unaware of the cost-effectiveness implications that alternative scenarios have, or the key inputs in the EAG analysis that drive cost-effectiveness results in the Biogen analysis. An indication or explanation of the impact of key scenarios would allow Roche, and other stakeholders, to prepare to input and respond as best as possible. Roche would welcome the sharing of magnitude and direction of change associated with alternative scenarios to aid interpretation of model drivers. Roche fails to understand how the committee will use the various (potentially conflicting outcomes) for decision making. It is imperative that NICE come to a coherent, trustworthy and timely recommendation for this important and underserved SMA population. The NICE process for this MTA has already been considerably delayed, causing untold uncertainty, anxiety and stress on the clinical, patient and carer communities. Roche advocates for timely positive guidance for both treatments so the community can realise the importance of these transformative treatments for people with SMA. Negative guidance would only serve to increase uncertainty and anxiety for patients and their carers and risk the regression of substantial clinical improvements these treatments have allowed.
8	<u>Summary of Roche position on 'Exploratory analyses'</u> The EAG report makes it clear that the EAG's position in this appraisal is to ignore reasonable, methodologically robust analyses comparing DMTs to each other. As in response to the Warwick EAG report, Roche would like to highlight key areas associated with the ITC analyses conducted by Roche to facilitate these comparisons. We would like to highlight two key areas regarding ITC and population adjustment methods, as they are crucial for informing models and aiding decision makers. The current evidence in the models has limitations, such as small sample sizes and heterogeneity in baseline characteristics across studies, which we have acknowledged in our published work and agree with the EAG assessment. 1. Our feasibility assessment of conducting Matching-Adjusted Indirect Comparisons (MAIC) to compare treatment efficacy in infants treated with risdiplam to those treated with nusinersen or gene therapy showed that numerical differences in baseline characteristics, including prognostic and predictive factors, further decreased the already small sample size by approximately 50%. Under these conditions, the existing literature does not support performing MAIC (or Simulated Treatment Comparisons) as the results may be biased or unstable due to the small sample size, and the findings may not be generalisable. This poses a risk that decisions based on limited evidence could lead to incorrect conclusions about the effectiveness or safety of treatments (17). Therefore, we propose that these limitations be acknowledged in the written report on the MAIC for the presymptomatic population. Results should be interpreted with caution and should be treated as exploratory and of limited statistical power, with the current evidence being insufficient to draw conclusions on efficacy or safety differences.

2. In our published work, “Long-Term Comparative Efficacy and Safety of Risdiplam and Nusinersen in Children with Type 1 Spinal Muscular Atrophy” (18), we conducted extensive scenario analyses for matching factors and outcomes to select the important prognostic and predictive factors for population adjustment, and highlight any possible biases due to factor selection in the outcome comparisons explicitly comparing children treated with risdiplam to those treated with nusinersen. To avoid overfitting (due to correlations in the baseline characteristics) and improve the reliability of the results, our main model only included factors with the highest contribution towards population imbalances at baseline. Including all available factors was in fact one of our scenarios and did not show significant impact or deviation from the results of the main model. Additionally, we accounted for differences in assessment schedules and matched for these to limit bias in outcome comparisons due to more frequent visits. We propose that the risks of matching for all available baseline characteristics be highlighted in the written report and suggest considering only those factors contributing to population imbalance. Furthermore, the importance of matching for differences in schedules should be emphasised to minimise bias. Addressing these points will ensure that the comparisons more accurately reflect the true treatment effect. Therefore, we propose that the methods and results from our peer-reviewed publication pertaining to the type 1 population on risdiplam versus nusinersen to be used to inform the cost-effectiveness model and decision making for this particular population.

As in the two points given in response to the Warwick EAG report, Roche acknowledges the important differences in trial populations and highlights the extensive sensitivity analyses and testing performed in order to facilitate a comparison between risdiplam and other DMTs.

Roche would argue that the current Newcastle EAG approach moves further away from facilitating a robust informative comparison. The current approach has limited ‘base case’ analyses to risdiplam versus BSC and nusinersen versus BSC only. The EAG's methods to facilitate this comparison opts to use each individual company model separately. Roche argues this lacks validity, goes against the spirit of the MTA process, and does not solve the underlying issues associated with differences in trial populations.

Roche struggle to understand how the analyses presented by the EAG:

- 3 ‘base case’ analyses comparing risdiplam and BSC in the Roche cost-effectiveness model
- 3 ‘base case’ analyses comparing risdiplam and BSC in the Biogen cost-effectiveness model
- 3 ‘exploratory’ analyses comparing risdiplam, nusinersen and onasemnogene abeparvovec in the Roche cost-effectiveness model

will be used to inform committee decision making. The current EAG approach of comparing cost-effectiveness outcomes generated in these standalone models does not solve the uncertainty associated with notable differences in the eligibility criteria between nusinersen and risdiplam. This EAG approach, the MTA process more generally, and the need to protect commercial information makes it very difficult to validate and verify analyses using Biogen’s models.

	Roche argues that the most appropriate comparison, and one that fully addresses the final NICE scope and remit for this MTA appraisal, is a single model that includes a full comparison between the interventions.
9	Comparison to best supportive care As outlined in the previous response to the Warwick EAG report, and stated in response to Newcastle EAG clarification questions, Roche questions the relevance of a cost-effectiveness comparison against best supportive care (BSC). However, the statements in the current EAG report miss the nuance of our stance on BSC, such as "*The base-case submitted by Roche for the presymptomatic population did not include BSC as an appropriate comparator*". The company base case analysis provides cost-effectiveness results to all treatments included in the NICE scope, i.e. BSC, nusinersen and onasemnogene abeparvovec. As explained in response to Newcastle EAG's clarification questions earlier this year, as there is no newborn screening for SMA in the UK, the only patients that could be considered 'truly' presymptomatic would be those who are specifically tested prenatally or at birth as they have parents or siblings with SMA. Even then, there is clinical theory that SMA-related damage could occur *in utero*. This population is extremely small in the UK and likely less than one incident patient per year. Therefore, for the majority of the 'presymptomatic' population, by nature of their presymptomatic state and lack of a diagnosis, patients would not be aware of their SMA until they become symptomatic and are diagnosed. Upon diagnosis, it is highly unlikely that any patient would opt for BSC. All patients would then likely start treatment with disease modifying treatments in line with the Type 1 or Type 2/3 models. For the few patients who are diagnosed presymptomatically, physicians would not recommend BSC as an option and it is highly unlikely that parents would opt for it. In the future, when newborn screening becomes available, this stance will not change. The company understands that this general assumption can be extended beyond the presymptomatic population to the Type 1 and Type 2/3 symptomatic populations. Roche understands that the vast majority of patients engaging in an SMA clinical pathway are treated with DMTs. So, any comparison to best supportive care is likely irrelevant to the NHS and the vast majority of people with SMA. This view has been validated and confirmed when speaking to the wider patient, carer and clinical SMA community who believe that BSC is not a relevant or clinically acceptable treatment option for most people with SMA. This view was presented in response to the 2024 Warwick EAG report and reiterated to Newcastle EAG in the two rounds of clarification questions in early 2025. Published research and national reports have shown that there is significant variation across the UK in neuromuscular standards of care and services both regionally and between paediatric and adult services. Many adults cannot access BSC on the NHS, and BSC requires a multidisciplinary approach and is tailored for individual patients. This includes the monitoring and support of patients in the absence of active disease modifying treatment and relies on the prevention and treatment of co-morbidities such as swallowing and feeding difficulties, scoliosis and thoracic deformity, contractures, and respiratory insufficiency. Roche has heard from the SMA community that access to BSC is not consistent across the country and many patients struggle to benefit from consistent care. The 2022 Muni-Lofra publication reported limited

access to care and provision for patients with SMA, with half of the study population consistently not accessing full multidisciplinary care (19).Since the start of the managed access period, the proportion of SMA patients accessing care through DMTs has increased. With increased use of DMTs, the prognosis of people with SMA has increased, which should be celebrated.

Now, as the managed access period is reaching its conclusion, Roche has been collecting insights from clinical experts on whether a population of patients exists who are:

1. Eligible for treatment with a DMT, and
2. Not previously treated with, and discontinued from, a DMT, and
3. Engaged in the healthcare service and are actively opting to receive BSC over one of the available DMTs.

Led by insights from patient advocacy groups and clinical experts, Roche believes that this population exists only for a very small proportion of patients currently engaged with a specialist centre. Market research through conversations with multiple clinicians, responsible for the care of over 300 SMA patients, it is clearly indicated that this proportion is very small.

REACH registry data (Table 1), as well as clinical opinion and Roche market forecasting data (Table 2) indicates that the vast majority of patients with SMA are receiving treatment with disease modifying therapies. For example, clinical opinion to the company backed up by data gathering in key treatment centres in the UK from October 2024 indicated that 0 eligible paediatric patients receive BSC over disease modifying therapies (Table 2). This is also supported by patient and carer advocacy groups who promote early intervention with disease modifying therapy.

For the adult population, data gathered through clinical conversations, presented in Table 2, suggests that only [redacted] of [redacted] ([redacted]%) patients sampled were receiving BSC instead of a disease modifying therapy and, when accounting for those who had previously discontinued a disease modifying therapy, this number shrinks to [redacted] of [redacted] ([redacted]%). Furthermore, the June 2024 REACH report, presented in Table 4, indicated that only 33 of 426 (7.7%) are still classed as 'natural history', which the company interprets to relate to BSC. The REACH data covered more sites than the Roche gathered data, but there was strong alignment in rates of BSC in centres that featured in both datasets.

Therefore, for the overall population sampled in Roche data gathering, only [redacted] of [redacted] ([redacted]%) people with SMA were receiving BSC instead of disease modifying therapy at first line (Table 2).

So, to summarise:

	• In the presymptomatic and Type 1 populations, there are likely to be <1% of patients who engage in the healthcare system and actively choose BSC as their initial treatment option, this would only be the case if patients are so severely affected at the time of diagnosis that palliation is the route of choice. • In the Type 2/3 paediatric population, the clinical opinion and evidence allude to a rate of 0%. The proportion is slightly higher (<5%) in the adult Type 2/3 population, but still very small. This indicates the importance of intervention with disease modifying therapies to patients, carers and their clinicians. It also calls into question the relevance of a cost-effectiveness comparison to BSC when it is not a reasonable treatment option for over 95% of the eligible population. Given the very small proportion of patients who receive BSC as first-line treatment, Roche question the appropriateness of an incremental comparison to BSC. Roche would like to understand why the EAG think a comparison to BSC is the most appropriate, other than ease of analysis. Roche understands that a comparison versus BSC may well be easiest from a process point of view, but this in of itself is not a reason to base an important appraisal in a rare and underserved population on cost-effectiveness analyses against an irrelevant comparator. Roche believes that the most appropriate comparison for NICE to consider the vast majority of the SMA clinical care pathway is one that reflects the true proportion of care in the NHS.
10	<u>Uncertainties</u> The EAG have highlighted a list of key issues and uncertainties in their analysis. However, Roche considers it important to reference the original list of uncertainties outlined by the NICE committee in TA755 and consider the extent to which these have been resolved or reduced by the period of managed access. In the risdiplam Managed Access Agreement, Section 5.1, the committee listed: • The suitability of the model for decision-making. • Long-term benefits with risdiplam are uncertain. • Methodological challenges and uncertainty associated with inclusion of caregiver utility values. • The approach to account for risdiplam's additional benefits that currently are not captured in the clinical outcomes and economic model. • The committee expect further data collection will allow for a new model to be presented when the guidance is updated. Roche considers that these uncertainties should have featured in the EAG's decision problem, and the efforts made by the company to resolve overarching uncertainty during the period of managed access should have been discussed. To summarise: • To address the suitability of the model for decision making:

- Roche conducted a workshop including a range of health economics and patient experts, to advise on the uncertainties flagged by the committee as part of TA755 and how these could be addressed. The feedback received during this workshop was subsequently considered for updating the economic analyses ahead of the resubmission (please also refer to CS Document B, Section B.3.2.2, for additional details). It was discussed that an economic model cannot capture all aspects of SMA (also mentioned in CS Document B, Section B.3.13), and is a well-documented challenge, particularly in the case of rare diseases.
- All models were subject to an external quality assurance procedure, which included technical validation of key model inputs and calculations. Any issues or errors were documented and addressed in the final version of the models.
- Roche further conducted dedicated HCRU (informing the base case health state costs across all three economic analyses) and utility studies (informing scenario analyses for caregiver utilities across all three economic analyses).
- Efforts undertaken by Roche to validate the originally submitted models, and update them in line with expert advice and available data, appears to also have been recognised by the EAG who decided to use these models (with relatively limited additional changes) as the basis for their preferred analyses. The EAG explained that they considered that the models were reasonable and captured the clinical pathways well.
- *Roche considers this issue has been resolved.*

- To reduce uncertainty in the long-term benefits of risdiplam:
  - Further data were collected in the SUNFISH, FIREFISH and RAINBOWFISH trials, which, alongside the SMA REACH real world evidence, has shown that motor function, survival and quality-of-life benefits with risdiplam have been maintained over the long term.
  - It was also possible to incorporate longer term data from more recent SUNFISH, FIREFISH and RAINBOWFISH data cuts, where available, into the economic analyses; in addition, data from SMA REACH were used in selected scenario analyses and otherwise used to validate selected assumptions in the models (around treatment discontinuation).
  - Roche considers the longer-term data collected in the managed access period goes some way to resolving this issue, however it is unlikely that further data collection will resolve long-term uncertainty entirely.

- To investigate and address the methodological challenges and uncertainty associated with inclusion of caregiver utility values:
  - During the managed access period, Roche conducted a new utility study to collect data for SMA patients and their caregivers. Health economic and academic experts specialising in utility methods, alongside SMA patient groups, were consulted to determine the most appropriate methodology to collect the data.
  - Methodological challenges and uncertainty associated with the modelling of caregiver utility values were also investigated during managed access in order to overcome the “QALY trap” around life extension for patients and carers, including investigating the health effects associated with bereavement (e.g. depression, anxiety and inability to participate in usual

activities due to grief), consideration of wellbeing as an alternative to health-related quality-of-life and carer modifier/multiplier for family health spillovers (as detailed in Section B.3.3.5). This also informed a peer-reviewed publication (20).
    - Despite these efforts, ultimately the data was limited by small sample sizes. Whilst robust data to inform economic analyses from this research was limited, the work helps to further highlight and define the continued uncertainty around patient and caregiver quality-of-life for people with SMA and their caregivers, and rare diseases more generally.
    - Roche consider that this was implausible to resolve during the managed access period and requires broader long term health system collaboration.

- To account for risdiplam's additional benefits that currently are not captured in clinical outcomes and economic model:
    - Roche undertook healthcare resource use and patient and carer utility studies, as well as Delphi panels and validation, to understand the originally uncaptured benefits' impact on the healthcare system, people with SMA and their caregivers. Roche is aware that these efforts only scratch the surface considering the complexity of SMA. Unfortunately, none of the efforts to capture these additional benefits in the economic analyses made it into the final models due to limited data to inform a robust economic analysis. Examples include the stratification by treatment response, modelling of upper limb function, and additional QALY benefits associated with risdiplam. The re-submitted models included incremental utility impacts for disease-related effects, so Roche is saddened to read that some of the impacts Roche had attempted to quantify have been dismissed by the EAG in their report.
    - *Roche considers that this was implausible to resolve during the managed access period and requires broader long term health system collaboration.*
    - A new updated model has been presented, including longer term follow-up data from SUNFISH and FIREFISH studies, and an additional presymptomatic analysis with RAINBOWFISH data.
    - *Roche considers this issue has been resolved.*

From a broader process perspective, Roche considers it highly important that the activities outlined above are documented in the assessment report and considered by the NICE committee at ACM1. The purpose of managed access is to give people faster access to promising new treatments whilst more evidence is collected to address the uncertainties identified by the NICE committee. Roche considers that, by not highlighting the committee's original views and the progress that has been made towards resolving any uncertainties, there is no differentiation between a new evaluation and a managed access review. This approach runs the risk that uncertainties which were resolved at the first appraisal, or during managed access, are reopened/re-discussed at committee, resulting in a delay to a routine commissioning decision. This also ignores the time and level of funding this data collection has required, undermining the energy and effort of all stakeholders involved. Roche would implore the EAG and NICE to:

	• Consider the activity and progress detailed above in the assessment report. • Recognise the efforts made by the SMA clinical and patient community to close evidence gaps and reduce/manage uncertainty during the managed access period. • Consider pragmatism in decision-making with regards to the uncertainties for which a resolution was highly unlikely to be achieved during a managed access time frame. • More broadly, consider the process for managed access review and how to link the re-appraisal to the original NICE evaluation. Roche would like to take this opportunity to thank the SMA community for their time, commitment and collaboration in facilitating data collection during managed access, acknowledging that this placed additional burden on the patient and caregiver community, and the NHS. The managed access period has, amongst other things, served to highlight the difficulty in generating robust evidence for rare diseases, particularly in children and their caregivers, and there are limitations to fully resolving some of the overarching uncertainties over a data collection period of 3 years.
11	<u>Carer health-related quality of life</u> As explained in CS Section B.3.3.5, given the substantial amount of care that SMA patients require from family members or professional carers, and in line with the approach taken in TA588, TA755 and the NICE reference case, HSUVs are included in the model base case for both patients and carers. Section 3.14 of TA755 final guidance outlines that the original company base case used an additive approach and assumed that caregiver health-related quality of life increased linearly with each motor milestone that was met. There were discussions during TA755 regarding the appropriateness of an additive or decrement approach to capture carer quality of life. As part of the data collection period, Roche committed to conducting a new utility study to collect new utility data for both SMA patients and their respective carers (discussed in CS Section B.3.3.5). Methodological challenges and uncertainty associated with the modelling of caregiver utility values were also investigated during the MAA period, in order to overcome the 'QALY trap' around life extension for patients and carers. Various methods were explored, including accounting for the health effects associated with bereavement (e.g. depression, anxiety, and inability to participate in usual activities due to grief), consideration of wellbeing as an alternative to HRQoL and carer modifier/multiplier for family health spillovers. In this consultation step, NICE and the EAG have asked Roche and Biogen to consider the most appropriate approach to capture important carer health-related quality of life. In the Roche submitted approach as explained above, following efforts made in the data collection period, the Roche approach for this appraisal considered consistency with the previous NICE appraisals. Carer utility from Bastida et al. was assigned to the lowest health state, general

	population utility assigned to highest health state, values for intermediate health states were evenly distributed, applied as a decrement. The analysis considered different utility values between presymptomatic/Type 1 SMA and late onset SMA, assuming that the level of carer impacts are different dependent on population. The EAG's interpretation that the analysis doesn't account for bereavement effect or carer 'QALY trap' as per expert opinion is not entirely correct, the model does have the option to limit the application of carer disutilities (to the period of BSC life expectancy) and/or bereavement disutilities (to the period of extended life expectancy with risdiplam). In contrast, the Biogen approach was described as a 'novel approach' to avoid the carer 'QALY trap'. In Biogen's approach, the caregiver utility value for lowest health state is used as baseline, then a utility increment for each health state is calculated and applied, general population utility is used for highest health state. The Biogen approach uses equivalent utility values for each SMA type, assuming it is the health state that drives utility for carers. Finally, carer utility is not captured upon patient death, which avoids favouring highest mortality interventions and avoiding the carer QALY trap. Roche would argue that the Biogen approach is similar to the Roche approach submitted by the company in TA755, described above. Roche understands that the decrement and increment approach should result in similar outcomes. Roche understands that the Biogen approach rewards occupancy of the better states via incremental gains and the Roche approach penalises occupancy of the worse states through decrements. This can lead to different outcomes due to the predicted survival and health state occupancy over time in the different arms of the different models. In the interest of consistency between company approaches, Roche believe that the Biogen is an appropriate method to capture carer quality of life, and advocates for the EAG to use this method consistently in their base case analyses in Roche and Biogen models. It is imperative that the EAG consider the health-related quality of life of, not only people with SMA, but their wider caring support network. Carers play a highly important role in the lives of people with SMA, and it is important that the benefits of DMTs on the lives of carers are captured in the analysis. In addition, Roche would advise the EAG to consult with their clinical experts to understand whether the assumption that carer impacts are the same across SMA Types i.e. applied consistently by health state (would "Not Sitting" present the same burden to carers for Type 1 vs Type 2/3 patients?).
12	<u>Severity</u> In this consultation step, NICE and the EAG have asked Roche and Biogen to consider the most appropriate approach to capture severity in the company models. The EAG highlighted that the Roche approach was inappropriate, as the severity modifiers were applied to patient and carer QALYs, not patients only.

	Roche confirms that the Roche models have been adjusted so that the severity modifier is not applied to caregiver QALYs. Instead, caregiver QALYs are added to the patient QALYs as part of the ICER calculation after the application of the modifier to patient QALYs. This approach aligns with the recommendations outlined in TSD23 (21). In the updated Roche models, the presymptomatic and Type 1 models estimate a 1.7x modifier and the Type 2/3 model estimates a 1.2x modifier. Regarding the Type 2/3 model, the EAG's base case assumptions return an absolute shortfall of 17.16 QALYs, just short of the 18 absolute short fall threshold for a 1.7x modifier. As highlighted in other comments, Roche believe that the EAG analysis is not capturing the true value of DMTs. We believe that if these benefits could be captured in the models, the absolute shortfall would be greater than 18 and a 1.7x modifier would be appropriate. Roche advocates for a consistent severity modifier to be applied in each SMA type. Given the severity of the condition and the impact to both life expectancy and health-related quality of life, Roche believes that the most appropriate modifier to reflect the totality of the condition would be 1.7x. Roche believes a 1.7x modifier should be used consistently in all Roche and Biogen analyses. Roche do not believe how a condition such as SMA does not meet the highest severity criteria and strongly suggests the most appropriate modifier to be 1.7x.
13	<u>Resource administration cost</u> Section 6.3.2.8 states the resource administration cost of nusinersen in the Biogen and EAG models is £836 per administration (using diagnostic spinal puncture as a proxy). This does not align with the resource administration costs that were confirmed in writing by the NHS England Highly Specialised Services team (email received by Roche on 14 March 2024), which states: [redacted] The EAG's application of the proxy administration costs for nusinersen underestimates the resource costs for nusinersen in both the first year of administration (6x treatment administrations total, including 4x initial loading doses) and maintenance years (3x treatment administrations). Hence, the resource costs for nusinersen presented in the assessment report and total administration costs calculated in the models are not an accurate reflection of the true costs to the NHS.

14	Uncertainty in patient costs for severe health states During the managed access period to address uncertainty highlighted by the committee in the original risdiplam and nusinersen appraisals, Roche conducted a HCRU study. As detailed extensively in CS Section B.3.5.2, robust evidence was sparse following the cost and resource-use SLR, particularly in relation to indirect (non-medical) costs associated with SMA, despite patients' requirement for a substantial amount of care and support. Although not specified in the risdiplam data collection agreement, due to the uncertainty around previous costs published in SMA and uncertainties highlighted in the previous NICE appraisals, the feasibility of different methodology types were explored to capture this data to inform the cost-effectiveness models. Initially, a database study feasibility assessment was conducted to understand if healthcare resource use data could be collected through Clinical Practice Research Datalink (CPRD) Gold, CPRD Aurum and Health Episode Statistics (HES), which are linked databases reporting data from a subset of primary care centres and secondary care data from all hospitals in England. An initial feasibility analysis indicated that estimates for important categories of HCRU, such as ventilation procedures, surgeries and respiratory tests, would be captured in these databases. Additionally, patients could be identified with available SMA-specific diagnosis codes (International Classification of Diseases, 10th Revision [ICD-10], Read or SNOMED). However, during the initial stages of the CPRD study, challenges arose in identifying patients belonging to the different health states. This was due to the defining of motor milestones in each health state not being explicitly recorded in the CPRD/HES routine care datasets. Alongside consulting clinical experts, multiple approaches were sought to determine how to define the motor milestone health states using the information provided within the database, via proxy variables. The challenges faced were issues around recursive analysis, inability to reliably differentiate between patients of different health states using individual HCRU items or recorded comorbidities and using an assumption of a linear, positive correlation between broader HCRU types such as hospital visits – which may in fact not be valid for all health states. Due to the challenges of the database study, a *de novo* modified Delphi panel was conducted between November 2023 and March 2024 with the objective of collecting quantitative expert clinical opinion on the amount of healthcare resource use (HCRU) associated with the management of SMA Types 1 and 2/3 in the UK. The detailed methodology can be found in the report on file. In brief, a pre-specified protocol was designed outlining eligibility criteria for participation, methods of data collection and analysis of results. A lead consultant neurologist and expert in SMA, as well as two representatives from SMA patient advocacy groups (PAG) were consulted on the scope and design of the questionnaire. The modified Delphi panel consisted of two rounds with the aim of trying to achieve consensus on the resource use estimates. In each round, geographically-spread invited participants individually responded to one of three questionnaires, respectively covering paediatric patients with SMA Type 1, paediatric patients with SMA Type 2/3 or adult patients with SMA Type 2/3, to reflect expected differences in clinical

	practice and HCRU needs in these populations. In total, 34 out of 36 (97%) invited participants completed the Round 1 survey and 28 out of 34 (82%) invited participants completed the Round 2 survey. Following completion of the two Delphi rounds, the aggregate results were shared at a clinical expert advisory board meeting which took place in March 2024. Discussions centred around the results for items which had not reached consensus during the two preceding rounds, as well as providing interpretation and validation for consensus values achieved. The results were also contextualised and validated with the two PAG representatives, as informed by providing patients' real-world experiences. The results showed that healthcare resource use was high in patients with SMA, with frequent planned and unplanned healthcare visits, tests or procedures for the condition along with many costs around the funding and purchasing of equipment that is currently not accounted for. Unit costs were sourced from NHS reference costs and applied to the proportion and frequencies (per cycle) of healthcare resource utilisation derived from the survey results. The resulting total costs for presymptomatic and Type 1, and Type 2/3 SMA were used in the base case analysis. The EAG expressed their concern regarding the differences in monthly costs between TA588 and those in the Roche base case analysis sourced from the HCRU study. So, to maintain consistency with the current company submission and previous SMA appraisals, the EAG used health state costs from the latest NICE submission in this area (HST24). Roche acknowledges the remaining uncertainty regarding HCRU costs, however, does not see the rationale for ignoring new alternative data. The EAG reasoning regarding the substantial differences between the HCRU data and HST24 values could be extended here, with HST24 values substantially higher than all other health state costs. The EAG approach utilising HST24 on precedent only is a common approach in NICE appraisals, and one that often results in inappropriate, outdated estimates used in decision making. It is unclear how the costs sourced from HST24 were originally calculated, as there is relatively sparse information on the exact costing approach used. So, there is a substantial lack of transparency with the EAG approach. Roche feels that precedent alone should not serve to reason for model assumptions. As in the company Comment 3, Roche is also disappointed that the EAG has excluded methods used by the company to account for disease-related complications, such as scoliosis, respiratory support and bulbar function. Roche appreciates that data for these complications is limited but feels that the EAG approach moves the analysis further away from capturing the full scale of SMA and the true value of DMTs. Roche advocate for the EAG to further justify the appropriateness of using the HST24 values, and provide an explanation as to how these costs were originally calculated and then applied in their analyses so stakeholders can understand their appropriateness. As HCRU costs have been an outstanding uncertainty in all SMA appraisals, Roche also call for alternative values to be considered in scenario analyses.
15	Lack of trust in EAG analyses

	Following a technical quality check of the confidential risdiplam EAG model (received 27 August 2025), Roche have identified some areas of concern in the EAG approach. These issues raise concerns with the remaining model changes, and changes Roche are unable to validate in the Biogen models. Please see technical comments (Comments 16-20) below. In addition, EAG adjustments to the cost-effectiveness models contain a large number of hard coding values and lack of referencing making it difficult to quickly infer the appropriateness of their changes.
16	<u>Modelling of motor milestone decline</u> Type 2/3 • In the Roche Type 2/3 model, after 26 months, patients receiving risdiplam were modelled to remain stable and not change health state. This aligns with the approach taken in TA588 and TA755, and was informed by UK clinical expert opinion.(22, 23) • By comparison, the EAG have adjusted the Type 2/3 model to include a probability of stabilisation with risdiplam of 58% after 24 months, sourced from Oskuoi et al. 2023.(24) However, Roche have identified several issues with this adaptation. Firstly, this statistic has not been correctly integrated into the model. Given the 58% statistic relates to the percentage of stabilised patients with risdiplam at 24 months, the rate of decline would theoretically be calculated be '1– 0.58' instead of '1 – 0.42'. Secondly, the calculated value is used as a multiplication factor applied to the transition probabilities for BSC to generate risdiplam transition probabilities. However, this approach is not methodologically appropriate given the statistic does not directly relate to a relative treatment effect. Finally, the Oskuoi et al. paper also mentions that 32% of patients improve after 24 months, alongside the 58% who stabilise.(24) However, this improvement is not modelled, which suggests that the EAG may have selectively focussed on certain inputs rather than fully aligning with the source. Therefore, the EAG's adaptations to long-term risdiplam transition probabilities in the Type 2/3 model make it currently unsuitable for decision-making. • Roche advocates for the EAG to use assumptions from the company base case analysis, i.e. following the original assumption of milestone maintenance (after 96 months). As noted below, Roche have provided a switch in the model to revert back to company-submitted assumptions. Type 1 • In the Roche Type 1 model, after 66 months, patients receiving risdiplam were modelled to remain stable and not change motor milestone. This again aligns with the approach taken in TA588 and TA755, and was informed by UK clinical expert opinion.(22, 23)

	• In the EAG model, data from Ribero et al. 2022 are used to inform the relative long-term transitions of risdiplam.(25) This was achieved through the application of MAIC-weighted proportion of HINE-2 responders applied as a multiplier to BSC transition probabilities. Similar to the Type 2/3 model, it is unclear where this approach is methodologically appropriate as it does not account for the fact that this statistic is not directly related to the relative treatment effect. • As with Type 2/3, Roche have provided a switch in the model to revert back to company-submitted assumptions. Roche have conducted pragmatic scenarios, replacing the modelling of long-term decline in the risdiplam arm with our original assumption of milestone maintenance in each Type 1 and Type 2/3 models. In both of these scenarios, cost-effectiveness outcomes improve for risdiplam versus BSC. These scenarios are present in the updated company models included in the company response documents.
17	<u>BSC long-term transition probabilities</u> Type 2/3 • Roche would like to provide clarification on the source of inputs for long-term transitions for BSC in the EAG-adapted Type 2/3 model. According to the EAG report (Table 84), Wadman et al. 2018 is identified as the source for long-term transition probabilities for BSC beyond 96 months.(26) However, the model is designed to always utilise the higher of the two transition probabilities — either from Wadman et al. or transition probabilities derived from SUNFISH data — for each health state.(26) In all health states, the SUNFISH-based transition results were greater than the Wadman et al. -derived transition probabilities, making SUNFISH the source used for long-term BSC transition probabilities in the model for all health states. It should be noted that this approach also indirectly affects transition probability estimates for risdiplam, as the EAG's method applies a relative effect modifier to the BSC transition probabilities to model the effects of risdiplam (as described above). • It is important that the Committee understands the correct sources informing the transition probability inputs. Type 1 • Roche would similarly like to provide clarification on the source of inputs for long-term transitions for BSC in the EAG-adapted Type 1 model. The approach for modelling long-term transition probabilities in the Type 1 model for BSC, whereby the highest transition probabilities for each health state are selected, is the same as for Type 2/3 model (see the row above). Accordingly, in the EAG-adapted Type 1 model, Wadman et al. is used only for the walking-to-standing probability, as the Wadman et al. decline probabilities are higher than the MAIC-derived BSC probabilities (Roche base case) for this health state transition only.(26) This is mostly inconsequential since no BSC Type 1 patients are reaching the walking state, but it is important the committee understand this nuance.

	• Additionally, there is uncertainty regarding the EAG's adaptation whereby a MAIC-derived relative treatment effect (based on Ribero et al.(25)) for risdiplam is applied to BSC transition probabilities in order to generate transition probabilities for risdiplam. These BSC probabilities are themselves derived from FIREFISH risdiplam data, calculated using a MAIC-based odds ratio method. This layered approach amplifies uncertainty around the long-term transition probabilities for risdiplam, further reducing the validity of the underlying assumptions and the overall methodology employed by the EAG for long-term efficacy. • As above, it is important that the Committee understands the correct sources informing the transition probability inputs.
18	<u>Alignment of timepoint of no further improvement in motor milestone for risdiplam with trial data availability (all models)</u> In the EAG-adapted Roche models, the choice of the timepoint at which no further improvement in motor milestones can be assumed has been updated to align with the approach used in the Biogen models, which is to reflect length of data availability from the relevant trial. While this method is based on the availability of trial data, it can be considered somewhat arbitrary and may not fully capture clinical considerations. For instance, in the Type 2/3 model, a 96-month timepoint was used instead of 26 months (selected originally by Roche based on clinical expert opinion). However, if the model is adjusted back to 26 months, it results in an increased number of LYs for risdiplam, i.e. implying shorter treatment duration increases efficacy—which is not clinically valid—highlighting the limitations of the assumptions made by the EAG regarding long-term transition probabilities. In the Type 1 model, the EAG reduced the timepoint from 66 to 60 months, and in the pre-symptomatic model, the selected timepoint is 72 months instead of 12 months to align with trial data availability. Again, Roche argue these changes are somewhat arbitrary and highlight flaws in the EAG analyses. With all arbitrary timepoints, Roche feel it is important to flag that Roche and clinical experts consulted by the company believe that patients will continue to receive benefit while on treatment with risdiplam. The selection of a timepoint to 'switch off' improvements was made for modelling reasons only and it is important for the committee to understand that benefit is not just achieved through continuing improvement. Maintenance of achieved benefit is equally as important for people with SMA and their carers. The company understands that there is always going to be a ceiling of improvement and the framing of benefit for people with SMA is important and is often missed in degenerative conditions such as SMA.
19	<u>Survival</u> Type 2/3 Roche's original approach to modelling Type 2 survival was based on an SLR of Type 2 survival data in the literature. The EAG replaced this with a single-source extrapolation from HST24, citing the need to ensure consistency across appraisals in SMA.(27) However, Roche do not

	consider changing the methodology solely for consistency is not clinically valid, particularly when existing survival data are available. Roche calls on the EAG to further justify and validate the appropriateness of the HST24 methodology and explain why it is preferred over the original company approach. Type 1 Roche's original approach to modelling Type 1 survival was based on PNCR natural history data. The EAG replaced this with using a single-source extrapolation from HST24 to maintain consistency, as per the approach for Type 2/3 modelling discussed above.(27) However, as discussed above, consistency alone is not necessarily a clinically valid reason for selecting these data over modelling based on natural history data. Roche calls on the EAG to further justify and validate the appropriateness of the HST24 methodology and explain why it is preferred over the original company approach.
20	<u>Discontinuation</u> The EAG report states that there is no discontinuation of risdiplam in the Roche models (pages 145, 223, and 425 for the pre-symptomatic model; pages 164, 225, and 428 for the Type 1 model; and pages 184, 228, and 430 for the Type 2/3 model; as well as pages 20 and 418 summarising the approach across all models). This is incorrect. The Roche models do incorporate health-state-specific stopping rules, whereby patients in lower health states no longer incur treatment costs once the treatment effect is lost, reflecting treatment discontinuation. In contrast, the EAG models do not include these rules and appear to assume lifelong treatment, which confuses their statements in the EAG report and does not align with the original Roche approach. Roche suggests that the EAG approach reverts back to discontinuation assumptions used in the company base case to better reflect treatment stopping decisions in clinical practice. As with Company Comment 16, Roche have conducted pragmatic scenarios replacing the EAG discontinuation assumptions with our original approach in each Type 1 and Type 2/3 models. In both of these scenarios, cost-effectiveness outcomes improve for risdiplam versus BSC. Roche argue that the company approach is more appropriate as it captures the proportion of patients who would discontinue in clinical practice based on health state dependent stopping rules. These scenarios are present in the updated company models included in the company response documents.
21	<u>Conclusions and recommendations for further research</u> The EAG's conclusions and recommendations for future research outline that, in general, there is strong clinical evidence for risdiplam and nusinersen. The EAG also highlight areas where evidence is lacking, for example a lack of longitudinal and comparative data for both

	nusinersen and risdiplam. Roche believe that the EAG should include caveats to these criticisms to highlight that these gaps are often common issues in rare disease conditions such as SMA and should acknowledge the difficulty in filling these data gaps with robust evidence. In general, Roche feel these caveats are important whenever the EAG highlights their concerns with the evidence base, when these data limitations are an expected feature given the rarity of the disease and the partially paediatric population.

NICE National Institute for Health and Care Excellence

Corrections and clarifications on the External Assessment Report

Corrections and clarifications		
Page	**Issue**	**Response**
Page 24, Section 3: Plain English Summary, Main results of the MTA	"*More people who received nusinersen survived for longer, but there was less information about survival for people taking risdiplam*."	It should be clarified if this interpretation is based upon the duration of data (i.e. longer term data available for nusinersen than risdiplam) rather than survival outcomes.
Page 69, Table 9: Overview of the results from the Biogen company submission	Comparators for the Type 1 population have been incorrectly defined as SUNFISH Part II for HINE-2 and overall survival.	A correction is needed: The risdiplam study with Type 1 SMA should be corrected to FIREFISH.
Page 137, Section 7.3.2.1.2 Health states and transitions	"*Probabilities were estimated for the 2 SMN copies group and the > 2 SMN group, and used a weighted average based on 2 SMN group proportions from RAINBOWFISH*."	A correction is needed: it is the *SMN2* gene copies that should be specified, not SMN.
Page 137, Section 7.3.2.1.2 Health states and transitions	"*For risdiplam treatment effectiveness was assumed to last 72 months by the EAG, similar to the available follow-up data for nusinersen, - which is a favourable assumption to risdiplam, given that the follow-up from RAINBOWFISH was only 12 months*."	Roche argues that, while on treatment, patients will continue to receive benefit and refute the framing of a cap on risdiplam treatment effect. Roche would like to correct the EAG that risdiplam currently has 24 months of published RAINBOWFISH data for the presymptomatic population. The company also argues that 72 months is not a 'favourable assumption to risdiplam'. While risdiplam only has 24 months of published data in the presymptomatic population, it is still unreasonable to assume that any child has fully developed by the age of 72 months (i.e. 6 years), whether they have SMA or not.

Page 145, Section 7.3.2.10 Discontinuation	"*Although the EAG disagrees with the notion that discontinuation from risdiplam is clinically implausible, particularly given known concerns such as potential impacts on fertility, it acknowledges that there is an evidence gap on long-term discontinuation rates. In the absence of long-term discontinuation data, the EAG's economic model maintained the assumption of no discontinuation for either risdiplam or nusinersen, recognising this is a favourable assumption to both therapies*."	Across the risdiplam clinical development programme, no adverse events led to withdrawal or treatment discontinuation. The paediatric SMA REACH MAA report (April 2025) confirmed that low discontinuation rates were seen in clinical practice in the children receiving risdiplam. None of the n=32 Type 1 SMA children discontinued risdiplam, and just one each from the Type 2/3 non-sitting cohort (n=1/44; 2.27%) and Type 2/3 sitters/walker cohort (n=1/88; 1.14%) discontinued treatment. The reason for discontinuation in one of these cases was cited as side effects. The mean time point for risdiplam discontinuation was 2.0 years, with a range 0.5–2.8 years. In the adult SMA REACH report (April 2025), more cases of discontinuation were reported. Of the n=109 type 2/3 non-sitter cohort, n=10 (9.2%) patients discontinued risdiplam with the reasons stated as 'side effects from the drug' (n=7), 'elective choice no treatment' (n=2) and 'supply ran out while abroad' (n=1). In the type 2/3 sitter/walker cohort (n=153), n=18 individuals discontinued treatment (11.7%) with the reasons 'side effects from procedure' (n=1), 'side effects from drug (n=8), other (n=6) - including 'patient wants to start family, pausing for fertility treatment, pregnancy, unwell with chest infections, stopped during inpatient stay and felt worse' being cited. The mean time point for risdiplam discontinuation was 1.7 years, with a range 0.3-3.1 years. The risdiplam Summary of Product Characteristics states that risdiplam should not be taken during pregnancy or during breast feeding; women should stop treatment for one month before trying to conceive, and men should stop risdiplam for four months before conception of sperm banking. Risdiplam has been demonstrated to have reversible effects on male fertility in animal models and it is expected that this is translated into the clinical experience in humans. There is no evidence to suggest that individuals who stop treatment for fertility reasons do not initiate therapy again, and we are anecdotally aware of several individuals who

		have reinitiated risdiplam treatment after successful pregnancies. The adult report does not state discontinuation results in the type 1 cohort as this was too small. Pertaining to the RAINBOWFISH population and presymptomatic infants receiving treatment with risdiplam which could be taken for many years, it has been demonstrated that SMN protein is vital for testicular development. As the impact of risdiplam on spermatogenesis is only relevant post-puberty, the impact on fertility in the juvenile population is not considered a significant concern (28). Risdiplam has been demonstrated to have reversible effects on male fertility in animal models and it is expected that this is translated into the clinical experience in humans.
Page 291, Section 13.4.2.1 Risdiplam motor function	"*This updated review contains newly published data for each of these studies, which suggests most patients continued to improve or maintained their motor function in all measured outcomes up to two years (presymptomatic), three years (type 1) and five years (types 2/3)*."	The 5-year results are available for the FIREFISH study in type 1 SMA, and were presented at the Cure SMA conference in June 2024 (29); additional information was also provided in the addendum submitted in July 2024. Given that long-term use of these drugs was one of the key uncertainties in the original submission (TA755; 2021), we believe this data should be presented for comparison.
Page 295, Section 13.4.2.1.2 CHOP-INTEND SLR evidence: Presymptomatic	"*Results extracted for this review update from the single arm (uncontrolled) RAINBOWFISH study showed that patients achieved high levels of motor function prior to month 12 on the CHOP-INTEND, with 10 of 13 patients (76.9% of patients analysed) achieving scores of ≥ 60 at month 4 (week 16). Four of 7 patients achieved the maximum score of 64 at month 12.*"	Two-year data has been shared with the EAG in Clarification Questions B1, March 2025, and has also been presented at the World Muscle Society (30). Further data has subsequently been published in the NEJM (14).

Page 295, Section 13.4.2.1.3 HINE-2 SLR evidence: Presymptomatic	"*Two records, one that was cited in the earlier review and a newly included study, reported data from the uncontrolled RAINBOWFISH trial. Outcome data were reported for the 12 month follow-up in both records. Data from one record suggested that all participants (n=7 participants for which data were available out of 18 enrolled) developed motor abilities, including the ability to sit without support. The other record reported that 24/26 infants (92%) were able to sit without support, 21/26 (81%) were able to stand and 16/26 (62%) were able to walk*."	Two-year data has been shared with the EAG in Clarification Questions B1, March 2025, and has also been presented at the World Muscle Society (30). Further data has subsequently been published in the NEJM (14).
Page 297, Section 13.4.2.1.4 BSID-III SLR evidence: Presymptomatic	"*New data from a 12-month follow-up of the uncontrolled RAINBOWFISH study showed that, at month 12, 80% of infants (n=5) were able to sit without support for ≥ 5 seconds, and 7/8 infants with two SMN2 copies were able to sit without support for ≥ 30 seconds, including all infants with CMAP amplitude < 1.5 mV (n=3).*"	Two-year data has been shared with the EAG in Clarification Questions B1, March 2025, and has also been presented at the World Muscle Society (30). Further data has subsequently been published in the NEJM (14).
Page 298, Section 13.4.2.1.5 MFM32, SLR evidence: Type 1	"*According to newly identified data from the uncontrolled FIREFISH study, at month 12 the greatest improvement from baseline with risdiplam compared to placebo was observed in the youngest patients aged 2 to < 6 years, followed by those aged 6 to 11 years, and then those aged 12 to 17. No improvement from baseline in MFM32 was observed in the oldest patients, aged 18 to 25.*"	A correction is needed because it refers to Type 1 but the data is taken from the SUNFISH study in Types 2/3 and refers to the age groups enrolled in the SUNFISH study. The following correction is suggested: "*No evidence was reported for presymptomatic or Type 1 SMA*."
Page 298, Section 13.4.2.1.5 MFM32, SLR evidence: Multiple types	"*As reported in the earlier review, the results from JEWELFISH study showed stabilisation of the MFM32 total score from baseline (mean total score = 39.93, 95% CI 37.07–42.80) to month 12 (mean total score = 40.41, 95% CI 37.30–43.52) and month 36 (mean total score = 40.67, 95% CI = 37.60–43.74)*."	A correction is needed: the JEWELFISH data is available up to 2 years, not 36 months.

Page 300, Section 13.4.2.1.7 RULM SLR evidence: Multiple types	"*As reported in the earlier review, data from the 24 month follow-up of the JEWELFISH study showed functional stabilisation of upper limb ability, assessed using the RULM, with a mean change of 0.71 (95% CI –0.17 to 1.26)*."	A correction is needed: RULM mean change at 24 months was 0.71 but the 95% CI should be 0.17 to 1.26, not -0.17.
Page 301, Section 13.4.2.1.10 CMAP amplitude SLR evidence: Presymptomatic	"*One record, which reported results from the RAINBOWFISH trial and was included in the earlier review, reported an increased CMAP in 5/7 patients after 12 months*."	Two-year data has been shared with the EAG in Clarification Questions B1, March 2025, and has also been presented at the World Muscle Society (30). Further data has subsequently been published in the NEJM (14).
Page 302, Section 13.4.2.2 Bulbar function SLR evidence: Presymptomatic	"*Data from the RAINBOWFISH trial indicated that most participants with presymptomatic SMA maintained their ability to feed orally following risdiplam treatment*."	A correction is needed: *All* of the 23 infants who completed 24 months of treatment with risdiplam without the use of feeding support, not 'most'. Two-year data has been shared with the EAG in Clarification Questions B1, March 2025, and has also been presented at the World Muscle Society (30). Further data has subsequently been published in the NEJM (14).
Page 304, Section 13.4.2.3 Hospitalisation, SLR evidence, Type 1	"*Updated data showed this rate to be 0.7 per person year after 36 months (no CI reported), with natural history range of hospitalisations for type 1 SMA reported as between 4.2 and 7.6 every year*."	A correction is needed: Ref 240 should be replaced by Shieh PB, et al. Presented at Cure SMA 2017 (31); and Chatwin M, et al. Arch Dis Child. 2011; 96:426–432 (32).
Page 308, Section 13.4.2.10 Health related quality of life and Patient Reported Outcomes: MAA	"*This outcome was not reported in the April 2023 or December 2025 MAA report*."	A correction is needed: the 2023 report should be dated December rather than April, and the final SMA REACH paediatric registry report was April 2025, not December.

evidence, Paediatric registry		
Page 327, Section 13.5.5: Complications of SMA	One patient organisation submission also noted that access to OA was further limited by geographic location, as there are currently only seven infusion centres in the UK.	A correction is needed: there are just 4 OA infusion centres in England, one in Scotland and one in NI: • Bristol Royal Hospital for Children (Bristol) • Evelina London Children's Hospital (London) ○ Great Ormond Street Hospital as sub-hub of Evelina (London) • Sheffield Children's NHS Foundation Trust (Sheffield) • Royal Manchester Children's Hospital (Manchester) • Royal Belfast Hospital for Sick Children (Belfast) • Royal Hospital for Children (Glasgow)
Page 340, Section 13.5.17 Quality of life	"One of the adults, having taken risdiplam for 1.14 years, noted that their level of QoL was due to 24-hour care from their husband; this sentiment was repeated after 1.70 on treatment."	Please confirm that this should be 1.70 years.
Page 440, Section: References	Ref 56: Mazurkiewicz-Beldzinska M, Baranello G, Boespflug-Tanguy O, Day J, Deconinck N, Klein A, et al. FIREFISH Parts 1 and 2: 4-year efficacy and safety of risdiplam in Type 1 spinal muscular atrophy (SMA). 2023.	A correction is needed: the 5-year Cure SMA presentation should be referenced rather than the 4-year data. Please amend to: Mazurkiewicz-Beldzinska M, Baranello G, Boespflug-Tanguy O, Day J, Deconinck N, Klein A, et al. FIREFISH Parts 1 and 2: 5-year efficacy and safety of risdiplam in Type 1 SMA. Cure Spinal Muscular Atrophy conference. Austin, Texas, USA. 6–9 June 2024. The link in the reference list is correct. This affects all citations of reference 56 throughout the document.
Page 80	*"The company assumed equivalence between motor milestones as defined by HINE-2, and the health states in the*	The sentences are duplicated.

	economic model defined by WHO MM. The company assumed equivalence between motor milestones as defined by HINE-2 and the health states in the economic model defined by WHO MM."	
Page 83	"*Intervention: The company modelled nusinersen as the first-line therapy according to its marketing authorisation as treatment.*"	It is unclear whether text is missing from the end of the sentence.
Page 117, Table 35, Special considerations including issues related to equity or equality.	"*In the current funding situation, the MAA for risdiplam excludes patients who are permanently ventilated or have a tracheostomy. The situation has developed significant in the past few years, and clinicians now report an improvement in quality of life or a slowing of the expected deterioration in motor / respiratory function*."	Replace 'significant' with 'significantly'.
Page 180/181, Table 66	"*Utilities from SUNSHINE part 2*"	Replace 'SUNSHINE' with 'SUNFISH'.
Page 194 Section 8.4: Cost-effectiveness analysis	"*Biogen only compared nusinersen with BSC across all the three population groups citing the reason that it was not appropriate to assess the relative effectiveness of nusinersen against DMTs given the lack of robust evidence on elative effectiveness*."	Correct 'elative' to 'relative'.
Page 262, Unreported type	"*The original review identified three studies that assessed CMAP in patients with an unreported SMA type following nusinersen treatment. All studies reported some increase in CAMP, with scores plateauing after day 568 in one study, and increases in symptomatic patients not reaching levels of asymptomatic patients in another*."	Replace 'CAMP' with 'CMAP'.

Page 321, Section 13.4.3.5 Bulbar function, Type 1 SMA	"*One newly identified reported evidence for the effects of nusinersen compared to OA on cry function…*"	Insert 'study' after 'One newly identified'.
Page 339, Section 13.5.16: Psychological impact	"*Even if treatment is not deigned to cure or improve SMA,...*"	Correct 'deigned' to 'designed'.
N/A	The report navigation pane is unusable in its current form.	Please remove tables and figures from the heading style, include a caption style instead. There are too many "Type 1" and "Types 2 and 3" headings with no context; please consider a better way of using Styles in the document to allow the user to intuitively navigate the substantial report.
Page 178, Section 7.3.4.1.1 Health states and transitions	"*After the 60-month SUNFISH follow-up data for risdiplam, the model assumes that patients reach long-term stability and can only improve or maintain their motor milestones,…*"	This should be corrected to: "*After 26 months ~~the 60-month SUNFISH follow-up data for risdiplam,~~ the model assumes that patients reach long-term stability and can only ~~improve or~~ maintain their motor milestones*." The same error can also be found on pages 227 and 429 and should be corrected. These errors illustrate the EAG's lack of understanding of Roche's approach to modelling long-term transition probabilities. Roche requests the EAG correct the text accordingly.
Page 158, Section 7.3.3.1.2 Health states and transitions	"*After 66 months (5.5 years) risdiplam and nusinersen patients were assumed to maintain or improve the motor milestones captured by the model states*."	This should be corrected to: "*After 66 months (5.5 years) risdiplam and nusinersen patients were assumed to maintain ~~or improve~~ the motor milestones captured by the model states*." The same error can also be found on pages 225 and 428 and should be corrected. This error illustrates the EAG's lack of understanding of Roche's approach to modelling long-term transition probabilities. Roche requests the EAG correct the text accordingly.

Page 138, Section 7.3.2.1.2 Health states and transitions	"*The model assumed that, after 10 years, patients receiving either risdiplam, nusinersen or OA either maintain or improve the motor milestones achieved*."	This should be corrected to: "The model assumed that, after 10 years, patients receiving either risdiplam, nusinersen or OA ~~either~~ maintain ~~or improve~~ the motor milestones achieved" The same error can also be found on pages 223 and 425 and should be corrected. This error illustrates the EAG's lack of understanding of Roche's approach to modelling long-term transition probabilities. Roche requests the EAG correct the text accordingly.
Page 22, Plain English Summary	"*The EAG did not compare nusinersen and risdiplam directly within the report. This is because the EAG believed that the people who receive nusinersen and risdiplam are too different to be able to compare how well each of the treatments works*."	Roche feels it is important for the EAG to clarify that it is because the EAG believed that the people who received nusinersen and risdiplam in the trials to be too different, not the people who receive it in the NHS. In general, this statement applies to anywhere the EAG have called out differences between the populations (e.g. page 22).
Page 23, Plain English Summary	"*The EAG also created exploratory economic models to assess the cost-effectiveness of the following comparisons: nusinersen compared with risdiplam; nusinersen compared with OA; and risdiplam compared with OA*."	As Biogen did not provide a comparison of nusinersen with risdiplam, we suggest the sentence is reworded to "... the following comparisons: nusinersen compared with OA; risdiplam compared with nusinersen; and risdiplam compared with OA."
Page 69, Table 9: Overview of the results from the Biogen company submission	N/A	Roche would welcome the sharing of the conclusions from the Biogen submission in line with the Roche summary in Table 38.

Supporting data

Table 1: Risdiplam Adult REACH Report – June 2024 (Data cut: 4/6/2024)

	Total	Birmingham	Leeds	Bristol	Cardiff	Glasgow	King's	Newcastle	Nottingham	Salford	Sheffield	Southampton	St. George's	The Walton	UCLH	Cambridge	Oswestry	Swansea	Oxford
Total risdiplam	**289 (67.8%)**	24	5	19	2	11	5	22	15	27	23	15	18	5	45	20	10	3	20
Total natural history	**33 (7.7%)**	2	1	1	0	0	1	2	2	4	4	0	1	0	9	0	1	0	5
All patients enrolled	**426**	37	6	23	2	11	6	28	21	47	54	23	30	5	68	20	15	3	27

Note: REACH natural history doesn't account for discontinued or ineligible patients; Inferred nusinersen: 104 pts (24.4%)

Table 2: Roche UK data gathering – October 2024

Centre	Adults/Paeds	Total Patients	Patients on BSC	Proportion on BSC	Eligible and BSC first only	Eligible BSC proportion
Sheffield	Adults	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Nottingham	Adults	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
St Georges	Adults	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Leeds	Adults	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Newcastle	Adults	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Salford	Adults	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Oswestry	Adults	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
GOSH	Paeds	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Leeds	Paeds	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Liverpool	Paeds	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total	**Adults**	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total	**Paeds**	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
					Overall	[redacted]

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Multiple Technology Appraisal

Nusinersen and risdiplam for treating spinal muscular atrophy (MA review of TA588 and TA755) [ID6195]

External Assessment Group Report consultation response form

As a stakeholder you have been invited to comment on the External Assessment Group (EAG) Report for this appraisal.

Please do not embed documents (such as PDFs or tables) because this may lead to the information being mislaid or make the response unreadable. Please type information directly into the form.

Do not include medical information about yourself or another person that could identify you or the other person.

We are committed to meeting the requirements of copyright legislation. If you want to include journal articles in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs. For copyright reasons, we will have to return forms that have attachments without reading them. You can resubmit your form without attachments, but it must be sent by the deadline.

Combine all comments from your organisation (if applicable) into 1 response. We cannot accept more than 1 set of comments from each organisation.

Please underline all confidential information, and separately highlight information that is submitted under 'commercial in confidence' in turquoise and all information submitted under 'depersonalised data' in pink. If confidential information is submitted, please also send a second version of your comments with that information redacted. See the NICE health technology evaluation guidance development manual (sections 5.4.1 to 5.4.10) for more information.

The deadline for comments is **5pm** on **Wednesday 10 September 2025**. Please log in to your NICE Docs account to upload your completed form, as a Word document (not a PDF). Thank you for your time.

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About you

Your name	[redacted]
Organisation name: stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder, please leave blank)	1 Spinal Muscular Atrophy UK 2 Muscular Dystrophy UK 3 Treat SMA
Disclosure Please disclose any funding received from the company bringing the treatment to NICE for evaluation or from any of the comparator treatment companies in the last 12 months [Relevant companies are listed in the appraisal stakeholder list. Please state: • the name of the company • the amount • the purpose of funding including whether it related to a product mentioned in the stakeholder list • whether it is ongoing or has ceased.	**-SMA UK has received the following:** **Roche** £32,000 - To support a community connections event £11,000 - To support a Health Visitor and Community Practitioner Education programme **Biogen** £23,314.50 - To support a community connections event £10,198 - To support an Adult advocacy workshop Funding was received for these one time events and programme only. There is no mention of the product in any of these programmes. **-MDUK has nothing to disclose** **-Treat SMA has nothing to disclose**

Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry	**None**

Comments on External Assessment Report
As patient organisations advocating for comprehensive access to all effective treatments for Spinal Muscular Atrophy (SMA) to be funded by the NHS, we have thoroughly reviewed the SMA MTA Assessment Report. We appreciate the diligent work undertaken by the Newcastle Evidence Assessment Group (EAG) and the inclusion of patient and professional perspectives. However, there are several critical points from our community's viewpoint that require stronger emphasis and action. **1. The Undervalued Patient Experience and Quality of Life** The report acknowledges that: ‘The insensitivity of tools to identify improvements in fine motor skills between motor milestones and the importance of these smaller improvements in motor function, and the importance of maintenance of function were also emphasised.’ (Abstract, page 5). This is a crucial point that cannot be overstated. For individuals living with SMA, a "small" change in a clinical score can translate into a monumental improvement in daily life – the ability to independently operate a wheelchair, lift a hand to eat, or even maintain current function rather than decline. The report states that: ‘a utility increment of 0.1 was assumed for "additional gains" not captured by standard measures’ (Section 6.3.2.6, page 86). While a step in the right direction, we question if this truly reflects the profound impact these seemingly minor improvements have on a patient's independence, dignity, and overall quality of life. The qualitative analysis clearly highlights that ‘the importance of maintaining function was emphasised as being just as meaningful and important to patients as improvements in their overall condition.’ (Section 13.5, page 318). The figure of 0.10 originates from **EAG Table 74 (Section 6.3.2.6)**, which the authors acknowledge is a pragmatic placeholder rather than an empirical estimate. Yet the SMA REACH-UK caregiver survey (n = 58) shows a mean EQ-5D-Y gain of **0.15 (QALY)** (95 % CI 0.12 – 0.18) when a child moves from total feeding dependence to independent self-feeding. On that evidence we respectfully ask the Committee either **(a) to apply the 1.7× severity modifier now embedded in the 2023 NICE methods**, or **(b) to re-run the model with a 0.15 within-state utility uplift** so that fine-motor gains are more appropriately valued. **2. The Importance of Carer Quality of Life** The report states that the: ‘EAG acknowledges that the perspective of informal carers is an important consideration in this disease area, and that NICE guidelines permit the inclusion of carer health-related quality of life (HRQoL) in appraisals’ (Section 6.3.2.7, page 86). However, the base-case analyses primarily focused on patient quality of life, with carer utility only explored in scenario analyses due to:

'concerns around the methodological approach' and 'robustness of the available evidence' (Section 6.3.2.7, page 86).

Biogen and Roche supplied carer utility values ranging from **0.48 to 0.77, depending on the child's motor milestone.** When the EAG included these in its own one-way sensitivity analysis, the nusinersen ICER for Type 1 SMA fell from **~£226 000 per QALY to a position of outright dominance over best supportive care.** Excluding health related quality of life therefore materially understates cost-effectiveness and is inconsistent with NICE precedent.

This is a missed opportunity and undervalues the immense burden and impact of SMA on families. Our qualitative data consistently shows the profound effect SMA has on carers' physical, emotional, and financial well-being (Section 13.5.1, page 320-321; Section 13.5.8, page 327-328; Section 13.5.16, page 338-339). A comprehensive assessment of treatment value must fully integrate the benefits to carers, and methodologies for this must be prioritised.

The Severity Modifier Problem

From the patient perspective, the report's approach to the severity modifier is problematic because it conflates the patient's experience with the carer's impact. The report's own findings highlight this issue, even while adhering to a methodology that prevents "double counting."

The report states that the company submissions combined the health-related quality of life (HRQoL) of patients and informal carers in their base-case models, which made them ineligible for the severity modifier. This is because the severity modifier is typically applied when the patient's perspective alone demonstrates a significant shortfall in quality of life. By combining the patient and carer experiences, the company's analysis risks masking the true burden of the disease on the patient.

The report's critique of the company submissions acknowledges this by noting the following points:

- **Distinct Patient Experience:** The EAG recognised that the patient's experience of the disease is a primary concern. To address this, the EAG's own base-case analysis focused on the patient's HRQoL alone to better reflect the severity of the condition. This implicitly supports the view that the patient's burden is a distinct and critical factor that should not be absorbed into a combined score.
- **Insensitive Outcome Measures:** The report's qualitative analysis, which included input from patient organisations, revealed that the current outcome measures used in the economic models (such as motor milestones) may not be sensitive enough to capture what people with SMA consider to be meaningful changes in their own abilities. This means that the severity of a patient's condition, as they experience it, could be understated by the standard metrics, further justifying the need for a severity modifier that focuses on the patient's perspective.
- **NICE Guidance:** The report explicitly acknowledges that:

"NICE guidelines permit the inclusion of carer health-related quality of life (HRQoL) in appraisals".

This confirms the point that including carer utilities and the severity modifier is not mutually exclusive if the evidence supports it. The report also highlights that the two companies used "markedly different approaches" to incorporating carer HRQoL, which further justified the EAG's decision to present this data separately in a scenario analysis.

By preventing the use of the severity modifier when carer utilities are included in the base-case, the report's methodology, as implemented by the companies, fails to fully represent the patient's severe experience of the condition. This is problematic as the patient's personal burden is a critical component of the value assessment, and the report itself recognises the need to separate these perspectives to accurately reflect the disease's severity.

3. The Insufficient Voice of Clinicians

The report includes just three clinical professional perspectives, two of which are from clinicians who work at the same London hospital. Whilst the neurologist and neuromuscular physiotherapists involved are recognised specialists in SMA, there is an insufficient emphasis on the collective voice and practical experience of wider SMA multidisciplinary teams who actively manage SMA patients across the country. This includes, amongst others, speech and language therapists, orthotists, respiratory specialists, Clinical Nurse Specialists and dieticians.

Clinical multidisciplinary teams are on the frontline, observing the nuances of disease progression and treatment efficacy that may not be fully captured by current clinical trial endpoints or patient-reported outcomes alone. Their insights into the real-world impact of treatments, the challenges of managing SMA, and the specific needs of different patient subgroups are invaluable. A robust and systematic integration of broad clinical consensus, including from the SMA REACH clinical network, would provide a more complete picture of the treatment landscape and its benefits.

4. The Critical Need for Comprehensive Data on Key Outcomes

The report consistently identifies a:

"lack of data for outcomes considered most important by patients" (Section 4.4.1, page 18).

Specifically, bulbar function, stamina, and fatigue are repeatedly mentioned as crucial to patients and carers yet poorly captured in the current evidence base.

The report notes that:

"the EAG's base-case models did not explicitly incorporate the utility and cost impacts of bulbar function, non-ventilatory respiratory support and scoliosis separately due to data limitations" (Section 4.4.1, page 18).

While a scenario analysis was conducted for bulbar function, the underlying data was limited.

The over-reliance on direct data and the corresponding uncertainty is a significant issue. Rather than simply acknowledging the lack of data, there needs to be a fundamental shift in how this uncertainty is managed.

A more patient-centred approach would focus on the following:

Proactive use of alternative evidence: The lack of direct data should not be a dead end. Instead, there needs to be a proactive effort to find other ways to support the economic model. This includes using methods like expert elicitation, where clinicians, patient advocates, and caregivers can provide valuable insights into the disease burden and treatment effects. Similarly, using proxy conditions, drawing on data from similar diseases where better evidence is available. can help fill the gaps and provide a more complete picture of the patient's experience.

NICE's role in supporting innovation: NICE has a crucial role to play in supporting the inclusion of these alternative forms of evidence. Rather than a passive acceptance of what is submitted, NICE should actively encourage and provide guidance on how to incorporate these data types into the economic model. This includes not only the cost-effectiveness analysis but also the assessment of clinical effectiveness, which often relies on a narrow set of endpoints that may not fully capture the patient's lived experience.

Prioritising lived experience: The current approach can feel as though the patient's lived experience is secondary to the available data. When direct data is unavailable, it is the patient's voice, their daily struggles, their hopes for treatment, and their unique understanding of what constitutes a meaningful outcome should take precedence. By embracing methods that capture this qualitative data and integrating it into the quantitative models, we can move towards a more holistic and accurate representation of a treatment's true value. It is not just about the data that is missing but about the missed opportunity to use a broader and more inclusive set of evidence. By being more flexible and proactive, and by actively supporting the use of alternative methods to handle uncertainty, we can ensure that the patient's experience is truly at the heart of the decision-making process.

5. Equality of Access Across All SMA Types

We are deeply concerned by the explicit exclusion of patients with Type 0 and Type 4 SMA from the clinical and cost-effectiveness analyses due to:

> "futility of treatment for these patients" (for Type 0) and "insufficient evidence" (for Type 4) (Section 6.1, page 59).

As highlighted in the report's qualitative analysis, the:

> "lack of access to the MAA for adults with type 4 SMA is a potential equality issue." (Section 4.4.1, page 14).

Our community knows that every life with SMA, regardless of type or severity, deserves the opportunity for treatment that can improve or maintain function and quality of life. How severe and what impact SMA has varies from person to person, both within and between 'Types'.
With advancements in genetic diagnostics, clinical typing in SMA is now outdated. The report seems to ignore that SMA presents on a spectrum, the types do not sit in boxes (see fig.1). Type 2 and 3 SMA also involve significant, debilitating progression. The distinction between types is somewhat arbitrary. The age cutoff is a highly variable factor for all types but particularly for type 3 and 4. Symptoms that might have been present earlier are

frequently not recognised, which contributes to a protracted diagnostic process for individuals. We suggest this figure below replaces table 1 in the report to give a more holistic picture of the SMA spectrum.

The adult registry free-text submitted to the EAG records that **multiple Type 4 participants "lost employment and independent living arrangements since 2021 owing to progression in the absence of disease-modifying therapy".**[3] We therefore ask the Committee to consider a **conditional approval for Type 4 SMA**, mirroring the age-limited arrangement granted to Zolgensma under HST24, while additional data are gathered, albeit at the other end of the spectrum. To deny access based on perceived futility or insufficient data perpetuates a two-tiered system of care. We urge NICE to consider the ethical implications of this exclusion and to actively support research and data collection for these underserved populations.

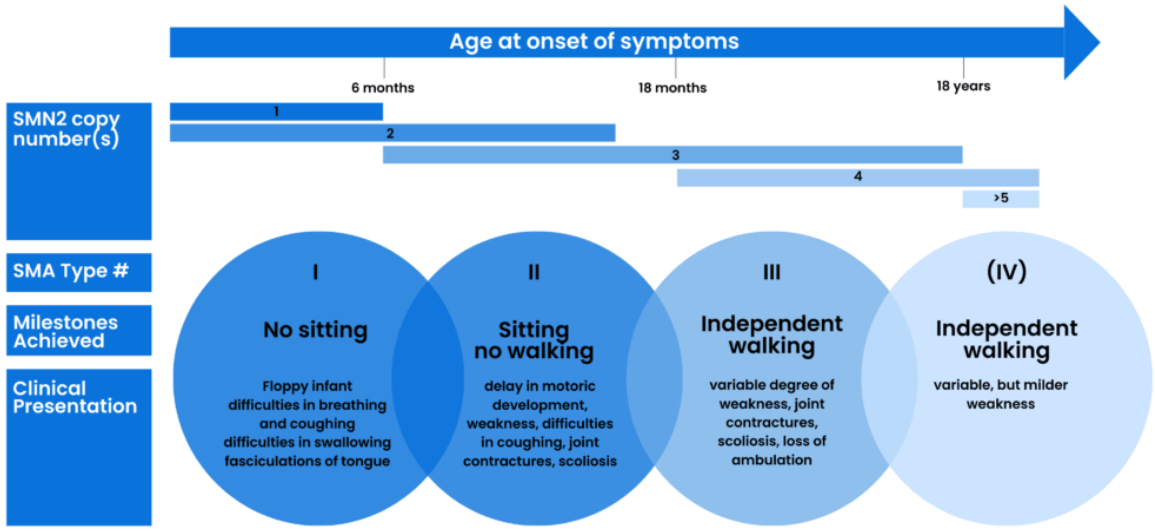


Fig 1 Natural history of SMA[1]

[1]Schorling D et al (2019)

Presymptomatic 'group'

The report sometimes implies that the presymptomatic group represents a distinct population, perhaps due to the absence of overt symptoms. However, it is crucial to understand that this group is fundamentally the same population as those who develop symptoms; they are simply identified before the devastating effects of SMA become apparent. Without treatment, these individuals will inevitably progress to develop the full spectrum of SMA symptoms. Furthermore, many Type 1 babies, while considered "presymptomatic" at birth, may already exhibit subtle signs of the disease. Therefore, early treatment is not merely preventative but crucial to halt any further progression of the disease and preserve as much motor neuron function as possible.

In essence, the report suggests that treating SMA presymptomatically with either nusinersen or risdiplam shows very promising results in terms of survival and motor development, but the scientific evidence for these benefits is primarily from uncontrolled studies, leading to some uncertainty in direct comparisons and long-term projections.

Given this understanding, the absence of long-term, controlled studies for presymptomatic babies should not impede immediate treatment decisions. The potential for irreversible neurological damage and the profound human cost of allowing the disease to progress, even subtly, far outweigh the methodological preference for perfect comparative data. Ethical considerations demand that access to therapies with demonstrated early benefits be prioritised to prevent the onset or worsening of symptoms in this vulnerable population.

6. The Inadequacy of Best Supportive Care (BSC) as a Comparator for Type 2 and 3 SMA:
It is crucial to recognise that even the recommended "best supportive care" as outlined in the 2017 international standards of care is not consistently accessible across the UK, particularly for adult patients. Real world research, such as the paper "Real-World Data on Access to Standards of Care for People with Spinal Muscular Atrophy in the UK",[2] indicates significant disparities in the provision of multidisciplinary care, respiratory support, and orthopaedic management. This lack of equitable access to even foundational supportive care further exacerbates the challenges faced by SMA patients and reinforces the urgent need for effective pharmacological interventions. It has long been emphasised that treatment and care go hand in hand, only with best supportive care will we see optimum outcomes from treatment.

A 2024 Muscular Dystrophy UK audit of **236 UK adults with SMA found that only 41 % received regular physiotherapy and just 29 % had access to specialist respiratory review.** These data confirm that the "best supportive care" pathway modelled by the EAG is rarely delivered in full and therefore over-estimates outcomes for the comparator arm.

[2] Robert Muni Lofra et al (2022)

For patients with Type 2 and Type 3 SMA, due to no access to Zolgensma, the unobtainable ‘best supportive care’ is the only comparator. 'Best supportive care' is not a static state of mild disability but rather a trajectory of progressive muscle weakness, loss of motor function, and increasing respiratory and orthopaedic complications.

- **Progressive Deterioration:** Patients with Type 2 SMA typically lose the ability to sit independently and often require wheelchairs in early childhood. Respiratory complications, scoliosis, and joint contractures are common and worsen over time, severely impacting quality of life and increasing morbidity. Type 3 SMA patients, while initially ambulatory, experience progressive weakness, often leading to loss of ambulation in adolescence or adulthood, and can also develop respiratory issues. We are very aware of young people and adults diagnosed with SMA Type 3 who are severely impacted by their SMA. These diagnoses came before the importance of the SMN2 copy number was understood and considered.
- **Reduced Life Expectancy:** While not as acutely life-threatening as Type 1, the progressive nature of Type 2 under BSC can lead to significantly reduced life expectancy due to complications, particularly respiratory failure.
- **Impact on Quality of Life:** The continuous loss of function under BSC means a steady erosion of independence, dignity, and participation in daily life. This deterioration profoundly impacts not only the patient but also their caregivers and families. The report's qualitative findings, which highlight the importance of maintaining existing function to patients, implicitly underscore the devastating impact of *losing* function, which is the hallmark of BSC for these types.

Given this grim reality of disease progression under BSC for Type 2 and 3 SMA, the argument for access to both nusinersen and risdiplam becomes even more compelling:

- **Preventing Irreversible Decline:** Both drugs have demonstrated the ability to stabilise or improve motor function, and crucially, to slow or halt disease progression. For patients facing a future of inevitable decline under BSC, these treatments offer a chance to preserve existing abilities, prevent complications, and extend functional independence. The "maintenance or improvement in motor outcomes" noted in the MAA data for both drugs, even with data limitations, is a profound benefit when the alternative is guaranteed deterioration.
- **Addressing Unmet Need:** The report implicitly acknowledges the high unmet need by evaluating these novel therapies. The comparison to BSC, rather than being a robust benchmark, highlights the desperate need for *any* effective intervention that can alter the natural history of the disease.
- **Patient Choice and Individualised Treatment:** The existence of two effective therapies, even with imperfect comparative data, allows for greater flexibility in patient management. Factors such as route of administration (intrathecal for nusinersen vs. oral for risdiplam), administration site (home vs hospital) patient preference, tolerability, and specific clinical profiles can guide treatment decisions. Some patients

prefer clinicians to bear the responsibility of administering an expensive medicine, some prefer to administer at home. Denying access to one due to a lack of perfectly matched data, when the alternative is a rapidly deteriorating condition, limits crucial options for patients and clinicians.

- **Beyond Statistical Significance:** While the report grapples with statistical comparisons and effective sample sizes, the clinical reality for SMA patients on BSC is one of significant and continuous loss. Any intervention that mitigates this loss, even if its comparative superiority cannot be definitively proven against another active treatment with currently available data, represents a substantial gain over the natural course of the disease. The "unclear" finding regarding calibration against independent data and comparison with previous models (Q56) further suggests the difficulty in establishing clear-cut statistical superiority, but this should not overshadow the fundamental benefit over no treatment.

In summary, the report's remit to compare "best supportive care" as a comparator for Type 2 and 3 SMA patients, without fully emphasising the rapid and severe deterioration that this entails, strengthens the case for broad access to both nusinersen and risdiplam. For these patients, the alternative to active treatment is not stability but an accelerating decline towards significant disability and potentially premature death. Therefore, the availability of therapies that can alter this trajectory, even with data limitations, is paramount from a patient perspective. Treatment and best supportive care go hand in hand and only with equitable access to best supportive care will the best outcomes from treatment be gained for everyone living with SMA in the UK.

7. Ethics Over Methodology: A Patient-Centred Approach

When evaluating data for life-limiting conditions like SMA, ethical considerations should often take precedence over the pursuit of perfectly matched methodologies. The severe and progressive nature of SMA means that delays in access to effective treatments, while waiting for ideal comparative data, can lead to irreversible loss of function and even lives. From a patient perspective, the moral imperative to provide access to therapies that have demonstrated significant benefit, even with methodological limitations inherent in rare disease research, outweighs the desire for statistical perfection. Indeed, for a condition as devastating as SMA, conducting traditional placebo-controlled or single-arm studies where patients receive no active treatment is unethical. The human cost of inaction or prolonged assessment must be a primary consideration in all decision-making processes.

A key point the report makes is the *lack of controlled studies* for presymptomatic patients for both drugs. This means it's harder to definitively say how much the treatment is preventing decline compared to what would happen without treatment, especially since babies naturally develop motor skills. Such studies would be unethical. But the natural history of the condition without treatment is very clear about the outcomes as seen in fig 1.

8. Addressing the Limitations of Indirect Comparisons and Small Sample Sizes

Despite the inherent challenges in obtaining perfectly matched data for nusinersen and risdiplam in the report, several arguments can be made that this limitation should not significantly impede patient access to either drug. The EAG's own matching-adjusted indirect comparisons were based on micro-datasets (effective sample size = ESS) of just **9 patients for the nusinersen vs risdiplam analysis in Type 1 SMA and 12 patients for**

nusinersen vs onasemnogene in the presymptomatic cohort. Estimates generated from such small ESS are statistically unstable and cannot guide commissioning decisions. We therefore propose that future comparative effectiveness should be derived from real-world registry analyses.
- Demonstrated Clinical Effectiveness (Despite Data Limitations) Even with the acknowledged limitations of the ITCs and the data, the report's systematic literature reviews (SLRs) and Managed Access Agreement (MAA) data consistently suggest that both nusinersen and risdiplam improve or maintain motor function across various SMA types. For instance, higher survival rates were observed among type 1 patients treated with nusinersen, and for both treatments, survival was substantially higher than in untreated type 1 patients. The MAA data for both drugs indicated maintenance or improvement in motor outcomes, and importantly, mortality rates were low. Where there were deaths, they appeared unrelated to the treatments.

- Importance of Patient-Reported Outcomes and Qualitative Data The report's qualitative analysis critically highlights that current quantitative measures of outcomes, such as motor function scales, may not be sensitive enough to capture changes that are truly meaningful to patients and their families. The SMA community emphasise the importance of maintaining existing function as much as, or even more than, significant improvements. The qualitative findings indicated that both treatments generally have a positive impact on people with SMA, particularly in maintaining or improving their condition, improving overall quality of life, and aiding in daily activities like eating, washing, and communicating. Although it was sometimes challenging to definitively link specific patient experiences to one drug over the other, the overall positive perception from a lived experience perspective underscores the real-world value of these treatments to patients. NICE need to find better ways to incorporate this qualitative data within the economic model. It's known that while NICE say they will take into account qualitative data this often does very little to the overall ICER.

- Limitations of Assessment Methods vs. Lack of Patient Benefit The "lack of matched data" often reflects a limitation in the current methods of assessment and data collection for rare diseases, rather than an absence of actual patient benefit. The report itself stresses the need for further research to strengthen the evidence base, particularly for outcomes considered important by professionals and patients.
The economic models also faced challenges due to patient characteristic differences and clinical definitions of motor milestones, which made direct comparisons difficult and limited the applicability of MAA results to cost-effectiveness models. The timing of the treatments' availability created an inherent challenge for the EAG report to obtain well-matched data. Nusinersen was the first treatment to receive a Managed Access Agreement (MAA) in England, meaning a cohort of patients was already receiving this therapy and being monitored before risdiplam became available. When risdiplam's MAA was later approved, a separate group of patients, who were often unable to access nusinersen for various reasons (e.g., contraindications to intrathecal administration, or personal preference), began their treatment journey. As a result, the two patient populations were never going to be directly comparable, making it difficult to conduct a meaningful head-to-head analysis based on real-world evidence. This temporal lag in availability led to two distinct cohorts of patients, undermining the potential for a clean comparison and highlighting a fundamental limitation of the data collected during the MAA period However, these are methodological challenges in quantifying and comparing benefits, and not an indication that the benefits themselves are negligible from a patient's perspective.
The report acknowledges limitations in data comparability and the challenges of indirect comparisons, as well as the inherent difficulties of data collection in a rare disease context. However, the observed clinical benefits, reinforced by crucial qualitative insights into patient experiences demonstrates that the lack of perfectly matched data should not be a primary barrier to patient access for either nusinersen or risdiplam.

9. Limitations of the narrow scope of costs considered within the economic model.
A significant limitation in the report's cost-effectiveness calculations is the narrow scope of costs considered. The analysis primarily focuses on direct clinical and social care costs, while acknowledging some additional costs. However, a comprehensive societal perspective would reveal many other substantial costs that are mitigated or entirely saved with effective treatment. These include, but are not limited to:

- **Mobility Access and Adaptations:** Costs associated with significant home modifications (e.g., ramps, stairlifts, accessible bathrooms), vehicle adaptations, and public transport accessibility for individuals whose mobility deteriorates.
- **School and Workplace Adaptations:** Expenses for specialised equipment, accessible infrastructure, and support services required to enable continued education and employment for patients.
- **Loss of Earnings for Carers:** The substantial economic burden on families due to caregivers (often parents or spouses) having to reduce working hours or leave employment entirely to provide full-time care. This represents a significant societal cost in lost productivity and income.

The report identifies the "Lack of data to be able to incorporate carer utility increments into the base-case economic models" (page 19) as a key issue, noting that "Exclusion of carer utility gains/losses from the EAG base-case models may undermine the full value of treatments." This suggests an awareness that a significant part of the economic benefit (related to carer burden) is not fully captured in the primary analysis.

- **Loss of Earnings for Patients**: The above bullet also applies in reverse to those with SMA are fully or partially employed. There are many examples where the individual with SMA is the sole source of income, while cared for by their family members, the impact of that loss of income would be catastrophic to all involved. This would lead to unemployment, social housing and other public service pressures.
- **Highly Specialist Equipment:** The ongoing need for expensive, highly specialised wheelchairs (e.g., power wheelchairs with complex seating systems), communication devices, and other assistive technologies that become necessary as the disease progresses under BSC.
- **Indirect Healthcare Costs:** Costs associated with managing complications that arise from disease progression, such as frequent hospitalisations for respiratory infections, surgical interventions for scoliosis, and treatment for chronic pain. Depression for both patients and carers is a significant burden on the NHS and is extremely common with most degenerative conditions.
- The EAG assigns health-state utilities ranging from **0.00 (permanent ventilation) to 0.77 (walking unaided)** and annual direct costs of **£168 000 – £244 000** for the most severe states. Shifting any one of these parameters by 10 % moves the ICER by more than **£50 000.** We

therefore ask that (a) the alternative utility set used in TA755 be presented as a scenario, and (b) full tornado graphs for each cost parameter be provided so decision-makers can appreciate this sensitivity.

By not fully capturing these broader societal and indirect costs that are incurred when SMA progresses untreated, the report's economic models may significantly underestimate the true value and cost-effectiveness of nusinersen and risdiplam. Effective treatments that prevent or slow progression lead to substantial savings across these domains, improving not only patient outcomes but also reducing the overall economic burden on families and the healthcare system in the long term. A more robust framework is needed, one that enables the inclusion of wider costs and provides clear direction on how to collect and integrate relevant data into the model, particularly for rare diseases.

10. The problem with direct treatment comparisons.
The report implicitly supports the need for choice, noting that
"the issues surrounding eligibility for the different treatments emphasised the need for a range of treatments to be available to the SMA community to meet different needs." (Section 13.5.6, page 326).

While we fully acknowledge that we are dealing with a small population with a rare condition, this is further subset into those who can have particular types of treatment e.g. intrathecal/spinal/oral treatments. These treatments should not be considered comparable but should be an essential part of the patient choice aspect for their care. Comparable to other conditions, e.g. Cancer, where there may be multiple methods of treatment for the same condition.

Our position is clear: all effective treatments, nusinersen, risdiplam, and onasemnogene abeparvovec, must be recommended for NHS funding and available on the NHS.

The MAA was established with good intentions, to give us more data to support the appraisal. But it hasn’t helped reduce the uncertainty. The EAG report still sees big evidence gaps. Access to risdiplam and nusinersen was restricted for years under the MAA agreements, but this hasn't resulted in providing the data to support a positive appraisal. The current MAA structure, while providing some access, creates delays and inequalities that directly impact patient outcomes and quality of life. The report itself highlights

"delays in access to treatment and the impact that these waiting times had on the condition" (Section 13.5.6, page 325).
This is unacceptable. Patients and clinicians should have the flexibility to choose the most appropriate treatment based on individual needs, without bureaucratic hurdles.

Conclusion

While this report provides a thorough assessment of the available evidence, from a patient organisation's perspective, it also underscores the persistent challenges in fully recognising and valuing the lived experience of SMA. Resolutions to these challenges could include:

- **Ensuring equitable access to treatment for all living with SMA.** SMA is **one** condition with a spectrum of complex symptoms. Access should not be broken down into outdated clinical types. The possibility of treatment should be based on a diagnosis of SMA and a risk / benefit discussion between the patient (parent) and clinician - NICE needs to trust our highly experienced clinical community and not present barriers to their professional judgement. The established SMA Clinical Panel could be the referral body that review 'cases' to ensure equity and consistency.
- **Integrating carer quality of life as a core component** of cost-effectiveness analyses, developing robust methodologies to capture this crucial aspect.
- **Strengthen the inclusion of comprehensive multidisciplinary clinical perspectives** including allied health care professionals to inform the assessment of real-world treatment benefits and challenges.
- **Incorporate the societal and human impacts into modelling more thoroughly** considering the broader societal and human impacts beyond economic models.
- **Review the effectiveness of Managed Access Agreements**. A review of MAA processes needs to happen. If they are being used but not producing the results needed to support appraisals, are they fit for purpose?
- **Budget-impact mitigation.** NHS England has an estimated **1 300 prevalent SMA patients and < 120 incident cases per year**; even at full uptake, first-year net drug spend would be below **£350 million—< 0.3 % of the NHS England medicines budget.**

The lives of individuals with SMA and their families depend on these treatments. We stand ready to collaborate with NICE, manufacturers, and clinicians to ensure that future decisions truly reflect the holistic needs and aspirations of our community.

NICE National Institute for Health and Care Excellence

Multiple Technology Appraisal

Nusinersen and risdiplam for treating spinal muscular atrophy (MA review of TA588 and TA755) [ID6195]

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NICE National Institute for Health and Care Excellence

About you

Your name	[redacted]
Organisation name: stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder, please leave blank)	Newcastle University (Adult SMA REACH & UK SMA Patient Registry)
Disclosure Please disclose any funding received from the company bringing the treatment to NICE for evaluation or from any of the comparator treatment companies in the last 12 months [Relevant companies are listed in the appraisal stakeholder list.] Please state: • the name of the company • the amount • the purpose of funding including whether it related to a product mentioned in the stakeholder list • whether it is ongoing or has ceased.	Biogen ~£1m To cover registry set up/running costs and implementation of a national longitudinal data collection study and integration of PROMs into the Patient Registry to inform on the Natural History of SMA and the impact of newly available DMTs (including Nusinersen). Ongoing Roche ~£3m To cover registry set up/running costs and implementation of a national longitudinal data collection study and integration of PROMs into the Patient Registry to inform on the Natural History of SMA and the impact of newly available DMTs (including Risdiplam). Ongoing
Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry	N/A

Comments on the External Assessment Report

Comments on External Assessment Report
The report contains a repeated misinterpretation, and then misrepresentation, of the adult PROMs data submitted to the EAG in April 2025, in stating that certain data points refer to an overall total of respondents (patients), implying the inclusion of one response per patient over the course of the entire data collection period, when the data points in question actually refer to an overall total of responses (allowing for the inclusion of multiple responses per patient over the course of the data collection period – but limited to one response per 6-month timepoint). The discussion and tables included in the report for the adult EQ-5D-5L, EQ VAS, and SMAIS data therefore require revision. In the attached document ('Adult PROMs revised tables – EAG response'), we have included recommended revised versions of each discussion paragraph and table where relevant, which we believe more accurately represents the PROMs data provided. The following pages of the EAG report are affected: Page 281 (final two paragraphs) | [Nusinersen – EQ-5D-5L and EQ VAS] Page 282 (Table 94) | [Nusinersen – EQ-5D-5L] Page 287 (final paragraph) | [Nusinersen – SMAIS] Page 288 (Table 98) | [Nusinersen – SMAIS] Page 309 (final two paragraphs) | [Risdiplam – EQ-5D-5L and EQ VAS] Page 310 (Table 101) | [Risdiplam – EQ-5D-5L] Page 315 (final paragraph) | [Risdiplam – SMAIS] Page 316 (Table 105) | [Risdiplam – SMAIS] If the EAG should choose not to accept the recommended revised tables provided in the 'Adult PROMs revised tables – EAG response' document, and instead revise the tables in their own fashion, it should be noted that further incorrect data, unrelated to that discussed above, has been entered into Table 101, for Type 2/3 walkers at the 6 month and 1 year timepoints, which will need to be corrected regardless (see highlighted fields on page 10 of the 'Adult PROMs EAG revision' document).
The report contains multiple comparisons of the two treatments, however we agree with the statement on page 22 that "..people who receive nusinersen and risdiplam are too different to be able to compare..".

The current data does not allow for a comparison between the two drugs because the cohorts started on the two treatments are different since the two technologies became available at different time points and for example patient with complex spines may have been started on the oral drug whilst those with no or less severe scoliosis may have been started on the intrathecal drug.
In addition, there is an unmet need for the SMA type 4 population, who would in our opinion benefit from accessing Nusinersen (within the approved label), despite limited data is available. The national numbers for this cohort are small and are between 10-15 patients.
There is a need for both technologies to meet patient needs and to allow for patient choice since these have different mode of administration and different profile of side effects. We agree that in some instances it is difficult to capture benefit in a consistent way, where for examples outcome measures for stamina, fatigue or bulbar function have not yet been implemented.

NICE National Institute for Health and Care Excellence

Multiple Technology Appraisal

Nusinersen and risdiplam for treating spinal muscular atrophy (MA review of TA588 and TA755) [ID6195]

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About you

Your name	[redacted]
Organisation name: stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder, please leave blank)	Association of British Neurologists
Disclosure Please disclose any funding received from the company bringing the treatment to NICE for evaluation or from any of the comparator treatment companies in the last 12 months [Relevant companies are listed in the appraisal stakeholder list.] Please state: • the name of the company • the amount • the purpose of funding including whether it related to a product mentioned in the stakeholder list • whether it is ongoing or has ceased.	In the past 12 months, the ABN has received sponsorship from the following companies to support the ABN Annual Conference. Sponsorship companies have no editorial input, control over the agenda, speaker selection, content development nor opportunity to influence the conference. Sponsorship is £18,020 per company. • Abbvie • Alnylam • Angelini • argenx • Biogen • Eisai • Eli Lilly • Janssen • Pfizer • Roche • Sanofi • Teva • UCB
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Comments on the External Assessment Report

Comments on External Assessment Report

This form has been completed by the Neuromuscular Disorders Advisory Group on behalf of the Association of British Neurologists (ABN). We are consultant neurologists caring for adults with spinal muscular atrophy (SMA), including those receiving nusinersen and/or risdiplam via the NHS England Managed Access Agreements (MAAs). Our comments reflect this clinical perspective and do not focus on statistical or economic aspects of the Evidence Assessment Group (EAG) report.

This is a thorough and well-constructed report. The summary of key issues identified by the EAG (pp.18–20) accurately reflects many of the challenges faced when making decisions in clinical practice. We have not identified any critical omissions.

We welcome the description of clear evidence indicating that both nusinersen and risdiplam appear to help maintain or improve motor function in people living with SMA. We look forward to the translation of these findings into routine clinical care. However, the ongoing delays to the appraisal and approval processes are generating significant anxiety and uncertainty among our patient cohorts and we encourage your expediency in decision making and communication with medical and patient communities.

A major concern is the equity of access to treatment across different SMA clinical subgroups. The current categorisation of SMA into types 0–4 is arbitrary and often unhelpful in clinical practice. While this framework reflects historical age-of-onset and severity distinctions, the underlying genetic pathology is the same across subtypes. Clearly the report focuses on SMA types 1–3 due to data availability. Nonetheless, we believe pragmatic extrapolation to other subtypes—particularly type 4—should be seriously considered.

At present, adults with type 4 SMA are excluded from treatment, despite biological plausibility that they could benefit from increased SMN protein levels. Stabilising or improving function in this group, many of whom are of working age, could yield considerable economic and societal benefits.

We agree with the EAG's observation that the outcome measures used in the adult MAA are insufficiently sensitive to detect meaningful functional change over time. In particular, bulbar function is inadequately captured. Furthermore, small improvements in upper limb and hand function—even if not captured in standard outcome tools—can have a profound impact on independence, personal care needs, and the ability to remain economically active.

We concur that meaningful comparison between nusinersen and risdiplam is not currently possible, due to differences in patient populations and treatment timing. However, having a choice of disease-modifying therapies across the lifespan of a person with SMA is crucial. The different routes of administration and adverse effect profiles influence treatment decisions regardless of (likely small) differences in efficacy. For example, nusinersen may be preferred during childbearing periods, while risdiplam may be more suitable for individuals with comorbidities such as diabetes or renal impairment.

It is essential that patients retain access to a full range of therapeutic options over time, allowing treatment to be tailored to their clinical needs and personal circumstances throughout the course of their disease

NICE National Institute for Health and Care Excellence

Multiple Technology Appraisal

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About you

Your name	[redacted]
Organisation name: stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder, please leave blank)	(on behalf of) SMA REACH UK
Disclosure Please disclose any funding received from the company bringing the treatment to NICE for evaluation or from any of the comparator treatment companies in the last 12 months [Relevant companies are listed in the appraisal stakeholder list.] Please state: • the name of the company • the amount • the purpose of funding including whether it related to a product mentioned in the stakeholder list • whether it is ongoing or has ceased.	SMA REACH UK received funding from both Biogen (Nusinersen) and Roche (Risdiplam) in the last 12 months. The purpose of the funding from both companies was to support the SMA REACH UK network through site fee contributions, staff posts including PI's time, as well as training opportunities and other project-related wider meetings. These are aligned with milestones and deliverables to be reached that include data to be shared with the companies. In the last 12 months, Biogen has contributed £468,389.90 to the SMA REACH UK Project. This is due to a no-cost extension until 30th January 2023, a contact amendment in March 2023 to be backdated to 1st February 2023 and then an updated contract for 3 years was signed in November 2023. This was extended for a further year from January 2024-December 2025 and then a NCE from January 2025-March2025. SMA REACH UK is in contract with Biogen to cover a three-year period. In the last 12 months, Roche have contributed £641,296.94 to the SMA REACH UK Project. The contract with this manufacturer is for a 3-year period. SMA REACH UK also have a contract in place with Novartis Gene Therapies Inc. for the collection of data regarding onasemnogene abeparvovec. This includes contribution to the SMA REACH network to provide site support as well as covering positions within the project team. In the last 12 months, Novartis Gene Therapies Inc. have contributed £657,942 to the SMA REACH UK project.

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Comments on the External Assessment Report

Comments on External Assessment Report
The findings from our registry work have been interpreted and presented in a fair and balanced manner. The EAG demonstrates a deeper understanding of the disease compared to the previous report, and the challenges associated with evaluating real-world data in the context of a rare disease. Regarding clinical effectiveness, it is seen in both products, especially in terms of stabilization but also safety profile. Comparatives between drugs is on an exploratory level, while the main comparator is the SOC, which we think it is the correct possibility at the moment since the two cohorts differ, and a direct comparison would not be fair. The data collection was also not designed for drugs' comparison and therefore we would be cautious interpreting any comparison other than SOC. There is still lack of data on various aspects: bulbar function, stamina and fatigue, school/education as well as day-to-day care and burden of living with SMA, but this should not stop the process as we could implement collecting new data and exploratory data in due course. Evidence regarding SMA Type 0 was not part of the current appraisal and treatment not routinely offered (nor licenced) for this type of severe SMA. Since there are few international cases shared of treated SMA0 patients with one of the two disease modifying treatment, we would anticipate that in future systematic data collection from SMA type 0 will need to be implemented in the current registry. On the economic models, there are 6 different models mentioned with slightly different structures and redactions which were more difficult to evaluate. One thing to highlight, is that in the Roche product the "discontinuation model" is not applied and this will always give an apparent advantage especially in the SMA1 group. Commenting on the cost effectiveness is difficult with all the reductions and beyond the clinical evaluation, but it seems clear that while stabilization is of great value, larger improvement is seen mainly with early treatment and mostly in pre-symptomatic patients. Hence the urgence to implement a national NBS for this condition.

It is encouraging that qualitative assessments have been highlighted and incorporated into the report, and that parent/carer perspectives are represented. However, it is important to acknowledge that such information may be more subjective than clinically captured data, particularly as it was not collected in a blinded setting.

The report emphasises the importance of collecting reliable data on additional outcomes such as health-related quality of life (HRQL) and social interaction. However, it is important to recognise the additional burden and unmet resource needs required to support such efforts. It is important to consider that funding for the continued use of the registries and importance of this data collection should be considered by NICE/NHS England and should not rely exclusively on external company funding.

Points 2 and 3 highlight the significant challenges faced by families, and it may be that other supportive interventions, such as psychological or general support for parents and carers, may help alleviate some of these burdens. While this is especially important in SMA, it is also relevant in other paediatric conditions. Indirect benefits of treatment, which are likely to be confounded by various social factors, should therefore be interpreted alongside primary, direct clinical benefit, when evaluating clinical treatments. This may be challenging with the absence of a control or direct comparator group.

One recommendation was to conduct a study directly comparing the two treatments within this MAA, or to compare with OA. However, the feasibility of this, especially at the current stage of drug development, remains uncertain.

There is also an evident requirement for newborn screening for SMA in the UK and the swift introduction of such is advocated by the SMA RAECH UK network as well as the patient communities. Additional data on Quality of Life, disease' burden as well as defining the trajectories of bulbar function are all of interest and could be developed as observational study but would require additional support to the registry.

We would welcome further discussion regarding the above at the upcoming meetings regarding the MTA.

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About you

Your name	[redacted]
Organisation name: stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder, please leave blank)	Novartis Pharmaceuticals UK Limited
Disclosure Please disclose any funding received from the company bringing the treatment to NICE for evaluation or from any of the comparator treatment companies in the last 12 months [Relevant companies are listed in the appraisal stakeholder list.] Please state: • the name of the company • the amount • the purpose of funding including whether it related to a product mentioned in the stakeholder list • whether it is ongoing or has ceased.	Company holding market authorisation for the comparator treatment onasemnogene abeparvovec
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NICE National Institute for Health and Care Excellence

Comments on the External Assessment Report

Comments on External Assessment Report
On page 20, in the summary of EAG key issues: *"Roche did not account for treatment discontinuation in their economic model, reasoning that discontinuation from risdiplam was unlikely in clinical practice - a justification based on the trial data, REACH data, and clinical expert feedback.* *Why this is considered important:* *Not incorporating treatment discontinuation in the Roche models may favour risdiplam as the EAG's discussions with clinical experts suggested that people may discontinue or switch from risdiplam due to known adverse events, such as potential effects on fertility. The EAG also notes that the discontinuation data used in the models were based on short-term MAA follow-up, which may overestimate the sustained benefits from treatment over the patient's lifetime. In addition, discontinuation from nusinersen incorporated into the Biogen (nusinersen) model assume that patients discontinuing treatments would go on to receive BSC, accruing the costs and outcomes of BSC after discontinuation. However, in clinical practice, those discontinuing may switch to alternative DMTs rather than BSC alone. Due to the lack of robust evidence, the potential impact of treatment switching could not be modelled. Therefore, the EAG caution that assumptions surrounding treatment discontinuations may introduce additional uncertainty into the cost-effectiveness results."* Novartis agree with the EAGs conclusion that discontinuation of risdiplam is an important consideration for the economic analysis, given the impact that this would have on both costs and outcomes over a lifetime horizon.
In Table 2, on page 46, the eligibility criteria for treatment with onasemnogene abeparvovec is described as follows: *"If presymptomatic SMA develops into type 1 SMA, OA is an available treatment option in certain situations"* Novartis suggest the wording is amended to: *"Patients with type 1 SMA, if:* • *they are 6 months or younger, or* • *they are aged 7 to 12 months, and their treatment is agreed by the national multidisciplinary team."*[1] For clarity as to the 'certain situations' in which OA is recommended, and to avoid misunderstanding, as the current wording implies that a patient diagnosed with presymptomatic SMA may go on to develop type 1 SMA, whereas in practice a patient would be treated as soon as possible upon diagnosis, and a patient diagnosed pre-symptomatically would therefore be unlikely to go on to develop type 1 SMA. Type 1 SMA patients would likely be diagnosed symptomatically.

On page 47, footnote *a* to Table 2, the definition provided is that of unsuccessful treatment with OA (as detailed in Appendix A to the risdiplam MAA)[2], but the description states "successful treatment", this should be amended to "unsuccessful treatment".

In Table 7, on page 60, Biogen provided the following rationale for differences in the comparators considered in their analysis compared with those specified in the NICE scope:
"No direct evidence is currently available against risdiplam or onasemnogene abeparvovec; consequently, ITCs were performed with the aim to inform relative efficacy. However, limitations of the ITCs render them unsuitable to inform cost-effectiveness modelling. Therefore, this submission focuses on the comparison between nusinersen and BSC".

Conversely, Roche included OA as a comparator for risdiplam in the presymptomatic and type 1 SMA populations (pages 140 and 159):
"The company modelled nusinersen and OA as the comparators for presymptomatic populations. The decision model submitted by Roche included BSC as a comparator based on data from an internal natural history study. However, the company did not consider BSC a relevant comparator for the presymptomatic population, reasoning that patients are likely to receive a disease modifying therapy upon diagnosis of SMA, therefore overlooking the results comparing risdiplam with BSC"

In the changes made by the EAG to the Biogen presymptomatic and type 1 models (Table 79, pages 215-216, and Table 80, page 218, respectively) the EAG highlight that exploratory analysis for nusinersen vs OA was undertaken.

Additionally, on page 84, the EAG comment: *"Based on both the clinical context and the evidence available, the EAG cautions against the use of BSC as an appropriate comparator in the presymptomatic SMA population"*

Novartis agree with the EAGs decision to conduct exploratory analysis for nusinersen versus OA, in line with the NICE decision problem, despite the acknowledged uncertainties in the indirect treatment comparisons. OA is routinely commissioned by NICE for presymptomatic and type 1 SMA and is established in UK clinical practice for these populations, and should therefore be considered as a comparator per the NICE manual.[1, 3-4]

On page 87, and throughout the report, the EAG explain their decision not to consider caregiver utility in the base case analysis:
"The EAG acknowledges the importance of including the experience of informal carers in this appraisal; however, there are no standardised methodologies to quantify the impact on health-related quality of life from informal carers, and the data specific to SMA is scarce. Therefore, in the EAG base-case, models focussed primarily on the quality of life of patients. The data for informal carers were

used and presented as an additional scenario for the purposes of transparency, allowing an explicit assessment of the disease burden for patients alone, and for patients and their carers together" Additionally, on pages 12-13, the EAG describe further rationale for the decision not to consider caregiver HRQoL in the base case analysis: *"However, the two company submissions adopted markedly different approaches to incorporating informal carer HRQoL, relying on data elicited outside the clinical trials."* Novartis disagree that reliance on data elicited outside the clinical trials warrants exclusion of caregiver HRQoL from the base case analysis, given that the NICE reference case states *"If not available in the relevant clinical trials, EQ-5D data can be sourced from the literature"*.[5] Owing to the unavoidable small sample size in clinical trials in SMA due to the rare nature of the disease, HRQoL data elicited through trials would likely be associated with substantial uncertainty. As such, in the opinion of Novartis, reliance on HRQoL data elicited outside trials is necessary in SMA, for both patients and carers, in order to capture all relevant health effects of the disease, and should be considered in analyses given the substantial impact that SMA can have on caregivers.[6,7] Further, whilst the EAGs statement that there are no standardised methodologies to quantify the impact on health-related quality of life of informal carers is true, Novartis also do not believe this warrants exclusion of caregiver HRQoL from the base case analysis, as this would suggest that caregiver HRQoL should not be considered in the base case for any NICE appraisal, which does not align with the NICE reference case.[5] Rather than excluding caregiver HRQoL from both analyses, an alternative solution would be to explore scenarios for both treatments using the different approaches adopted by the two companies.
On page 89 and 100-101: *"it is likely that those discontinuing nusinersen may not transition to receive BSC alone, but instead may receive alternative disease modifying treatments. This would have implications for both the costs and outcomes, which are not fully captured in the current models"* Novartis agree with the EAGs conclusion that patients discontinuing nusinersen (or risdiplam) would not go on to receive BSC and would instead move on to subsequent treatment.
Sections 6.3.2.12 and 6.3.3.11, and described on page 89: *"The EAG considers the company's approach of incorporation of severity modifier in QALYs gains in treatment of SMA to be appropriate, given the severity of the condition. However, the EAG cautions that applying a severity modifier may risk double counting if the health state utility values used to calculate the QALYs already reflect disease*

severity. Therefore, for transparency and explicit assessments the EAG assessed the impact of incorporating the severity modifier only as an additional analysis presented alongside the base-case"

Novartis agree with the EAGs decision to consider the severity modifier as an additional analysis alongside the base case, rather than within the base case, for the reasons provided. However, Novartis query the appropriateness of application of severity weights of 1.2 and 1.7 in the presymptomatic and type 1 analyses, respectively, given the calculations are based on a comparison with BSC, rather than with OA. As stated in Novartis' comment on the comparators considered in the analysis, OA is routinely commissioned by NICE for presymptomatic and type 1 SMA and is established in UK clinical practice.[1,3] As such, the calculation of future QALYs for those with presymptomatic or type 1 SMA under current NHS treatment should be estimated based on treatment with OA, not with BSC.[8] Whilst acknowledging that Biogen did not include OA as a comparator and therefore cannot calculate comparator QALYs through their own analysis, in the opinion of Novartis it is not appropriate to substitute BSC as the comparator for the severity modifier calculation. This is supported by the EAG statement on page 145, discussing the application of the severity modifier in the Roche presymptomatic analysis: *"The base-case analysis presented comparing risdiplam with BSC met the criteria for a severity multiplier of 1.7 on the incremental QALYs; however, the BSC was not considered a relevant comparator in the presymptomatic population as almost all patients do get treated."*

On page 140, with regard to the comparators considered by Roche in the presymptomatic analysis, the EAG comment: *"The base-case submitted by Roche for the presymptomatic population did not include BSC as an appropriate comparator, arguing that in current clinical practice patients diagnosed with SMA are expected to receive a DMT. However, the EAG is concerned about the gaps in clinical evidence that make comparisons between risdiplam and other DMTs highly unreliable.*
Considering the limitations in relative effectiveness evidence between DMTs, the EAG decided to focus the economic decision problem in the presymptomatic population on comparing risdiplam against BSC for analytical purposes, while acknowledging that current clinical practice is constantly evolving. Comparisons between risdiplam and other DMTs will be presented as scenario analyses using the evidence available, highlighting the caveats around the potential for bias."

Whilst Novartis acknowledge data limitations making a robust comparison between risdiplam and OA challenging, given that OA is routinely commissioned for people with presymptomatic OA, in the opinion of Novartis the rationale that "*current clinical practice is constantly evolving"* does not justify exclusion of OA as a comparator in the base case analysis.

In Table 79 and Table 80 on pages 216 and 218, respectively, where describing the changes made to the presymptomatic and type 1 models, the EAG state that for their exploratory analysis vs. OA, *"the treatment effect duration and the relative rate of decline for OA was considered equal to nusinersen."*

Whilst both nusinersen and OA are disease modifying treatments, OA is a one-time gene therapy targeting *SMN1,* the genetic cause of SMA, whereas nusinersen is an *SMN2* splicing modifier, which does not address the genetic cause of SMA and does not fully restore SMN protein expression. Nusinersen requires chronic treatment and poses a risk of long-term motor milestone decline, as acknowledged by the EAG on page 95. As such, Novartis believe the assumption of equal treatment effect duration and equal relative rate of decline between the two treatments requires rationale.

Abbreviations: BSC – Best supportive care; DMT – Disease modifying treatment; EAG – External Assessment Group; HRQoL – Health-related quality of life; ITC – Indirect treatment comparison; MAA – Managed Access Agreement; NICE – National Institute for Health and Care Excellence; OA – onasemnogene abeparvovec; SMA – Spinal muscular atrophy.

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NICE National Institute for Health and Care Excellence

Multiple Technology Appraisal

Nusinersen and risdiplam for treating spinal muscular atrophy (MA review of TA588 and TA755) [ID6195]

External Assessment Group Report consultation responses

Report key: Commercial in confidence (CiC) data are highlighted in blue throughout the report.
Academic in confidence (AiC) data are highlighted in yellow throughout the report.
Any de-personalised data are highlighted in pink throughout the report.

Association of British Neurologists (ABN)

Comments on External Assessment Report	EAG response
This form has been completed by the Neuromuscular Disorders Advisory Group on behalf of the Association of British Neurologists (ABN). We are consultant neurologists caring for adults with spinal muscular atrophy (SMA), including those receiving nusinersen and/or risdiplam via the NHS England Managed Access Agreements (MAAs). Our comments reflect this clinical perspective and do not focus on statistical or economic aspects of the Evidence Assessment Group (EAG) report. This is a thorough and well-constructed report. The summary of key issues identified by the EAG (pp.18–20) accurately reflects many of the challenges faced when making decisions in clinical practice. We have not identified any critical omissions.	The EAG thanks the ABN for their comment.

Comments on External Assessment Report	EAG response
We welcome the description of clear evidence indicating that both nusinersen and risdiplam appear to help maintain or improve motor function in people living with SMA. We look forward to the translation of these findings into routine clinical care. However, the ongoing delays to the appraisal and approval processes are generating significant anxiety and uncertainty among our patient cohorts and we encourage your expediency in decision making and communication with medical and patient communities.	The EAG thanks the ABN for their comment.
A major concern is the equity of access to treatment across different SMA clinical subgroups. The current categorisation of SMA into types 0–4 is arbitrary and often unhelpful in clinical practice. While this framework reflects historical age-of-onset and severity distinctions, the underlying genetic pathology is the same across subtypes. Clearly the report focuses on SMA types 1–3 due to data availability. Nonetheless, we believe pragmatic extrapolation to other subtypes—particularly type 4—should be seriously considered. At present, adults with type 4 SMA are excluded from treatment, despite biological plausibility that they could benefit from increased SMN protein levels. Stabilising or improving function in this group, many of whom are of working age, could yield considerable economic and societal benefits.	The EAG thanks the ABN for their comment.
We agree with the EAG's observation that the outcome measures used in the adult MAA are insufficiently sensitive to detect meaningful functional change over time. In particular, bulbar function is inadequately captured. Furthermore, small improvements in upper limb and hand function—even if not captured in standard outcome	The EAG thanks the ABN for their comment.

Comments on External Assessment Report	EAG response
tools—can have a profound impact on independence, personal care needs, and the ability to remain economically active.	
We concur that meaningful comparison between nusinersen and risdiplam is not currently possible, due to differences in patient populations and treatment timing. However, having a choice of disease-modifying therapies across the lifespan of a person with SMA is crucial. The different routes of administration and adverse effect profiles influence treatment decisions regardless of (likely small) differences in efficacy. For example, nusinersen may be preferred during childbearing periods, while risdiplam may be more suitable for individuals with comorbidities such as diabetes or renal impairment.	The EAG thanks the ABN for their comment.
It is essential that patients retain access to a full range of therapeutic options over time, allowing treatment to be tailored to their clinical needs and personal circumstances throughout the course of their disease	The EAG thanks the ABN for their comment.

Biogen

General Comments	EAG response
Biogen appreciate the efforts from NICE and the EAG since re-commissioning a new report to engage with the SMA community including SMA patient organisations, SMA REACH, individual clinicians, and the manufacturers. This has contributed to a report which more appropriately contextualises SMA and the available treatments.	The EAG thanks Biogen for their comment.
Biogen agree with the EAG's assessment of the clinical effectiveness and safety data for nusinersen. We also agree with the EAG's critique of both manufacturers ITCs and the data limitations that inhibit a robust comparison of the interventions. We agree that comparisons against BSC are not ideal and do not reflect current UK clinical practice (either as first line or assuming BSC use when discontinuation of a DMT occurs), however such comparisons are a more appropriate use of the available data without introducing further complexity, assumption, and uncertainty.	The EAG thanks Biogen for their comment and their understanding of limitations of using BSC as a comparator, as well as the availability of data.
Biogen acknowledge the limited data available for nusinersen use in type 4 SMA patients is insufficient for health technology appraisal, however excluding type 4 patients from a recommendation may widen health inequality for SMA patients.	The EAG thanks Biogen for their comment and note that this is a matter of discussion for NICE.
Biogen agree with EAG base case and adaptations made to the Biogen economic models, except for excluding caregiver health-related quality of life. We acknowledge that different methods and data sources have been used across manufacturer submissions and that no NICE guidance exists for how this should be approached. Following a request from NICE, we have submitted an addendum which covers this topic in more detail and assesses the impact of the different manufacturer approaches on model outcomes.	The EAG thanks Biogen for their comment and for submitting the addendum on different methods of incorporating carers' health-related quality of life. Following discussions with NICE and the manufacturers, the EAG has conducted additional analyses using consistent methodological approaches to carers' quality of life for both manufacturers.

General Comments	EAG response
Biogen request the EAG include further narrative and critique of the different model health state definitions (with clinical expert input) including how well the data available to populate the models align with these definitions. The Biogen models use narrow definitions for motor milestones with clearer distinction between health states e.g. sitting without support, standing with assistance, and walking independently, whereas the Roche models use broad definitions e.g. sitting (with or without support), standing (with or without assistance) and walking (cruising or independently). We would therefore query how clinically distinct the health state definitions are in the Roche model (e.g. is there sufficient distinction between a patient who can stand unaided and those who can cruise), when each health state could include patients with a broad range of abilities and how well the associated costs and utilities reflect the potentially diverse populations within these health states.	The EAG thanks Biogen for their comment. We have already discussed the health state definitions, the supporting evidence, and the tools used to define them in each of the company models throughout our assessment report. Therefore, we believe that additional discussion of these issues may not be necessary.
Biogen acknowledge the efforts of the EAG to make the models as consistent as possible despite the different structures, however we request further narrative to be included in the report to explain the differences in model outcomes (note, only total life years and some QALY data are unredacted). For example in the EAG adapted presymptomatic models, the estimates for BSC are 19.84 and 12.91 years in the Biogen and Roche models, respectively. We presume this is predominantly driven by differences in the natural history data underpinning outcomes for BSC in addition to differences in the distribution of SMN2 copy numbers. Furthermore, the report would benefit from further investigation into discontinuations and specifically the assumption of no discontinuation for any DMT in the Roche models. Although short-term, data exists from the nusinersen MAA which highlights that discontinuation does occur, mainly due to scoliosis and the inability to continue to safely give nusinersen via intrathecal administration given current levels of service provision in UK clinical practice and the availability of alternative DMTs. However, the assumption of no discontinuation also means that patients receive the benefit of the 'on treatment' utility increment for the entire lifetime of the	The EAG thanks Biogen for their comment and recognising the need for consistency across the company models. The differences in QALY estimates for the BSC arm between the Biogen and Roche models are due to differences in patient characteristics and the underlying data. Throughout our report, we have discussed the variations in model structures and data used, and we have clearly stated that these results should be interpreted with caution, particularly considering the gaps in the evidence base. Additionally, we have discussed how incorporation and omission of treatment discontinuation in the models is likely to impact the results for each DMT. Therefore, we believe that the issues raised here have been adequately discussed in our report.

General Comments	EAG response
model (particularly in the case of OA in the Biogen economic models) which may overestimate the benefit of treatment.	
Biogen agree with the EAG that the symptomatic populations treated with nusinersen and risdiplam are clinically different, however we do not support the application of different severity modifiers. In table 106 of the EAG report, the severity modifiers are the same for type 1 and type 2/3, however the modifiers are different for the presymptomatic population (1.2 in the Biogen models vs 1.7 in the Roche models). Our understanding is that this is a consequence of different underlying natural history for the BSC arm as opposed to differences in the presymptomatic populations and therefore a consistent severity modifier should be applicable. At the request of NICE, Biogen have provided further detail on this issue in a separate addendum.	The EAG thanks Biogen for their comment and for submitting an addendum on the issue of using different severity modifiers in the Biogen and Roche models. The EAG has now conducted additional analyses to explore the use of a consistent severity modifier across both company models.
Biogen would like to re-emphasise that we still do not have access to sufficient data (despite requests to NICE and Roche) to understand the clinical and cost-effectiveness of nusinersen is being assessed using the Roche models due to the level of redaction. This therefore limits our ability to scrutinise data and assumptions for appropriateness. Should the Roche models be used to inform decision making for nusinersen without further information being provided to Biogen, we deem this procedurally unfair.	The EAG thanks Biogen for their comment. However, we note that this is a matter of discussion for NICE.

Text clarifications			
Page/ Paragraph	**Text/ Issue**	**Comment**	**EAG response**
P6, para 1	“A single study directly comparing nusinersen and risdiplam suggested no statistically significant differences between treatments but baseline imbalances in prognostic factors limit data comparability. “	Add SMA type and follow-up period: type 2/3 patients and 6 months.	The text has been amended to: “A single study directly comparing nusinersen and risdiplam suggested no statistically significant differences between treatments in people with types 2 and 3 SMA at the 6-month follow up,

Text clarifications			
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			but baseline imbalances in prognostic factors limit data comparability."
P8, para 3 (also applies to p55, para 1)	"The intrathecal injection (12 mg/5 mL) requires an initial loading phase of four doses, with the first three doses taken at 14-day intervals and the fourth dose 30 days after the third dose."	Typographical error, the 4th doses is given 35 days after the third dose, as per the license." Spinraza treatment should be initiated as early as possible after diagnosis with 4 loading doses on Days 0, 14, 28 and 63."	The text has been changed to: "The intrathecal injection (12 mg/5 mL) requires an initial loading phase of four doses on days 0, 14, 28 and 63. Maintenance doses are subsequently provided every four months."
P14, para 3	"While the adult registry for risdiplam extended to ~4 years, the patient numbers were smaller"	Clarify that patient numbers at 4 years were smaller, rather than patient numbers in the adult registry being overall smaller for risdiplam than for nusinersen.	We have edited the text to explicitly state risdiplam: "While the adult registry for risdiplam extended to ~4 years, the patient numbers were smaller at this point **for risdiplam** than those in the nusinersen MAA"
P17, para 3	"What is the issue: The EAG did not identify any evidence surrounding the effectiveness or cost-effectiveness of nusinersen or risdiplam in patients with SMA types 0 and 4. Why this is considered important: Patients with either type 0 or type 4 SMA are not represented within the clinical and cost-effectiveness sections of this report due to the lack of data. Representatives of patient organisations highlighted to	Biogen did submit available evidence for type 4 SMA patients from the SMARTCARE registry; however we acknowledge data are limited and likely insufficient for HTA purposes. Due to the mechanism of action of nusinersen increasing the levels of functional SMN protein, it is expected to have a treatment effect in type 4 SMA, however the magnitude is uncertain due to higher SMN2 copy numbers and unknown extent of neuronal changes prior to	We thank the company for highlighting this work. The study by Gunther et al (2024) included a mixed population of SMA types (1-4). Of these, 9 type 4 patients were included at baseline, 7 at 26 month analysis, and 2 at 38 month analysis. Subgroup analyses were not undertaken for SMA type 4; therefore, the effectiveness in this subpopulation cannot be determined (especially, as the company points out, given the small sample size).

Text clarifications			
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	the EAG that the lack of access to the MAA for adults with type 4 SMA is a potential equality issue. “	treatment initiation. However, excluding type 4 patients from any recommendation may increase health inequality among SMA patients.	
P18, para 2	“What is the issue: There are no controlled studies that include any therapy for presymptomatic patients. Risdiplam also lacked controlled studies for type 1 patients. Why this is considered important: The lack of data means that the evidence for this population is more uncertain.	Whilst factually accurate, conducting placebo/sham-controlled studies in presymptomatic SMA is considered unethical. Furthermore without treatment of presymptomatic patients, symptomatic SMA would be a certain eventuality for patients and the natural history of symptomatic forms are well characterised.	The EAG agrees that placebo-controlled trials in presymptomatic patients would likely be considered unethical, because later treatment leads to worse outcomes, there is data showing effectiveness for both drugs, and treating early improves cost-effectiveness. However, the fact remains that the existing evidence is more uncertain.
P19, para 3	“What is the issue: The effectiveness data (e.g. transitions, relative effect, decline in health states) used in the cost-effectiveness models largely come from single arm trials in the absence of RCTs. Why this is considered important: Whilst it may not always be feasible or ethical to conduct a RCT for treatments in rare diseases like 5q SMA, it therefore becomes necessary to use	Additional context should be added that the pivotal studies across the symptomatic SMA types for nusinersen were sham-controlled studies (ENDEAR and CHERISH).	The following text has been added to this section: “It should be noted, however, that the pivotal studies (ENDEAR; CHERISH) for the symptomatic SMA types (2/3) for nusinersen were sham-controlled studies.”

Text clarifications			
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	the effectiveness data coming from single arm trials. Using evidence from single arm trials may introduce bias in favour of the treatments under evaluation"		
P19, para 4	"What is the issue: The motor milestone scores used in defining disease progression in terms of model health states are derived from different tools which vary in their scoring system. Why this is considered important: The EAG note that assuming equivalence of health states defined by tools varying in their scoring system may add further uncertainty in motor functions, patient health states, and ultimately in the cost-effectiveness outcomes due to the sensitivity in how well the tools capture the true impact of the disease as valued by patients and carers. "	Additional context should be added that often the transition between tools is driven by age and functional status as per section 4.4. With regards to nusinersen, the transition from HINE-2 to the WHO motor milestones occurs in the type 1 model providing a patient could sit without support and was >2 years of age. The WHO motor milestones are potentially more permissive focusing on whether a child can demonstrate the skill e.g. for sitting without support, the Infant sits upright with head erect ≥10 seconds, without using arms/hands for support whereas in the HINE -2, the infant would be required to show stability and progression from prop (sitting with support) to stable/ pivot (sitting without support).	Whilst the EAG appreciates the comment, we wish to clarify that the issue concerns only the assumption regarding the equivalence of the tools in defining health states, not a comparison of their respective strengths and limitations. However, we note that this could be a matter of discussion for NICE.
P20, para 2	"What is the issue: Discontinuation from treatments were	MAA data reflect real world data collected in UK clinical practice and	The EAG thanks Biogen for their comment.

Text clarifications			
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	informed by the MAA data but were only incorporated into the Biogen model for nusinersen. Roche did not account for treatment discontinuation in their economic model, reasoning that discontinuation from risdiplam was unlikely in clinical practice - a justification based on the trial data, REACH data, and clinical expert feedback. Why this is considered important: Not incorporating treatment discontinuation in the Roche models may favour risdiplam as the EAG's discussions with clinical experts suggested that people may discontinue or switch from risdiplam due to known adverse events, such as potential effects on fertility. The EAG also notes that the discontinuation data used in the models were based on short-term MAA follow-up, which may overestimate the sustained benefits from treatment over the patient's lifetime. In addition, discontinuation from nusinersen incorporated into the Biogen (nusinersen) model assume that	should inform the cost-effectiveness models. The majority of patients who discontinued nusinersen during the MAA period did so due to scoliosis and the inability to safely administer intrathecally, part of which is linked to variable service provision across the UK for intrathecal administration for more complex cases. Biogen do not support the assumption of zero discontinuations in the Roche models and we agree this may overestimate the sustained benefits of treatment which is linked to an 'on treatment' utility benefit. Biogen agree that a patient discontinuing treatment would switch to an alternative DMT (if eligible) as opposed to BSC. Whilst trials are ongoing to assess the efficacy and safety of DMTs when used in sequence, there is currently limited data for use in economic models which would require further assumption and lead to more uncertainty. Furthermore, due to nusinersen being available earlier than both OA and risdiplam, treatment switches were often away	

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	patients discontinuing treatments would go on to receive BSC, accruing the costs and outcomes of BSC after discontinuation. However, in clinical practice, those discontinuing may switch to alternative DMTs rather than BSC alone. Due to the lack of robust evidence, the potential impact of treatment switching could not be modelled. Therefore, the EAG caution that assumptions surrounding treatment discontinuations may introduce additional uncertainty into the cost-effectiveness results. “	from nusinersen and switching back to nusinersen requires input from the NHSE clinical panel, making this more challenging.	
P43, para 1	“Type 1 SMA is the most common type of disease, occurring in 60% of cases.”	Clarify that type 1 SMA occurs in 60% of diagnosed cases, it does not represent the most comment type in the prevalent population due to high mortality rates in the absence of DMTs.	The EAG have clarified as follows: “Type 1 SMA is the most common type of diagnosed disease, occurring in 60% of cases.”
P45, table 2	Eligibility criteria This table states the different start criteria for the nusinersen and risdiplam MAA.	Aside from criteria regarding intrathecal administration, the eligibility criteria are identical despite not being written the same.	The eligibility criteria table reflects the phrasing of the NICE documentation.
P55, para 1	“The committee noted that there may be a delayed response to nusinersen	Please clarify what is meant by “some people.” Whilst motor	This is a direct quote from the TA588 guidance (point 3.11), in the context of a

Text clarifications			
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	for some people (for at least 2 years). “	improvements may continue to accrue beyond the completion of loading doses and across 12-24 months in older children and those with more advanced disease, this does not reflect a delayed response to treatment. Also, as noted in the EAG report, stabilisation of disease progression should be seen as a positive outcome when compared to natural history.	description of the SHINE extension study.
P63, para 8	“The restriction to studies that included at least 100 participants meant that a number of eligible smaller studies were omitted, but no controlled studies.”	Biogen acknowledge this may have led to the omission of some studies, however as stated in the company submission, this was done for pragmatic reasons given the volume of literature identified.	The EAG thanks Biogen for their clarification.
P77, para 1	“It should be noted, then, that the CHERISH trial is not generalisable to UK clinical practice because participants did not receive the relevant dose, and because of restrictions in eligibility around age, complications and ventilation requirements. “	Outside of age restrictions, participants do reflect the UK population treated with nusinersen (e.g. without severe scoliosis and contractures). It should be noted that the dose used in CHERISH is less than the licensed dose (3 loading doses and maintenance every 6 months vs 4 loading doses over 2 months and maintenance dosing every 4 months thereafter). Based on dose response relationships	We thank Biogen for their comment. The EAG is unable to comment on the impact on treatment effect with the use of the licensed dosing regimen in the absence of direct evidence. We have re-phrased the text in relation to generalisability issues relating to the eligibility criteria as follows: “*It should be noted that the enrolled population was more homogeneous than the population encountered in*

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		demonstrated in early phase studies, a greater treatment effect may be expected with use of the licensed dosing regimen. A protocol amendment was made in SHINE so that all patients received the licensed 4 monthly maintenance dose.	*clinical practice due to restrictions in the eligibility criteria (i.e., no severe contractures or scoliosis, respiratory insufficiency, or reliance on a gastric tube). Furthermore, the age profile of enrolled children was younger than would be seen in clinical practice.*" as acknowledged in Mercuri, Eugenio, et al. "Nusinersen versus sham control in later-onset spinal muscular atrophy." New England Journal of Medicine 378.7 (2018): 625-635.
P75,2	"The company reported that none of the presymptomatic patients had died or required permanent ventilation by a median age of 4.9 years (range 3.8 to 5.5 years), compared to an estimated average age of mortality from natural history of 19.2 months (SD 10.1 months).20 Children with three SMN2 copies were walking independently within normal developmental timeframes; 13 of the 15 children with two SMN2 copies achieved the WHO motor milestone of standing alone and walking alone, whilst 14 achieved hands and knees crawling and walking with assistance, and all achieved sitting without support and	Updated end of study results are available for NURTURE and have been provided to NICE. Biogen acknowledge the timing of study completion and CSR availability meant this data could not be incorporated into the current report but should be included in future updates.	The EAG thanks Biogen for their comment.

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	standing with assistance. A total of 88% of children achieved the maximum CHOP-INTEND score, and mean HFMSE scores showed continuous improvement. “		
P81, para 1	“Patients receiving nusinersen were assumed to have no risk of progression to ‘permanent ventilation’ based on results from NURTURE. “	This is factually accurate for the first 72 months i.e. the period of NURTURE only, in the long-term if a patient enters the non-sitting state depending on the rate of decline, they have a risk of entering the permanent ventilation state.	The EAG thanks Biogen for their comment. However, we highlight that the Biogen submitted report on page 146, section 3.3.1.4. in the second paragraph states that “No patients in the individual patient-level time-to-event data from the NURTURE clinical trial required permanent ventilation. Therefore, it was assumed that anyone receiving nusinersen would not progress to permanent ventilation.” This is also reflected in the company submitted model. Therefore, the comment does not align with what has been reported.
P82, para 4	“The HINE-2 outcome measure was collected in the NURTURE trial informing clinical effectiveness of nusinersen treatment and is considered more comprehensive than the WHO MM for its inclusion of voluntary grasp and head control”	Voluntary grasp and head control are not modelled health states. The attainment of milestones used to define health states should be considered similar across the WHO and HINE-2, although the former maybe more permissive.	The EAG thanks Biogen for their comment. We wish to clarify that the issue concerns only about the assumption regarding the equivalence of the tools in defining health states, not a comparison of their respective strengths and limitations. We have now rephrased our comment where we now say, “Whilst the WHO MM is based on typical age-related norms for motor

Text clarifications			
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			development, HINE-2 is based on clinically assessed scores."
P82, para 5	"The EAG understands there is a lack of data on patients with presymptomatic SMA receiving BSC however, cautions that adjustments to the state occupancy for patients receiving BSC in the presymptomatic model"	The adjustments made to the BSC arm were to avoid patients achieving milestones earlier than WHO developmental norms given the differences in the age for patients in ENDEAR/ CHERISH and the start age in the presymptomatic model.	The EAG thanks Biogen for their clarification.
P83, para 7	"Based on both the clinical context and the evidence available, the EAG cautions against the use of BSC as an appropriate comparator in the presymptomatic SMA population"	We agree the DMTs would be given to presymptomatic patients in addition to BSC, as opposed to BSC alone, however the choice for not including DMTs was based on data limitations and issues around comparability of populations and outcomes as highlighted in the ITCs.	The EAG thanks Biogen for their comment.
P83, para 7	"EAG notes that the company model relied on strong assumptions of outcomes under BSC"	These assumptions reflect the sham-control arms in ENDEAR and CHERISH where relevant, reflecting symptomatic forms of SMA which, without treatment, would be the certain outcome for patients not treated presymptomatically.	The EAG thanks Biogen for their comment. We have now revised the text to clarify that the assumptions reflect patients not on treatment.
P88, para 3	"However, it is likely that those discontinuing nusinersen may not transition to receive BSC alone, but instead may receive alternative	Biogen agree that a patient discontinuing treatment would switch to an alternative DMT (if eligible) as opposed to BSC. Whilst trials are	The EAG thanks Biogen for their comment.

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	disease modifying treatments. This would have implications for both the costs and outcomes, which are not fully captured in the current models. "	ongoing to assess the efficacy and safety of DMTs when used in sequence, there is currently limited data for use in economic models which would require further assumption and lead to more uncertainty.	
P109, para 2	"A hazard ratio was applied to these survival data to reflect those with England and Wales setting."	For clarity, the HR to reflect the England and Wales setting was not applied by Biogen. The survival curves were taken directly from HST24 which already included this adjustment (the HR is not reported within HST24 papers) as per p112: "For survival in this health state, data for patient cohorts (with SMA types 2a and 2b) are pooled from a recent natural history study based on a Dutch cohort (in which more recent clinical practice is reflected (3)). Due to few deaths in the type 2a population and zero events in the type 2b population, parametric curves fitted to the extracted data resulted in unrealistic flat curves and thus are not used directly in this model. Instead, parametric curves were fitted to the pooled data and then compared with the general population curve for the	The EAG thanks Biogen for the clarification regarding the hazard ratio used to derive the survival data. We have rephrased our comment to clarify that the survival data was taken directly from HST24, where the hazard ratio was not reported.

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		Netherlands. A constant hazard ratio was calculated relative to general population and applied to the UK general population life tables."	
P121, para 1	"For risdiplam compared to nusinersen, unanchored MAICs suggested a statistically significant difference between the treatments for CHOP-INTEND, HINE-2, adverse events and survival (see Table). The ESS for these analyses is >35, which suggest the potential for less bias and uncertainty in these results. "	It should be also noted that there are important differences in exclusion criteria between trials regarding pulmonary events and pulmonary function, which are key factors influencing outcomes such as permanent ventilation and overall survival. FIREFISH included more restrictive exclusion criteria than ENDEAR (e.g., excluded patients with hospitalisation for pulmonary event within the last 2 months; with invasive ventilation or tracheostomy; requiring non-invasive ventilation or hypoxemia with or without ventilator support; and history of respiratory failure or severe pneumonia and had not fully recovered their pulmonary function at time of screening vs. excluded patients with hypoxemia at screening). Incomparable exclusion criteria used in FIREFISH and ENDEAR may have enriched for a population in FIREFISH with less pulmonary burden compared to	We thank the company for their insight and agree that these are key things to consider within the analyses. Currently these differences are highlighted more implicitly (e.g. table 38). However, we agree that explicit details should be added, therefore, we have included the following text to summarise potential matching issues at the end of the aforementioned text: "Additionally, it worth noting that the trials included in this analysis (FIREFISH; risdiplam and ENDEA-SHINE; nusinersen) had different eligibility criteria and only considered matching on age at first dose, disease duration at baseline, and mean baseline total CHOP-INTEND score. Therefore, differences in the populations are likely not fully accounted for."

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		patients in ENDEAR that cannot be resolved through MAIC weighting. In addition, only three baseline variables were considered for weighting (age at first dose, disease duration at baseline and CHOP-INTEND score). The exclusion of important variables e.g. body weight and nutritional support may have introduced bias into the analysis. Furthermore post weighting, there were imbalances in baseline variables (e.g. sex and age at symptom onset). Lastly, there are differences in the schedule of assessments for motor endpoints which may have introduced further bias. Motor milestones were assessed at 12 months in FIREFISH whereas ENDEAR ended early with an average of 9 months follow-up (based on a positive benefit risk assessment of a prespecified interim analysis). However no additional follow-up data from SHINE was used to bridge this gap. Differences in the timing of assessment can have a meaningful impact as the attainment	

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		of motor milestones (e.g. sitting without support) are time dependent.	
P137, para 4	"For risdiplam treatment effectiveness was assumed to last 72 months by the EAG, similar to the available follow-up data for nusinersen,30- which is a favourable assumption to risdiplam, given that the follow-up from RAINBOWFISH was only 12 months."	We agree this is a strong assumption and should be validated against later data cuts for risdiplam.	The EAG thanks Biogen for their comment. We note that this could be a matter of discussion for NICE.
P143, Table 49 (also applicable to p181, table 68)	Cost per cycle from TA588	Could the EAG clarify these are 4 monthly cycle costs as opposed to monthly cycle costs in the Roche model or whether they have been adjusted for comparability.	The EAG thanks Biogen for their comment. We clarify that the costs used from TA588 in the Roche model are the monthly cycle costs.
P179, para 2	"An unanchored MAIC was used to compare RULM scores for risdiplam from the SUNFISH trial with RULM score for nusinersen from the CHERISH trial and present them as odds ratios (ORs). Although the company reported high uncertainties around the estimated results from the MAIC, these were used to estimate the relative effectiveness between risdiplam and nusinersen in the economic model. The economic model assumes a monthly relative	Biogen cannot see the data for nusinersen and it is unclear what the RULM scores relate to (change from baseline or > 2 points) and how well improvements in RULM scores correlate to moving between gross motor milestones.	The EAG thanks Biogen for their comment. We clarify that the analysis comparing risdiplam with nusinersen presented by Roche was based on an independent, unpublished analysis, therefore this analysis was commercial in confidence. Our preference in the EAG analysis was to use published evidence available in Ribero et al. 2022. [1]

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	risk of nusinersen versus risdiplam for improving to a higher motor milestone"		
p 213 table 79	In the exploratory analysis, it was considered inappropriate to have discontinuation from OA, as it is a one-off treatment.	Whilst we agree it is inappropriate to assume discontinuation from OA, consideration should be given to the on-utility treatment increment, as this would be assumed for the entire model horizon, potentially overestimating treatment effect and cost-effectiveness.	The EAG thanks Biogen for their comment. We note that the point raised here could be a matter of discussion for NICE.
P 277 para8	"Three randomised controlled trials (RCTs) were assessed using the Cochrane risk of bias tool (ROB 2.0): CHERISH, ENDEAR, and EMBRACE. All three trials were judged overall to have some concerns."	This contradicts the ratings given in table 86 p 229 which are noted as "serious".	Text amended to "Two of these trials (CHERISH and ENDEAR) were judged overall to have high risk of bias, one (EMBRACE) was judged overall to have some concerns."
P238, para 3	"The clinical trials reporting data for the effects of nusinersen on motor function were SM201 and NURTURE for patients with presymptomatic SMA"	NURTURE and SM201 are the same study.	The EAG have clarified as follows: "The clinical trials reporting data for the effects of nusinersen on motor function were NUTURE for patients with presymptomatic SMA, […]"
P238, para 3	"Another study reported significant increases in type 1 and 2 patients but not type 3 patients."	Consideration should be given to the baseline score and possible ceiling effects. Furthermore the CHOP-INTEND is unlikely to be administered to a type 3 patients.	It is beyond the scope of the EAG to comment on measurement limitations, including ceiling effects. However, the text has been changed to: "Another study that used standardised data from

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			three measures of motor function reported significant increases in type 1 and 2 patients. Type III patients, who had higher baseline motor function than type 1 and 2 patients overall, showed a trend towards improvement on motor scales, albeit that statistical significance was not reached (p = 0.051). [2]"
P239, para 1	"New final analysis data from NURTURE further supports the long-term benefit of nusinersen in presymptomatic patients."	This is not the final analysis of NURTURE, the final end of study data contains up to 8 years of data and has been provided to NICE, however Biogen acknowledge this was not available within the period needed for inclusion in this report.	Wording changed from "New final analysis data" to "Additional data".
P239, para 2	"No studies reported WHO motor milestones in type 1 patients"	WHO motor milestones for type 1 patients were reported in SHINE, however we acknowledge this falls under "mixed SMA types" in the report.	The wording has been changed to "No studies reported WHO motor milestones in type 1 patients specifically. However, data for this outcome and patient sub-group were reported in one record [3] that is included in the section "Multiple types", below."
P 241, Table 89	Type 1 EAP	context for type 1 EAP patients – please add a footnote or text to acknowledge that the data presented represents outcomes from entry into the MAA and not since the initiation of treatment. A further footnote should be added to highlight that type 2/3 walkers	We have added the details regarding EAP patients added to tables 89, 90, and 92 as footnotes. Additionally, we have added the details for type 2/3 walkers added to tables 89, 90 and 91.

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		cannot attain motor milestone beyond walking.	
P 246	"reported data from the RESPOND trial, showing that, at day 183 following nusinersen treatment, there were mean changes (SD) in CHOP INTEND scores of +6.7 ± 6.76 for people aged ≤ 9 months with 2 copies of SMN2 and +0.6 ± 5.50 for patients aged > 9 months with 2 SMN2 copies. Among non-sitters, the mean changes were +6.7 ± 6.76 for people aged ≤ 9 months with 2 copies of SMN2 and+3.6 ± 3.91 for those aged > 9 months with 2 copies of SMN2"	For context, it should be noted RESPOND is post OA use.	The EAG have clarified as follows: "reported data from the RESPOND trial (in post-OA use), […]".
P357, table 106	Difference in severity modifiers	Whilst the treated populations are different, SMA is a severe and debilitating disease across the spectrum – we do not see why presymptomatic treatment should have different severity modifiers and this calculation likely reflects differences in the model structure and underlying BSC disease progression rates which should be explored further. We have provided an appendix on this issue as requested by NICE.	The EAG thanks Biogen for their comment and for submitting an addendum on this. The EAG has now explored the use of consistent severity modifier across manufacturers as asked by NICE.

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Novartis

Comments on External Assessment Report	EAG response
On page 20, in the summary of EAG key issues: *"Roche did not account for treatment discontinuation in their economic model, reasoning that discontinuation from risdiplam was unlikely in clinical practice - a justification based on the trial data, REACH data, and clinical expert feedback.* *Why this is considered important:* *Not incorporating treatment discontinuation in the Roche models may favour risdiplam as the EAG's discussions with clinical experts suggested that people may discontinue or switch from risdiplam due to known adverse events, such as potential effects on fertility. The EAG also notes that the discontinuation data used in the models were based on short-term MAA follow-up, which may overestimate the sustained benefits from treatment over the patient's lifetime. In addition, discontinuation from nusinersen incorporated into the Biogen (nusinersen) model assume that patients discontinuing treatments would go on to receive BSC, accruing the costs and outcomes of BSC after discontinuation. However, in clinical practice, those discontinuing may switch to alternative DMTs rather than BSC alone. Due to the lack of robust evidence, the potential impact of treatment switching could not be modelled. Therefore, the EAG caution that assumptions surrounding treatment discontinuations may introduce additional uncertainty into the cost-effectiveness results."* Novartis agree with the EAGs conclusion that discontinuation of risdiplam is an important consideration for the economic analysis, given the impact that this would have on both costs and outcomes over a lifetime horizon.	The EAG thanks Novartis for their comment.
In Table 2, on page 46, the eligibility criteria for treatment with onasemnogene abeparvovec is described as follows:	The EAG have edited as suggested.

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"If presymptomatic SMA develops into type 1 SMA, OA is an available treatment option in certain situations" Novartis suggest the wording is amended to: *"Patients with type 1 SMA, if:* • *they are 6 months or younger, or* • *they are aged 7 to 12 months, and their treatment is agreed by the national multidisciplinary team."*[1] For clarity as to the 'certain situations' in which OA is recommended, and to avoid misunderstanding, as the current wording implies that a patient diagnosed with presymptomatic SMA may go on to develop type 1 SMA, whereas in practice a patient would be treated as soon as possible upon diagnosis, and a patient diagnosed pre-symptomatically would therefore be unlikely to go on to develop type 1 SMA. Type 1 SMA patients would likely be diagnosed symptomatically.	
On page 47, footnote *a* to Table 2, the definition provided is that of unsuccessful treatment with OA (as detailed in Appendix A to the risdiplam MAA)[2], but the description states "successful treatment", this should be amended to "unsuccessful treatment".	"successful treatment" has been amended to "non-successful treatment", which is the wording used in the risdiplam MAA.
In Table 7, on page 60, Biogen provided the following rationale for differences in the comparators considered in their analysis compared with those specified in the NICE scope: *"No direct evidence is currently available against risdiplam or onasemnogene abeparvovec; consequently, ITCs were performed with the aim to inform relative efficacy. However, limitations of the ITCs render them unsuitable to inform cost-effectiveness modelling. Therefore, this submission focuses on the comparison between nusinersen and BSC".* Conversely, Roche included OA as a comparator for risdiplam in the presymptomatic and type 1 SMA populations (pages 140 and 159): *"The company modelled nusinersen and OA as the comparators for presymptomatic*	The EAG thanks Novartis for their comment.

Comments on External Assessment Report	EAG response
populations. The decision model submitted by Roche included BSC as a comparator based on data from an internal natural history study. However, the company did not consider BSC a relevant comparator for the presymptomatic population, reasoning that patients are likely to receive a disease modifying therapy upon diagnosis of SMA, therefore overlooking the results comparing risdiplam with BSC" In the changes made by the EAG to the Biogen presymptomatic and type 1 models (Table 79, pages 215-216, and Table 80, page 218, respectively) the EAG highlight that exploratory analysis for nusinersen vs OA was undertaken. Additionally, on page 84, the EAG comment: *"Based on both the clinical context and the evidence available, the EAG cautions against the use of BSC as an appropriate comparator in the presymptomatic SMA population"* Novartis agree with the EAGs decision to conduct exploratory analysis for nusinersen versus OA, in line with the NICE decision problem, despite the acknowledged uncertainties in the indirect treatment comparisons. OA is routinely commissioned by NICE for presymptomatic and type 1 SMA and is established in UK clinical practice for these populations, and should therefore be considered as a comparator per the NICE manual.[1, 3-4]	
On page 87, and throughout the report, the EAG explain their decision not to consider caregiver utility in the base case analysis: *"The EAG acknowledges the importance of including the experience of informal carers in this appraisal; however, there are no standardised methodologies to quantify the impact on health-related quality of life from informal carers, and the data specific to SMA is scarce. Therefore, in the EAG base-case, models focussed primarily on the quality of life of patients. The data for informal carers were used and presented as an additional scenario for the purposes of*	The EAG thanks Novartis for their comment. The issue pointed out here could be a matter for discussion by NICE. However, in response to NICE's request, we have conducted additional analyses, using two different approaches to incorporating carer QALY increments and decrements.

Comments on External Assessment Report	EAG response
transparency, allowing an explicit assessment of the disease burden for patients alone, and for patients and their carers together" Additionally, on pages 12-13, the EAG describe further rationale for the decision not to consider caregiver HRQoL in the base case analysis: *"However, the two company submissions adopted markedly different approaches to incorporating informal carer HRQoL, relying on data elicited outside the clinical trials."* Novartis disagree that reliance on data elicited outside the clinical trials warrants exclusion of caregiver HRQoL from the base case analysis, given that the NICE reference case states *"If not available in the relevant clinical trials, EQ-5D data can be sourced from the literature"*.[5] Owing to the unavoidable small sample size in clinical trials in SMA due to the rare nature of the disease, HRQoL data elicited through trials would likely be associated with substantial uncertainty. As such, in the opinion of Novartis, reliance on HRQoL data elicited outside trials is necessary in SMA, for both patients and carers, in order to capture all relevant health effects of the disease, and should be considered in analyses given the substantial impact that SMA can have on caregivers.[6,7] Further, whilst the EAGs statement that there are no standardised methodologies to quantify the impact on health-related quality of life of informal carers is true, Novartis also do not believe this warrants exclusion of caregiver HRQoL from the base case analysis, as this would suggest that caregiver HRQoL should not be considered in the base case for any NICE appraisal, which does not align with the NICE reference case.[5] Rather than excluding caregiver HRQoL from both analyses, an alternative solution would be to explore scenarios for both treatments using the different approaches adopted by the two companies.	

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On page 89 and 100-101: *"it is likely that those discontinuing nusinersen may not transition to receive BSC alone, but instead may receive alternative disease modifying treatments. This would have implications for both the costs and outcomes, which are not fully captured in the current models"* Novartis agree with the EAGs conclusion that patients discontinuing nusinersen (or risdiplam) would not go on to receive BSC and would instead move on to subsequent treatment.	
Sections 6.3.2.12 and 6.3.3.11, and described on page 89: *"The EAG considers the company's approach of incorporation of severity modifier in QALYs gains in treatment of SMA to be appropriate, given the severity of the condition. However, the EAG cautions that applying a severity modifier may risk double counting if the health state utility values used to calculate the QALYs already reflect disease severity. Therefore, for transparency and explicit assessments the EAG assessed the impact of incorporating the severity modifier only as an additional analysis presented alongside the base-case"* Novartis agree with the EAGs decision to consider the severity modifier as an additional analysis alongside the base case, rather than within the base case, for the reasons provided. However, Novartis query the appropriateness of application of severity weights of 1.2 and 1.7 in the presymptomatic and type 1 analyses, respectively, given the calculations are based on a comparison with BSC, rather than with OA. As stated in Novartis' comment on the comparators considered in the analysis, OA is routinely commissioned by NICE for presymptomatic and type 1 SMA and is established in UK clinical practice.[1,3] As such, the calculation of future QALYs for those with presymptomatic or type 1 SMA under current NHS treatment should be estimated based on treatment with OA, not with BSC.[8] Whilst acknowledging that Biogen did not include OA as a comparator and therefore cannot calculate comparator QALYs through their own analysis, in the opinion of Novartis it is not appropriate to substitute BSC as the	The EAG thanks Novartis for their comment. The points raised here may be a matter for discussion by NICE; however, the EAG has now conducted additional analyses using consistent severity modifiers across both companies (as requested by NICE).

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comparator for the severity modifier calculation. This is supported by the EAG statement on page 145, discussing the application of the severity modifier in the Roche presymptomatic analysis: *"The base-case analysis presented comparing risdiplam with BSC met the criteria for a severity multiplier of 1.7 on the incremental QALYs; however, the BSC was not considered a relevant comparator in the presymptomatic population as almost all patients do get treated."*	
On page 140, with regard to the comparators considered by Roche in the presymptomatic analysis, the EAG comment: *"The base-case submitted by Roche for the presymptomatic population did not include BSC as an appropriate comparator, arguing that in current clinical practice patients diagnosed with SMA are expected to receive a DMT. However, the EAG is concerned about the gaps in clinical evidence that make comparisons between risdiplam and other DMTs highly unreliable.* *Considering the limitations in relative effectiveness evidence between DMTs, the EAG decided to focus the economic decision problem in the presymptomatic population on comparing risdiplam against BSC for analytical purposes, while acknowledging that current clinical practice is constantly evolving. Comparisons between risdiplam and other DMTs will be presented as scenario analyses using the evidence available, highlighting the caveats around the potential for bias."* Whilst Novartis acknowledge data limitations making a robust comparison between risdiplam and OA challenging, given that OA is routinely commissioned for people with presymptomatic OA, in the opinion of Novartis the rationale that "*current clinical practice is constantly evolving"* does not justify exclusion of OA as a comparator in the base case analysis.	The EAG thanks Novartis for their comment. Whilst we agree that OA should not be excluded as a comparator, there is currently limited evidence available to use it as a comparator in the base case. However, should relevant evidence become available in the future, OA should be used as a comparator. Despite the limited evidence, the EAG has conducted exploratory analyses using OA as comparator to both the Nusinersen and Risdiplam.
In Table 79 and Table 80 on pages 216 and 218, respectively, where describing the changes made to the presymptomatic and type 1 models, the EAG state that	The EAG thanks Novartis for their comment. Whilst we agree that assuming equivalence in treatment effect between Nusinersen and OA may not be justifiable, the

Comments on External Assessment Report	EAG response
for their exploratory analysis vs. OA, *"the treatment effect duration and the relative rate of decline for OA was considered equal to nusinersen."* Whilst both nusinersen and OA are disease modifying treatments, OA is a one-time gene therapy targeting *SMN1,* the genetic cause of SMA, whereas nusinersen is an *SMN2* splicing modifier, which does not address the genetic cause of SMA and does not fully restore SMN protein expression. Nusinersen requires chronic treatment and poses a risk of long-term motor milestone decline, as acknowledged by the EAG on page 95. As such, Novartis believe the assumption of equal treatment effect duration and equal relative rate of decline between the two treatments requires rationale.	assumption was made due to the lack of robust supporting evidence. Consequently, the comparison between Nusinersen and OA was evaluated only as a scenario analysis.

Roche

Clinical and economic comments		EAG response
Clinical effectiveness		
1a	Patient heterogeneity - the spectrum of SMA The EAG have reported on the spectrum of outcomes in individuals with SMA, which was highlighted by patient organisations and clinical experts and recognised by Roche. Timing of treatment initiation is another variable which has a significant impact on the outcomes of individuals with SMA. The awareness of SMA has increased in the UK, thanks to collaborative efforts of patient advocacy groups and clinical teams working with their community colleagues to educate on the early symptoms of the condition. There are anecdotal cases in neuromuscular centres of children being referred earlier than they would have been in previous years, however there are still sadly too many children who are diagnosed after symptoms have been present for weeks or even months. Between Jan 1, 2019, and Nov 1, 2024, 507 individuals with SMA were registered in the SMA REACH UK database. The mean age at diagnosis was 0·5 years (SD 0·4) for those with SMA type 1, 1·6 years (SD 0·8) for those with SMA type 2, and 2·9 years (SD 1·7) for those with SMA type 3 [4]. The effectiveness of newborn screening and impact of earlier treatment for infants with SMA in the real-world setting has been reported in a	The EAG thanks Roche for their comment.

Clinical and economic comments		EAG response
	nonrandomised controlled trial in Germany, Austria and Switzerland [5]. Patients born in two federal states in Germany underwent screening in a newborn screening pilot project (n=44 (18.8%)). All other patients were diagnosed after clinical symptom onset (n=190 children (81.2%)). All patients received standard care within the same health care system. Functional outcomes and thus the response to treatment were significantly better in the newborn screening cohort compared to the unscreened clinical symptom onset group. The mean (SD) age at start of treatment with 1 of the approved disease-modifying drugs was 1.3 (2.2) months in the newborn screening cohort and 10.7 (9.1) months in the clinical symptom onset cohort. In the newborn screening cohort, 40 of 44 children (90.9%) gained the ability to sit independently vs 141 of 190 (74.2%) in the clinical symptom onset cohort. For independent ambulation, the ratio was 28 of 40 (63.6%) vs 28 of 190 (14.7%). A UK government funded In-Service Evaluation of newborn screening for SMA has been announced, and supporters anticipate that this will lead to newborn screening being implemented across England and Wales in the coming years. As reported in the European nonrandomised controlled trial [5], treatment with a disease modifying therapy earlier in individuals with SMA will result in improved outcomes, which will have a positive effect on the individuals and families as well as reducing the cost and burden on the NHS and society [6]	
1b	<u>Patient heterogeneity - comparability of individuals receiving risdiplam or nusinersen in the real-world and in trials</u>	The EAG thanks Roche for their comments; we have responded to specific points within this comment below

Clinical and economic comments		EAG response
	The EAG has accurately reflected that the initial cohort of risdiplam treated individuals enrolled on the pre-licence Early Access to Medicines Scheme (EAMS) and NHS patients treated with risdiplam were more progressed compared to the nusinersen treated population. This is a direct result of the treatment landscape at the point at which risdiplam became available for use. As nusinersen was made routinely available in the UK before risdiplam and onasemnogene abeparvovec, any patients who were eligible for treatment were largely initiated on nusinersen. Historically (pre-licence), patients receiving risdiplam as part of the EAMS were ineligible for alternative licensed treatments, and inherently were either more progressed in their condition and couldn't receive nusinersen due to scoliosis or spinal surgery precluding intrathecal administration or had other clinical justification for not being able to receive nusinersen. The timing of availability of risdiplam compared with nusinersen has had an impact on the extent of the follow-up data available within the Managed Access Agreement data collection. The EAG stated that "From the paediatric registry, nusinersen had longer follow-up data available than risdiplam for motor outcomes (~4+ years vs ~1.5+ years, respectively)." Roche would like to confirm that longer term data has been reported in the SMA REACH paediatric report to NICE MAOG/EAG dated April 2025. The SMA REACH paediatric registry included 164 MAA cohort patients, and the most recent data cut taken in February 2025 included 3-year data for 17 individuals with SMA. Of these, n=3 were type 1, n=2 SMA types 2/3 non-sitters and n=12 type 2/3 sitters/walkers. The three-year available data set had been reduced from the numbers available at 30 months (n=50 all SMA	The EAG has changed the statement to "(~4+ years vs 3 years respectively)".

Clinical and economic comments		EAG response
	types, with n=6 type 1 SMA, n=14 type 2/3 SMA non sitters and n=30 type 2/3 sitters/walkers). Furthermore, the Managed Access Agreement heavily restricted patients (and their HCP) from switching therapies unless there was a strong clinical need to do so which means that the treatment landscape has been more static than other countries. As with the pivotal clinical trial data, the real-world evidence captured within the SMA REACH registry will have the initial cohort of risdiplam treated individuals representing a more progressed condition than those receiving nusinersen. In the current UK commissioning/ treatment landscape, patient selection for a DMT treatment is not driven by the status of a patient's condition (except in the case of scoliosis precluding IT access). Excluding SMA Types 0 and 4, the licensed indications and clinical eligibility criteria for nusinersen and risdiplam are identical, hence a new SMA type 1, 2 or 3 patient today would have the option for treatment with either DMT (with the further option of onasemnogene abeparvovec for Type 1 patients). Regarding the clinical development programmes for nusinersen and risdiplam, there were differences in the eligibility criteria for each of the studies that have been documented in the inclusion and exclusion criteria differences Tables 1, 2, and 3 in the April 2025 additional clarification questions submission document (4). The risdiplam clinical development programme enrolled a more heterogeneous, older population with more severe disability (scoliosis and contractures) compared to the clinical development programme for nusinersen, which makes comparison between the two treatments challenging, however an ITC of the two treatments is	The EAG noted the differences in eligibility criteria and agrees that the populations receiving the two drugs in the clinical development programmes were heterogeneous due largely to their respective timings. The EAG states their reasons for believing that an ITC is inappropriate in this case in section 11.6.2 of the report.

Clinical and economic comments		EAG response
	considered an appropriate and relevant methodological approach to assessing cost effectiveness - please refer to Company Comment 8. The EAG identified a single comparative study (5) and stated that the baseline imbalances in prognostic factors limited comparability. Roche would like to highlight that this study should be identified as investigating SMA Types 2 and 3. The children in the nusinersen group were on average 12 months younger at the start of treatment, far fewer had scoliosis, and scored about 10 points better in HFSME and RULM. The difference in RULM and HFMSE score after 3 and 6 months of treatment compared to the baseline showed significant changes in both groups (P-value <0.001). According to the results of the linear regression model, after adjusting for the baseline value of the HMFSE and RULM scores, no significant difference was observed between the two types of drugs used after three and six months in this study. When age of treatment, age of diagnosis, the number of SMN2 gene copies, and disease type was controlled, there was no significant difference in HMFSE and RULM scores between the two groups at 3 and 6 months (P-value >0.05). The differences in the populations on each treatment in the Ashrafi study reflects the real-world experience in the UK, with historically more severely affected individuals receiving treatment with risdiplam compared to those treated with nusinersen due to the eligibility criteria for the risdiplam Early Access to Medicines Scheme and the fact that nusinersen was the first disease modifying therapy available to people with SMA.	The EAG reported "…one study assessing the impact of both nusinersen (n=52) and risdiplam (n=73) treatment on **type 2/3** patients", and the numbers of types 2 and 3 patients are included in the characteristics of included studies in Appendix 6.

Clinical and economic comments		EAG response
2a	<u>Availability of data - lack of controlled trials for presymptomatic and type 1 SMA patients</u> Roche acknowledge that these were not placebo controlled trials as it was not considered appropriate or ethical to include a control arm within the RAINBOWFISH or FIREFISH studies due to the severity of the natural history of the condition, particularly as this natural history is very well established [7]. The randomised, sham-controlled trial of nusinersen in infants with type 1 SMA (ENDEAR) was terminated early after a positive interim analysis to allow for participants to enrol into an open label study [8]. Subsequent disease modifying therapy trials have not used a placebo arm. Survival data up to 60 months from the FIREFISH study has been shared with the EAG in the addendum dated July 2024 and the 24-month RAINBOWFISH data was submitted in the Clarification Questions response B1 in March 2025. Please see Company Comment 1 regarding a nonrandomised controlled trial investigating the effectiveness of newborn screening for infants with SMA in the real-world setting [5]. Functional outcomes and thus the response to treatment were significantly better in the newborn screening cohort compared to the unscreened clinical symptom onset group, with 40 of 44 children (90.9%) sitting independently vs 141 of 190 (74.2%) respectively, and 28 of 40 (63.6%) children identified by newborn screening walking independently vs 28 of 190 (14.7%) in those identified by clinical symptoms. Please see Company Comment 8 for the company position on ITCs. In addition, Roche does not think the statement "*Using evidence from single*	The EAG thanks Roche for their comment. The EAG acknowledges that it is not considered ethical to include a control arm in a trial of presymptomatic patients; however it remains the case that the results carry more uncertainty than a controlled trial. The EAG has included 5 year data from FIREFISH (for example in sections 13.4.2.1.2, 13.4.2.1.3, 13.4.2.2, 13.4.2.3, and so on). The final column in the table of included studies in Appendix 5 incorrectly states the follow-up time of FIREFISH to be 36 instead of 60 months, and this has now been changed. 24-month RAINBOWFISH data is included (as shown in the characteristics of studies table in Appendix 5 and sections 13.4.2.1.2, 13.4.2.1.3, 13.4.2.1.4, and so on).

Clinical and economic comments		EAG response
	arm trials may introduce bias in favour of the treatments under evaluation." is appropriate. It is uncertain if using evidence from single arm trials may bias in favour of the treatments under evaluation. The EAG's statement unnecessarily frames the evidence base as favouring risdiplam and nusinersen. The single arm studies may introduce uncertainty, but it is unclear whether using the evidence biases in favour or against the treatments and it is unfair for the EAG to conclude one way or another. Roche would also like to highlight that single arm evidence is appropriate in rare diseases where it would be unethical to withhold highly effective treatment to allow for a randomised controlled trial.	The EAG has edited this statement to read "… using evidence from single arm trials *where principles of randomisation and blinding cannot be applied*, may introduce bias *into the results, often* in favour of the treatments under evaluation" and added the following reference in support: Wang M, Ma H, Shi Y*, et al* Single-arm clinical trials: design, ethics, principles. *BMJ Supportive & Palliative Care* 2025;**15:**46-54.
2b	<u>Availability of data - lack of data in type 0 and type 4 SMA</u> The licence/marketing authorisation for risdiplam is for the treatment of 5q SMA in patients with a clinical diagnosis of SMA Type 1, Type 2 or Type 3 or with one to four *SMN2* copies. The risdiplam clinical trials included individuals with SMA types 1, 2 or 3 and presymptomatically those infants who had a genetic diagnosis of 5q-autosomal recessive SMA, including confirmation of homozygous deletion or compound heterozygosity predictive of loss of function of the *SMN1* gene - in the RAINBOWFISH study there was no maximum number of *SMN2* copies, though only 5/26 (19%) of the babies enrolled had 4 or more copies of the *SMN2* gene (and potentially could go on to develop SMA type 4) and no infant enrolled with fewer than 2 *SMN2* copies. Roche accept that there is no evidence from	We thank the company for their comment. The EAG agree that the marketing authorisation does not include type 0 or 4 SMA patients. However, as this was part of the NICE scope, the EAG must make reference to this matter.

Clinical and economic comments		EAG response
	pivotal clinical trials that demonstrates efficacy of risdiplam in individuals with SMA type 0 or type 4 - this is reflected in the marketing authorisation.	
3a	<u>Outcomes - lack of data considered important by individuals affected by SMA</u> With the evolving phenotype of SMA associated with DMT use, clinical and scientific understanding of outcomes and ability to capture data is also evolving. It is understandable that there is a relative paucity of evidence available on elements such as activities of daily living, ability to socialise, the impact on education or work engagement as well as the impact on carers and families, given the focus initially would have been demonstration of clinical efficacy and safety. Qualitative analysis of PROMs and the integration of PROM reporting within the MAA has meant that a narrative of these outcomes is included. The EAG highlight that "it was often not clear what treatments the people in the analyses were taking, making it challenging to find out more about what effect each of the treatments separately had on the lives of people with SMA and their carers" (Results; key findings, Qualitative analysis, pages 13-14). Roche appreciate that some of the verbatim submissions from the patient community may be challenging to attribute; there were attributable statements in the Patient Registry submission that clearly define the individual thoughts on risdiplam treatment, but the company does appreciate that it is not possible to draw conclusions from the limited data available. The paucity of data means that the holistic benefits of treatment are not possible to ascertain. The systematic literature review conducted by Warwick Evidence (MTA final	The EAG thanks Roche for their comment. The points raised here may be a matter for discussion by NICE.

Clinical and economic comments		EAG response
	protocol ID6195) incorporated exclusion criteria for published literature with a population who had received spinal fusion surgery following a diagnosis of scoliosis (due to its preclusion for safe administration of nusinersen), and history of surgery for scoliosis or hip fixation which may have led to exclusion of risdiplam publications. Evidence on risdiplam outcomes may have been missed for this reason. The paediatric SMA REACH April 2025 report (page 13) states: "... the initial treated cohort was mainly older and more chronic than more recently treated patients, they had more 'difficult' spines which prevented nusinersen treatment. Once the risdiplam drug approval was implemented and extended to babies younger than 6 weeks, the cohort of treated patients changed, becoming younger and therefore expected to have a better outcome." The nature of publication timelines may reflect this earlier cohort, potentiated by the global access to nusinersen prior to risdiplam authorisation; subsequently there may be a more balanced cohort of real-world outcomes available. Due to the evolving phenotype and increased scientific and clinical knowledge of SMA, there are evidence gaps around outcomes such as bulbar function, cognition, fatigability and patient reported outcomes within the registrational trials. These are particularly pertinent in the Type 1 patients who had historically passed away before these challenges became apparent. As we learn more about these outcomes, they may become a differentiating factor for treatment choice across the breadth of SMA types. However, there is no standardisation of bulbar functional tools that are	

Clinical and economic comments		EAG response
	assessed in clinical practice and hence real-world evidence publications report on different assessments in this domain. The trajectory of bulbar function deterioration is heterogeneous and disease modifying treatment intervention after SMA symptom onset has variable results in terms of bulbar function outcomes.	
3b	Respiratory function Evidence from the Clinical effectiveness SLR stated for nusinersen that "Stability or maintenance in respiratory function was generally suggested", (Results, key findings, page 12) is less definitive than the statement regarding respiratory function in the abstract ("Evidence also suggested that nusinersen provided stability for respiratory function"). For risdiplam, (Results, key findings, page 13) states "Evidence suggested maintenance of small increases or decreases in respiratory function, although evidence was sparse." Orthopaedic deformity progresses in children and adults with SMA, and respiratory impairment is a consequence of this as the thoracic cage is impacted as growth occurs. It could be postulated that the real-world evidence available in the literature reflects the use of risdiplam in those individuals who have spinal deformity and scoliosis and are unable to receive intrathecal administration of nusinersen. Roche would like to advocate for access to DMTs to be available for people who are on permanent ventilation or who have a tracheostomy. This was raised by a professional expert in the statement "Operating on the principle that those who are long term ventilated unnecessarily have a less good quality of life is an equality issue" (Page 327, section 13.5.6: Equality	The EAG thanks Roche for their comment. The points raised here may be a matter for discussion by NICE.

Clinical and economic comments		EAG response
	considerations). People with SMA types 1 and 2 who were on permanent ventilation or had a tracheostomy were eligible for enrolment in the risdiplam Early Access to Medicines Scheme (EAMS) - this was advocated for by the clinical and patient advocacy community when the EAMS was being set up in 2020. Twelve people (n=6 paediatric and n=6 adults) who were receiving ventilation support for more than 16 hours per day ('permanent ventilation') or had a tracheostomy ('SMA-PV') were enrolled in the risdiplam EAMS and have been receiving risdiplam through a compassionate supply scheme for almost five years. Ongoing supply has been reliant on the prescriber confirming that the individual has been obtaining clinical benefit from risdiplam treatment. SMA-PV was an exclusion criteria for pivotal clinical trials with DMTs due to permanent ventilation being an event to demonstrate disease progression. However, permanent ventilation or tracheostomy are not contraindications for risdiplam treatment. Motor function assessments mandated during the MAA have excluded individuals who were not able to perform the necessary movements, and permanent ventilation could be considered a proxy for severe disability associated with SMA and other neuromuscular conditions. There is paucity of published evidence of DMTs in SMA-PV. Roche Products Ltd. supported a Delphi consensus process with a panel of neurologists, respiratory consultants and physiotherapists with experience in managing individuals with SMA or SMA-PV. Statements that outline the clinical benefits associated with DMT use in people with SMA-PV and best practice recommendations regarding DMT use were developed through an evidence-based consensus process. Complete endorsement of the	

Clinical and economic comments		EAG response
	statement “PV alone should not preclude the use of DMTs in patients with SMA-PV” was achieved in the first voting round. Clinical benefits achieved from risdiplam treatment in SMA-PV includes stabilisation of motor function, and particularly upper limb function that has such an important role in maintaining a degree of independence. Examples within the Delphi consensus process included individuals who worked full time. Control of power chairs, computer mouses and communication technologies was called out as functions that have a disproportionate impact on severely disabled individuals' wellbeing. Stronger coughs, reduced salivary secretion and reduced suction requirements were also commented on, and this was postulated as a reason for fewer respiratory infections and associated hospitalisations. There are also reports of reduced fatigue and increased and clearer vocalisation. ATEND and the EK motor function scores were proposed as more appropriate assessment tools for individuals unable to perform RULM, CHOP-INTEND, or the RHS. It is important to remember that SMA is a progressive condition, whatever the baseline an individual is at when initiating a DMT, and without active treatment an individual will deteriorate and lose functions that are important to them. Stabilisation, or slowing down the deterioration, is valuable for the individual and access to DMTs should be based on a holistic appraisal and not just the requirement (or not) of permanent ventilation/tracheostomy [9].	
3c	<u>Fatigue and stamina</u> The EAG stated (Section 16.1.2: Clinical effectiveness - Fatigue and stamina) that “There was no available evidence for this outcome assessing	The text for this section has been edited to reflect differences between patient reported outcomes and clinical outcomes (i.e. 6MWT):

Clinical and economic comments		EAG response
	risdiplam treatment." Roche would like to highlight evidence available. In the JEWELFISH study, at 24 months an increase in the total distance walked in the six minute walk test (6MWT) was observed in ambulant patients. A decrease in fatigue was also observed (measured by change from baseline in the distance walked from the first to sixth minute of the 6MWT) [10].	With regards to patient reported fatigue and stamina, the evidence for nusinersen was mixed. Two studies among mixed type SMA reported improvement in fatigue, whilst one noted increased fatigue. There was no available patient reported evidence for this outcome assessing risdiplam treatment. For clinical measures of fatigue and stamina (i.e. 6MWT), nusinersen consistently showed improvements across different SMA types, while risdiplam had evidence from one study showing improvements in ambulant patients.
3d	<u>Impact on models</u> Please see Company Comment 4. Roche is disappointed that the EAG has excluded methods used by the company to account for disease-related complications, such as scoliosis, respiratory support and bulbar function. Roche appreciates that data for these complications is limited but feel that the EAG approach moves the analysis further away from capturing the full scale of SMA and the true value of DMTs. Roche has heard passionately from the SMA community of the importance that these disease impacts have on patient and carer quality-of-life (also see CS Document B, Section 3.13 [11]), and that there may be a general lack of understanding of the nuances of SMA. We have heard how loss or lack of mobility does not constitute the totality of the condition, and whether considering quality-of-life stratified by motor function only is appropriate. For example, the ability to breathe efficiently and swallow effectively are more likely to have a positive impact on the majority of people with SMA than the ability to walk or stand	The EAG thanks Roche for their comment. Whilst we agree that disease related complications such as scoliosis, respiratory support and bulbar function are likely to have a substantial impact on the patient quality of life, carer burden and healthcare costs, the supporting evidence is currently limited. The EAG was concerned the approach taken by Roche resulted in double-counting the disease-related burden in patient HRQoL in BSC, as the impact of disease-related events is likely to be included in HRQoL estimates of the disease. Moreover, there was a lack of evidence from the clinical studies around the impact of risdiplam on these disease-related events relative to BSC. Therefore, the EAG excluded the impact of these complications from the basecase analysis.

Clinical and economic comments		EAG response
	unaided, and impacts to bulbar and respiratory function are likely to have a substantial negative effect on patient quality-of-life and carer burden. During the managed access period, Roche made extensive efforts to generate additional informative data and improve the modelling of SMA as accurately as possible. This included conducting a utility study in people with SMA and their caregivers, but ultimately, due to data limitations, it was only possible to adopt a simplistic approach to modelling these benefits. Roche considers it inappropriate for the impact of these disease effects to not be considered in the EAG's model in any capacity. In line with the EAG, the company has removed these model features from the base case. However, the company emphasises that the economic results should be interpreted in the context of a rare disease, where the disease burden is significant and may not be fully reflected by the CEM. This is evident from the exclusion of factors such as bulbar function, respiratory support, and scoliosis from the model. So, the committee should consider the results alongside potential benefits that may extend beyond those explicitly captured in the model. While Roche recognises the limited data available specifically for these disease complications, we call for the EAG to acknowledge that the models, and the cost-effectiveness results, do not capture the full benefits associated with DMTs. Therefore any cost-effectiveness outcomes could be considered conservative. Additionally, it is unclear to the company why the EAG conducted a scenario analysis within the Type 2/3 models incorporating both utility decrement and additional healthcare costs associated with bulbar function only. Roche advocates for a model scenario	Additionally, it was important to exclude these complications from the base case to ensure consistency across the Biogen and Roche models. The EAG modelled the impact of bulbar dysfunction only in the scenario analyses for type 2/3 patients, based on consultations with the patients and carers. Nevertheless, we agree that the full burden of SMA cannot be adequately captured by cost-effectiveness models alone. This has been discussed alongside our findings from the qualitative research.

Clinical and economic comments		EAG response
	to be conducted in all models to consider the impacts of all disease complications. It is important for the committee to consider the potential benefits that may extend beyond those explicitly captured in the model.	
4	<u>Outcomes - insensitivity of tools to assess motor function to capture improvements considered important by patients, families and their carers</u> Roche agree with the EAG that the motor function assessments used within the MAA and clinical trials do not fully demonstrate the benefits that DMTs can bring to individuals with SMA due to the sensitivity of the scales used. We agree that the inclusion of the 0.1 utility increment may not adequately capture benefits for individuals with severe disability, and would like to emphasise the disproportionate impact of stabilisation/maintenance of small motor movements such as fingertip control have on independence in individuals who have very limited motor function. Similarly, the impact of improved secretion management on respiratory exacerbations is more significant in those severely affected individuals. Roche understand why the EAG attempted to use a pragmatic approach to capture the effect on patient health-related quality of life and agree with the 0.1 increment used to account for nuanced motor improvements. These nuances are described to great detail in the qualitative assessment in correspondence with patients, carers and clinical experts. This qualitative assessment is a real strength of the Newcastle EAG report. However, Roche is disappointed that the EAG has excluded methods used by the company to account for disease-related complications, such as	The EAG thanks Roche for their comment and would like to offer further clarification on this assumption. The EAG's analysis assumes that receiving a disease-modifying therapy, regardless of efficacy, increases patient HRQoL by 10%. Although this approach was not directly informed by trial evidence, the EAG implemented this as an assumption to capture additional treatment-related benefits not captured by improvements in motor function, therefore representing a favourable assumption to disease-modifying therapies. Please see the response to comment 3b on why the impact of disease related complications such as scoliosis, respiratory support and bulbar dysfunction was not included in the EAG's base-case.

Clinical and economic comments		EAG response
	scoliosis, respiratory support and bulbar function. Roche appreciates that data for these complications is limited, but feel that the EAG approach moves the analysis further away from capturing the full scale of SMA and the true value of DMTs. Roche has heard passionately from the SMA community of the importance that these disease impacts have on patient and carer quality-of-life (also see CS Document B, Section 3.13 [11]), and that there may be a general lack of understanding of the nuances of SMA. We have heard how loss or lack of mobility does not constitute the totality of the condition, and whether considering quality-of-life stratified by motor function only is appropriate. For example, the ability to breathe efficiently and swallow effectively are more likely to have a positive impact on the majority of people with SMA than the ability to walk or stand unaided, and impacts to bulbar and respiratory function are likely to have a substantial negative effect on patient quality-of-life and carer burden. During the managed access period, Roche made extensive efforts to generate additional informative data and improve the modelling of SMA as accurately as possible. This included conducting a utility study in people with SMA and their caregivers, but ultimately, due to data limitations, it was only possible to adopt a simplistic approach to modelling these benefits. Roche considers it inappropriate for the impact of these disease effects to not be considered in the EAG's model in any capacity. So, while Roche agree with the 0.1 utility increment to account for nuanced motor movements, Roche believe that the EAG should have included this in addition to capturing motor function health state utilities **and** impacts of disease-related complications or alternatively included a greater increment	

Clinical and economic comments		EAG response
	to account for the nuanced motor movements **and** impacts of disease-related complications that the EAG acknowledge are uncaptured as well.	
5	<u>Outcomes - heterogeneity in the motor milestones used to define disease progression in the model</u> Recommendations [12] made in the 2018 update on standards of care for SMA state that clinical assessments in SMA should focus on the musculoskeletal system and related functional impairments, assessing strength and range of joint motion, relevant motor functional scales and timed tests to monitor aspects of function that reflect activities of daily living. The choice of scale should be based on the patient's age, SMA type and neurological status and should objectively assess the individual's functional status. It has been highlighted by clinical experts and patient advocacy groups that SMA manifests as a spectrum, with individual variation around outcomes within definitions of the types of SMA. The motor function assessment conducted for each individual should be chosen depending on age and functional ability; there are acknowledged and reported advantages and disadvantages of each scoring system, such as behavioural states and compliance being taken into account, sensitivity, and which muscle groups are assessed and there is some overlap between the motor function assessments that may be used. However, each scale rates individuals' in a different way, and it is not possible to directly translate scores from one scale to another [13]. Roche has acknowledged this challenge (see Roche clarification responses	The EAG thanks Roche for their comment.

	Clinical and economic comments	EAG response
	March 2025, B1 [14]) - Roche advocated that clinical expert advice was sought to assess the appropriateness of comparing BSID-III or HINE-2 milestones with WHO milestones in the study cohort. Outcomes in the RAINBOWFISH study (published in the NEJM since our previous submission [15]), in which the Bayley Scales of Infant and Toddler Development (third edition, BSID-III) were used as the primary outcome measure; these were compared to the WHO windows for healthy children. Hammersmith Infant Neurological Examination, Module 2 (HINE-2) scoring of motor milestones was assessed as a secondary outcome in the RAINBOWFISH study. While HINE-2 milestone attainment could plausibly align with WHO motor milestones in the presymptomatic cohort, equivalence between the two scales has not been explored. Extreme caution should be taken in extrapolating the same connection for any symptomatic cohorts. The natural history of individuals with SMA type 2 and 3 suggests that they would experience declines in both RULM and MFM32 scores and appreciate the EAG highlighting that WHO motor milestones are insensitive to small changes [16,17].	
6	<u>Costs associated with administration of risdiplam</u> The EAG included comments regarding the administration and dispensing of risdiplam (Page 414, Section 15.3 Qualitative analyses surrounding economic impact and finances). "One patient expert submission (adult with SMA) noted that risdiplam would have less impact on the NHS because it is administered at home. However, a professional group submission also	The EAG thanks Roche for their comment.

Clinical and economic comments		EAG response
	noted that specialist pharmacy knowledge and dispensing was required when prescribing risdiplam, implying a greater level of training needed to dispense the treatment." The risdiplam licence states that "Treatment with Evrysdi should be initiated by a physician with experience in the management of SMA." Risdiplam is prescribed in neuromuscular specialist centres as required by the High Cost Drugs route via Blueteq, and the prescribing consultants manage the patients routinely with no onerous monitoring necessary. The vast majority of risdiplam (around 99%) is dispensed by a Roche funded homecare vendor who manage prescriptions, reconstitution and deliveries direct to patients homes through cold chain delivery. Home delivery/dispensing in the community addresses one of the key drivers in the NHS 10 year plan of more care being available on people's doorsteps, and also VAT savings are realised when risdiplam is not dispensed by hospital pharmacies. Risdiplam's oral route of administration offers patients convenience and avoids the need to travel (in some cases long distances, and often utilising NHS transport services due to the disabling nature of SMA and incurring significant personal costs when hotel accommodation and equipment hire is necessary) to a specialist neuromuscular centre to receive treatment. In addition, risdiplam's at home administration does not require any additional NHS capacity or resource to deliver, hence it does not have a treatment administration tariff. In the small number of cases where risdiplam is dispensed by the hospital pharmacy, reconstitution is required which takes a few minutes without	

Clinical and economic comments		EAG response
	specialist equipment being required. Instructions for reconstitution are clearly described in the Summary of Product Characteristics.	
Economic		
7	Summary of Roche position on economic models Roche understands that, as part of a multiple technology appraisal (MTA), a single analysis considering both treatments is required using one trusted and executable cost-effectiveness model. Roche is pleased to read that the EAG considers the Roche models were logical and appropriate. However, it is clear that facilitating an open and transparent appraisal of limited evidence in rare conditions is not without considerable challenges. For this iteration of EAG assessment, Newcastle have decided that the most appropriate mechanism to assess the cost-effectiveness of risdiplam and nusinersen for SMA is to consider the value of each treatment versus BSC in standalone models. As explained in Comment 8 and Comment 9, Roche has issues basing the whole cost-effectiveness value on obsolete and irrelevant BSC comparisons. However, Roche also considers the approach to consider cost-effectiveness of multiple treatments in separate models at odds with the reasoning, spirit and technical rigour expected in a multiple technology appraisal. A key challenge with the new EAG modelling approach is that, due to the range of alternative analyses in the various populations and the need now for the EAG to perform these in two separate confidential models, it is increasingly difficult to understand the real implications of alternative EAG	The EAG thanks Roche for their comment. We note that the points raised may be a matter for discussion by NICE.

Clinical and economic comments		EAG response
	assumptions. These results will be considered in committee decision making and the current approach means that Roche and other stakeholders will be entering the committee meeting without a full picture and little indication of the cost-effectiveness of risdiplam and other treatments for SMA and key drivers of model results. Roche is unaware of the cost-effectiveness implications that alternative scenarios have, or the key inputs in the EAG analysis that drive cost-effectiveness results in the Biogen analysis. An indication or explanation of the impact of key scenarios would allow Roche, and other stakeholders, to prepare to input and respond as best as possible. Roche would welcome the sharing of magnitude and direction of change associated with alternative scenarios to aid interpretation of model drivers. Roche fails to understand how the committee will use the various (potentially conflicting outcomes) for decision making. It is imperative that NICE come to a coherent, trustworthy and timely recommendation for this important and underserved SMA population. The NICE process for this MTA has already been considerably delayed, causing untold uncertainty, anxiety and stress on the clinical, patient and carer communities. Roche advocates for timely positive guidance for both treatments so the community can realise the importance of these transformative treatments for people with SMA. Negative guidance would only serve to increase uncertainty and anxiety for patients and their carers and risk the regression of substantial clinical improvements these treatments have allowed.	

Clinical and economic comments		EAG response
8	Summary of Roche position on 'Exploratory analyses' The EAG report makes it clear that the EAG's position in this appraisal is to ignore reasonable, methodologically robust analyses comparing DMTs to each other. As in response to the Warwick EAG report, Roche would like to highlight key areas associated with the ITC analyses conducted by Roche to facilitate these comparisons. We would like to highlight two key areas regarding ITC and population adjustment methods, as they are crucial for informing models and aiding decision makers. The current evidence in the models has limitations, such as small sample sizes and heterogeneity in baseline characteristics across studies, which we have acknowledged in our published work and agree with the EAG assessment. 1. Our feasibility assessment of conducting Matching-Adjusted Indirect Comparisons (MAIC) to compare treatment efficacy in infants treated with risdiplam to those treated with nusinersen or gene therapy showed that numerical differences in baseline characteristics, including prognostic and predictive factors, further decreased the already small sample size by approximately 50%. Under these conditions, the existing literature does not support performing MAIC (or Simulated Treatment Comparisons) as the results may be biased or unstable due to the small sample size, and the findings may not be generalisable. This poses a risk that decisions based on limited evidence could lead to incorrect conclusions about the effectiveness or safety of treatments [18].	The EAG thanks Roche for their comment. We note that the points raised may be a matter for discussion by NICE.

Clinical and economic comments	EAG response
Therefore, we propose that these limitations be acknowledged in the written report on the MAIC for the presymptomatic population. Results should be interpreted with caution and should be treated as exploratory and of limited statistical power, with the current evidence being insufficient to draw conclusions on efficacy or safety differences. 2. In our published work, "Long-Term Comparative Efficacy and Safety of Risdiplam and Nusinersen in Children with Type 1 Spinal Muscular Atrophy" [19], we conducted extensive scenario analyses for matching factors and outcomes to select the important prognostic and predictive factors for population adjustment, and highlight any possible biases due to factor selection in the outcome comparisons explicitly comparing children treated with risdiplam to those treated with nusinersen. To avoid overfitting (due to correlations in the baseline characteristics) and improve the reliability of the results, our main model only included factors with the highest contribution towards population imbalances at baseline. Including all available factors was in fact one of our scenarios and did not show significant impact or deviation from the results of the main model. Additionally, we accounted for differences in assessment schedules and matched for these to limit bias in outcome comparisons due to more frequent visits. We propose that the risks of matching for all available baseline characteristics be highlighted in the written report and suggest considering only those factors contributing to population imbalance. Furthermore, the importance of matching for differences in schedules should be emphasised to minimise bias. Addressing	

Clinical and economic comments		EAG response
	these points will ensure that the comparisons more accurately reflect the true treatment effect. Therefore, we propose that the methods and results from our peer-reviewed publication pertaining to the type 1 population on risdiplam versus nusinersen to be used to inform the cost-effectiveness model and decision making for this particular population. As in the two points given in response to the Warwick EAG report, Roche acknowledges the important differences in trial populations and highlights the extensive sensitivity analyses and testing performed in order to facilitate a comparison between risdiplam and other DMTs. Roche would argue that the current Newcastle EAG approach moves further away from facilitating a robust informative comparison. The current approach has limited 'base case' analyses to risdiplam versus BSC and nusinersen versus BSC only. The EAG's methods to facilitate this comparison opts to use each individual company model separately. Roche argues this lacks validity, goes against the spirit of the MTA process, and does not solve the underlying issues associated with differences in trial populations. Roche struggle to understand how the analyses presented by the EAG: • 3 'base case' analyses comparing risdiplam and BSC in the Roche cost-effectiveness model • 3 'base case' analyses comparing risdiplam and BSC in the Biogen cost-effectiveness model	

Clinical and economic comments		EAG response
	• 3 'exploratory' analyses comparing risdiplam, nusinersen and onasemnogene abeparvovec in the Roche cost-effectiveness model will be used to inform committee decision making. The current EAG approach of comparing cost-effectiveness outcomes generated in these standalone models does not solve the uncertainty associated with notable differences in the eligibility criteria between nusinersen and risdiplam. This EAG approach, the MTA process more generally, and the need to protect commercial information makes it very difficult to validate and verify analyses using Biogen's models. Roche argues that the most appropriate comparison, and one that fully addresses the final NICE scope and remit for this MTA appraisal, is a single model that includes a full comparison between the interventions.	
9	<u>Comparison to best supportive care</u> As outlined in the previous response to the Warwick EAG report, and stated in response to Newcastle EAG clarification questions, Roche questions the relevance of a cost-effectiveness comparison against best supportive care (BSC). However, the statements in the current EAG report miss the nuance of our stance on BSC, such as "*The base-case submitted by Roche for the presymptomatic population did not include BSC as an appropriate comparator*". The company base case analysis provides cost-effectiveness results to all treatments included in the NICE scope, i.e. BSC, nusinersen and onasemnogene abeparvovec. As explained in response to Newcastle EAG's clarification questions earlier this year, as there is no newborn	The EAG thanks Roche for their comment. We note that the points raised may be a matter for discussion by NICE. We have clearly stated in our report that BSC may not be an appropriate comparator treatment in SMA patients. However, to maintain consistency and comparability of company models, we have used BSC as a treatment comparator in order to facilitate this MTA.

Clinical and economic comments		EAG response
	screening for SMA in the UK, the only patients that could be considered 'truly' presymptomatic would be those who are specifically tested prenatally or at birth as they have parents or siblings with SMA. Even then, there is clinical theory that SMA-related damage could occur *in utero*. This population is extremely small in the UK and likely less than one incident patient per year. Therefore, for the majority of the 'presymptomatic' population, by nature of their presymptomatic state and lack of a diagnosis, patients would not be aware of their SMA until they become symptomatic and are diagnosed. Upon diagnosis, it is highly unlikely that any patient would opt for BSC. All patients would then likely start treatment with disease modifying treatments in line with the Type 1 or Type 2/3 models. For the few patients who are diagnosed presymptomatically, physicians would not recommend BSC as an option and it is highly unlikely that parents would opt for it. In the future, when newborn screening becomes available, this stance will not change. The company understands that this general assumption can be extended beyond the presymptomatic population to the Type 1 and Type 2/3 symptomatic populations. Roche understands that the vast majority of patients engaging in an SMA clinical pathway are treated with DMTs. So, any comparison to best supportive care is likely irrelevant to the NHS and the vast majority of people with SMA. This view has been validated and confirmed when speaking to the wider patient, carer and clinical SMA community who believe that BSC is not a relevant or clinically acceptable treatment option for most people with SMA. This view was presented in	

Clinical and economic comments		EAG response
	response to the 2024 Warwick EAG report and reiterated to Newcastle EAG in the two rounds of clarification questions in early 2025. Published research and national reports have shown that there is significant variation across the UK in neuromuscular standards of care and services both regionally and between paediatric and adult services. Many adults cannot access BSC on the NHS, and BSC requires a multidisciplinary approach and is tailored for individual patients. This includes the monitoring and support of patients in the absence of active disease modifying treatment and relies on the prevention and treatment of co-morbidities such as swallowing and feeding difficulties, scoliosis and thoracic deformity, contractures, and respiratory insufficiency. Roche has heard from the SMA community that access to BSC is not consistent across the country and many patients struggle to benefit from consistent care. The 2022 Muni-Lofra publication reported limited access to care and provision for patients with SMA, with half of the study population consistently not accessing full multidisciplinary care [20].Since the start of the managed access period, the proportion of SMA patients accessing care through DMTs has increased. With increased use of DMTs, the prognosis of people with SMA has increased, which should be celebrated. Now, as the managed access period is reaching its conclusion, Roche has been collecting insights from clinical experts on whether a population of patients exists who are: 1. Eligible for treatment with a DMT, and 2. Not previously treated with, and discontinued from, a DMT, and	

Clinical and economic comments	EAG response
3. Engaged in the healthcare service and are actively opting to receive BSC over one of the available DMTs. Led by insights from patient advocacy groups and clinical experts, Roche believes that this population exists only for a very small proportion of patients currently engaged with a specialist centre. Market research through conversations with multiple clinicians, responsible for the care of over 300 SMA patients, it is clearly indicated that this proportion is very small. REACH registry data (**Error! Reference source not found.**), as well as clinical opinion and Roche market forecasting data (**Error! Reference source not found.**) indicates that the vast majority of patients with SMA are receiving treatment with disease modifying therapies. For example, clinical opinion to the company backed up by data gathering in key treatment centres in the UK from October 2024 indicated that 0 eligible paediatric patients receive BSC over disease modifying therapies (**Error! Reference source not found.**). This is also supported by patient and carer advocacy groups who promote early intervention with disease modifying therapy. For the adult population, data gathered through clinical conversations, presented in **Error! Reference source not found.**, suggests that only [redacted] of [redacted] ([redacted]%) patients sampled were receiving BSC instead of a disease modifying therapy and, when accounting for those who had previously discontinued a disease modifying therapy, this number shrinks to [redacted] of [redacted] ([redacted]%). Furthermore, the June 2024 REACH report, presented in Table 4, indicated that only 33 of 426 (7.7%) are still classed as 'natural history', which the company interprets to relate to BSC. The REACH data covered	

Clinical and economic comments	EAG response
more sites than the Roche gathered data, but there was strong alignment in rates of BSC in centres that featured in both datasets. Therefore, for the overall population sampled in Roche data gathering, only [redacted] of [redacted] ([redacted]%) people with SMA were receiving BSC instead of disease modifying therapy at first line (**Error! Reference source not found.**). So, to summarise: • In the presymptomatic and Type 1 populations, there are likely to be <1% of patients who engage in the healthcare system and actively choose BSC as their initial treatment option, this would only be the case if patients are so severely affected at the time of diagnosis that palliation is the route of choice. • In the Type 2/3 paediatric population, the clinical opinion and evidence allude to a rate of 0%. The proportion is slightly higher (<5%) in the adult Type 2/3 population, but still very small. This indicates the importance of intervention with disease modifying therapies to patients, carers and their clinicians. It also calls into question the relevance of a cost-effectiveness comparison to BSC when it is not a reasonable treatment option for over 95% of the eligible population. Given the very small proportion of patients who receive BSC as first-line treatment, Roche question the appropriateness of an incremental comparison to BSC. Roche would like to understand why the EAG think a comparison to BSC is the most appropriate, other than ease of analysis. Roche understands that a comparison versus BSC may well be easiest from a process point of view, but this in of itself is not a reason to base an	

Clinical and economic comments		EAG response
	important appraisal in a rare and underserved population on cost-effectiveness analyses against an irrelevant comparator. Roche believes that the most appropriate comparison for NICE to consider the vast majority of the SMA clinical care pathway is one that reflects the true proportion of care in the NHS.	
10	<u>Uncertainties</u> The EAG have highlighted a list of key issues and uncertainties in their analysis. However, Roche considers it important to reference the original list of uncertainties outlined by the NICE committee in TA755 and consider the extent to which these have been resolved or reduced by the period of managed access. In the risdiplam Managed Access Agreement, Section 5.1, the committee listed: • The suitability of the model for decision-making. • Long-term benefits with risdiplam are uncertain. • Methodological challenges and uncertainty associated with inclusion of caregiver utility values. • The approach to account for risdiplam's additional benefits that currently are not captured in the clinical outcomes and economic model. • The committee expect further data collection will allow for a new model to be presented when the guidance is updated.	The EAG thanks Roche for their comment. We believe that we have highlighted and discussed all the key issues with respect to the current MTA, and to the best of our knowledge, in our assessment report. However, we agree anything that we may not have covered is a matter for discussion by NICE.

Clinical and economic comments		EAG response
	Roche considers that these uncertainties should have featured in the EAG's decision problem, and the efforts made by the company to resolve overarching uncertainty during the period of managed access should have been discussed. To summarise: • To address the suitability of the model for decision making: ○ Roche conducted a workshop including a range of health economics and patient experts, to advise on the uncertainties flagged by the committee as part of TA755 and how these could be addressed. The feedback received during this workshop was subsequently considered for updating the economic analyses ahead of the resubmission (please also refer to CS Document B, Section B.3.2.2, for additional details). It was discussed that an economic model cannot capture all aspects of SMA (also mentioned in CS Document B, Section B.3.13), and is a well-documented challenge, particularly in the case of rare diseases. ○ All models were subject to an external quality assurance procedure, which included technical validation of key model inputs and calculations. Any issues or errors were documented and addressed in the final version of the models. ○ Roche further conducted dedicated HCRU (informing the base case health state costs across all three economic analyses) and utility studies (informing scenario analyses for caregiver utilities across all three economic analyses).	

Clinical and economic comments	EAG response
○ Efforts undertaken by Roche to validate the originally submitted models, and update them in line with expert advice and available data, appears to also have been recognised by the EAG who decided to use these models (with relatively limited additional changes) as the basis for their preferred analyses. The EAG explained that they considered that the models were reasonable and captured the clinical pathways well. ○ *Roche considers this issue has been resolved.* • To reduce uncertainty in the long-term benefits of risdiplam: ○ Further data were collected in the SUNFISH, FIREFISH and RAINBOWFISH trials, which, alongside the SMA REACH real world evidence, has shown that motor function, survival and quality-of-life benefits with risdiplam have been maintained over the long term. ○ It was also possible to incorporate longer term data from more recent SUNFISH, FIREFISH and RAINBOWFISH data cuts, where available, into the economic analyses; in addition, data from SMA REACH were used in selected scenario analyses and otherwise used to validate selected assumptions in the models (around treatment discontinuation). ○ Roche considers the longer-term data collected in the managed access period goes some way to resolving this	

Clinical and economic comments	EAG response
issue, however it is unlikely that further data collection will resolve long-term uncertainty entirely. • To investigate and address the methodological challenges and uncertainty associated with inclusion of caregiver utility values: o During the managed access period, Roche conducted a new utility study to collect data for SMA patients and their caregivers. Health economic and academic experts specialising in utility methods, alongside SMA patient groups, were consulted to determine the most appropriate methodology to collect the data. o Methodological challenges and uncertainty associated with the modelling of caregiver utility values were also investigated during managed access in order to overcome the "QALY trap" around life extension for patients and carers, including investigating the health effects associated with bereavement (e.g. depression, anxiety and inability to participate in usual activities due to grief), consideration of wellbeing as an alternative to health-related quality-of-life and carer modifier/multiplier for family health spillovers (as detailed in Section B.3.3.5). This also informed a peer-reviewed publication [21]. o Despite these efforts, ultimately the data was limited by small sample sizes. Whilst robust data to inform economic analyses from this research was limited, the work helps to further highlight and define the continued uncertainty around	

Clinical and economic comments		EAG response
	patient and caregiver quality-of-life for people with SMA and their caregivers, and rare diseases more generally. ○ Roche consider that this was implausible to resolve during the managed access period and requires broader long term health system collaboration. • To account for risdiplam's additional benefits that currently are not captured in clinical outcomes and economic model: ○ Roche undertook healthcare resource use and patient and carer utility studies, as well as Delphi panels and validation, to understand the originally uncaptured benefits' impact on the healthcare system, people with SMA and their caregivers. Roche is aware that these efforts only scratch the surface considering the complexity of SMA. Unfortunately, none of the efforts to capture these additional benefits in the economic analyses made it into the final models due to limited data to inform a robust economic analysis. Examples include the stratification by treatment response, modelling of upper limb function, and additional QALY benefits associated with risdiplam. The re-submitted models included incremental utility impacts for disease-related effects, so Roche is saddened to read that some of the impacts Roche had attempted to quantify have been dismissed by the EAG in their report. ○ *Roche considers that this was implausible to resolve during the managed access period and requires broader long term health system collaboration.*	

Clinical and economic comments		EAG response
	○ A new updated model has been presented, including longer term follow-up data from SUNFISH and FIREFISH studies, and an additional presymptomatic analysis with RAINBOWFISH data. ○ *Roche considers this issue has been resolved.* From a broader process perspective, Roche considers it highly important that the activities outlined above are documented in the assessment report and considered by the NICE committee at ACM1. The purpose of managed access is to give people faster access to promising new treatments whilst more evidence is collected to address the uncertainties identified by the NICE committee. Roche considers that, by not highlighting the committee's original views and the progress that has been made towards resolving any uncertainties, there is no differentiation between a new evaluation and a managed access review. This approach runs the risk that uncertainties which were resolved at the first appraisal, or during managed access, are reopened/re-discussed at committee, resulting in a delay to a routine commissioning decision. This also ignores the time and level of funding this data collection has required, undermining the energy and effort of all stakeholders involved. Roche would implore the EAG and NICE to: • Consider the activity and progress detailed above in the assessment report. • Recognise the efforts made by the SMA clinical and patient community to close evidence gaps and reduce/manage uncertainty during the managed access period.	

Clinical and economic comments		EAG response
	• Consider pragmatism in decision-making with regards to the uncertainties for which a resolution was highly unlikely to be achieved during a managed access time frame. • More broadly, consider the process for managed access review and how to link the re-appraisal to the original NICE evaluation. Roche would like to take this opportunity to thank the SMA community for their time, commitment and collaboration in facilitating data collection during managed access, acknowledging that this placed additional burden on the patient and caregiver community, and the NHS. The managed access period has, amongst other things, served to highlight the difficulty in generating robust evidence for rare diseases, particularly in children and their caregivers, and there are limitations to fully resolving some of the overarching uncertainties over a data collection period of 3 years.	
11	<u>Carer health-related quality of life</u> As explained in CS Section B.3.3.5, given the substantial amount of care that SMA patients require from family members or professional carers, and in line with the approach taken in TA588, TA755 and the NICE reference case, HSUVs are included in the model base case for both patients and carers. Section 3.14 of TA755 final guidance outlines that the original company base case used an additive approach and assumed that caregiver health-related quality of life increased linearly with each motor milestone that was met. There were discussions during TA755 regarding the appropriateness of an additive or decrement approach to capture carer quality of life.	The EAG thanks Roche for their comment. We have now considered the methodological differences between Roche and Biogen in calculating carer quality and conducted additional analyses using both decrement and increment approaches, as agreed with NICE. However, anything beyond that may be a matter for discussion by NICE.

Clinical and economic comments		EAG response
	As part of the data collection period, Roche committed to conducting a new utility study to collect new utility data for both SMA patients and their respective carers (discussed in CS Section B.3.3.5). Methodological challenges and uncertainty associated with the modelling of caregiver utility values were also investigated during the MAA period, in order to overcome the 'QALY trap' around life extension for patients and carers. Various methods were explored, including accounting for the health effects associated with bereavement (e.g. depression, anxiety, and inability to participate in usual activities due to grief), consideration of wellbeing as an alternative to HRQoL and carer modifier/multiplier for family health spillovers. In this consultation step, NICE and the EAG have asked Roche and Biogen to consider the most appropriate approach to capture important carer health-related quality of life. In the Roche submitted approach as explained above, following efforts made in the data collection period, the Roche approach for this appraisal considered consistency with the previous NICE appraisals. Carer utility from Bastida et al. was assigned to the lowest health state, general population utility assigned to highest health state, values for intermediate health states were evenly distributed, applied as a decrement. The analysis considered different utility values between presymptomatic/Type 1 SMA and late onset SMA, assuming that the level of carer impacts are different dependent on population. The EAG's interpretation that the analysis doesn't account for bereavement effect or carer 'QALY trap' as per expert opinion is not entirely correct, the model does have the option to limit the application of carer	

Clinical and economic comments		EAG response
	disutilities (to the period of BSC life expectancy) and/or bereavement disutilities (to the period of extended life expectancy with risdiplam). In contrast, the Biogen approach was described as a 'novel approach' to avoid the carer 'QALY trap'. In Biogen's approach, the caregiver utility value for lowest health state is used as baseline, then a utility increment for each health state is calculated and applied, general population utility is used for highest health state. The Biogen approach uses equivalent utility values for each SMA type, assuming it is the health state that drives utility for carers. Finally, carer utility is not captured upon patient death, which avoids favouring highest mortality interventions and avoiding the carer QALY trap. Roche would argue that the Biogen approach is similar to the Roche approach submitted by the company in TA755, described above. Roche understands that the decrement and increment approach should result in similar outcomes. Roche understands that the Biogen approach rewards occupancy of the better states via incremental gains and the Roche approach penalises occupancy of the worse states through decrements. This can lead to different outcomes due to the predicted survival and health state occupancy over time in the different arms of the different models. In the interest of consistency between company approaches, Roche believe that the Biogen is an appropriate method to capture carer quality of life, and advocates for the EAG to use this method consistently in their base case analyses in Roche and Biogen models. It is imperative that the EAG consider the health-related quality of life of, not only people with SMA, but their wider caring support network. Carers play a highly important role in the	

Clinical and economic comments		EAG response
	lives of people with SMA, and it is important that the benefits of DMTs on the lives of carers are captured in the analysis. In addition, Roche would advise the EAG to consult with their clinical experts to understand whether the assumption that carer impacts are the same across SMA Types i.e. applied consistently by health state (would "Not Sitting" present the same burden to carers for Type 1 vs Type 2/3 patients?).	
12	<u>Severity</u> In this consultation step, NICE and the EAG have asked Roche and Biogen to consider the most appropriate approach to capture severity in the company models. The EAG highlighted that the Roche approach was inappropriate, as the severity modifiers were applied to patient and carer QALYs, not patients only. Roche confirms that the Roche models have been adjusted so that the severity modifier is not applied to caregiver QALYs. Instead, caregiver QALYs are added to the patient QALYs as part of the ICER calculation after the application of the modifier to patient QALYs. This approach aligns with the recommendations outlined in TSD23 [22]. In the updated Roche models, the presymptomatic and Type 1 models estimate a 1.7x modifier and the Type 2/3 model estimates a 1.2x modifier. Regarding the Type 2/3 model, the EAG's base case assumptions return an absolute shortfall of 17.16 QALYs, just short of the 18 absolute short fall threshold for a 1.7x modifier. As highlighted in other comments, Roche believe that the EAG analysis is not capturing the true value of DMTs. We believe that if these benefits could	The EAG thanks Roche for their comment and adjustments/updates in their model. The EAG have undertaken additional work to align the use of severity modifiers across the Roche and Biogen models as requested by NICE.

Clinical and economic comments		EAG response
	be captured in the models, the absolute shortfall would be greater than 18 and a 1.7x modifier would be appropriate. Roche advocates for a consistent severity modifier to be applied in each SMA type. Given the severity of the condition and the impact to both life expectancy and health-related quality of life, Roche believes that the most appropriate modifier to reflect the totality of the condition would be 1.7x. Roche believes a 1.7x modifier should be used consistently in all Roche and Biogen analyses. Roche do not believe how a condition such as SMA does not meet the highest severity criteria and strongly suggests the most appropriate modifier to be 1.7x.	
13	<u>Resource administration cost</u> Section 6.3.2.8 states the resource administration cost of nusinersen in the Biogen and EAG models is £836 per administration (using diagnostic spinal puncture as a proxy). This does not align with the resource administration costs that were confirmed in writing by the NHS England Highly Specialised Services team (email received by Roche on 14 March 2024), which states: [redacted]	The EAG thanks Roche for their comment. The costs used for the EAG's base-case analysis were based on the latest publicly available evidence from the NHS National Tariffs. We were unable to validate the resources administration costs estimate from the NHS England Highly Specialised Services team, therefore we maintain the base-case assumption. However, this may be a matter for discussion by NICE.

	Clinical and economic comments	EAG response
	[redacted] The EAG's application of the proxy administration costs for nusinersen underestimates the resource costs for nusinersen in both the first year of administration (6x treatment administrations total, including 4x initial loading doses) and maintenance years (3x treatment administrations). Hence, the resource costs for nusinersen presented in the assessment report and total administration costs calculated in the models are not an accurate reflection of the true costs to the NHS.	
14	<u>Uncertainty in patient costs for severe health states</u> During the managed access period to address uncertainty highlighted by the committee in the original risdiplam and nusinersen appraisals, Roche conducted a HCRU study. As detailed extensively in CS Section B.3.5.2, robust evidence was sparse following the cost and resource-use SLR, particularly in relation to indirect (non-medical) costs associated with SMA, despite patients' requirement for a substantial amount of care and support. Although not specified in the risdiplam data collection agreement, due to the uncertainty around previous costs published in SMA and uncertainties highlighted in the previous NICE appraisals, the feasibility of different	The EAG thanks Roche for their comment and appreciates the research they have conducted on costs and resource use. The approach we have taken in the EAG adapted model is to ensure consistency across the two company models and is in line with previous TAs. Furthermore, we reject the suggestion that new cost data provided from Roche were ignored; these values were used as alternative scenarios in all populations in section 15.2 and increased the ICER against risdiplam in Presymptomatic and Type 1, therefore the assumption in the EAG's base-case is considered favourable.

Clinical and economic comments		EAG response
	methodology types were explored to capture this data to inform the cost-effectiveness models. Initially, a database study feasibility assessment was conducted to understand if healthcare resource use data could be collected through Clinical Practice Research Datalink (CPRD) Gold, CPRD Aurum and Health Episode Statistics (HES), which are linked databases reporting data from a subset of primary care centres and secondary care data from all hospitals in England. An initial feasibility analysis indicated that estimates for important categories of HCRU, such as ventilation procedures, surgeries and respiratory tests, would be captured in these databases. Additionally, patients could be identified with available SMA-specific diagnosis codes (International Classification of Diseases, 10th Revision [ICD-10], Read or SNOMED). However, during the initial stages of the CPRD study, challenges arose in identifying patients belonging to the different health states. This was due to the defining of motor milestones in each health state not being explicitly recorded in the CPRD/HES routine care datasets. Alongside consulting clinical experts, multiple approaches were sought to determine how to define the motor milestone health states using the information provided within the database, via proxy variables. The challenges faced were issues around recursive analysis, inability to reliably differentiate between patients of different health states using individual HCRU items or recorded comorbidities and using an assumption of a linear, positive correlation between broader HCRU types such as hospital visits – which may in fact not be valid for all health states.	Regarding the exclusion of disease related complications such as scoliosis, respiratory support and bulbar function, we have already explained above that their exclusion was due to limited evidence and the need to maintain consistency between the two company models.

Clinical and economic comments		EAG response
	Due to the challenges of the database study, a *de novo* modified Delphi panel was conducted between November 2023 and March 2024 with the objective of collecting quantitative expert clinical opinion on the amount of healthcare resource use (HCRU) associated with the management of SMA Types 1 and 2/3 in the UK. The detailed methodology can be found in the report on file. In brief, a pre-specified protocol was designed outlining eligibility criteria for participation, methods of data collection and analysis of results. A lead consultant neurologist and expert in SMA, as well as two representatives from SMA patient advocacy groups (PAG) were consulted on the scope and design of the questionnaire. The modified Delphi panel consisted of two rounds with the aim of trying to achieve consensus on the resource use estimates. In each round, geographically-spread invited participants individually responded to one of three questionnaires, respectively covering paediatric patients with SMA Type 1, paediatric patients with SMA Type 2/3 or adult patients with SMA Type 2/3, to reflect expected differences in clinical practice and HCRU needs in these populations. In total, 34 out of 36 (97%) invited participants completed the Round 1 survey and 28 out of 34 (82%) invited participants completed the Round 2 survey. Following completion of the two Delphi rounds, the aggregate results were shared at a clinical expert advisory board meeting which took place in March 2024. Discussions centred around the results for items which had not reached consensus during the two preceding rounds, as well as providing interpretation and validation for consensus values achieved. The results were also contextualised and validated with the two PAG representatives, as informed by providing patients' real-world experiences. The results showed that healthcare resource use was high in	

Clinical and economic comments		EAG response
	patients with SMA, with frequent planned and unplanned healthcare visits, tests or procedures for the condition along with many costs around the funding and purchasing of equipment that is currently not accounted for. Unit costs were sourced from NHS reference costs and applied to the proportion and frequencies (per cycle) of healthcare resource utilisation derived from the survey results. The resulting total costs for presymptomatic and Type 1, and Type 2/3 SMA were used in the base case analysis. The EAG expressed their concern regarding the differences in monthly costs between TA588 and those in the Roche base case analysis sourced from the HCRU study. So, to maintain consistency with the current company submission and previous SMA appraisals, the EAG used health state costs from the latest NICE submission in this area (HST24). Roche acknowledges the remaining uncertainty regarding HCRU costs, however, does not see the rationale for ignoring new alternative data. The EAG reasoning regarding the substantial differences between the HCRU data and HST24 values could be extended here, with HST24 values substantially higher than all other health state costs. The EAG approach utilising HST24 on precedent only is a common approach in NICE appraisals, and one that often results in inappropriate, outdated estimates used in decision making. It is unclear how the costs sourced from HST24 were originally calculated, as there is relatively sparse information on the exact costing approach used. So, there is a substantial lack of transparency with the EAG approach. Roche feels that precedent alone should not serve to reason for model assumptions.	

Clinical and economic comments		EAG response
	As in the company Comment 3, Roche is also disappointed that the EAG has excluded methods used by the company to account for disease-related complications, such as scoliosis, respiratory support and bulbar function. Roche appreciates that data for these complications is limited but feels that the EAG approach moves the analysis further away from capturing the full scale of SMA and the true value of DMTs. Roche advocate for the EAG to further justify the appropriateness of using the HST24 values, and provide an explanation as to how these costs were originally calculated and then applied in their analyses so stakeholders can understand their appropriateness. As HCRU costs have been an outstanding uncertainty in all SMA appraisals, Roche also call for alternative values to be considered in scenario analyses.	
15	<u>Lack of trust in EAG analyses</u> Following a technical quality check of the confidential risdiplam EAG model (received 27 August 2025), Roche have identified some areas of concern in the EAG approach. These issues raise concerns with the remaining model changes, and changes Roche are unable to validate in the Biogen models. Please see technical comments (Comments 16-20) below. In addition, EAG adjustments to the cost-effectiveness models contain a large number of hard coding values and lack of referencing making it difficult to quickly infer the appropriateness of their changes.	The EAG thanks Roche for their comment. We respond to your comments below.

	Clinical and economic comments	EAG response
16	<u>Modelling of motor milestone decline</u> Type 2/3 • In the Roche Type 2/3 model, after 26 months, patients receiving risdiplam were modelled to remain stable and not change health state. This aligns with the approach taken in TA588 and TA755, and was informed by UK clinical expert opinion.[23,24] • By comparison, the EAG have adjusted the Type 2/3 model to include a probability of stabilisation with risdiplam of 58% after 24 months, sourced from Oskuoi et al. 2023.[25] However, Roche have identified several issues with this adaptation. Firstly, this statistic has not been correctly integrated into the model. Given the 58% statistic relates to the percentage of stabilised patients with risdiplam at 24 months, the rate of decline would theoretically be calculated be '1–0.58' instead of '1 – 0.42'. Secondly, the calculated value is used as a multiplication factor applied to the transition probabilities for BSC to generate risdiplam transition probabilities. However, this approach is not methodologically appropriate given the statistic does not directly relate to a relative treatment effect. Finally, the Oskuoi et al. paper also mentions that 32% of patients improve after 24 months, alongside the 58% who stabilise.[25] However, this improvement is not modelled, which suggests that the EAG may have selectively focussed on certain inputs rather than fully aligning with the source. Therefore, the EAG's adaptations to long-term risdiplam transition	The EAG appreciates the thorough review and validation made by Roche of our economic model. We want to address some of the points for concern raised: Type 2/3: Due to the absence of long-term data from the clinical trials and the communication between the EAG and clinicians, professional and patient organisations, the risk of motor decline remained a key point of concern across all stakeholders. Assumptions about the risk of decline were based on the best evidence available which for the Type 2/3 population was Oskoui et al. 2023. The EAG acknowledges the appropriate parameter is '1-42', but maintains its base-case assumption. Type 1: The EAG does not consider the issues raised by Roche to be a factual inaccuracy but rather a matter of judgement, therefore we maintain the EAG's base-case assumptions of long-term decline.

Clinical and economic comments	EAG response
probabilities in the Type 2/3 model make it currently unsuitable for decision-making. • Roche advocates for the EAG to use assumptions from the company base case analysis, i.e. following the original assumption of milestone maintenance (after 96 months). As noted below, Roche have provided a switch in the model to revert back to company-submitted assumptions. Type 1 • In the Roche Type 1 model, after 66 months, patients receiving risdiplam were modelled to remain stable and not change motor milestone. This again aligns with the approach taken in TA588 and TA755, and was informed by UK clinical expert opinion.[23,24] • In the EAG model, data from Ribero et al. 2022 are used to inform the relative long-term transitions of risdiplam.[26] This was achieved through the application of MAIC-weighted proportion of HINE-2 responders applied as a multiplier to BSC transition probabilities. Similar to the Type 2/3 model, it is unclear where this approach is methodologically appropriate as it does not account for the fact that this statistic is not directly related to the relative treatment effect. • As with Type 2/3, Roche have provided a switch in the model to revert back to company-submitted assumptions. Roche have conducted pragmatic scenarios, replacing the modelling of long-term decline in the risdiplam arm with our original assumption of	

Clinical and economic comments		EAG response
	milestone maintenance in each Type 1 and Type 2/3 models. In both of these scenarios, cost-effectiveness outcomes improve for risdiplam versus BSC. These scenarios are present in the updated company models included in the company response documents.	
17	<u>BSC long-term transition probabilities</u> Type 2/3 • Roche would like to provide clarification on the source of inputs for long-term transitions for BSC in the EAG-adapted Type 2/3 model. According to the EAG report (Table 84), Wadman et al. 2018 is identified as the source for long-term transition probabilities for BSC beyond 96 months.[27] However, the model is designed to always utilise the higher of the two transition probabilities — either from Wadman et al. or transition probabilities derived from SUNFISH data — for each health state.[27] In all health states, the SUNFISH-based transition results were greater than the Wadman et al. -derived transition probabilities, making SUNFISH the source used for long-term BSC transition probabilities in the model for all health states. It should be noted that this approach also indirectly affects transition probability estimates for risdiplam, as the EAG's method applies a relative effect modifier to the BSC transition probabilities to model the effects of risdiplam (as described above). • It is important that the Committee understands the correct sources informing the transition probability inputs.	The EAG accepts the request from Roche to improve the transparency of reporting our base-case assumptions and has amended the report as follows: Section 12.2.2.1, page 228, Table 82: "Assumption of long-term risk of losing motor milestones based on the Roche internal natural history data and Wadman et al. 2018[28] using the higher risk estimate available." Section 12.2.2.2, page 231, Tabe 83: "Risdiplam: 60 months; BSC: 12 months. BSC long-term risk of decline based on data from FIREFISH[29] and Wadman et al. 2018[28] using the higher risk estimate from the two after this period." Section 12.2.2.3, page 234, Tabe 84: " BSC long-term risk of decline based on the BSC arm of SUNFISH and Wadman et al.[28] using the higher risk estimate from the two after this period"

Clinical and economic comments		EAG response
	Type 1 • Roche would similarly like to provide clarification on the source of inputs for long-term transitions for BSC in the EAG-adapted Type 1 model. The approach for modelling long-term transition probabilities in the Type 1 model for BSC, whereby the highest transition probabilities for each health state are selected, is the same as for Type 2/3 model (see the row above). Accordingly, in the EAG-adapted Type 1 model, Wadman et al. is used only for the walking-to-standing probability, as the Wadman et al. decline probabilities are higher than the MAIC-derived BSC probabilities (Roche base case) for this health state transition only.[27] This is mostly inconsequential since no BSC Type 1 patients are reaching the walking state, but it is important the committee understand this nuance. • Additionally, there is uncertainty regarding the EAG's adaptation whereby a MAIC-derived relative treatment effect (based on Ribero et al.[26]) for risdiplam is applied to BSC transition probabilities in order to generate transition probabilities for risdiplam. These BSC probabilities are themselves derived from FIREFISH risdiplam data, calculated using a MAIC-based odds ratio method. This layered approach amplifies uncertainty around the long-term transition probabilities for risdiplam, further reducing the validity of the underlying assumptions and the overall methodology employed by the EAG for long-term efficacy.	

Clinical and economic comments		EAG response
	• As above, it is important that the Committee understands the correct sources informing the transition probability inputs.	
18	<u>Alignment of timepoint of no further improvement in motor milestone for risdiplam with trial data availability (all models)</u> In the EAG-adapted Roche models, the choice of the timepoint at which no further improvement in motor milestones can be assumed has been updated to align with the approach used in the Biogen models, which is to reflect length of data availability from the relevant trial. While this method is based on the availability of trial data, it can be considered somewhat arbitrary and may not fully capture clinical considerations. For instance, in the Type 2/3 model, a 96-month timepoint was used instead of 26 months (selected originally by Roche based on clinical expert opinion). However, if the model is adjusted back to 26 months, it results in an increased number of LYs for risdiplam, i.e. implying shorter treatment duration increases efficacy—which is not clinically valid—highlighting the limitations of the assumptions made by the EAG regarding long-term transition probabilities. In the Type 1 model, the EAG reduced the timepoint from 66 to 60 months, and in the pre-symptomatic model, the selected timepoint is 72 months instead of 12 months to align with trial data availability. Again, Roche argue these changes are somewhat arbitrary and highlight flaws in the EAG analyses. With all arbitrary timepoints, Roche feel it is important to flag that Roche and clinical experts consulted by the company believe that patients will continue to receive benefit while on treatment with risdiplam. The selection	The EAG has detailed its decision to include a long-term risk of losing motor function in the EAG report, section 7.3.2.1.2. Under the lack of long-term evidence beyond the follow-up of the clinical trials assumptions of life-long benefit from decision-modifying therapies are highly uncertain.

Clinical and economic comments		EAG response
	of a timepoint to 'switch off' improvements was made for modelling reasons only and it is important for the committee to understand that benefit is not just achieved through continuing improvement. Maintenance of achieved benefit is equally as important for people with SMA and their carers. The company understands that there is always going to be a ceiling of improvement and the framing of benefit for people with SMA is important and is often missed in degenerative conditions such as SMA.	
19	<u>Survival</u> Type 2/3 Roche's original approach to modelling Type 2 survival was based on an SLR of Type 2 survival data in the literature. The EAG replaced this with a single-source extrapolation from HST24, citing the need to ensure consistency across appraisals in SMA.[30] However, Roche do not consider changing the methodology solely for consistency is not clinically valid, particularly when existing survival data are available. Roche calls on the EAG to further justify and validate the appropriateness of the HST24 methodology and explain why it is preferred over the original company approach. Type 1 Roche's original approach to modelling Type 1 survival was based on PNCR natural history data. The EAG replaced this with using a single-source extrapolation from HST24 to maintain consistency, as per the approach for Type 2/3 modelling discussed above.[30] However, as discussed above, consistency alone is not necessarily a clinically valid reason for	The EAG acknowledges the justification behind the survival assumptions in the decision model Type 1 and Type 2/3 was primarily for pragmatic purposes (specifically to generate consistency between the decision models), and does not indicate that one approach is more clinically valid. As the survival assumptions available from HST24 were not considered a key issue by the committee and are accessible from the NICE submission, we opted for this approach.

Clinical and economic comments		EAG response
	selecting these data over modelling based on natural history data. Roche calls on the EAG to further justify and validate the appropriateness of the HST24 methodology and explain why it is preferred over the original company approach.	
20	Discontinuation The EAG report states that there is no discontinuation of risdiplam in the Roche models (pages 145, 223, and 425 for the pre-symptomatic model; pages 164, 225, and 428 for the Type 1 model; and pages 184, 228, and 430 for the Type 2/3 model; as well as pages 20 and 418 summarising the approach across all models). This is incorrect. The Roche models do incorporate health-state-specific stopping rules, whereby patients in lower health states no longer incur treatment costs once the treatment effect is lost, reflecting treatment discontinuation. In contrast, the EAG models do not include these rules and appear to assume lifelong treatment, which confuses their statements in the EAG report and does not align with the original Roche approach. Roche suggests that the EAG approach reverts back to discontinuation assumptions used in the company base case to better reflect treatment stopping decisions in clinical practice. As with Company Comment 16, Roche have conducted pragmatic scenarios replacing the EAG discontinuation assumptions with our original approach in each Type 1 and Type 2/3 models. In both of these scenarios, cost-effectiveness outcomes improve for risdiplam versus BSC. Roche argue that the company approach is more appropriate as it captures the proportion of patients who would discontinue in clinical practice based on	The approach proposed by the company assumes that patients do not receive therapy in either “permanent ventilation” or “not sitting”. This is a departure from the Roche submission which in section 3.3.1, page 225, states that: “Combined with clinical expert feedback, it was concluded that discontinuation of risdiplam was unlikely to take place in clinical practice, and therefore no discontinuation was assumed”. Moreover, this approach has an impact on health-care costs only, while the impact of discontinuation on clinical effectiveness is not explicitly accounted for. As we were unable to include assumptions around the impact of discontinuation on the effectiveness of risdiplam, we maintain our position that the EAG’s base-case assumption is likely to be favourable to risdiplam compared to BSC.

Clinical and economic comments		EAG response
	health state dependent stopping rules. These scenarios are present in the updated company models included in the company response documents.	
21	Conclusions and recommendations for further research The EAG's conclusions and recommendations for future research outline that, in general, there is strong clinical evidence for risdiplam and nusinersen. The EAG also highlight areas where evidence is lacking, for example a lack of longitudinal and comparative data for both nusinersen and risdiplam. Roche believe that the EAG should include caveats to these criticisms to highlight that these gaps are often common issues in rare disease conditions such as SMA and should acknowledge the difficulty in filling these data gaps with robust evidence. In general, Roche feel these caveats are important whenever the EAG highlights their concerns with the evidence base, when these data limitations are an expected feature given the rarity of the disease and the partially paediatric population.	The EAG thanks Roche for their comment. We have now added text in our report in Section 17.1 acknowledging the challenges of conducting RCTs in rare diseases like SMA. The text added at the end of the paragraph now reads "However, the EAG acknowledges that there could be challenges in conducting RCTs for treatments of rare diseases like SMA."

Corrections and clarifications			
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Page 24, Section 3: Plain English Summary, Main	"*More people who received nusinersen survived for longer, but there was less*	It should be clarified if this interpretation is based upon the duration of data (i.e. longer term data available for	The EAG have clarified as follows: " More people who received nusinersen survived for longer, but there was less information about survival for people taking risdiplam, though there was longer-term data available for nusinersen"

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results of the MTA	*information about survival for people taking risdiplam*."	nusinersen than risdiplam) rather than survival outcomes.	
Page 69, Table 9: Overview of the results from the Biogen company submission	Comparators for the Type 1 population have been incorrectly defined as SUNFISH Part II for HINE-2 and overall survival.	A correction is needed: The risdiplam study with Type 1 SMA should be corrected to FIREFISH.	The EAG have adjusted Table 9 in the Report to reflect that the different HINE-2 measurements and overall survival were based on FIREFISH as opposed to SUNFISH Part II.
Page 137, Section 7.3.2.1.2 Health states and transitions	"*Probabilities were estimated for the 2 SMN copies group and the > 2 SMN group, and used a weighted average based on 2 SMN group proportions from RAINBOWFISH*."	A correction is needed: it is the *SMN2* gene copies that should be specified, not SMN.	The EAG have clarified this point as follows: "Probabilities were estimated for the 2 SMN2 copies group and the > 2 SMN2 group, and used a weighted average based on 2 SMN2 group proportions from RAINBOWFISH"
Page 137, Section 7.3.2.1.2 Health states and transitions	"*For risdiplam treatment effectiveness was assumed to last 72 months by the EAG, similar to the available follow-up data for*	Roche argues that, while on treatment, patients will continue to receive benefit and refute the framing of a cap on risdiplam treatment effect.	The EAG thanks Roche for their comment. We want to clarify that the EAG model was based on the data available at the time of assessment. As far as the assumption of 72 months of treatment effect is concerned, we do not think it undermines risdiplam. However, this may be a matter for discussion by NICE.

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	nusinersen, - which is a favourable assumption to risdiplam, given that the follow-up from RAINBOWFISH was only 12 months."	Roche would like to correct the EAG that risdiplam currently has 24 months of published RAINBOWFISH data for the presymptomatic population. The company also argues that 72 months is not a 'favourable assumption to risdiplam'. While risdiplam only has 24 months of published data in the presymptomatic population, it is still unreasonable to assume that any child has fully developed by the age of 72 months (i.e. 6 years), whether they have SMA or not.	
Page 145, Section 7.3.2.10 Discontinuation	"*Although the EAG disagrees with the notion that discontinuation from risdiplam is clinically implausible, particularly given known concerns such as potential impacts on fertility, it acknowledges that there is an evidence*	Across the risdiplam clinical development programme, no adverse events led to withdrawal or treatment discontinuation. The paediatric SMA REACH MAA report (April 2025) confirmed that low discontinuation rates were seen in clinical practice in the children receiving risdiplam. None of the n=32 Type 1 SMA	After consultations with clinicians and assessing the qualitative evidence, the EAG considers there is still a risk of discontinuation from risdiplam, which does not negate the high rates of treatment adherence from registry data, therefore we do not consider this to be an inaccuracy, but a matter of judgement.

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	gap on long-term discontinuation rates. In the absence of long-term discontinuation data, the EAG's economic model maintained the assumption of no discontinuation for either risdiplam or nusinersen, recognising this is a favourable assumption to both therapies."	children discontinued risdiplam, and just one each from the Type 2/3 non-sitting cohort (n=1/44; 2.27%) and Type 2/3 sitters/walker cohort (n=1/88; 1.14%) discontinued treatment. The reason for discontinuation in one of these cases was cited as side effects. The mean time point for risdiplam discontinuation was 2.0 years, with a range 0.5–2.8 years. In the adult SMA REACH report (April 2025), more cases of discontinuation were reported. Of the n=109 type 2/3 non-sitter cohort, n=10 (9.2%) patients discontinued risdiplam with the reasons stated as 'side effects from the drug' (n=7), 'elective choice no treatment' (n=2) and 'supply ran out while abroad' (n=1). In the type 2/3 sitter/walker cohort (n=153), n=18 individuals discontinued treatment (11.7%) with the reasons 'side effects from procedure' (n=1), 'side	

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		effects from drug (n=8), other (n=6) - including 'patient wants to start family, pausing for fertility treatment, pregnancy, unwell with chest infections, stopped during inpatient stay and felt worse' being cited. The mean time point for risdiplam discontinuation was 1.7 years, with a range 0.3-3.1 years. The risdiplam Summary of Product Characteristics states that risdiplam should not be taken during pregnancy or during breast feeding; women should stop treatment for one month before trying to conceive, and men should stop risdiplam for four months before conception of sperm banking. Risdiplam has been demonstrated to have reversible effects on male fertility in animal models and it is expected that this is translated into the clinical experience in humans. There is no evidence to suggest that	

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		individuals who stop treatment for fertility reasons do not initiate therapy again, and we are anecdotally aware of several individuals who have reinitiated risdiplam treatment after successful pregnancies. The adult report does not state discontinuation results in the type 1 cohort as this was too small. Pertaining to the RAINBOWFISH population and presymptomatic infants receiving treatment with risdiplam which could be taken for many years, it has been demonstrated that SMN protein is vital for testicular development. As the impact of risdiplam on spermatogenesis is only relevant post-puberty, the impact on fertility in the juvenile population is not considered a significant concern [31]. Risdiplam has been demonstrated to have reversible effects on male fertility in animal models and it	

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		is expected that this is translated into the clinical experience in humans.	
Page 291, Section 13.4.2.1 Risdiplam motor function	"*This updated review contains newly published data for each of these studies, which suggests most patients continued to improve or maintained their motor function in all measured outcomes up to two years (presymptomatic), three years (type 1) and five years (types 2/3)*."	The 5-year results are available for the FIREFISH study in type 1 SMA, and were presented at the Cure SMA conference in June 2024 [32]; additional information was also provided in the addendum submitted in July 2024. Given that long-term use of these drugs was one of the key uncertainties in the original submission (TA755; 2021), we believe this data should be presented for comparison.	The 5 year data from the FIREFISH study was included in the EAG review. Text changed to: "This updated review contains newly published data for each of these studies, which suggests most patients continued to improve or maintained their motor function in all measured outcomes up to two years (presymptomatic) and five years (types 1-3)."
Page 295, Section 13.4.2.1.2 CHOP-INTEND	"*Results extracted for this review update from the single arm (uncontrolled) RAINBOWFISH study showed that patients*	Two-year data has been shared with the EAG in Clarification Questions B1, March 2025, and has also been presented at the World Muscle Society [33]. Further	The following text has been added: "At month 24, 22 out of 23 infants (96%) met the CHOP-INTEND stopping criteria for assessment: they were able to sit without support and achieved a total CHOP-INTEND score of ≥60 at two consecutive visits."

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SLR evidence: Presymptomatic	*achieved high levels of motor function prior to month 12 on the CHOP-INTEND, with 10 of 13 patients (76.9% of patients analysed) achieving scores of ≥ 60 at month 4 (week 16). Four of 7 patients achieved the maximum score of 64 at month 12.*"	data has subsequently been published in the NEJM [15].	
Page 295, Section 13.4.2.1.3 HINE-2 SLR evidence: Presymptomatic	"*Two records, one that was cited in the earlier review and a newly included study, reported data from the uncontrolled RAINBOWFISH trial. Outcome data were reported for the 12 month follow-up in both records. Data from one record suggested that all participants (n=7 participants for which*	Two-year data has been shared with the EAG in Clarification Questions B1, March 2025, and has also been presented at the World Muscle Society [33]. Further data has subsequently been published in the NEJM [15].	The following text has been added: " When assessed with the HINE-2 at month 24, a total of 21 of 23 infants (91%) could stand unaided and 20 of 23 (87%) walked independently."

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	data were available out of 18 enrolled) developed motor abilities, including the ability to sit without support. The other record reported that 24/26 infants (92%) were able to sit without support, 21/26 (81%) were able to stand and 16/26 (62%) were able to walk."		
Page 297, Section 13.4.2.1.4 BSID-III SLR evidence: Presymptomatic	"*New data from a 12-month follow-up of the uncontrolled RAINBOWFISH study showed that, at month 12, 80% of infants (n=5) were able to sit without support for ≥ 5 seconds, and 7/8 infants with two SMN2 copies were able to sit without support for ≥ 30 seconds, including all infants with CMAP*	Two-year data has been shared with the EAG in Clarification Questions B1, March 2025, and has also been presented at the World Muscle Society [33]. Further data has subsequently been published in the NEJM [15].	The following text has been added: "At month 24, of 21 of 23 infants (91%) were able to stand alone (BSID-III Item 40) and walk alone (BSID-III Item 42)."

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	amplitude < 1.5 mV (n=3)."		
Page 298, Section 13.4.2.1.5 MFM32, SLR evidence: Type 1	"*According to newly identified data from the uncontrolled FIREFISH study, at month 12 the greatest improvement from baseline with risdiplam compared to placebo was observed in the youngest patients aged 2 to < 6 years, followed by those aged 6 to 11 years, and then those aged 12 to 17. No improvement from baseline in MFM32 was observed in the oldest patients, aged 18 to 25.*"	A correction is needed because it refers to Type 1 but the data is taken from the SUNFISH study in Types 2/3 and refers to the age groups enrolled in the SUNFISH study. The following correction is suggested: "*No evidence was reported for presymptomatic or Type 1 SMA*."	Text replaced with "*No evidence was reported for presymptomatic or Type 1 SMA*."
Page 298, Section 13.4.2.1.5 MFM32, SLR evidence: Multiple types	"*As reported in the earlier review, the results from JEWELFISH study showed stabilisation of the MFM32 total score*	A correction is needed: the JEWELFISH data is available up to 2 years, not 36 months.	Text changed from "month 36" to "month 24"

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	from baseline (mean total score = 39.93, 95% CI 37.07–42.80) to month 12 (mean total score = 40.41, 95% CI 37.30–43.52) and month 36 (mean total score = 40.67, 95% CI = 37.60–43.74)."		
Page 300, Section 13.4.2.1.7 RULM SLR evidence: Multiple types	"*As reported in the earlier review, data from the 24 month follow-up of the JEWELFISH study showed functional stabilisation of upper limb ability, assessed using the RULM, with a mean change of 0.71 (95% CI –0.17 to 1.26)*."	A correction is needed: RULM mean change at 24 months was 0.71 but the 95% CI should be 0.17 to 1.26, not -0.17.	Text changed from –0.17 to 0.17
Page 301, Section 13.4.2.1.10 CMAP amplitude	"*One record, which reported results from the RAINBOWFISH trial and was included in the earlier review,*	Two-year data has been shared with the EAG in Clarification Questions B1, March 2025, and has also been presented at the World	The following text has been added: "Another record, which reported data from the RAINBOWFISH trial up to month 24, reported a mean change from baseline in ulnar CMAP amplitude of 1.76 (±1.76) at 12 months and 2.43 (±2.01) at 24 months."

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SLR evidence: Presymptomatic	*reported an increased CMAP in 5/7 patients after 12 months*."	Muscle Society [33]. Further data has subsequently been published in the NEJM [15].	
Page 302, Section 13.4.2.2 Bulbar function SLR evidence: Presymptomatic	"*Data from the RAINBOWFISH trial indicated that most participants with presymptomatic SMA maintained their ability to feed orally following risdiplam treatment*."	A correction is needed: *All* of the 23 infants who completed 24 months of treatment with risdiplam without the use of feeding support, not 'most'. Two-year data has been shared with the EAG in Clarification Questions B1, March 2025, and has also been presented at the World Muscle Society [33]. Further data has subsequently been published in the NEJM [15].	Text updated to: ''Data from the RAINBOWFISH trial indicated that all of the 23 infants who completed 24 months of treatment with risdiplam were able to feed without support."
Page 304, Section 13.4.2.3 Hospitalisation, SLR evidence, Type 1	"*Updated data showed this rate to be 0.7 per person year after 36 months (no CI reported), with natural history range of hospitalisations for type 1 SMA reported*	A correction is needed: Ref 240 should be replaced by Shieh PB, et al. Presented at Cure SMA 2017 [34]; and Chatwin M, et al. Arch Dis Child. 2011; 96:426–432 [35].	These references have been updated as per the company's request.

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	as between 4.2 and 7.6 every year."		
Page 308, Section 13.4.2.10 Health related quality of life and Patient Reported Outcomes: MAA evidence, Paediatric registry	"*This outcome was not reported in the April 2023 or December 2025 MAA report*."	A correction is needed: the 2023 report should be dated December rather than April, and the final SMA REACH paediatric registry report was April 2025, not December.	We thank the company for highlighting this error. This has been amended.
Page 327, Section 13.5.5: Complications of SMA	One patient organisation submission also noted that access to OA was further limited by geographic location, as there are currently only seven infusion centres in the UK.	A correction is needed: there are just 4 OA infusion centres in England, one in Scotland and one in NI: • Bristol Royal Hospital for Children (Bristol) • Evelina London Children's Hospital (London) ○ Great Ormond Street Hospital as sub-hub of Evelina (London)	The EAG have reflected on the submission and coding of this aspect of the qualitative data and can confirm that in the joint submission from SMA UK, MD UK and Treat SMA they stated that there were seven infusion centres. Due to the nature of qualitative analysis, the EAG would prefer not to change the current wording as it reflects what was provided within the submissions.

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		• Sheffield Children's NHS Foundation Trust (Sheffield) • Royal Manchester Children's Hospital (Manchester) • Royal Belfast Hospital for Sick Children (Belfast) Royal Hospital for Children (Glasgow)	
Page 340, Section 13.5.17 Quality of life	"One of the adults, having taken risdiplam for 1.14 years, noted that their level of QoL was due to 24-hour care from their husband; this sentiment was repeated after 1.70 on treatment."	Please confirm that this should be 1.70 years.	The EAG can confirm that the company is correct and have amended appropriately.
Page 440, Section: References	Ref 56: Mazurkiewicz-Beldzinska M, Baranello G, Boespflug-Tanguy O, Day J, Deconinck N, Klein A, et al.	A correction is needed: the 5-year Cure SMA presentation should be referenced rather than the 4-year data. Please amend to:	Reference number 56 from the original report has been amended to: Mazurkiewicz-Beldzinska M, Baranello G, Boespflug-Tanguy O, Day J, Deconinck N, Klein A, et al. FIREFISH Parts 1 and 2: 5-year efficacy and safety of risdiplam in Type 1 SMA. 2024. Available at: https://medically.roche.com/content/dam/pdmahub/restricted/neurology/cure-

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	FIREFISH Parts 1 and 2: 4-year efficacy and safety of risdiplam in Type 1 spinal muscular atrophy (SMA). 2023.	Mazurkiewicz-Beldzinska M, Baranello G, Boespflug-Tanguy O, Day J, Deconinck N, Klein A, et al. FIREFISH Parts 1 and 2: 5-year efficacy and safety of risdiplam in Type 1 SMA. Cure Spinal Muscular Atrophy conference. Austin, Texas, USA. 6–9 June 2024. The link in the reference list is correct. This affects all citations of reference 56 throughout the document.	sma-2024/CURESMA-2024-presentation-mazurkiewicz-FIREFISH-parts-1-and-2-5-year-efficacy.pdf
Page 80	*"The company assumed equivalence between motor milestones as defined by HINE-2, and the health states in the economic model defined by WHO MM. The company assumed equivalence between motor milestones as defined by HINE-2 and the health states in the*	The sentences are duplicated.	The EAG have removed the duplicated sentence.

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	economic model defined by WHO MM."		
Page 83	"*Intervention: The company modelled nusinersen as the first-line therapy according to its marketing authorisation as treatment.*"	It is unclear whether text is missing from the end of the sentence.	The EAG have revised this sentence as below: *The company modelled nusinersen as the first-line therapy according to its marketing authorisation as SMA treatment*
Page 117, Table 35, Special considerations including issues related to equity or equality.	"*In the current funding situation, the MAA for risdiplam excludes patients who are permanently ventilated or have a tracheostomy. The situation has developed significant in the past few years, and clinicians now report an improvement in quality of life or a slowing of the expected deterioration in motor / respiratory function*."	Replace 'significant' with 'significantly'.	The EAG have made this suggested correction.

Corrections and clarifications			
Page	**Issue**	**Response**	**EAG response**
Page 180/181, Table 66	"*Utilities from SUNSHINE part 2*"	Replace 'SUNSHINE' with 'SUNFISH'.	The EAG have made this correction.
Page 194 Section 8.4: Cost-effectiveness analysis	"*Biogen only compared nusinersen with BSC across all the three population groups citing the reason that it was not appropriate to assess the relative effectiveness of nusinersen against DMTs given the lack of robust evidence on elative effectiveness*."	Correct 'elative' to 'relative'.	The EAG have amended this typo.
Page 262, Unreported type	"*The original review identified three studies that assessed CMAP in patients with an unreported SMA type following nusinersen treatment. All studies reported some increase in CAMP, with scores plateauing after day 568 in one study, and increases in*	Replace 'CAMP' with 'CMAP'.	The EAG have amended this typo.

Corrections and clarifications			
Page	**Issue**	**Response**	**EAG response**
	symptomatic patients not reaching levels of asymptomatic patients in another."		
Page 321, Section 13.4.3.5 Bulbar function, Type 1 SMA	"*One newly identified reported evidence for the effects of nusinersen compared to OA on cry function…*"	Insert 'study' after 'One newly identified'.	The EAG have amended this typo.
Page 339, Section 13.5.16: Psychological impact	"*Even if treatment is not deigned to cure or improve SMA,...*"	Correct 'deigned' to 'designed'.	The EAG have amended this typo.
N/A	The report navigation pane is unusable in its current form.	Please remove tables and figures from the heading style, include a caption style instead. There are too many "Type 1" and "Types 2 and 3" headings with no context; please consider a better way of using Styles in the document to allow the user to intuitively navigate the substantial report.	The EAG have used the heading styles recommended by NICE. Although the EAG appreciate that the Report is substantial, the EAG also believe the current format is necessary to adequately differentiate the evidence on different types of SMA for each outcome for both nusinersen and risdiplam, particularly within the clinical effectiveness section.

Corrections and clarifications			
Page	**Issue**	**Response**	**EAG response**
Page 178, Section 7.3.4.1.1 Health states and transitions	"*After the 60-month SUNFISH follow-up data for risdiplam, the model assumes that patients reach long-term stability and can only improve or maintain their motor milestones,…*"	This should be corrected to: "*After 26 months ~~the 60-month SUNFISH follow-up data for risdiplam,~~ the model assumes that patients reach long-term stability and can only ~~improve or~~ maintain their motor milestones*." The same error can also be found on pages 227 and 429 and should be corrected. These errors illustrate the EAG's lack of understanding of Roche's approach to modelling long-term transition probabilities. Roche requests the EAG correct the text accordingly.	The EAG accepted this correction and has amended the text as follows: Section 7.3.2.1.2, page 140: "The model assumed that, after 10 years, patients receiving either risdiplam, nusinersen or OA maintain the motor milestones achieved." Section 7.3.3.1.2, page 162: "After 24 months (2 years), the model assumes patients do not lose the motor milestones gained from a DMT, and after 66 months (5.5 years) risdiplam and nusinersen patients were assumed to only maintain the motor milestones captured by the model states." Section 7.3.4.1.1, page 181: "After 24 months (2 years), the model assumes patients do not lose the motor milestones gained from a DMT, and after the 26 months the model assumes that patients reach long-term stability and can only maintain their motor milestones, the equivalent long-term assumption is applied to nusinersen." The text in Table 82, Table 83, and Table 84 have also been amended as follows: Table 82: "After 10 years receiving DMTs only maintained the motor milestones achieved." Table 83: "After 5.5 years receiving DMTs only maintained the motor milestones achieved." Table 84: "After 60 months receiving DMTs only maintained the motor milestones achieved."
Page 158, Section 7.3.3.1.2 Health	"*After 66 months (5.5 years) risdiplam and nusinersen patients were assumed to*	This should be corrected to: "*After 66 months (5.5 years) risdiplam and nusinersen patients were assumed to*	The EAG acknowledged this as an error and has amended the text in the report as described above. This error did not change the assumptions in the EAG's base-case analysis and had not impact on our conclusions.

Corrections and clarifications			
Page	**Issue**	**Response**	**EAG response**
states and transitions	*maintain or improve the motor milestones captured by the model states*." The same error can also be found on pages 225 and 428 and should be corrected. This error illustrates the EAG's lack of understanding of Roche's approach to modelling long-term transition probabilities. Roche requests the EAG correct the text accordingly.	*maintain ~~or improve~~ the motor milestones captured by the model states*."	
Page 138, Section 7.3.2.1.2 Health states and transitions	"*The model assumed that, after 10 years, patients receiving either risdiplam, nusinersen or OA either maintain or improve the motor milestones achieved*." The same error can also be found on pages 223 and 425 and should be corrected. This error illustrates the EAG's lack of understanding of Roche's approach to modelling long-term transition probabilities. Roche requests the EAG correct the text accordingly.	This should be corrected to: "The model assumed that, after 10 years, patients receiving either risdiplam, nusinersen or OA ~~either~~ maintain ~~or improve~~ the motor milestones achieved"	The EAG acknowledged this as an error and has amended the text in the report as described above. This error did not change the assumptions in the EAG's base-case analysis and had not impact on our conclusions.

Corrections and clarifications			
Page	**Issue**	**Response**	**EAG response**
Page 22, Plain English Summary	"*The EAG did not compare nusinersen and risdiplam directly within the report. This is because the EAG believed that the people who receive nusinersen and risdiplam are too different to be able to compare how well each of the treatments works*."	Roche feels it is important for the EAG to clarify that it is because the EAG believed that the people who received nusinersen and risdiplam in the trials to be too different, not the people who receive it in the NHS. In general, this statement applies to anywhere the EAG have called out differences between the populations (e.g. page 22).	The EAG has added to this sentence: "This is because the EAG believed that the people in the trials who receive nusinersen and risdiplam are too different". In other places (e.g. section 11.6.2) the populations are discussed in the context of the trials.
Page 23, Plain English Summary	"*The EAG also created exploratory economic models to assess the cost-effectiveness of the following comparisons: nusinersen compared with risdiplam; nusinersen compared with OA; and risdiplam compared with OA*."	As Biogen did not provide a comparison of nusinersen with risdiplam, we suggest the sentence is reworded to "... the following comparisons: nusinersen compared with OA; risdiplam compared with nusinersen; and risdiplam compared with OA."	This sentence refers to the exploratory analyses from the EAG and not those of either company. Therefore, we believe that the current text does not need amendment.
Page 69, Table 9: Overview of	N/A	Roche would welcome the sharing of the conclusions from	The EAG suggests that this is for discussion with NICE.

Corrections and clarifications			
Page	**Issue**	**Response**	**EAG response**
the results from the Biogen company submission		the Biogen submission in line with the Roche summary in Table 38.	

Spinal Muscular Atrophy UK (SMA UK), Muscular Dystrophy UK (MD UK) and Treat SMA

Comments on External Assessment Report	EAG response
As patient organisations advocating for comprehensive access to all effective treatments for Spinal Muscular Atrophy (SMA) to be funded by the NHS, we have thoroughly reviewed the SMA MTA Assessment Report. We appreciate the diligent work undertaken by the Newcastle Evidence Assessment Group (EAG) and the inclusion of patient and professional perspectives. However, there are several critical points from our community's viewpoint that require stronger emphasis and action.	The EAG thanks SMA UK, MD UK and Treat SMA for their comment.
1. The Undervalued Patient Experience and Quality of Life The report acknowledges that: ‘The insensitivity of tools to identify improvements in fine motor skills between motor milestones and the importance of these smaller improvements in motor function, and the importance of maintenance of function were also emphasised.’ (Abstract, page 5). This is a crucial point that cannot be overstated. For individuals living with SMA, a "small" change in a clinical score can translate into a monumental improvement in daily life – the ability to independently operate a wheelchair, lift a hand to eat, or even maintain current function rather than decline. The report states that: ‘a utility increment of 0.1 was assumed for "additional gains" not captured by standard measures’ (Section 6.3.2.6, page 86). While a step in the right direction, we question if this truly reflects the profound impact these seemingly minor improvements have on a patient's independence, dignity, and overall quality of life. The qualitative analysis clearly highlights that	The EAG thanks SMA UK, MD UK and Treat SMA for their comment. Whilst we understand your concerns that a utility increment of 0.1 may not fully capture the additional benefits of treatment, we would like to clarify that this was a pragmatic decision. However, the use of utility increment is not expected to substantially affect the results or alter the conclusion of our findings. This may be a matter for discussion by NICE.

Comments on External Assessment Report	EAG response
'the importance of maintaining function was emphasised as being just as meaningful and important to patients as improvements in their overall condition.' (Section 13.5, page 318). The figure of 0.10 originates from **EAG Table 74 (Section 6.3.2.6)**, which the authors acknowledge is a pragmatic placeholder rather than an empirical estimate. Yet the SMA REACH-UK caregiver survey (n = 58) shows a mean EQ-5D-Y gain of **0.15 (QALY)** (95 % CI 0.12 – 0.18) when a child moves from total feeding dependence to independent self-feeding. On that evidence we respectfully ask the Committee either **(a) to apply the 1.7× severity modifier now embedded in the 2023 NICE methods**, or **(b) to re-run the model with a 0.15 within-state utility uplift** so that fine-motor gains are more appropriately valued.	
2. The Importance of Carer Quality of Life The report states that the: 'EAG acknowledges that the perspective of informal carers is an important consideration in this disease area, and that NICE guidelines permit the inclusion of carer health-related quality of life (HRQoL) in appraisals' (Section 6.3.2.7, page 86). However, the base-case analyses primarily focused on patient quality of life, with carer utility only explored in scenario analyses due to: 'concerns around the methodological approach' and 'robustness of the available evidence' (Section 6.3.2.7, page 86). Biogen and Roche supplied carer utility values ranging from **0.48 to 0.77, depending on the child's motor milestone.** When the EAG included these in its own one-way sensitivity analysis, the nusinersen ICER for Type 1 SMA fell from **~£226 000 per QALY to a position of outright dominance over best supportive care.** Excluding health related quality of life therefore materially understates cost-effectiveness and is inconsistent with NICE precedent.	The EAG thanks SMA UK, MD UK and Treat SMA for their comment. Whilst we understand your concerns that a utility increment of 0.1 may not fully capture the additional benefits of treatment, we would like to clarify that this was a pragmatic decision. However, the use of utility increment is not expected to substantially affect the results or alter the conclusion of our findings. This may be a matter for discussion by NICE.

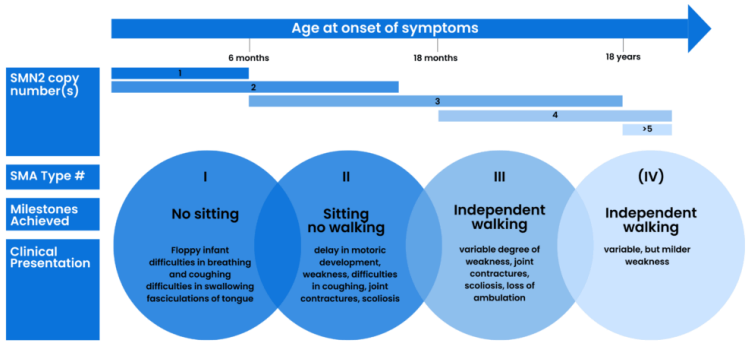
Comments on External Assessment Report	EAG response
This is a missed opportunity and undervalues the immense burden and impact of SMA on families. Our qualitative data consistently shows the profound effect SMA has on carers' physical, emotional, and financial well-being (Section 13.5.1, page 320-321; Section 13.5.8, page 327-328; Section 13.5.16, page 338-339). A comprehensive assessment of treatment value must fully integrate the benefits to carers, and methodologies for this must be prioritised.	
The Severity Modifier Problem From the patient perspective, the report's approach to the severity modifier is problematic because it conflates the patient's experience with the carer's impact. The report's own findings highlight this issue, even while adhering to a methodology that prevents "double counting." The report states that the company submissions combined the health-related quality of life (HRQoL) of patients and informal carers in their base-case models, which made them ineligible for the severity modifier. This is because the severity modifier is typically applied when the patient's perspective alone demonstrates a significant shortfall in quality of life. By combining the patient and carer experiences, the company's analysis risks masking the true burden of the disease on the patient. The report's critique of the company submissions acknowledges this by noting the following points: • **Distinct Patient Experience:** The EAG recognised that the patient's experience of the disease is a primary concern. To address this, the EAG's own base-case analysis focused on the patient's HRQoL alone to better reflect the severity of the condition. This implicitly supports the	The EAG thanks SMA UK, MD UK and Treat SMA for their comment and appreciates the importance of benefits to carers. We want to clarify that, in response to NICE's request, we have conducted additional exploratory analyses on the impact of incorporating carer utility, using varying methodological approaches.

Comments on External Assessment Report	EAG response
view that the patient's burden is a distinct and critical factor that should not be absorbed into a combined score. • **Insensitive Outcome Measures:** The report's qualitative analysis, which included input from patient organisations, revealed that the current outcome measures used in the economic models (such as motor milestones) may not be sensitive enough to capture what people with SMA consider to be meaningful changes in their own abilities. This means that the severity of a patient's condition, as they experience it, could be understated by the standard metrics, further justifying the need for a severity modifier that focuses on the patient's perspective. • **NICE Guidance:** The report explicitly acknowledges that: "NICE guidelines permit the inclusion of carer health-related quality of life (HRQoL) in appraisals". This confirms the point that including carer utilities and the severity modifier is not mutually exclusive if the evidence supports it. The report also highlights that the two companies used "markedly different approaches" to incorporating carer HRQoL, which further justified the EAG's decision to present this data separately in a scenario analysis. By preventing the use of the severity modifier when carer utilities are included in the base-case, the report's methodology, as implemented by the companies, fails to fully represent the patient's severe experience of the condition. This is problematic as the patient's personal burden is a critical component of the value assessment, and the report itself recognises the need to separate these perspectives to accurately reflect the disease's severity.	

Comments on External Assessment Report	EAG response
3. The Insufficient Voice of Clinicians The report includes just three clinical professional perspectives, two of which are from clinicians who work at the same London hospital. Whilst the neurologist and neuromuscular physiotherapists involved are recognised specialists in SMA, there is an insufficient emphasis on the collective voice and practical experience of wider SMA multidisciplinary teams who actively manage SMA patients across the country. This includes, amongst others, speech and language therapists, orthotists, respiratory specialists, Clinical Nurse Specialists and dieticians. Clinical multidisciplinary teams are on the frontline, observing the nuances of disease progression and treatment efficacy that may not be fully captured by current clinical trial endpoints or patient-reported outcomes alone. Their insights into the real-world impact of treatments, the challenges of managing SMA, and the specific needs of different patient subgroups are invaluable. A robust and systematic integration of broad clinical consensus, including from the SMA REACH clinical network, would provide a more complete picture of the treatment landscape and its benefits.	The EAG wish to highlight Table 76 of the Report (Section 9), in which the EAG detail their interactions with various key interest-holders including clinicians and professional organisations. Alongside considering written submissions from clinicians and professional organisations provided to NICE for the MTA, the EAG also held three additional meetings with groups of clinicians and professional organisations to discuss the approach the EAG was taking during the MTA and interim results, including from the SMA registries. Alongside this, the EAG engaged with individual clinicians and specialist physiotherapists to further discuss specific clinical factors that may have impacted on the EAG's approach and assumptions. The EAG appreciate that the engagement may potentially not have captured all perspectives (e.g. from speech and language therapists or dieticians) but that our engagement with individual clinicians and organisations, alongside patient organisations and the companies, means that our approach to the MTA and the qualitative section have been substantially shaped by key interest-holders.
4. The Critical Need for Comprehensive Data on Key Outcomes The report consistently identifies a: "lack of data for outcomes considered most important by patients" (Section 4.4.1, page 18). Specifically, bulbar function, stamina, and fatigue are repeatedly mentioned as crucial to patients and carers yet poorly captured in the current evidence base. The report notes that: "the EAG's base-case models did not explicitly incorporate the utility and cost impacts of bulbar function, non-ventilatory respiratory support and scoliosis separately due to data limitations" (Section 4.4.1, page 18).	The EAG thanks SMA UK, MD UK and Treat SMA for their comment. Whilst the EAG has explored the best possible options based on available data, we would like to clarify that our report highlights that the cost-effectiveness model alone may not capture the nuanced benefits of treatments. Therefore, any judgements on treatments should also take other relevant factors into account. The EAG made sustained efforts to obtain alternative data sources, both quantitative and qualitative and to incorporate these into the report as comprehensively as possible. We acknowledge that better data would permit more sensitive

Comments on External Assessment Report	EAG response
While a scenario analysis was conducted for bulbar function, the underlying data was limited. The over-reliance on direct data and the corresponding uncertainty is a significant issue. Rather than simply acknowledging the lack of data, there needs to be a fundamental shift in how this uncertainty is managed. A more patient-centred approach would focus on the following: **Proactive use of alternative evidence:** The lack of direct data should not be a dead end. Instead, there needs to be a proactive effort to find other ways to support the economic model. This includes using methods like expert elicitation, where clinicians, patient advocates, and caregivers can provide valuable insights into the disease burden and treatment effects. Similarly, using proxy conditions, drawing on data from similar diseases where better evidence is available. can help fill the gaps and provide a more complete picture of the patient's experience. **NICE's role in supporting innovation:** NICE has a crucial role to play in supporting the inclusion of these alternative forms of evidence. Rather than a passive acceptance of what is submitted, NICE should actively encourage and provide guidance on how to incorporate these data types into the economic model. This includes not only the cost-effectiveness analysis but also the assessment of clinical effectiveness, which often relies on a narrow set of endpoints that may not fully capture the patient's lived experience. **Prioritising lived experience:** The current approach can feel as though the patient's lived experience is secondary to the available data. When direct data is unavailable, it is the patient's voice, their daily struggles, their hopes for treatment, and their unique understanding of what constitutes a meaningful outcome should take precedence. By embracing methods that capture this	appraisal of the impact of treatments. The EAG believes that some of these points are a matter for consideration by NICE.

Comments on External Assessment Report	EAG response
qualitative data and integrating it into the quantitative models, we can move towards a more holistic and accurate representation of a treatment's true value. It is not just about the data that is missing but about the missed opportunity to use a broader and more inclusive set of evidence. By being more flexible and proactive, and by actively supporting the use of alternative methods to handle uncertainty, we can ensure that the patient's experience is truly at the heart of the decision-making process.	
5. Equality of Access Across All SMA Types We are deeply concerned by the explicit exclusion of patients with Type 0 and Type 4 SMA from the clinical and cost-effectiveness analyses due to: "futility of treatment for these patients" (for Type 0) and "insufficient evidence" (for Type 4) (Section 6.1, page 59). As highlighted in the report's qualitative analysis, the: "lack of access to the MAA for adults with type 4 SMA is a potential equality issue." (Section 4.4.1, page 14). Our community knows that every life with SMA, regardless of type or severity, deserves the opportunity for treatment that can improve or maintain function and quality of life. How severe and what impact SMA has varies from person to person, both within and between 'Types'. With advancements in genetic diagnostics, clinical typing in SMA is now outdated. The report seems to ignore that SMA presents on a spectrum, the types do not sit in boxes (see fig.1). Type 2 and 3 SMA also involve significant, debilitating progression. The distinction between types is somewhat arbitrary. The age cutoff is a highly variable factor for all types but particularly for type 3 and 4. Symptoms that might have been present earlier are frequently not recognised, which contributes to a protracted diagnostic process for individuals. We suggest this figure below replaces table 1 in the report to give a more holistic picture of the SMA spectrum.	The EAG agrees that the lack of evidence for patients with Type 4 SMA is unfortunate and a potential equality issue. The use of 'Types' is common and is used in the scoping document for this project. Table 1 is taken from a 2022 paper, which is more recent than the Schorling paper from which the alternative figure is taken. However, we have added a footnote to Table 1 acknowledging that the distinction between types is somewhat arbitrary and that an alternative view is provided in Schorling 2020 (note that the final published version of this paper is referenced as 2020 Advances in Treatment of Spinal Muscular Atrophy – New Phenotypes, New Challenges, New Implications for Care).

Comments on External Assessment Report	EAG response
The adult registry free-text submitted to the EAG records that **multiple Type 4 participants "lost employment and independent living arrangements since 2021 owing to progression in the absence of disease-modifying therapy".[3]** We therefore ask the Committee to consider a **conditional approval for Type 4 SMA**, mirroring the age-limited arrangement granted to Zolgensma under HST24, while additional data are gathered, albeit at the other end of the spectrum. To deny access based on perceived futility or insufficient data perpetuates a two-tiered system of care. We urge NICE to consider the ethical implications of this exclusion and to actively support research and data collection for these underserved populations.  *Fig 1 Natural history of SMA*[1]	
Presymptomatic 'group' The report sometimes implies that the presymptomatic group represents a distinct population, perhaps due to the absence of overt symptoms. However, it	The EAG agrees that treatment should not be withheld from presymptomatic patients; our report simply reflects the fact that the evidence for this group is subject to more uncertainty than elsewhere.

[1]Schorling D et al (2019)

Comments on External Assessment Report	EAG response
is crucial to understand that this group is fundamentally the same population as those who develop symptoms; they are simply identified before the devastating effects of SMA become apparent. Without treatment, these individuals will inevitably progress to develop the full spectrum of SMA symptoms. Furthermore, many Type 1 babies, while considered "presymptomatic" at birth, may already exhibit subtle signs of the disease. Therefore, early treatment is not merely preventative but crucial to halt any further progression of the disease and preserve as much motor neuron function as possible. In essence, the report suggests that treating SMA presymptomatically with either nusinersen or risdiplam shows very promising results in terms of survival and motor development, but the scientific evidence for these benefits is primarily from uncontrolled studies, leading to some uncertainty in direct comparisons and long-term projections. Given this understanding, the absence of long-term, controlled studies for presymptomatic babies should not impede immediate treatment decisions. The potential for irreversible neurological damage and the profound human cost of allowing the disease to progress, even subtly, far outweigh the methodological preference for perfect comparative data. Ethical considerations demand that access to therapies with demonstrated early benefits be prioritised to prevent the onset or worsening of symptoms in this vulnerable population.	
6. The Inadequacy of Best Supportive Care (BSC) as a Comparator for Type 2 and 3 SMA: It is crucial to recognise that even the recommended "best supportive care" as outlined in the 2017 international standards of care is not consistently accessible across the UK, particularly for adult patients. Real world research, such as the paper "Real-World Data on Access to Standards of Care for	The EAG thanks SMA UK, MD UK and Treat SMA for laying out the issues with ‘best supportive care’ and reinforcing the fact that a good outcome of these drugs is stability, as without them patients undergo rapid decline. The EAG suggest that this may be a matter for consideration by NICE.

Comments on External Assessment Report	EAG response
People with Spinal Muscular Atrophy in the UK",[2] indicates significant disparities in the provision of multidisciplinary care, respiratory support, and orthopaedic management. This lack of equitable access to even foundational supportive care further exacerbates the challenges faced by SMA patients and reinforces the urgent need for effective pharmacological interventions. It has long been emphasised that treatment and care go hand in hand, only with best supportive care will we see optimum outcomes from treatment. A 2024 Muscular Dystrophy UK audit of **236 UK adults with SMA found that only 41 % received regular physiotherapy and just 29 % had access to specialist respiratory review.** These data confirm that the “best supportive care” pathway modelled by the EAG is rarely delivered in full and therefore over-estimates outcomes for the comparator arm. For patients with Type 2 and Type 3 SMA, due to no access to Zolgensma, the unobtainable ‘best supportive care’ is the only comparator. 'Best supportive care' is not a static state of mild disability but rather a trajectory of progressive muscle weakness, loss of motor function, and increasing respiratory and orthopaedic complications. • **Progressive Deterioration:** Patients with Type 2 SMA typically lose the ability to sit independently and often require wheelchairs in early childhood. Respiratory complications, scoliosis, and joint contractures are common and worsen over time, severely impacting quality of life and increasing morbidity. Type 3 SMA patients, while initially ambulatory, experience progressive weakness, often leading to loss of ambulation in adolescence or adulthood, and can also develop respiratory issues. We are very aware of young people and adults diagnosed with SMA Type 3 who are severely impacted by their SMA.	

[2] Robert Muni Lofra et al (2022)

Comments on External Assessment Report	EAG response
These diagnoses came before the importance of the SMN2 copy number was understood and considered. • **Reduced Life Expectancy:** While not as acutely life-threatening as Type 1, the progressive nature of Type 2 under BSC can lead to significantly reduced life expectancy due to complications, particularly respiratory failure. • **Impact on Quality of Life:** The continuous loss of function under BSC means a steady erosion of independence, dignity, and participation in daily life. This deterioration profoundly impacts not only the patient but also their caregivers and families. The report's qualitative findings, which highlight the importance of maintaining existing function to patients, implicitly underscore the devastating impact of *losing* function, which is the hallmark of BSC for these types. Given this grim reality of disease progression under BSC for Type 2 and 3 SMA, the argument for access to both nusinersen and risdiplam becomes even more compelling: • **Preventing Irreversible Decline:** Both drugs have demonstrated the ability to stabilise or improve motor function, and crucially, to slow or halt disease progression. For patients facing a future of inevitable decline under BSC, these treatments offer a chance to preserve existing abilities, prevent complications, and extend functional independence. The "maintenance or improvement in motor outcomes" noted in the MAA data for both drugs, even with data limitations, is a profound benefit when the alternative is guaranteed deterioration. • **Addressing Unmet Need:** The report implicitly acknowledges the high unmet need by evaluating these novel therapies. The comparison to	

Comments on External Assessment Report	EAG response
BSC, rather than being a robust benchmark, highlights the desperate need for *any* effective intervention that can alter the natural history of the disease. • **Patient Choice and Individualised Treatment:** The existence of two effective therapies, even with imperfect comparative data, allows for greater flexibility in patient management. Factors such as route of administration (intrathecal for nusinersen vs. oral for risdiplam), administration site (home vs hospital) patient preference, tolerability, and specific clinical profiles can guide treatment decisions. Some patients prefer clinicians to bear the responsibility of administering an expensive medicine, some prefer to administer at home. Denying access to one due to a lack of perfectly matched data, when the alternative is a rapidly deteriorating condition, limits crucial options for patients and clinicians. • **Beyond Statistical Significance:** While the report grapples with statistical comparisons and effective sample sizes, the clinical reality for SMA patients on BSC is one of significant and continuous loss. Any intervention that mitigates this loss, even if its comparative superiority cannot be definitively proven against another active treatment with currently available data, represents a substantial gain over the natural course of the disease. The "unclear" finding regarding calibration against independent data and comparison with previous models (Q56) further suggests the difficulty in establishing clear-cut statistical superiority, but this should not overshadow the fundamental benefit over no treatment.	

Comments on External Assessment Report	EAG response
In summary, the report's remit to compare "best supportive care" as a comparator for Type 2 and 3 SMA patients, without fully emphasising the rapid and severe deterioration that this entails, strengthens the case for broad access to both nusinersen and risdiplam. For these patients, the alternative to active treatment is not stability but an accelerating decline towards significant disability and potentially premature death. Therefore, the availability of therapies that can alter this trajectory, even with data limitations, is paramount from a patient perspective. Treatment and best supportive care go hand in hand and only with equitable access to best supportive care will the best outcomes from treatment be gained for everyone living with SMA in the UK	
7. Ethics Over Methodology: A Patient-Centred Approach When evaluating data for life-limiting conditions like SMA, ethical considerations should often take precedence over the pursuit of perfectly matched methodologies. The severe and progressive nature of SMA means that delays in access to effective treatments, while waiting for ideal comparative data, can lead to irreversible loss of function and even lives. From a patient perspective, the moral imperative to provide access to therapies that have demonstrated significant benefit, even with methodological limitations inherent in rare disease research, outweighs the desire for statistical perfection. Indeed, for a condition as devastating as SMA, conducting traditional placebo-controlled or single-arm studies where patients receive no active treatment is unethical. The human cost of inaction or prolonged assessment must be a primary consideration in all decision-making processes. A key point the report makes is the *lack of controlled studies* for presymptomatic patients for both drugs. This means it's harder to definitively say how much the treatment is preventing decline compared to what would happen without treatment, especially since babies naturally develop motor	The EAG agrees that placebo-controlled studies would be unethical, but it is important to point out that the existing uncontrolled evidence carries more uncertainty; this is a matter of fact and while the EAG accept that there are reasons for the nature of the current evidence base this does not obviate the implications of study designs for evidence certainty.

Comments on External Assessment Report	EAG response
skills. Such studies would be unethical. But the natural history of the condition without treatment is very clear about the outcomes as seen in fig 1.	
8. Addressing the Limitations of Indirect Comparisons and Small Sample Sizes Despite the inherent challenges in obtaining perfectly matched data for nusinersen and risdiplam in the report, several arguments can be made that this limitation should not significantly impede patient access to either drug. The EAG's own matching-adjusted indirect comparisons were based on micro-datasets (effective sample size = ESS) of just **9 patients for the nusinersen vs risdiplam analysis in Type 1 SMA and 12 patients for nusinersen vs onasemnogene in the presymptomatic cohort.** Estimates generated from such small ESS are statistically unstable and cannot guide commissioning decisions. We therefore propose that future comparative effectiveness should be derived from real-world registry analyses. **- Demonstrated Clinical Effectiveness (Despite Data Limitations)** Even with the acknowledged limitations of the ITCs and the data, the report's systematic literature reviews (SLRs) and Managed Access Agreement (MAA) data consistently suggest that both nusinersen and risdiplam improve or maintain motor function across various SMA types. For instance, higher survival rates were observed among type 1 patients treated with nusinersen, and for both treatments, survival was substantially higher than in untreated type 1 patients. The MAA data for both drugs indicated maintenance or improvement in motor outcomes, and importantly, mortality rates were low. Where there were deaths, they appeared unrelated to the treatments. **- Importance of Patient-Reported Outcomes and Qualitative Data** The report's qualitative analysis critically highlights that current quantitative measures of outcomes, such as motor function scales, may not be sensitive enough to capture changes that are truly meaningful to patients and their	The EAG thanks the SMA UK, MD UK and Treat SMA for reinforcing the methodological limitations of approaches to comparing treatments within the current evidence base, and highlighting effectiveness of the drugs for some outcomes, with few adverse events. We acknowledge that this reflects issues common to rare diseases but note that the fact that there are valid reasons for the limited data does not obviate the impact of this on certainty in the analyses. The EAG fully appreciate the points about relevance of outcomes to patients and have made sustained efforts to capture information on this within the report.

Comments on External Assessment Report	EAG response
families. The SMA community emphasise the importance of maintaining existing function as much as, or even more than, significant improvements. The qualitative findings indicated that both treatments generally have a positive impact on people with SMA, particularly in maintaining or improving their condition, improving overall quality of life, and aiding in daily activities like eating, washing, and communicating. Although it was sometimes challenging to definitively link specific patient experiences to one drug over the other, the overall positive perception from a lived experience perspective underscores the real-world value of these treatments to patients. NICE need to find better ways to incorporate this qualitative data within the economic model. It's known that while NICE say they will take into account qualitative data this often does very little to the overall ICER. **- Limitations of Assessment Methods vs. Lack of Patient Benefit** The "lack of matched data" often reflects a limitation in the current methods of assessment and data collection for rare diseases, rather than an absence of actual patient benefit. The report itself stresses the need for further research to strengthen the evidence base, particularly for outcomes considered important by professionals and patients. The economic models also faced challenges due to patient characteristic differences and clinical definitions of motor milestones, which made direct comparisons difficult and limited the applicability of MAA results to cost-effectiveness models. The timing of the treatments' availability created an inherent challenge for the EAG report to obtain well-matched data. Nusinersen was the first treatment to receive a Managed Access Agreement (MAA) in England, meaning a cohort of patients was already receiving this therapy and being monitored before risdiplam became available. When risdiplam's MAA was later approved, a separate group of patients, who were often unable to access nusinersen for various reasons (e.g., contraindications to intrathecal administration, or personal preference), began their treatment journey. As a result, the two patient populations were never going to be directly comparable,	

Comments on External Assessment Report	EAG response
making it difficult to conduct a meaningful head-to-head analysis based on real-world evidence. This temporal lag in availability led to two distinct cohorts of patients, undermining the potential for a clean comparison and highlighting a fundamental limitation of the data collected during the MAA period However, these are methodological challenges in quantifying and comparing benefits, and not an indication that the benefits themselves are negligible from a patient's perspective. The report acknowledges limitations in data comparability and the challenges of indirect comparisons, as well as the inherent difficulties of data collection in a rare disease context. However, the observed clinical benefits, reinforced by crucial qualitative insights into patient experiences demonstrates that the lack of perfectly matched data should not be a primary barrier to patient access for either nusinersen or risdiplam.	
9. Limitations of the narrow scope of costs considered within the economic model. A significant limitation in the report's cost-effectiveness calculations is the narrow scope of costs considered. The analysis primarily focuses on direct clinical and social care costs, while acknowledging some additional costs. However, a comprehensive societal perspective would reveal many other substantial costs that are mitigated or entirely saved with effective treatment. These include, but are not limited to: • **Mobility Access and Adaptations:** Costs associated with significant home modifications (e.g., ramps, stairlifts, accessible bathrooms), vehicle adaptations, and public transport accessibility for individuals whose mobility deteriorates.	The EAG thanks SMA UK, MD UK and Treat SMA for their comment. The EAG understands your concerns however, we conducted the assessment from the NHS perspective, in line with NICE requirements. As such, the assessment does not include costs or outcomes that fall outside this perspective.

Comments on External Assessment Report	EAG response
• **School and Workplace Adaptations:** Expenses for specialised equipment, accessible infrastructure, and support services required to enable continued education and employment for patients. • **Loss of Earnings for Carers:** The substantial economic burden on families due to caregivers (often parents or spouses) having to reduce working hours or leave employment entirely to provide full-time care. This represents a significant societal cost in lost productivity and income. The report identifies the "Lack of data to be able to incorporate carer utility increments into the base-case economic models" (page 19) as a key issue, noting that "Exclusion of carer utility gains/losses from the EAG base-case models may undermine the full value of treatments." This suggests an awareness that a significant part of the economic benefit (related to carer burden) is not fully captured in the primary analysis. • **Loss of Earnings for Patients**: The above bullet also applies in reverse to those with SMA are fully or partially employed. There are many examples where the individual with SMA is the sole source of income, while cared for by their family members, the impact of that loss of income would be catastrophic to all involved. This would lead to unemployment, social housing and other public service pressures. • **Highly Specialist Equipment:** The ongoing need for expensive, highly specialised wheelchairs (e.g., power wheelchairs with complex seating systems), communication devices, and other assistive technologies that become necessary as the disease progresses under BSC. • **Indirect Healthcare Costs:** Costs associated with managing complications that arise from disease progression, such as frequent	

Comments on External Assessment Report	EAG response
hospitalisations for respiratory infections, surgical interventions for scoliosis, and treatment for chronic pain. Depression for both patients and carers is a significant burden on the NHS and is extremely common with most degenerative conditions. • The EAG assigns health-state utilities ranging from **0.00 (permanent ventilation) to 0.77 (walking unaided)** and annual direct costs of **£168 000 – £244 000** for the most severe states. Shifting any one of these parameters by 10 % moves the ICER by more than **£50 000.** We therefore ask that (a) the alternative utility set used in TA755 be presented as a scenario, and (b) full tornado graphs for each cost parameter be provided so decision-makers can appreciate this sensitivity. By not fully capturing these broader societal and indirect costs that are incurred when SMA progresses untreated, the report's economic models may significantly underestimate the true value and cost-effectiveness of nusinersen and risdiplam. Effective treatments that prevent or slow progression lead to substantial savings across these domains, improving not only patient outcomes but also reducing the overall economic burden on families and the healthcare system in the long term. A more robust framework is needed, one that enables the inclusion of wider costs and provides clear direction on how to collect and integrate relevant data into the model, particularly for rare diseases.	
10. The problem with direct treatment comparisons. The report implicitly supports the need for choice, noting that "the issues surrounding eligibility for the different treatments emphasised the need for a range of treatments to be available to the SMA community to meet different needs." (Section 13.5.6, page 326).	The EAG thanks SMA UK, MD UK and Treat SMA for their comment. We think this may be a matter for discussion by NICE.

Comments on External Assessment Report	EAG response
While we fully acknowledge that we are dealing with a small population with a rare condition, this is further subset into those who can have particular types of treatment e.g. intrathecal/spinal/oral treatments. These treatments should not be considered comparable but should be an essential part of the patient choice aspect for their care. Comparable to other conditions, e.g. Cancer, where there may be multiple methods of treatment for the same condition. Our position is clear: all effective treatments, nusinersen, risdiplam, and onasemnogene abeparvovec, must be recommended for NHS funding and available on the NHS. The MAA was established with good intentions, to give us more data to support the appraisal. But it hasn't helped reduce the uncertainty. The EAG report still sees big evidence gaps. Access to risdiplam and nusinersen was restricted for years under the MAA agreements, but this hasn't resulted in providing the data to support a positive appraisal. The current MAA structure, while providing some access, creates delays and inequalities that directly impact patient outcomes and quality of life. The report itself highlights "delays in access to treatment and the impact that these waiting times had on the condition" (Section 13.5.6, page 325). This is unacceptable. Patients and clinicians should have the flexibility to choose the most appropriate treatment based on individual needs, without bureaucratic hurdles.	
Conclusion While this report provides a thorough assessment of the available evidence, from a patient organisation's perspective, it also underscores the persistent challenges in fully recognising and valuing the lived experience of SMA. Resolutions to these challenges could include:	The EAG thanks SMA UK, MD UK and Treat SMA for their comment. We think this may be a matter for discussion by NICE.

Comments on External Assessment Report	EAG response
• **Ensuring equitable access to treatment for all living with SMA.** SMA is **one** condition with a spectrum of complex symptoms. Access should not be broken down into outdated clinical types. The possibility of treatment should be based on a diagnosis of SMA and a risk / benefit discussion between the patient (parent) and clinician - NICE needs to trust our highly experienced clinical community and not present barriers to their professional judgement. The established SMA Clinical Panel could be the referral body that review 'cases' to ensure equity and consistency. • **Integrating carer quality of life as a core component** of cost-effectiveness analyses, developing robust methodologies to capture this crucial aspect. • **Strengthen the inclusion of comprehensive multidisciplinary clinical perspectives** including allied health care professionals to inform the assessment of real-world treatment benefits and challenges. • **Incorporate the societal and human impacts into modelling more thoroughly** considering the broader societal and human impacts beyond economic models. • **Review the effectiveness of Managed Access Agreements**. A review of MAA processes needs to happen. If they are being used but not producing the results needed to support appraisals, are they fit for purpose? • **Budget-impact mitigation.** NHS England has an estimated **1 300 prevalent SMA patients and < 120 incident cases per year**; even at	

Comments on External Assessment Report	EAG response
full uptake, first-year net drug spend would be below **£350 million—< 0.3 % of the NHS England medicines budget.** The lives of individuals with SMA and their families depend on these treatments. We stand ready to collaborate with NICE, manufacturers, and clinicians to ensure that future decisions truly reflect the holistic needs and aspirations of our community.	

SMA Reach

Comments on External Assessment Report	EAG response
The report contains a repeated misinterpretation, and then misrepresentation, of the adult PROMs data submitted to the EAG in April 2025, in stating that certain data points refer to an overall total of respondents (patients), implying the inclusion of one response per patient over the course of the entire data collection period, when the data points in question actually refer to an overall total of responses (allowing for the inclusion of multiple responses per patient over the course of the data collection period – but limited to one response per 6-month timepoint). The discussion and tables included in the report for the adult EQ-5D-5L, EQ VAS, and SMAIS data therefore require revision. In the attached document ('Adult PROMs revised tables – EAG response'), we have included recommended revised versions of each discussion paragraph and table where relevant, which we believe more accurately represents the PROMs data provided. The following pages of the EAG report are affected: Page 281 (final two paragraphs) | [Nusinersen – EQ-5D-5L and EQ VAS] Page 282 (Table 94) | [Nusinersen – EQ-5D-5L] Page 287 (final paragraph) | [Nusinersen – SMAIS] Page 288 (Table 98) | [Nusinersen – SMAIS] Page 309 (final two paragraphs) | [Risdiplam – EQ-5D-5L and	We thank the SMA Reach registry for providing clarity around these results. The suggested changes have been incorporated within the report in the appropriate sections.

EQ VAS] Page 310 (Table 101) | [Risdiplam – EQ-5D-5L] Page 315 (final paragraph) | [Risdiplam – SMAIS] Page 316 (Table 105) | [Risdiplam – SMAIS] If the EAG should choose not to accept the recommended revised tables provided in the 'Adult PROMs revised tables – EAG response' document, and instead revise the tables in their own fashion, it should be noted that further incorrect data, unrelated to that discussed above, has been entered into Table 101, for Type 2/3 walkers at the 6 month and 1 year timepoints, which will need to be corrected regardless (see highlighted fields on page 10 of the 'Adult PROMs EAG revision' document).	
The report contains multiple comparisons of the two treatments, however we agree with the statement on page 22 that "..people who receive nusinersen and risdiplam are too different to be able to compare..". The current data does not allow for a comparison between the two drugs because the cohorts started on the two treatments are different since the two technologies became available at different time points and for example patient with complex spines may have been started on the oral drug whilst those with no or less severe scoliosis may have been started on the intrathecal drug.	The EAG thanks SMA REACH for their comment.

In addition, there is an unmet need for the SMA type 4 population, who would in our opinion benefit from accessing Nusinersen (within the approved label), despite limited data is available. The national numbers for this cohort are small and are between 10-15 patients.	The EAG thanks SMA REACH for their comment; the report reflects the lack of existing data in this population.
There is a need for both technologies to meet patient needs and to allow for patient choice since these have different mode of administration and different profile of side effects. We agree that in some instances it is difficult to capture benefit in a consistent way, where for examples outcome measures for stamina, fatigue or bulbar function have not yet been implemented.	The EAG thanks SMA REACH for their comment and note that we have attempted to capture these elements within the report through sustained engagement with patients and professionals.

SMA REACH UK

Comments on External Assessment Report	EAG response
The findings from our registry work have been interpreted and presented in a fair and balanced manner. The EAG demonstrates a deeper understanding of the disease compared to the previous report, and the challenges associated with evaluating real-world data in the context of a rare disease. Regarding clinical effectiveness, it is seen in both products, especially in terms of stabilization but also safety profile. Comparatives between drugs is on an exploratory level, while the main comparator is the SOC, which we think it is the correct possibility at the moment since the two cohorts differ, and a direct comparison would not be fair. The data collection was also not designed for drugs' comparison and therefore we would be cautious interpreting any comparison other than SOC. There is still lack of data on various aspects: bulbar function, stamina and fatigue, school/education as well as day-to-day care and burden of living with SMA, but this should not stop the process as we could implement collecting new data and exploratory data in due course. Evidence regarding SMA Type 0 was not part of the current appraisal and treatment not routinely offered (nor licenced) for this type of severe SMA. Since there are few international	The EAG thanks SMA REACH for their comment. These points are likely to be for discussion with NICE and other national stakeholders.

Comments on External Assessment Report	EAG response
cases shared of treated SMA0 patients with one of the two disease modifying treatment, we would anticipate that in future systematic data collection from SMA type 0 will need to be implemented in the current registry. On the economic models, there are 6 different models mentioned with slightly different structures and redactions which were more difficult to evaluate. One thing to highlight, is that in the Roche product the “discontinuation model” is not applied and this will always give an apparent advantage especially in the SMA1 group. Commenting on the cost effectiveness is difficult with all the reductions and beyond the clinical evaluation, but it seems clear that while stabilization is of great value, larger improvement is seen mainly with early treatment and mostly in pre-symptomatic patients. Hence the urgence to implement a national NBS for this condition.	
It is encouraging that qualitative assessments have been highlighted and incorporated into the report, and that parent/carer perspectives are represented. However, it is important to acknowledge that such information may be more subjective than clinically captured data, particularly as it was not collected in a blinded setting. The report emphasises the importance of collecting reliable data on additional outcomes such as health-related quality of life (HRQL) and social interaction. However, it is important to	The EAG appreciate this comment and acknowledge that there are inherent issues with including patient perspectives particularly when data were not collected for specific research purposes. However we believe that the benefits of reflecting lived experience substantively outweigh the downsides of not including it, in the absence of data from more rigorously designed approaches. Discussion with NICE and other stakeholders may be beneficial to supporting additional data acquisition.

Comments on External Assessment Report	EAG response
recognise the additional burden and unmet resource needs required to support such efforts. It is important to consider that funding for the continued use of the registries and importance of this data collection should be considered by NICE/NHS England and should not rely exclusively on external company funding. Points 2 and 3 highlight the significant challenges faced by families, and it may be that other supportive interventions, such as psychological or general support for parents and carers, may help alleviate some of these burdens. While this is especially important in SMA, it is also relevant in other paediatric conditions. Indirect benefits of treatment, which are likely to be confounded by various social factors, should therefore be interpreted alongside primary, direct clinical benefit, when evaluating clinical treatments. This may be challenging with the absence of a control or direct comparator group. One recommendation was to conduct a study directly comparing the two treatments within this MAA, or to compare with OA. However, the feasibility of this, especially at the current stage of drug development, remains uncertain.	

Comments on External Assessment Report	EAG response
There is also an evident requirement for newborn screening for SMA in the UK and the swift introduction of such is advocated by the SMA RAECH UK network as well as the patient communities. Additional data on Quality of Life, disease' burden as well as defining the trajectories of bulbar function are all of interest and could be developed as observational study but would require additional support to the registry. We would welcome further discussion regarding the above at the upcoming meetings regarding the MTA.	

NICE

Comments on External Assessment Report	EAG response
To calculate severity weights as per TSD 23 and include in EAG base case, make clear in EAG report post consultation what weights the EAG calculated and used alongside weights the company's used.	The EAG has reported the severity weights in our analysis in section 15, Table 15.1. In addition, the EAG has added a further clarification about differences in the severity modifiers and reported the approaches by the manufacturers and the EAG in section 15.5
If calculated severity weights differ for the same populations in the different models, to provide explanations why this is the case, and provide a scenario for committee using the same weight for the same population across models (noting this is a basic approach and not adjusting underlying data)	Additional details and clarifications around the severity modifiers were included in section 15.5.
To share scenarios with the alternative approach to carer QALYs for each model (using incremental QALYs if decremental QALYs used in base case and vice versa, being mindful of number of carers when changing approach)	The EAG has included the results of additional scenarios requested by NICE in the Addendum to the EAG report after the report's consultation. Additional clarification to the EAG's approach to carer QALYs has been included in section 12.2.3. The additional scenarios requested by NICE have been included in the EAG's scenario analyses and reported for Biogen in section 15.1 Table 15.4, Table 15.8, and Table 15.12; and for Roche in section 15.2, Table 15.15, Table 15.19, and Table 15.23

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NICE National Institute for Health and Care Excellence

Multiple Technology Appraisal

Nusinersen and risdiplam for treating spinal muscular atrophy (MA review of TA588 and TA755) [ID6195]

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Combine all comments from your organisation (if applicable) into 1 response. We cannot accept more than 1 set of comments from each organisation.

Please underline all confidential information, and separately highlight information that is submitted as 'confidential [CON]' in turquoise, and all information submitted as 'depersonalised data [DPD]' in pink. If confidential information is submitted, please also

send a second version of your comments with that information redacted. See Health technology evaluations: interim methods and process guide for the proportionate approach to technology appraisals (section 3.2) for more information.

The deadline for your response is **5pm** on **Wednesday 29 May 2024.** Please log in to your NICE Docs account to upload your completed form, as a Word document (not a PDF).

Thank you for your time.

We reserve the right to summarise and edit comments received, or not to publish them at all, if we consider the comments are too long, or publication would be unlawful or otherwise inappropriate.

Comments received are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the comments we received, and are not endorsed by NICE, its officers or advisory committees.

NICE National Institute for Health and Care Excellence

Part 1: Treating spinal muscular atrophy and current treatment options

Table 1 About you, aim of treatment, place and use of technology, sources of evidence and equality

1. Your name	Dr Channa Hewamadduma
2. Name of organisation	University of Sheffield and Sheffield Teaching Hospitals Foundation NHS Trust
3. Job title or position	Lead Clinician for Neuromuscular Disorders, Consultant Neurologist
4. Are you (please tick all that apply)	☐ An employee or representative of a healthcare professional organisation that represents clinicians? ☒ A specialist in the treatment of people with spinal muscular atrophy? ☒ A specialist in the clinical evidence base for spinal muscular atrophy, nusinersen or risdiplam? ☐ Other (please specify):
5. Do you wish to agree with your nominating organisation's submission? (We would encourage you to complete this form even if you agree with your nominating organisation's submission)	☒ Yes, I agree with it ☐ No, I disagree with it ☐ I agree with some of it, but disagree with some of it ☐ Other (they did not submit one, I do not know if they submitted one etc.)
6. If you wrote the organisation submission and/or do not have anything to add, tick here. (If you tick this box, the rest of this form will be deleted after submission)	☐ Yes
7. Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	None
8. What is the main aim of treatment for spinal muscular atrophy? (For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability)	Depending on the subgroup of patients – slowing or preventing progression, achieving stability and in a subset improvement in motor functions.

	Especially in the adult cohort slowing progression and maintaining motor functions in the longer term is key.
9. What do you consider a clinically significant treatment response? (For example, a reduction in tumour size by x cm, or a reduction in disease activity by a certain amount)	In a disease where there is the possibility of progressive decline reducing the rate of decline is significant treatment response. The outcome measures we have adopted from paediatric clinical trials may not always reflect a treatment response in the adult. Therefore taking into consideration patient reported outcomes will help guide establishing the significance of a treatment response.
10. In your view, is there an unmet need for patients and healthcare professionals in spinal muscular atrophy?	Patients with complex spines can only access Risdiplam with relative ease. Longer acting ASO or one off therapies are needed as alternatives.
11. How is spinal muscular atrophy currently treated in the NHS? • Are any clinical guidelines used in the treatment of the condition, and if so, which? • Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please state if your experience is from outside England.) • What impact would the technology have on the current pathway of care?	We refer to the international SMA care standards. UK care standards are being reviewed. Treatment of SMA in the UK is more harmonised since the treatments for adult SMA patients became available and we formed SMAREACH network. Here we share best practice and experience. NHSE clinical panel also provides a forum for discussion and generate national (England) alignment when managing challenging cases. Managed access oversight guidelines provided clear starting and stopping criteria which I think also provided a frame work for managing adult SMA patients, where over 80% of my cohort of north of England SMA patients known to our service is on treatment (rest- ineligible, intolerant or patients choice). Most adult centres have formed the carepathways that meet their resources and patient care needs. Improvement in care standards need to happen in key areas such as respiratory care, bone/spine and hip management and reproductive health pathways. Effort is afoot to bridge these gaps via SMA care UK.

12. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice? • How does healthcare resource use differ between the technology and current care? • In what clinical setting should the technology be used? (for example, primary or secondary care, specialist clinic) • What investment is needed to introduce the technology? (for example, for facilities, equipment, or training)	Over the last 5 years a frame work of specialist centres has been formed and the clinical practice network of hub and spoke referral model has worked to help SMA patients access treatments. Risdiplam is delivered to patients home and only require patients to attend to centres for assessments and monitoring.
13. Do you expect the technology to provide clinically meaningful benefits compared with current care? • Do you expect the technology to increase length of life more than current care? • Do you expect the technology to increase health-related quality of life more than current care?	Current care is modified since pre 2019 where the care for SMA is planned around the availability and access to disease modifying therapies. Services have begun to reorganise themselves to address the care needs. Biggest change that has happened as an indirect consequence of the DMTs is the increase in the clinic appointment duration times allowing better discussion and identification of care needs for the SMA patients. This compares to having only 15min to address the complexities of SMA patients. Previous care for SMA in the adult clinics was extremely limited, to the point it has been reactive to firefight acute changes. Current provision of care paradigm is significantly different compared to 2019 for adults with SMA.
14. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	In the adult SMA currently there are no real predictors of who will do best with which technology. General real world evidence points towards magnitude of response if greater with higher baseline motor function (Lancet 2020), however it appears that stability is seen across all functional status' over longer periods of review (Lancet regional health 2024)
15. Will the technology be easier or more difficult to use for patients or healthcare professionals than	Of course to do something compared to do nothing is always going to be difficult and challenging. Allowing for this philosophical challenge with anything, the availability of disease modifying therapy for SMA has been a life time aspiration

current care? Are there any practical implications for its use? (For example, any concomitant treatments needed, additional clinical requirements, factors affecting patient acceptability or ease of use or additional tests or monitoring needed)	for almost all adult SMA patients and their families (as an adult neurologist my references are for adult SMA patients). Making the DMTs available for our SMA patients within MAA criteria is the duty of the neuromuscular centres selected for delivering such therapies. Whilst nusinersen therapy was supported with a special tariff, Risdiplam wasn't. Special tariff for nusinersen has significantly helped delivery of this therapy
16. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	This is well defined is MAA agreement. Complex patients are discussed at the NHSE clinical panel which from informal feedback, has certainly helped adult neuromuscular colleagues significantly. Post MAA , SMAREACH network established consensus to continue it (SMAREACH adult network meeting 2023/2024)
17. Do you consider that the use of the technology will result in any substantial health-related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation? • Do the instruments that measure quality of life fully capture all the benefits of the technology or have some been missed? For example, the treatment regimen may be more easily administered (such as an oral tablet or home treatment) than current standard of care	Improved strength and stability can release carer burden. This is not necessarily captured in the EQ5D in the absence of carer reported QOL instrument. Risdiplam is certainly administered at home and delivered to the patient minimising the clinic/hospital visit related burden.
18. Do you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits and how might it improve the way that current need is met? • Is the technology a 'step-change' in the management of the condition? • Does the use of the technology address any particular unmet need of the patient population?	This is a well settled matter in my opinion. Therapies are innovative and targeted.
19. How do any side effects or adverse effects of the technology affect the management of the condition and the patient's quality of life?	Both Risdiplam and Nusinersen can be associated with adverse events. Both treatments with continued treatment the adverse effects tend to settle and not be bothersome. Proportions of patients on Nusinersen continue this treatment in

	spite of side effects of the procedure (difficult lumbar puncture) due to stability and/or improvement of the motor function. Evidence for this question is well covered by published evidence.
20. Do the clinical trials on the technology reflect current UK clinical practice? • If not, how could the results be extrapolated to the UK setting? • What, in your view, are the most important outcomes, and were they measured in the trials? • If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes? • Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	No But that is due to trial design complexities in rare disease and need to demonstrate the maximum effect in the shorter duration of the study.
21. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	There is significant amount of RWE to support the benefits of Nusinersen in Adults with SMA. Risdiplam RWE is limited to small studies with shorter follow up duration.
22. Are you aware of any new evidence for the comparator treatment (onasemnogene abeparvovec) since the publication of NICE technology appraisal guidance [HST15, HST24]?	Yes to some extent. There is some evidence from the STEER (however its Intra thecal Onasemnogene) which included patients up to 18 yrs of age who were treatment naïve. Patients were non ambulant and therefore perhaps could be compared indirectly with SUNFISH part 2 study. This is a suggestion but will need statistical analysis such as network meta analysis.
23. How do data on real-world experience compare with the trial data?	No new safety signals identified for both Risdiplam and Nusinersen. Both therapies are well tolerated. Efficacy of Nusinersen in the adult SMA patients is well reported. But patient populations are not comparable to pivotal studies conducted in very young SMA children. RWE for Risdiplam is not robust as the studies are limited to small cohorts with shorter follow up durations. In the UK patients I have treated (approx. 24) and through independently analysing the UK cohort of Risdiplam patients (n=268 from May data cut), there appears to be stability if not improvement in some motor function.

24. NICE considers whether there are any equalities issues at each stage of an evaluation. Are there any potential equality issues that should be taken into account when considering this condition and this treatment? Please explain if you think any groups of people with this condition are particularly disadvantaged. Equality legislation includes people of a particular age, disability, gender reassignment, marriage and civil partnership, pregnancy and maternity, race, religion or belief, sex, and sexual orientation or people with any other shared characteristics. Please state if you think this evaluation could • exclude any people for which this treatment is or will be licensed but who are protected by the equality legislation • lead to recommendations that have a different impact on people protected by the equality legislation than on the wider population • lead to recommendations that have an adverse impact on disabled people. Please consider whether these issues are different from issues with current care and why. More information on how NICE deals with equalities issues can be found in the NICE equality scheme. Find more general information about the Equality Act and equalities issues here.	Type 4 SMA patients and those who are on ventilation for more than 16 hours. There are a few patients on Risdiplam [via CUP] who appear to be doing well with improved swallowing and truncal strength. Overall my observation as a nonexpert in health economics indexed QUALY threshold of £20-30,000 which appears arbitrary and set in stone as it were over 15-20years ago, for rare diseases like SMA, is an inequitable approach to assessing cost effectiveness.

Part 2: Key messages

In up to 5 sentences, please summarise the key messages of your statement:

Risdiplam and Nusinersen have significantly changed how we treat adult SMA patients in the UK and in the world.

Progressive SMA is stabilised in most and improved in some with the new therapies.

Outcome measures used for adult are derived from paediatric setting are too stiff to demonstrate significant improvements in adults.

Patients report meaningful improvements which are not captured adequately via the existing PROMs or motor function tests

Click or tap here to enter text.

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Your privacy

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☒ **Please tick this box** if you would like to receive information about other NICE topics.

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NICE National Institute for Health and Care Excellence

Multiple Technology Appraisal

Nusinersen and risdiplam for treating spinal muscular atrophy (MA review of TA588 and TA755) [ID6195]

Clinical expert statement

Information on completing this form

In part 1 we are asking for your views on this technology. The text boxes will expand as you type.

In part 2 we are asking you to provide 5 summary sentences on the main points contained in this document.

Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable. Please type information directly into the form.

Do not include medical information about yourself or another person that could identify you or the other person.

We are committed to meeting the requirements of copyright legislation. If you want to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs. For copyright reasons, we will have to return forms that have attachments without reading them. You can resubmit your form without attachments, but it must be sent by the deadline.

Combine all comments from your organisation (if applicable) into 1 response. We cannot accept more than 1 set of comments from each organisation.

Please underline all confidential information, and separately highlight information that is submitted as 'confidential [CON]' in turquoise, and all information submitted as 'depersonalised data [DPD]' in pink. If confidential information is submitted, please also

send a second version of your comments with that information redacted. See Health technology evaluations: interim methods and process guide for the proportionate approach to technology appraisals (section 3.2) for more information.

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Part 1: Treating spinal muscular atrophy and current treatment options

Table 1 About you, aim of treatment, place and use of technology, sources of evidence and equality

1. Your name	Mariacristina SCOTO
2. Name of organisation	Great Ormond Street Hospital, London UK
3. Job title or position	Consultant in Neuromuscular Translational Research
4. Are you (please tick all that apply)	☐ An employee or representative of a healthcare professional organisation that represents clinicians? ☒ A specialist in the treatment of people with spinal muscular atrophy? ☒ A specialist in the clinical evidence base for spinal muscular atrophy, nusinersen or risdiplam? ☐ Other (please specify):
5. Do you wish to agree with your nominating organisation's submission? (We would encourage you to complete this form even if you agree with your nominating organisation's submission)	☒ Yes, I agree with it ☐ No, I disagree with it ☐ I agree with some of it, but disagree with some of it ☐ Other (they did not submit one, I do not know if they submitted one etc.)
6. If you wrote the organisation submission and/or do not have anything to add, tick here. (If you tick this box, the rest of this form will be deleted after submission)	☐ Yes
7. Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	I have received honoraria for presentation at meetings and scientific advisory boards of Biogen, Novartis and Roche.
8. What is the main aim of treatment for spinal muscular atrophy?	The aim of the treatment is to improve outcome of patients affected by SMA. Both nusinersen and risdiplam have clearly demonstrated a very statistically

(For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability)	robust and clinically meaningful effect on improving clinical outcomes of infants, children and adults affected by SMA. This includes the slowing progression of motor, respiratory and bulbar function shown in both clinical trials and real-world evidence for both treatments. In some cases, dependent on age of treatment initiation, not only was progression stopped but new milestones and improvements have been observed. In some cases, preserving ability to move fingers has meant the difference between operating a powered wheelchair/computer or not.
9. What do you consider a clinically significant treatment response? (For example, a reduction in tumour size by x cm, or a reduction in disease activity by a certain amount)	• In early symptomatic individuals: slowing/stopping disease progression; achievement of novel motor milestones completely uncharacteristic for the classical disease course (e.g. sitting or standing with support and 4-point increase score on CHOP INTEND); and improved (or prevention of) respiratory and bulbar weakness/ feeding difficulties. • For symptomatic patients: slowing/stopping disease progression; changes in the trajectories of loss of motor function; reduced hospitalisation has been clearly documented in our clinical real-world experience, and peer reviewed in publications. • For pre-symptomatic patients: a clinically significant response would include acquiring motor milestones as well as maintaining independent respiratory and feeding abilities.
10. In your view, is there an unmet need for patients and healthcare professionals in spinal muscular atrophy?	• Untreated patients have an immense unmet need • Symptomatically treated patients have less unmet needs but still have some unmet needs • Pre-symptomatically treated patients – depending on the *SMN2* copy numbers- may have no or modest unmet needs according to publications with any of the 3 Disease Modifying Treatments, including Risdiplam and nusinersen

	• The lack of newborn screening is definitely an unmet need; early diagnosis and early recognition of initial symptoms is still difficult. • Orthotics provision is fragmented nationally as well as management of orthopaedic problems. • Those who are long term ventilated are not eligible through the MAA and this denies this cohort a meaningful quality of life as being long term ventilated does not necessarily mean someone cannot have some independence e.g. ability to speak, operate a powered wheelchair, attend school. • The only other treatment available – onasemnogene abeparvovec is only available to those with Type 1 SMA under 21kg, and not all of those who fall in this category can be treated because of contraindications. • For as long as SMA is diagnosed through symptoms rather than routine screening, there will be significant unmet need as it is vital to keep all three treatment options given incidence of contraindications exist. • Treatment cannot reverse nerve cell death, and we need to continue to explore whether there are additional strategies that can optimise treatment response – both in terms of supportive care and other medications e.g. myostatin inhibition, currently ongoing clinical trials • Implementation of bulbar function monitoring pre-post treatment • Proper rehabilitative plan post treatment Without treatment, these patients will continue to deteriorate in terms of motor, respiratory and bulbar function. Even when the scales used in clinic to capture response to treatment, are not able to detect any significant changes, patients tend to report perceived benefits and gaining of activities of daily living that are critical for their quality of life.
11. How is spinal muscular atrophy currently treated in the NHS?	Almost all patients with SMA are diagnosed after symptoms onset; depending on the age of the patient, general health at baseline and *SMN2* copy numbers there

• Are any clinical guidelines used in the treatment of the condition, and if so, which? • Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please state if your experience is from outside England.) • What impact would the technology have on the current pathway of care?	are three treatments available. Risdiplam and Nusinersen are both available within the framework provided by NICE. The compliance with therapies is excellent. Onasemnogene abeparvovec is also available to Type 1 SMA patients under 21kg (if not contraindicated). Palliative care is also considered and discussed with families. All patients will continue to also receive standard of care: BiPAP ventilation when needed, gastrostomy when indicated, physiotherapy rehabilitation (eg use of KAFOs to aid standing), surgical procedures (i.e. scoliosis surgery). Those not eligible through MAA may be on treatment on compassionate grounds/ EAMS scheme but switching treatment within these schemes is very challenging.
12. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice? • How does healthcare resource use differ between the technology and current care? • In what clinical setting should the technology be used? (for example, primary or secondary care, specialist clinic) • What investment is needed to introduce the technology? (for example, for facilities, equipment, or training)	These 2 therapies are now well embedded in most regional centres in the UK. Compared with no treatment (natural history): reduced hospital admissions, motor improvement and improved independence; improved speech and possibility to attend school/receive proper education. All therapies will need a level of surveillance such as blood tests monitoring for safety and continue monitoring progression. The clinical setting should remain in specialised centres as these are still relatively new treatments and administration can be difficult (i.e. lumbar puncture).

13. Do you expect the technology to provide clinically meaningful benefits compared with current care? • Do you expect the technology to increase length of life more than current care? • Do you expect the technology to increase health-related quality of life more than current care?	The QALY calculation will maximally benefit when newborn screening will be implemented in England. Compared to standard of care alone, there is prove from trials and real-world data of improved survival; slowed disease progression and improved respiratory progression. For patients who are long-term ventilated, the benefits might include enabling continuing use of powered wheelchairs or computer controls. This is unlikely to be captures in existing QALY.
14. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	• More effective: Pre-symptomatic cases diagnosed with newborn screening. Outside NBS, all newly diagnosed patients should be initiated on a treatment as soon as possible • Less effective: SMA type 0, i.e. those with very severe neonatal onset but data on this group of patients are scarse. .
15. Will the technology be easier or more difficult to use for patients or healthcare professionals than current care? Are there any practical implications for its use? (For example, any concomitant treatments needed, additional clinical requirements, factors affecting patient acceptability or ease of use or additional tests or monitoring needed)	These 2 therapies are now well embedded in most regional centres in the UK.

16. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	The NICE Start-Stop rules are helpful but not fully comprehensive and exclude patients (i.e. ventilated) who will benefit from the medications. There are defined rules in the MAA but this could be left to clinician discretion. NHSE could appoint a centralised body to consider this – using the existing clinical panel for example. Stopping treatment should be discussed with families/patients as well as the possibility of switching from one treatment to another. An adverse event/ side effect linked to the technology could be a reason for considering discontinuation/switching treatment. No response and/or no perceived benefits from treatment together with increased burden for the patient/family could also lead to discontinuation/switching treatment. Additionally, some guidance about combination therapy, switching and identifying non-responders will be helpful so that the same criteria can be used across the UK.
17. Do you consider that the use of the technology will result in any substantial health-related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation? • Do the instruments that measure quality of life fully capture all the benefits of the technology or have some been missed? For example, the treatment regimen may be more easily administered (such as an oral tablet or home treatment) than current standard of care	The QALY calculation will maximally benefit when newborn screening will be implemented in England. For patients who are long-term ventilated, the benefits might include enabling continuing use of powered wheelchairs or computer controls. This is unlikely to be captures in existing QALY.
18. Do you consider the technology to be innovative in its potential to make a significant and substantial	These 2 therapies have dramatically changed the way SMA progresses to the point that some of the classical descriptions do not apply any more- especially

impact on health-related benefits and how might it improve the way that current need is met? • Is the technology a 'step-change' in the management of the condition? • Does the use of the technology address any particular unmet need of the patient population?	for treatments initiated early. Reducing diagnostic delay will lead to improved outcomes.
19. How do any side effects or adverse effects of the technology affect the management of the condition and the patient's quality of life?	Nusinersen is typically well tolerated with very scarce drug related adverse events. However, there are adverse events related to the route of administration. Risdiplam is generally well tolerated although in some patients, adverse events require discontinuation. Having both options available for HCP and patients is important. So far both technologies have been well tolerated; only a few patients have stopped treatment in the UK. If one is not well tolerated then the alternative may be considered.
20. Do the clinical trials on the technology reflect current UK clinical practice? • If not, how could the results be extrapolated to the UK setting? • What, in your view, are the most important outcomes, and were they measured in the trials? • If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes? • Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	Yes, especially for symptomatic treated patients. For pre-symptomatic treated patients there is not much data in the UK since there is not NBS but the expectation is that real-world will largely follow the experience in the trials.
21. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	NO
22. Are you aware of any new evidence for the comparator treatment (onasemnogene abeparvovec)	NO

since the publication of NICE technology appraisal guidance [HST15, HST24]?	
23. How do data on real-world experience compare with the trial data?	They parallel the trials' xperience, especially for symptomatic treated patients. For pre-symptomatic treated patients there is not much data in the UK since there is not NBS but the expectation is that real-world will largely follow the experience in the trials.
24. NICE considers whether there are any equalities issues at each stage of an evaluation. Are there any potential equality issues that should be taken into account when considering this condition and this treatment? Please explain if you think any groups of people with this condition are particularly disadvantaged. Equality legislation includes people of a particular age, disability, gender reassignment, marriage and civil partnership, pregnancy and maternity, race, religion or belief, sex, and sexual orientation or people with any other shared characteristics. Please state if you think this evaluation could exclude any people for which this treatment is or will be licensed but who are protected by the equality legislation lead to recommendations that have a different impact on people protected by the equality legislation than on the wider population lead to recommendations that have an adverse impact on disabled people. Please consider whether these issues are different from issues with current care and why.	Both should be available as some patients cannot tolerate or access one (for example after spinal fusion). Operating on the principle that those who are long term ventilated unnecessarily have a less good quality of life is an equality issue.

More information on how NICE deals with equalities issues can be found in the NICE equality scheme. Find more general information about the Equality Act and equalities issues here.	

Part 2: Key messages

In up to 5 sentences, please summarise the key messages of your statement:

Click or tap here to enter text.

Click or tap here to enter text.

Click or tap here to enter text.

Click or tap here to enter text.

Click or tap here to enter text.

Thank you for your time.

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NICE National Institute for Health and Care Excellence

Multiple Technology Appraisal

Nusinersen and risdiplam for treating spinal muscular atrophy (MA review of TA588 and TA755) [ID6195]

Patient expert statement

Thank you for agreeing to give us your views on these treatments and their possible use in the NHS.

Your comments are really valued. You can provide a unique perspective on conditions and their treatment that is not typically available from other sources

Information on completing this form

In part 1 we are asking you about living with spinal muscular atrophy or caring for a patient with spinal muscular atrophy. The text boxes will expand as you type.

In part 2 we are asking you to provide 5 summary sentences on the main points contained in this document.

Help with completing this form

If you have any questions or need help with completing this form please email the public involvement (PIP) team at pip@nice.org.uk (please include the ID number of your appraisal in any correspondence to the PIP team).

Please use this questionnaire with our hints and tips for patient experts. You can also refer to the Patient Organisation submission guide. **You do not have to answer every question** – they are prompts to guide you. There is also an opportunity to raise issues that are important to patients that you think have been missed and want to bring to the attention of the committee.

NICE National Institute for Health and Care Excellence

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Your response should not be longer than 15 pages.

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Part 1: Living with this condition or caring for a patient with spinal muscular atrophy

Table 1 About you, spinal muscular atrophy, current treatments and equality

1. Your name	Andrew Thornton
2. Are you (please tick all that apply)	☒ A patient with spinal muscular atrophy ? ☒ A patient with experience of the treatment(s) being evaluated? ☐ A carer of a patient with spinal muscular atrophy? ☒ A patient organisation employee or volunteer? ☐ Other (please specify):
3. Name of your nominating organisation	Treat SMA
4. Has your nominating organisation provided a submission? (please tick all options that apply)	☐ No (please review all the questions and provide answers when possible) ☒ Yes, my nominating organisation has provided a submission ☐ I agree with it and **do not wish to** complete a patient expert statement ☒ Yes, I authored / was a contributor to my nominating organisations submission ☐ I agree with it and **do not wish to** complete this statement ☒ I agree with it and **will be** completing
5. How did you gather the information included in your statement? (please tick all that apply)	☒ I am drawing from personal experience ☐ I have other relevant knowledge or experience (for example, I am drawing on others' experiences). Please specify what other experience: ☐ I have completed part 2 of the statement **after attending** the expert engagement teleconference

Patient expert statement

	☐ I have completed part 2 of the statement **but was not able to attend** the expert engagement teleconference ☐ I have not completed part 2 of the statement
6. What is your experience of living with spinal muscular atrophy? **If you are a carer (for someone with spinal muscular atrophy) please share your experience of caring for them**	I was born in 1974 and diagnosed at approximately 18 months of age with type II Spinal muscular Atrophy. The condition has had a profound impact on all aspects of my life from childhood through to the age I am now. Living with SMA means dealing with loss of strength and mobility; experiencing serious or life-threatening episodes of respiratory illness; having to rely on other people for personal care and daily living; having to fight to get the necessary equipment to maximise independence. Being a physical condition, the emotional and mental health aspect of SMA is often overlooked. As the condition does not impact on my cognitive abilities, I am acutely aware of their limitations and that they likely impact of their condition in the future. SMA Being a progressive condition always means that individuals are often faced with the knowledge that you are soon to lose another everyday function, but without any indication as to when. For example, I may be able to clean their teeth myself today but I know at some point in the future this will be impossible. I often refer to this as having a constant “sword of Damocles” hanging over my head as to what function I am going to lose next, all of which has an indescribable impact on my mental health. It is often said that someone who is in an accident, and perhaps loses the ability to walk, there is a grieving process for the loss of that function. This can take months if not years to recover from. Those with SMA face this continuous grieving process over and over again throughout their entire life due to the progressive ongoing loss of different functions over time. This is often described as a “chronic sorrow” by those with the condition, a recurring sadness created by the loss of functions and is often considered and treated as a form of depression. Sadly very few benefit from treatment for depression as depression is generally considered treatment of a steady-state, whereas the chronic sorrow caused by this ongoing grief continues to progress.

	As you lose these functions you also lose social elements that go with them, which can leave you feeling quite isolated. For example, when I lost the ability to feed or provide drink myself, I no longer take part in social or work events due to the stigma of needing help with such simple things. While people around me would be sure to understand the circumstances, for my own mental health and feeling of worth, it isn't something that I want people to see. I'm fortunate enough to have had a long and successful career working in the NHS, and somewhat ironically, as I have increased in my responsibility managerial the physical requirements of the job has reduced. My role is far more focused around management and leadership these days rather than actually doing, which fits with the natural progression of the condition. This means I am able to continue with my career with very limited functional use, for example, the ability to use a mouse with one hand. I no longer have the ability to type, I use voice recognition, but the ability to manipulate a computer easily using a mouse sustains my role. Yes, something as simple as that, these are the details that people do not understand. If I was to lose the ability to use that mouse there is a good chance I would lose my ability to do my job, as the sole bread winner within my family this would have a catastrophic impact on not only my own life but my family's. The ramifications are huge, financial consequences of not being able to sustain my family, potential loss of house and so much more, all pivotal on such a simple function of using a mouse. While clearly SMA is a physical condition the emotional and mental well-being side of it cannot be ignored. Since starting treatment in December 2020 I have not lost a single function, and despite my age, have actually gained some ability. But probably more importantly is my outlook on life its self. I was told I would not live beyond the age of five, then in my 20s I was told probably not beyond 40, all of these have had massive impacts on my life constantly being concerned about getting close to dying. Now all of a sudden my outlook on life has changed. Treatment has now given me hope that while I may not live to 100, there is now no predefined expiry date that I am living to. My stamina has increased, I have greater strength, when breathing is better I can eat and drink without worrying about the potential consequences of

	choking and no longer do I have to consider the thought of dying each time I sit down for a meal. It's really hard to articulate these things to those who don't necessarily understand the gravity behind what is that I'm talking about. But ultimately, I no longer have that sword of Damocles hanging over me, no longer am I waking up in the morning wondering if I have lost a function, no longer only grieving what I have lost, I am able completely focused on what I have and look forward to the rest of my life.
7a. What do you think of the current treatments and care available for spinal muscular atrophy on the NHS? **7b. How do your views on these current treatments compare to those of other people that you may be aware of?**	Zolgensma is something I have limited knowledge of as this is only available to a very small subset of the population. This kind of medical breakthrough is fantastic in the longer term and is exactly why the UK genomics program has been set up, to champion this kind of genetic advancements in treatment. However, it is far from adequate for the rest of the population. Spinraza has a very good track record and was obviously the 1st to market in terms of the wider population. This has been available for longer than the other treatment and therefore there is greater data and evidence to suggest efficacy. However, a fundamental flaw with this particular treatment is the method of delivery. Delivered primarily through spinal injection/lumbar puncture significantly limits the population able to take advantage of this particular treatment. The majority of patients with SMA have at some point received a spinal fusion which means that access to the spinal canal is extremely limited, if not impossible. Therefore this treatment has been predominantly used on those younger individuals where any treatment is likely to show more pronounced improvement. The other concern relating to Spinraza is the potential support services required to deliver on the treatment. For example, it is not unusual to need CT guidance with regards to spinal injections, there is also an on-site element of the treatment that requires supporting. All of this plays a pivotal role due to the pressures on the NHS. Evrysdi I personally believe is groundbreaking in the way that the treatment is delivered at home with minimal impact from the NHS. The treatment is easy to take, there are no risks associated with lumbar punctures, the treatment is easily stored and is stable and provides the flexibility for people to travel and still receive

	treatment. This treatment is absolutely essential to those who accessing the spinal canal through injections is impossible, but not only that, to those who feel that this is a safer and better option than attending hospital on a regular basis. It's acknowledged that the majority of those on this particular treatment are likely to be of the older population and therefore the perceived efficacy may be somewhat less, but I can tell you from personal experience, that is far from the truth. This deliver stability and that is what we should be looking to deliver with regards to treatment. Yes improvements are a bonus, but stability maintains lives, livelihoods, relationships and everything else. People should be given the choice as to how they receive treatment, and while globally efficacy may show slightly lesser benefit there are plenty of examples of children on this particular treatment who have seen massive improvements in their strength and abilities.
8. If there are disadvantages for patients of current NHS treatments for spinal muscular atrophy (for example, how they are given or taken, side effects of treatment, and any others) please describe these	The biggest disadvantage from my perspective is the use of hospital resources. The regular need for spinal injections, the associated support required to facilitate these, the potential risks and consequences associated with these I think presents a significant disadvantage.
9a. If there are advantages of nusinersen and/or risdiplam over current treatments on the NHS please describe these. For example, the effect on your quality of life, your ability to continue work, education, self-care, and care for others? **9b. If you have stated more than one advantage, which one(s) do you consider to be the most important, and why?** **9c. Does nusinersen and/or risdiplam help to overcome or address any of the listed disadvantages of current treatment that you have described in question 8? If so, please describe these**	Just to be clear for the purposes of discussion, there are no other NHS treatment available other than those being described in this document for adults. By far the biggest advantage with regards to the two treatments is that Evrysdi is a home based treatment that requires no additional support services for delivery. There are inherent risks attached with lumbar punctures and spinal injections and therefore Spinraza requires a much more holistic MDT style approach when it comes to administration. While lumbar punctures are generally well tolerated in youngsters there are also challenges that this can become more difficult as patients get older. As Spinraza was 1st to market there is a lot of evidence with regards to efficacy in young children however this information can also be found in a smaller scale with regards to Evrysdi.

10. If there are disadvantages of nusinersen and/or risdiplam over current treatments on the NHS please describe these. For example, are there any risks with nusinersen and/or risdiplam? If you are concerned about any potential side effects you have heard about, please describe them and explain why	See above
11. Are there any groups of patients who might benefit more from nusinersen or risdiplam, or any who may benefit less? If so, please describe them and explain why Consider, for example, if patients also have other health conditions (for example difficulties with mobility, dexterity or cognitive impairments) that affect the suitability of different treatments	Yes! Spinraza is not a practical treatment for those who have had significant spinal surgery, particularly those aged 25+. Many patients who have had spinal fusion received surgery in a way that limits access to the lumbar area of the spine as there was no treatment available and no necessity to maintain access. While all patients with SMA would be able to receive Evrysdi this is not the case with regards to Spinraza. Administration of Spinraza is a lot more complex as it requires hospital visits, potential CT services, short-term day case bed capacity, transport, patient support and numerous other elements. A patient receiving this medication must have a robust and supportive network around them to assist with receiving treatment. Unfortunately this isn't necessarily the case with all patients. Some patients did not have the adequate support network around them to receive such complex treatment and therefore the home delivery nature of Evrysdi provides significant advantages.
12. Are there any potential equality issues that should be taken into account when considering spinal muscular atrophy, nusinersen and risdiplam? Please explain if you think any groups of people with this condition are particularly disadvantage Equality legislation includes people of a particular age, disability, gender reassignment, marriage and civil partnership, pregnancy and maternity, race, religion or	The biggest equality issue relating to equity of access would be age. Should Evrysdi not receive approval then this would remove available treatment for those who have spinal fusions, particularly those of older generation when there wasn't a requirement to maintain spinal access. This means that patients over the age of 25/30 would not have equal access to treatment compared to those who do have access to receive lumbar punctures.

belief, sex, and sexual orientation or people with any other shared characteristics More information on how NICE deals with equalities issues can be found in the NICE equality scheme Find more general information about the Equality Act and equalities issues here.	
13. Are there any other issues that you would like the committee to consider?	

Part 2: Key messages

In up to 5 sentences, please summarise the key messages of your statement:

- Every patient should be given the right to receive treatment in a way that best suits their own personal circumstances and lifestyle choices.
- Failure to approve Evrysdi would create inequality in access to treatment for those with complex spinal fusions
- The UK government has invested heavily into genomic medicine in recent years, culminating in the establishment of a hub and spoke National genomic model. If the UK does not take advantage of associated genomic development what is the point in investing in translational medicine.
- The mental health impact of treatment should not be underplayed when decision-making. While SMA is a physical condition the mental health aspects that sit alongside it have huge impacts on those both with and caring for those with SMA.
- Every patient with SMA should be entitled to treatment regardless of age, type or personal circumstances and should also have the right to switch between treatments to determine which is the most appropriate for their own benefit.

Thank you for your time.

Your privacy

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NICE National Institute for Health and Care Excellence

Multiple Technology Appraisal

Nusinersen and risdiplam for treating spinal muscular atrophy (MA review of TA588 and TA755) [ID6195]

Patient expert statement

Thank you for agreeing to give us your views on these treatments and their possible use in the NHS.

Your comments are really valued. You can provide a unique perspective on conditions and their treatment that is not typically available from other sources

Information on completing this form

In part 1 we are asking you about living with spinal muscular atrophy or caring for a patient with spinal muscular atrophy. The text boxes will expand as you type.

In part 2 we are asking you to provide 5 summary sentences on the main points contained in this document.

Help with completing this form

If you have any questions or need help with completing this form please email the public involvement (PIP) team at pip@nice.org.uk (please include the ID number of your appraisal in any correspondence to the PIP team).

Please use this questionnaire with our hints and tips for patient experts. You can also refer to the Patient Organisation submission guide. **You do not have to answer every question** – they are prompts to guide you. There is also an opportunity to raise issues that are important to patients that you think have been missed and want to bring to the attention of the committee.

NICE National Institute for Health and Care Excellence

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Your response should not be longer than 15 pages.

The deadline for your response is **5pm** on **Wednesday 29 May 2024.** Please log in to your NICE Docs account to upload your completed form, as a Word document (not a PDF).

Thank you for your time.

We reserve the right to summarise and edit comments, or not to publish them at all, if we consider the comments are too long, or publication would be unlawful or otherwise inappropriate.

Comments received are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the comments we received, and are not endorsed by NICE, its officers or advisory committees.

Part 1: Living with this condition or caring for a patient with spinal muscular atrophy

Table 1 About you, spinal muscular atrophy, current treatments and equality

1. Your name	Lucy Frost
2. Are you (please tick all that apply)	☐ A patient with spinal muscular atrophy ? ☐ A patient with experience of the treatment(s) being evaluated? ☒ A carer of a patient with spinal muscular atrophy? ☐ A patient organisation employee or volunteer? ☐ Other (please specify):
3. Name of your nominating organisation	Treat SMA
4. Has your nominating organisation provided a submission? (please tick all options that apply)	☐ No (please review all the questions and provide answers when possible) ☒ Yes, my nominating organisation has provided a submission ☐ I agree with it and **do not wish to** complete a patient expert statement ☐ Yes, I authored / was a contributor to my nominating organisations submission ☐ I agree with it and **do not wish to** complete this statement ☒ I agree with it and **will be** completing
5. How did you gather the information included in your statement? (please tick all that apply)	☒ I am drawing from personal experience ☐ I have other relevant knowledge or experience (for example, I am drawing on others' experiences). Please specify what other experience: ☐ I have completed part 2 of the statement **after attending** the expert engagement teleconference

	☐ I have completed part 2 of the statement **but was not able to attend** the expert engagement teleconference ☐ I have not completed part 2 of the statement
6. What is your experience of living with spinal muscular atrophy? **If you are a carer (for someone with spinal muscular atrophy) please share your experience of caring for them**	My son, George, has spinal muscular atrophy type 2. He was diagnosed at the age of 1, however; this was a traumatic experience as it took over 3 months for my concerns to be heard. During this time, George underwent multiple, invasive tests only to be told that he had arthritis and to go home. It was only because I demanded a day transfer to Great Ormond Street Hospital, that George was then diagnosed. If it wasn't for my persistence, George would have remained undiagnosed and would've missed out on possible help. Prior to George receiving treatment at the age of 7, I watched him deteriorate and lose many abilities such as: crawling, high kneeling, rolling, arm strength and neck strength. I also had to watch his respiratory system decline which resulted in multiple hospital admissions, which showed declining lung capacity and a swallow that was weakening which led to George aspirating and chest infections. As a parent, not being able to help your child or have any control over their health was devastating and took its toll physically and mentally. Alongside this, I also had the pressures of multiple, weekly appointments, the fight to get George the support he needed and the financial implications this all had, especially when trying to source vital equipment that the NHS would not supply. I had to fundraise as this was my only option to purchase this equipment, which was another thing I had to take ownership of. George also has a sister, who is only 11 months older than him. Her emotional and physical needs still had to be met but often there was an immense feeling of guilt as I had to prioritise George. George's care for the first 7 years of his life was immense. I navigated my way through a minefield of learning and educating myself on how to take care of my son and meet his needs. His physical needs consisted of dressing, toileting, bathing, washing, assisting with meals and snacks throughout the day, getting George anything he needed, changing his position throughout the day from the floor, to wheelchairs or turning him throughout the night. Ultimately, being there to assist him 24 hours a day. Monitoring George's respiratory health was so important in order to

	keep him alive, that my own mental health suffered, which then impacted my physical health too. I have been diagnosed with PTSD, anxiety and fibromyalgia. However, my health issues always come second, as my children will always comes first but also the lack of care available in order for me to seek help or rest. George's respiratory care is continuous throughout the year to act as a preventative and then if he does get ill, that care and machines involved escalate to around the clock care. Even when I can sleep, I cannot for fear of me not hearing him or not being able to act quick enough. Since George has been on risdiplam, he has not had a hospital admission, his lung capacity has increased, he has regained his swallow and the threat to his life is no longer as severe. This has had a massive impact on not only his quality of life but his family's too. His physical abilities have got stronger in some areas and have maintained in the rest. I feel this is due to the medicine itself and as he is well the majority of time, he is able to participate in physical activities and physio. This improved strength has allowed me to be needed less and therefore I have more quality time with my daughter. Knowing your child's condition will not deteriorate, is a heavy weight lifted on what I have to carry as a parent. This has eradicated the fear of wondering what George may lose from one day to the next. George's mental health is amazing and although he has always had a positive outlook, this treatment has only improved this further since he has gained more independence and confidence in himself. His school attendance has risen from 27% to 98% and he is currently now one of the top students in his class. Spinal muscular atrophy is beyond devastating and the impact doesn't just stop at the person diagnosed or immediate family. Receiving treatment has only made things better, not only for George but for everyone who cares for him.
7a. What do you think of the current treatments and care available for spinal muscular atrophy on the NHS?	The only current approved treatment on the NHS is zolgensma, which has a strict criteria and eliminates the majority of the current SMA community. Therefore, this drug is completely unsuitable and would leave hundreds of people at the mercy of this terrible condition.

7b. How do your views on these current treatments compare to those of other people that you may be aware of?	Both risdiplam and nusinersen, which are being accessed via MAA have transformed the lives of children and adults living with SMA for the better. I have experienced risdiplam due to George being on it for the last 5 years. This is extremely easy to take as it is just an oral solution. The medication is couriered to your home and is simply stored in the fridge. It is completely non-invasive and has not caused my son any stress. Nor does it require him to go into hospital in order to receive it and doesn't pose the risk of any infection nor take resources away from the NHS. George has never had any side effects from this treatment. Risdiplam has transformed George's life for the better and continues to gain strength and new abilities along with this treatment and regular physio. Unfortunately, physio comes in blocks on the NHS so it is not continuous throughout the year. These voids are filled with paid, private physio. George receives orthotics to keep his contractures in line and although these services have always been good for George. I do know, this differs for others across the UK. I believe that SMA needs to be treated as rehabilitation rather than managing a physical decline with more educated services available to do that and get the best out of the treatment.
8. If there are disadvantages for patients of current NHS treatments for spinal muscular atrophy (for example, how they are given or taken, side effects of treatment, and any others) please describe these	My son personally hasn't experienced any side effects whilst taking this drug but for others side effects will always depend on the individual person due to there always being different variables to consider such as other medical conditions. Risdiplam is the easiest treatment to take as stated above and the way it is administered allows for no risks. Nusinersen is a more invasive procedure that requires you to travel to a hospital 4 times a year and there can be side effects associated with the lumbar puncture. However, the positives of the treatment will always outweigh any of this. Without either of these treatments, the alternative is living with SMA which is forever a risk to life and shorter life expectancy.
9a. If there are advantages of nusinersen and/or risdiplam over current treatments on the NHS please describe these. For example, the effect on your quality of life, your ability to continue work, education, self-care, and care for others?	The only other treatment on the NHS is zolgensma and this is only accessible for young children with SMA type 1 that fall within a certain weight limit. This eliminates nearly all of the current SMA community so the positives of risdiplam and nusinersen is that they come with no type of weight restriction and will allow all of those with SMA to be treated. Neither risdiplam or nusinersen pose a major health risk, like zolgensma so there is not the aftercare required or medication. Risdiplam doesn't impact our daily life and therefore, George's education, social life and self-

9b. If you have stated more than one advantage, which one(s) do you consider to be the most important, and why? **9c. Does nusinersen and/or risdiplam help to overcome or address any of the listed disadvantages of current treatment that you have described in question 8? If so, please describe these**	care are met. It is important that all three treatments are available. Firstly, so people have the right to choose their treatment. Secondly, to swap treatments if one no longer works, if there are any side effects and if administering the drug is impossible via lumbar puncture. The right to choose is very important.
10. If there are disadvantages of nusinersen and/or risdiplam over current treatments on the NHS please describe these. For example, are there any risks with nusinersen and/or risdiplam? If you are concerned about any potential side effects you have heard about, please describe them and explain why	Although zolgensma is a one-off treatment, there is no long-term data to show the long-term impact. Therefore, regularly receiving treatment ensures a long-term guarantee.
11. Are there any groups of patients who might benefit more from nusinersen or risdiplam, or any who may benefit less? If so, please describe them and explain why Consider, for example, if patients also have other health conditions (for example difficulties with mobility, dexterity or cognitive impairments) that affect the suitability of different treatments	No. All will benefit equally in their own way. Although starting treatment younger, may show better physical results, treatments started later where someone regains their hand movement means they can operate a computer, phone and power wheelchair. This will lead to greater communication, work and education opportunities and mobility advantages.
12. Are there any potential equality issues that should be taken into account when considering spinal muscular atrophy, nusinersen and risdiplam? Please explain if you think any groups of people with this condition are particularly disadvantage Equality legislation includes people of a particular age, disability, gender reassignment, marriage and civil	People living with SMA type 4 currently do not have access to treatment which they could benefit from.

partnership, pregnancy and maternity, race, religion or belief, sex, and sexual orientation or people with any other shared characteristics More information on how NICE deals with equalities issues can be found in the NICE equality scheme Find more general information about the Equality Act and equalities issues here.	
13. Are there any other issues that you would like the committee to consider?	

Part 2: Key messages

In up to 5 sentences, please summarise the key messages of your statement:

- SMA has an impact on mental health as much as physical health.
- SMA impacts an entire family not just the person diagnosed.
- The added financial burden that SMA brings directly and indirectly.
- The right to access treatment and choose your treatment.
- All type and ages will benefit from treatments which will impact their lives positively.

Thank you for your time.

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Part 1: Living with this condition or caring for a patient with spinal muscular atrophy

Table 1 About you, spinal muscular atrophy, current treatments and equality

1. Your name	Mrs Portia Thorman
2. Are you (please tick all that apply)	☐ A patient with spinal muscular atrophy ? ☐ A patient with experience of the treatment(s) being evaluated? ☒ A carer of a patient with spinal muscular atrophy? ☒ A patient organisation employee or volunteer? ☐ Other (please specify):
3. Name of your nominating organisation	
4. Has your nominating organisation provided a submission? (please tick all options that apply)	☐ No (please review all the questions and provide answers when possible) ☒ Yes, my nominating organisation has provided a submission ☐ I agree with it and **do not wish to** complete a patient expert statement ☒ Yes, I authored / was a contributor to my nominating organisations submission ☐ I agree with it and **do not wish to** complete this statement ☒ I agree with it and **will be** completing
5. How did you gather the information included in your statement? (please tick all that apply)	☒ I am drawing from personal experience ☒ I have other relevant knowledge or experience (for example, I am drawing on others' experiences). Please specify what other experience: ☐ I have completed part 2 of the statement **after attending** the expert

	engagement teleconference ☒ I have completed part 2 of the statement **but was not able to attend** the expert engagement teleconference ☐ I have not completed part 2 of the statement
6. What is your experience of living with spinal muscular atrophy? **If you are a carer (for someone with spinal muscular atrophy) please share your experience of caring for them**	**Diagnosis** My son, Ezra was born in November 2016. Five weeks later he caught RSV, his first common cold and was transferred from our local hospital and intubated in intensive care. Despite concerns raised about his lack of tone, we were discharged back to our local hospital and then home. Ezra lost an enormous amount of strength over the 2 weeks in hospital and continued to do so rapidly. Three different health visitors and his GP put this down to his time in hospital and assured me his strength would return. By February 2017, at just 3 months old, he could only move his forearms, could not put his hand to his mouth, completely stopped moving his legs, was choking on his feed and was 'belly breathing'. At this point we insisted on a referral to our local hospital which was done immediately. The next day we were urgently called in to the Evelina Childrens Hospital. After an agonising two week wait for the results of a blood test, in March 2017, at 4 months old, Ezra was diagnosed with SMA type 1, a condition that we had never heard of. We were told the devastating news that he would not make it to his second birthday. At diagnosis, however, we were also told that Ezra met the criteria for access to a new drug, nusinersen, through the Expanded Access Programme (EAP), enabling him to receive the drug on compassionate grounds. With limited clinical evidence, this was a difficult decision to make. **Treatment Initiation**

	Just weeks after diagnosis, before treatment could start, in April 2017, Ezra caught ERV, another common cold virus and again needed the support of a ventilator in PICU. This admission filled us with fear as we knew the impact of an SMA diagnosis on the chances of his recovery On the 11th April 2017, despite his compromised condition, the Multi Disciplinary Team agreed that Ezra could go ahead with nusinersen treatment. As a family, we refused palliation and made the decision to go ahead with treatment. This was a very stressful time for not only us as parents but for Ezra's 3 siblings who had watched his deterioration and had their own questions about SMA, Ezra's prognosis and the new treatment. Aged 16, 13 and 3 at the time, these were extremely difficult conversations. **Adjustment** The next month in hospital was a whirlwind. Nusinersen treatment continued. A videofluoroscopy revealed an unsafe swallow - accepting the fact that Ezra would now not be able to eat anything orally was incredibly difficult. We went from breast feeding to tube feeding at six months old, this was hugely psychologically damaging for me as a mother and one of the hardest times of the whole journey. I had to accept the reality that I would have to give up my career as a primary school teacher to care for Ezra full time. This put enormous strain on our finances and caused a significant amount of stress. Unfortunately, the remainder of 2017 saw three further long PICU admissions throughout which we were trained how to use a bi-pap ventilator, a cough assist machine and how to administer aggressive respiratory physiotherapy and invasive deep suction. All of these interventions would now be needed routinely to keep Ezra safely at home. Not really understanding what a care package was, I refused to wait for one to be arranged before being discharged home in July 2017, where his room now looked like a hospital with a ventilator for sleeping, a suction machine, cough assists and a saturation monitor. Sleeping was not easy for any of us!

	That was not the end of our time in intensive care, but the admissions did become shorter and less frequent. We had three admissions in 2018, then none at all for a year and a half until January 2020 and again in June 2021. All of these hospital admissions in London weighed extremely heavily on my husband and three daughters who tried their best to continue a normal life at home, travelling several hours to London to visit when they were able to at the weekend. My eldest daughters went through GCSE's and A-levels, revising at Ezra's bedside, managing the trauma of his condition and the impact on their daily lives, alongside exam stress. **Day to day living with SMA** Ezra is now 7 and since he was 3, he has not had any more admissions to hospital. With a dedicated team of NHS funded home nurses providing 12 hour 1:1 overnight care as well as a 1:1 nurse and TA at school, Ezra is thriving. Life is very busy and with no daytime care support at weekends and during school holidays it is difficult to get any free time. Holidays are difficult. We are yet to strike up the courage and the energy to take a trip abroad. Even local trips require meticulous planning, organising and packing, taking a myriad of machines, wheelchairs, medical feed and extra medical stock to ensure any eventuality is catered for. Daytrips are similarly stressful and frustrating for my 10-year-old daughter, with so many activities out of bounds for us as a family. It is very difficult to spend any quality time with my husband as one of us must always be in the house with the nurse to fulfil the conditions of his care package. We have not had any support for our mental health. Mobility Unable to bear any weight through his legs, Ezra relies on a powered wheelchair to get around, having started learning at the age of 3 he is an incredibly proficient driver and enjoys exploring his environment in his Tiny Trax wheelchair which enables him to go offroad and up small kerbs. With no statutory provision for these

	wheelchairs, we have had to fundraise as well as contributing a significant amount of money ourselves. Transferring Ezra is becoming more and more difficult, now at 24kg we should be hoisting him for transfers but practically, with a busy family, lifting him saves time. This is having a detrimental effect on my back. We have recently received our first wheelchair accessible van, which has improved our ability to go out and about with all his kit. Not being eligible for a grant meant we had to find £5000 as a one off downpayment. Ezra can not travel in a car seat for more than about 30 minutes as it hurts his back, therefore for longer journeys we use a specialist harness that enables him to lie flat across the back seat. If I am travelling alone with Ezra, I always put his bi-pap ventilator on him for safety and peace of mind. Respiratory Health Ezra is dependent on his bi-pap ventilator overnight and requires routine nebulisers, chest physiotherapy and cough assist every morning and again before bed. Over time, the pressures required on his ventilator have reduced, until his scoliosis became more pronounced recently when the pressures had to be increased again. If Ezra catches a cold, he may require 24hr bipap ventilation, increased respiratory physio and nebulisers. It is always an anxious time as he can tire easily, becoming very poorly very quickly. I have to remove my emotional 'mum hat' and put on my 'nurse hat', a coping strategy I have developed over time that enables me to carry out these distressing procedures on my son . However, nusinersen treatment, along with nursing support overnight at home and our growing understanding and acceptance of his condition, has had a positive impact on his respiratory health. For the last 3 years we have managed all his coughs and colds at home with no hospital admissions. Ezra is extremely self-aware of his respiratory health and will ask for his bi-pap if he feels he needs it and is able to suction himself orally with support. Contractures and Scoliosis

	Ezra has significant contractures which restrict mobility in his knees, ankles, hips and shoulders. For his knees, this is managed with regular stretching, daily standing frame practise and gaiters worn overnight. Access to appropriate physiotherapy is limited, and professional hydrotherapy non-existent, so we have invested in a hot tub which Ezra adores. In the water he is able to move independently and recently he has learnt to swim underwater which I believe is strengthening his respiratory muscles and supporting his secretion management. Despite wearing an orthotic spinal brace since he was 2 years old, Ezra's scoliosis has progressed significantly and now he lives with a 70 degree curve which is impacting his lung capacity. He regularly complains of back pain and is finding his spinal brace, which he wears all day, harder to tolerate. He also has significant kyphosis which is not addressed with the spinal brace. Spinal surgery is therefore inevitable. I hope that Ezra's clinicians can find a way to do this that allows him to continue nusinersen treatment. Swallowing With an unsafe swallow, Ezra has been entirely peg fed since he was 6 months old and requires regular suctioning to manage his secretions. He finds this difficult to accept and does not like me telling people that he can not swallow. He thoroughly enjoys tasting food and is very happy to munch on anything and then spit it out. His unsafe swallow, however, means that any tasting has to be very carefully monitored due to the high risk of choking. He is also at risk of choking on his own secretions which are often copious. Clinicians have struggled to agree what treatment can alleviate Ezra's secretion load as thickening it could put him at increased risk of a severe aspiration and any intervention involving botox could impact his already compromised facial muscles. At school Ezra stays in the classroom with his nurse to have his lunch feed and his ventilator on. He enjoys this opportunity to rest and have some peace from the noisy classroom environment. However, it does mean he misses out on socialising.

	Speech and language and cognition With a weak tongue, facial muscles and reduced lung capacity, Ezra's articulation and volume of speech are significantly affected by SMA. However, he has a huge vocabulary, above average for his age and is able to hold meaningful, interesting and often witty conversations. If you know Ezra well, it is easy to understand him; for others he can require interpretation. Now in year two, academically Ezra is excelling, working at above age-related expectations in reading and writing. He can write with a pencil but is very slow and his letter formation poor which frustrates him. With the help of some assistive technology however, he is able to keep up with his peers. Ezra's speech difficulties, his mobility issues and the fact that he always has an adult with him means that socialising with his able-bodied peers will always be challenging, However, their acceptance of him and the way the staff and the pupils have embraced and normalised his condition and his medical kit has been fantastic.
7a. What do you think of the current treatments and care available for spinal muscular atrophy on the NHS?	**Nusinersen treatment and effective management strategies have enabled Ezra to not only live but to live a happy and full life as you can see on Instagram @ezrasadventures_smatype1.** **Treatment** Over the 7 years that Ezra has been receiving nusinersen, the management and efficiency of the appointments has gradually improved. The injections themselves are done considerately with Ezra's welfare considered. Due to the expertise of the treating consultant, his ever-increasing scoliosis curve does not seem to have impacted the intrathecal process. Ezra understands what his 'muscle juice' is for and is incredibly tolerant of the invasive procedure, he remains awake throughout with only anaesthetic cream to manage procedural discomfort. We are usually in and out of the hospital within about 4 hours with no side-effects. After significant rises in his physio assessment scores over Ezra's first 5 years, they have now plateaued, with no significant changes in his motor function over the last

	couple of years. The volume and diction of his voice has improved which has had a positive impact on his socialisation He has become more able to manage his secretions with less incidents of aspiration and he has had far less severe respiratory infections. The physio assessments for the MAA are limited and do not capture the holistic picture of his improvements and their impact on our quality of life. **Disease management and Care coordination** Ezra receives multi-disciplinary care across different sites, managing these appointments is time consuming and requires Ezra to miss a significant amount of school. **At his specialist hospital we travel 2-3 hours for:** -Nusinersen treatment: 4x per year -Orthotics and orthopaedics: approx. 2x per year -Neuromuscular physiotherapy: 2 x per year (All the time in these appointments is taken up with Managed Access Agreement assessments rather than giving specialist support which is a great shame) -Neurology: 2x per year -Long term ventilation and respiratory inc. sleep studies: 2x per year These appointments are in the same hospital; unfortunately, poor coordination of appointments means we have to travel to London, on average, 10 times a year. **Locally, at our disabled children's centre we receive support from:** -Dietician -Speech and language therapist (Ezra has now been discharged form this service- with a lack of clinical evidence they do not know how to help him) -Physiotherapist (6x week block every 3 months if their capacity allows) -Occupational therapists -OT and PT sessions are split between home, school and at their site.

7b. How do your views on these current treatments compare to those of other people that you may be aware of?	Ezra does not receive enough physiotherapy. We have had periods of up to 2 years without seeing a community physiotherapist. With a lack of clinical evidence in SMA type 1, the care pathways differ across the UK, with some community physios following inappropriate cerebral palsy pathways. There does not seem to be any direction from specialist to community physios. The quality of orthotic bracing also varies depending on where you live. Influential families on social media raise awareness of expensive private providers that they consider to be superior, many families pay a significant amount of money for private physiotherapy and orthotics based on social media opinion and not on clinical evidence. This causes a lot of stress for many families. There are also huge geographical inequities in access to care support. The criteria to access Continuing Care funding appears to differ across the UK and access to appropriate social care is becoming more and more difficult. There is not enough mental health support for people living with SMA or their families. My views on the current treatments reflect those of the many other people living with SMA that I know. Both risdiplam and nusinersen have been transformative for the SMA community. The challenge now is to create, collect and share clinical research that will lead to best practice for management strategies, enabling the best outcomes from these treatments as possible.
8. If there are disadvantages for patients of current NHS treatments for spinal muscular atrophy (for example, how they are given or taken, side effects of treatment, and any others) please describe these	Anecdotally, risdiplam has given a minority of patients a range of side effects, many of which seem to be very individualised. The most commonly reported side effects, particularly in adults, are gastro related. This is difficult to manage when you live with limited strength and mobility. Nusinersen involves an invasive procedure that requires travel to a specialist centre 4 times a year. However, for me and for many, this disruption and discomfort is both manageable and justifiable due to the efficacy experienced. Adults have reported headaches and fatigue associated with the lumbar puncture; this is less common in children.

9a. If there are advantages of nusinersen and/or risdiplam over current treatments on the NHS please describe these. For example, the effect on your quality of life, your ability to continue work, education, self-care, and care for others? **9b. If you have stated more than one advantage, which one(s) do you consider to be the most important, and why?** **9c. Does nusinersen and/or risdiplam help to overcome or address any of the listed disadvantages of current treatment that you have described in question 8? If so, please describe these**	Zolgensma is the only other treatment available on the NHS, this is only accessible for young children who have SMA Type 1 and who fall within the restrictive weight limit. Therefore, the greatest advantage of these two treatments is that they come with no type restriction when symptomatic. This means that having all 3 drugs allows potential for all diagnosed with SMA type 1-3 to be treated. Nusinersen and risdiplam both act on the SMN2 gene. As such, there is scope for them to be used in combination with Zolgensma which acts on the SMN1 gene. Zolgensma is a one-off treatment, with limited long term efficacy data. Both risdiplam and nusinersen could be used to treat those who do not respond or who do not continue to respond to Zolgensma in the future. Neither risdiplam nor nusinersen have health risks like those associated with gene therapy administration, so do not require such a rigorous post treatment monitoring schedule, nor any steroid use causing immunosuppression which can result in whole families shielding for long periods of time. Whilst nusinersen takes a whole day or two out of our schedule once every 4 months, between these treatment days we do not have to think about a treatment regime. Risdiplam becomes a daily routine, individually designed to fit around eating, working and school. The perspective of the impact of treatment on daily life and quality of life is subjective and another reason for the importance of choice. Having three treatments available means that if a person does not get on with one or cannot have it there is the option of the other. For Ezra it will be vital that if his spinal curvature or any surgery prevents the use of nusinersen, he still has the option of risdiplam.
10. If there are disadvantages of nusinersen and/or risdiplam over current treatments on the NHS please describe these. For example, are there any risks with nusinersen and/or risdiplam? If you are concerned about any potential side	As continual treatments, risdiplam and nusinersen have a higher impact on daily life than Zolgensma, a one off treatment. Personally however, there is a peace of mind that comes with knowing Ezra's treatment is continually 'topped up'.

effects you have heard about, please describe them and explain why	
11. Are there any groups of patients who might benefit more from nusinersen or risdiplam, or any who may benefit less? If so, please describe them and explain why Consider, for example, if patients also have other health conditions (for example difficulties with mobility, dexterity or cognitive impairments) that affect the suitability of different treatments	Babies who are diagnosed and treated through newborn screening benefit most from treatment. For all three treatments, evidence shows that the earlier the treatment, the better the treatment outcome. If my son had accessed treatment when he was first hospitalised at 5 weeks old, he most likely would have retained more function and might not be living with the complex needs he has today. However, the value to an older individual of not losing a critical ability such as the movement in a finger to control a powerchair or the ability to swallow food, cannot be emphasised enough.
12. Are there any potential equality issues that should be taken into account when considering spinal muscular atrophy, nusinersen and risdiplam? Please explain if you think any groups of people with this condition are particularly disadvantage Equality legislation includes people of a particular age, disability, gender reassignment, marriage and civil partnership, pregnancy and maternity, race, religion or belief, sex, and sexual orientation or people with any other shared characteristics More information on how NICE deals with equalities issues can be found in the NICE equality scheme Find more general information about the Equality Act and equalities issues here.	People living with SMA type 4 currently can not access any treatment, despite it being a milder and rarer form of the disease. It can leave adults unable to continue work and becoming reliant on family and friends to meet their needs. Psychologically, with the condition appearing later in life, when they are accustomed to full independence - the acceptance of this progressive condition is hard. It is extremely distressing for them to be excluded from treatment that could halt the progression of their condition. Classed as 5Q SMA, those living with SMA type 4 could technically access treatment under the nusinersen label which is not limited to any specific type.

13. Are there any other issues that you would like the committee to consider?	

Part 2: Key messages

In up to 5 sentences, please summarise the key messages of your statement:

- An SMA diagnosis impacts the whole family and their support network. Treatment brings hope.
- Living with SMA brings huge amounts of stress, anxiety and financial burden. With treatment it can also bring huge amounts of pride, joy and a new appreciation of every moment.
- There are huge geographical inequities in care and management strategies for those living with SMA in the UK.
- All people living with SMA need the choice of available treatments to find them one that works best for them and fits their individual needs.
- To get the best outcomes from treatment, there needs to be more research into standards of care in SMA across the UK.

Thank you for your time.

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NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Multiple technology appraisal

Nusinersen for treating spinal muscular atrophy. Review of TA588

Addendum

Summary of Additional Analysis for NICE Committee

December 2025

File name	Version	Contains confidential information	Date
ID6195 Nusinersen for treating 5qSMA_Post ACM1 Addendum_Redacted_Severity Modifier Updates	**Final**	**Yes**	**7 January 2026**

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Description of the issue

Following the Appraisal Committee Meeting held on 11 November 2025, NICE has requested that Biogen provides additional analyses to help to address outstanding key issues. Therefore, a series of model updates have been made as described in Section 1.1. Additionally, scenario analyses have been completed to further explore the key discussion points as described in Section 1.2.

Section 1.1 Updated base case analysis

All updated analyses are based on the EAG versions of the Biogen models as provided on 27th August 2025. These models were the basis for the EAG analysis for nusinersen in the MTA EAG Assessment Report. To provide the requested analyses, and to align with the NICE committee preferences, it was necessary to make a number of changes in the EAG models. These were as follows:

- Onasemnogene abeparvovec (OA) was included as a comparator in the pre-symptomatic (PS) and type 1 models in scenario analyses by the EAG. Data from the adjusted MAIC conducted by Biogen as part of the MTA submission was used to compare OA with nusinersen, however the reported risk difference was misinterpreted (see later section on “treatment effect”). Based on recommendations from the NICE committee, the severity modifier was not applied for all comparisons of nusinersen and OA.

- The “on treatment” absolute utility increment was applied to people who were actively receiving nusinersen or had received OA (but capped by general population utility). This was amended from the EAG approach which used a utility increment of 10% of the respective health state utility.

- The caregiver age and utility values were updated to align with the data used in the models originally submitted by Biogen (sourced from Tappenden et al. [2021]) as the EAG withdrew their preference for Lo et al. [2024] prior to the first committee meeting.

- Caregiver utility increments were included in the base case analysis.

- The number of caregivers in the base case was increased from 1 to 2.

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- Severity modifiers were applied to the total QALYs for the person with SMA (not the caregiver QALYs). The selected severity modifier aligned with the EAG preferences: presymptomatic = 1.7, type 1 = 1.7 and type 2/3 = 1.2 (for the comparison of nusinersen and BSC only, not relevant for the OA comparison).

- Lower hospitalisation rates and resulting health state costs were applied for people receiving nusinersen and OA, versus BSC.

Treatment effect (nusinersen vs. OA)

Biogen maintain that comparisons between DMTs based on the available clinical trials are inappropriate given significant differences in inclusion/ exclusion criteria, assessment timepoints, definitions for baseline characteristics and outcome measures, as referenced in the original company submission. Resulting outputs from the matching adjusted indirect comparisons (MAICs) are based on small effective sample sizes and associated with high risk of bias. Nevertheless, as per the request of NICE, Biogen have conducted exploratory scenario analyses comparing nusinersen and OA.

The EAG versions of the PS and type 1 models used the treatment effect for nusinersen compared with OA as reported in the MAICs provided by Biogen in Appendix D of the MTA Assessment Report. The relevant data from the MAIC is reported in Table 1 for pre-symptomatic SMA and Table 2 for type 1 SMA.

It is important to highlight that Appendix D of the MTA Assessment Report reported the risk difference as decimals. For example, the adjusted risk difference in the PS sub-population comparing nusinersen with OA for the WHO motor milestone ‘standing with support’, at 18 months was [redacted], equivalent to [redacted]. The EAG models instead applied a risk difference of [redacted] to each timepoint in the efficacy data. Therefore, it is believed that the EAG misinterpreted the outputs of the MAICs. The data have subsequently been corrected in the latest versions of the models.

Following these corrections, the OA population were able to both achieve motor milestones ahead of the general population (which was deemed implausible) and negative numbers appeared in the efficacy data.

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To avoid these limitations, the method in which the MAIC data was applied has been updated using the following assumptions:

- The efficacy of OA was assumed to be equivalent to nusinersen up until 18 months (the published time point at which the study cohorts were assessed).
- From 18 months onwards, the risk difference value for nusinersen vs OA was applied to all cycles, until Month 60. Thereafter, patients on treatment could only maintain or lose motor milestones aligned with the original Biogen submission.
- To avoid the total health state occupancy for OA exceeding 100% (effectively creating more people), the data has been adjusted to prioritise the more advanced motor milestone. For example, if the OA data stated that 80% of people achieved ‘walking independently’ and 40% achieved ‘standing with support’ then the standing with support figure was adjusted to 20% to ensure the value of the two did not exceed 100%.

Additionally, for pre-symptomatic SMA, it was only possible to undertake a MAIC for people with 2 copies of SMN2. A MAIC for people with 3 copies of SMN2 was not feasible as all participants achieved walking independently and no permanent ventilation or death events occurred. Therefore, the risk difference from the MAIC was applied to the nusinersen efficacy data for the 2 SMN2 copy sub-population to estimate the effectiveness of OA in this sub- population. In the absence of any MAIC data, the efficacy data for OA in the 3 SMN2 copy sub-population was assumed to be equivalent to nusinersen. A weighted average was taken over the two sub-populations to derive the efficacy for the total pre-symptomatic population.

The derived efficacy data for OA in the PS and type 1 sub-populations are presented in Table 3 and Table 4, respectively.

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Table 1. MAIC results for presymptomatic SMA

Efficacy measure	Nusinersen individual patient level data source	OA published aggregated data (AgD) source	Time point	Effective sample size	Adjusted risk difference (95% CI)
WHO motor milestones: Standing with support	NURTURE	SPR1NT (2 SMN2 copies cohort)	18 months	8.78	[redacted]
WHO motor milestones: Walking independently	NURTURE	SPR1NT (2 SMN2 copies cohort)	18 months	8.78	[redacted]

Table 2. MAIC results for type 1 SMA

Efficacy measure	Nusinersen individual patient level data source	OA published aggregated data (AgD) source	Time point	Effective sample size	Adjusted risk difference (95% CI)
BSID-III/WHO: Sitting without support	CS3-A, CS3-B	STR1VE-EU STR1VE-US	18 months	12.61	[redacted]
BSID-III/WHO: Standing with support	CS3-A, CS3-B	STR1VE-EU STR1VE-US	18 months	12.61	[redacted]
BSID-III/WHO: Walking independently	CS3-A, CS3-B	STR1VE-EU STR1VE-US	18 months	12.61	[redacted]

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Table 3. OA efficacy data derived from the Biogen MAIC – Pre-symptomatic population

Time point	Not sitting	Sitting without support	Standing with support	Walking independently
Baseline	[redacted]	[redacted]	[redacted]	[redacted]
Month 6	[redacted]	[redacted]	[redacted]	[redacted]
Month 9	[redacted]	[redacted]	[redacted]	[redacted]
Month 12	[redacted]	[redacted]	[redacted]	[redacted]
Month 15	[redacted]	[redacted]	[redacted]	[redacted]
Month 18	[redacted]	[redacted]	[redacted]	[redacted]
Month 24	[redacted]	[redacted]	[redacted]	[redacted]
Month 36	[redacted]	[redacted]	[redacted]	[redacted]
Month 48	[redacted]	[redacted]	[redacted]	[redacted]
Month 60	[redacted]	[redacted]	[redacted]	[redacted]
Month 72	[redacted]	[redacted]	[redacted]	[redacted]

Table 4. OA efficacy data derived from the Biogen MAIC – Type 1 population

Time point	Not sitting	Sitting without support	Standing with support	Walking independently
Baseline	[redacted]	[redacted]	[redacted]	[redacted]
Month 3	[redacted]	[redacted]	[redacted]	[redacted]
Month 6	[redacted]	[redacted]	[redacted]	[redacted]
Month 9	[redacted]	[redacted]	[redacted]	[redacted]
Month 12	[redacted]	[redacted]	[redacted]	[redacted]
Month 18	[redacted]	[redacted]	[redacted]	[redacted]
Month 24	[redacted]	[redacted]	[redacted]	[redacted]
Month 30	[redacted]	[redacted]	[redacted]	[redacted]
Month 36	[redacted]	[redacted]	[redacted]	[redacted]
Month 42	[redacted]	[redacted]	[redacted]	[redacted]
Month 48	[redacted]	[redacted]	[redacted]	[redacted]
Month 60	[redacted]	[redacted]	[redacted]	[redacted]

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Utility increments

The application of an on-treatment utility increment was a key discussion point during the Appraisal Committee Meeting, aimed at capturing improvements in fine motor milestone skills whilst on treatment but remaining in the same WHO motor milestone health state. In the original Biogen submission, a utility increment of 0.10 was applied, whereas the EAG preferred a 10% increment. During the Committee Meeting there was a consensus that it was more appropriate to replace the 10% approach adopted by the EAG with the Biogen methods. However, it was also discussed whether a value of 0.10 may potentially undervalue the impact of treatment on health-related quality of life and NICE requested Biogen explore the use of higher values. For example, SMA UK proposed using a within state uplift of 0.15 (as reported on slide 42 of the Committee slides). Therefore, in the updated base case reported here, an on-treatment utility of 0.15 has been applied.

Additionally, the previous methods used to add the treatment-specific utility increment allowed for the utility values of people with SMA to exceed that of the general population in certain instances. In particular, people in the ‘walking independently’ state already have utility that aligns with the general population.

Following further consideration, it was judged that it would lack face validity if people with SMA could have a utility value that exceeds that of the general population. Therefore, the calculations in all models have been modified to ensure the utilities, including on-treatment utilities, are bound by the general population.

Number of caregivers

In the base case models, Biogen assumed people with SMA had 1 primary caregiver. However, members of the Committee and key stakeholders highlighted that it was likely people, particularly those in the ‘not sitting’ and ‘sitting without support’ health states, would need more than 1 caregiver. Roche assumed an average of 2.2 informal caregivers needed per person with SMA, informed by their internal burden of illness study.

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Biogen acknowledge that the number of caregivers may be greater than 1, depending upon disease severity. However, because of the novel increment approach to caregiver utilities, if a differential number of caregivers are utilised for each health state this produces results that lack face validity (i.e. more QALYs generated when people are in the most severe health states). Therefore, Biogen has updated the base case to include 2 caregivers for all health states, and scenarios have been completed with higher (3 caregivers) and lower values (1 caregiver). An additional scenario has been conducted using disutilities rather than utility increments.

Health state costs

Biogen and the EAG opted to apply motor-milestone specific health state costs originally derived from HST15, which were subsequently used in HST24 (both NICE appraisals analysing OA in separate SMA sub-populations). Within these appraisals, a micro-costing approach was used to derive annual costs associated with each SMA type (T1, T2 and T3 SMA). Costs were applied to UK-specific health care resource use (HCRU) estimates. The HCRU was categorised into key items:

1. Consultations with the multidisciplinary team responsible for the care of SMA (e.g. neuromuscular specialists, respiratory physicians, physiotherapists, nutritionists, nurses [community and hospital based] etc.)

2. Hospitalisations (including accident and emergency department visits and overnight admissions)

3. Pharmacotherapies for treatment of SMA-related symptoms and comorbidities

4. Tests, devices and surgeries – including those required for ventilatory and nutritional support

5. Community and social care services (including personal and respite care)

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To determine the total cost associated with each item, the company designed and implemented a de novo HCRU study, based in the UK, in which 16 clinical experts were interviewed. The aim of the study was to determine the specific HCRU costs under each of the items above associated with people receiving BSC for T1, T2 and T3 SMA.

The resource use for each type was used as a proxy for the not sitting, sitting without support, and walking independently health states, respectively. Costs for each resource were sourced from the NHS Schedule of Reference Costs (cost year 2019/20), Prescription Cost Analysis (PCA) 2021/22 data and published, peer reviewed publications. Where applicable, costs were inflated to 2019/20 cost year using NHS Cost Inflation Index (NHSCII) as published by the Unit Costs of Health and Social Care (2021). Feedback provided by the EAG and NICE committee in the previous appraisals, related to these health state costs, is summarised below.

During HST15, the EAG commented that the methods used by the company to generate health state costs was “overly complex”. In particular, the EAG referred to the methods that were used to convert the resource use values from the original HCRU study to match the categories that were used for the model health states. It was specifically noted that this approach lacked transparency. In terms of the methods of the original HCRU study, the EAG noted that the opinions of the clinical experts could have been elicited using formal elicitation techniques, such as SHELF.

The EAG subsequently ran a small number of scenarios related to the model health state costs to explore the impact. Once the scenarios were run, the base case ICER varied within a range of -22% to +12%. The NICE committee noted that there is uncertainty about the true health state costs associated with SMA, whilst acknowledging that the company had carried out an extensive costing analysis.

During HST24, the EAG only had one comment related to the health state costs, namely that the social care component was uncertain. This is because the value presented by the company could not be validated against the original article (Noyes et al 2006). Therefore, a scenario was completed in which social care cost component was set to £0 (results were redacted so the level of impact is uncertain).

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The NICE committee had no comments on the health state costs that were applied in HST24.

Altogether, Biogen concluded that the data from HST15 and HST24 was the most robust source to inform the health state costs for the current model. However, it should be noted that the health state costs from HST15 are expected to reflect the experience of people with SMA who are not receiving disease modifying therapy, i.e. reflective of best supportive care. In the committee meeting for the current nusinersen appraisal, patients and caregivers testified to the benefits of treatment outside of motor milestone attainment, most notably, a reduction in hospitalisations for respiratory events. Therefore, the total health state costs from HST15, and applied in the current analysis, are likely to overestimate these costs for people receiving nusinersen and this will have affected all previous analyses undertaken by Biogen and the EAG.

This potential difference in health state costs for nusinersen versus BSC is shown by outputs from ENDEAR/SHINE and CHERISH/SHINE. The outputs from these studies showed that hospitalisation for serious respiratory events, a frequent basis for SMA-related hospital admissions (particularly in type 1 SMA), which was a pre-specified analysis in the ENDEAR, CHERISH and SHINE studies, decreased in people with continued nusinersen treatment. This is important because hospitalisation costs contributed to a substantial percentage of the overall health state costs.

Hospitalisation data with nusinersen is available for up to 8 years from SHINE for both the type 1 and type 2/3 sub-populations. These data are presented in Table 1 and show that, across the full follow-up period in SHINE, the annualised rate of hospitalisation for serious respiratory events in people treated with nusinersen was [redacted] and [redacted] in the type 1 and type 2/3 sub-populations, respectively.

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Section B.2.4.3.1.10 and Section B.2.4.3.2.9 of Biogen's submission presented the annualised rate of hospitalisation for serious respiratory events in ENDEAR/SHINE and CHERISH/SHINE. This showed that the annualised rate of hospitalisation for serious respiratory events in the sham control arm of ENDEAR (type 1) and CHERISH (type 2/3) was [redacted] and [redacted], respectively. Therefore, when comparing this data with the annual hospitalisation rates with nusinersen across the full follow-up of SHINE, this indicates that the use of nusinersen led to an [redacted] % and [redacted] % reduction in this rate for the type 1 and type 2/3 sub-populations, respectively. Data specifically related to the pre-symptomatic sub-population are not available from SHINE and, therefore, a mean value for the percentage reduction in hospitalisations has been estimated ([redacted] %), based on data for the two other sub-populations.

Given the reduction in hospitalisations with nusinersen, as just described, it was judged that differential health state costs should be applied for people receiving disease modifying therapy versus BSC as this would better reflect the true cost of treating those with SMA. Therefore, the hospitalisation costs that were reported in HST24 were applied directly to people receiving BSC. For nusinersen, these health state costs were then amended as per the percentage reduction in the annualised rates of hospitalisation for serious respiratory events that are reported above (i.e. [redacted] %). Based on these adjustments, the hospitalisation costs for each health state are presented in Table 5. The subsequent total costs are presented in Table 6. These adjustments are based on the assumption that the hospitalisation rates reported in CHERISH & ENDEAR for BSC, and SHINE for nusinersen, remain constant for the full-time horizon of the model.

It should also be noted that the reduced health state costs for nusinersen have also been applied for OA, based on the assumption that OA will have a similar impact on the rate of hospitalisation due to the fact it is disease modifying treatment. This is a limitation of the comparison of nusinersen and OA and may over or underestimate the reduction in health state costs with OA.

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Table 1: Hospitalisations for serious respiratory events with nusinersen in pivotal clinical trials

	Study Follow-up (Days)								Total
	360	720	1080	1440	1800	2160	2520	2880	
ENDEAR/SHINE - type 1 sub-population									
Patients	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Hospitalisations	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total years followed	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Annualized hospitalisation rate	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
CHERISH/SHINE - type 2/3 sub-population									
Patients	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Hospitalisations	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total years followed	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Annualized hospitalisation rate	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Based on patients who received nusinersen in both ENDEAR, CHERISH and SHINE

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Table 5. The annualised hospitalisation health state costs for each model*

	BSC hospitalisation health state costs	Nusinersen hospitalisation health state costs		
		Presymptomatic	Type 1	Type 2/3
Permanent ventilation	[redacted]	[redacted]	[redacted]	[redacted]
Not sitting	[redacted]	[redacted]	[redacted]	[redacted]
Sitting without support	[redacted]	[redacted]	[redacted]	[redacted]
Standing with support	[redacted]	[redacted]	[redacted]	[redacted]
Walking independently	[redacted]	[redacted]	[redacted]	[redacted]

*Costs from HST24 have been inflated to reflect 2023/24 prices.

Table 6. The annualised overall health state costs for each model*

	BSC heath state costs	Nusinersen health state costs		
		Presymptomatic	Type 1	Type 2/3
Permanent ventilation	[redacted]	[redacted]	[redacted]	[redacted]
Not sitting	[redacted]	[redacted]	[redacted]	[redacted]
Sitting without support	[redacted]	[redacted]	[redacted]	[redacted]
Standing with support	[redacted]	[redacted]	[redacted]	[redacted]
Walking independently	[redacted]	[redacted]	[redacted]	[redacted]

*Costs from HST24 have been inflated to reflect 2023/24 prices.

Uncertainty remains in terms of the most appropriate social care costs to apply for SMA. In HST24, the EAG acknowledged that people with SMA are likely to rely heavily on social care and, therefore, they expect the costs to be substantial. However, as described previously, the EAG found that the methods employed by the company in HST24 lacked clarity. Therefore, the EAG conducted a scenario in which social service costs were set to £0 to understand whether social care costs would change the conclusions that can be drawn from model cost effectiveness results. The EAG found that uncertainties in the social service costs were unlikely to change the conclusions for OA.

To alleviate uncertainty associated with social care cost, a scenario has been conducted in which the social care costs were removed for all treatment arms.

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Section 1.2. New scenario analyses

Based on discussions with NICE, the following scenarios have been completed:

1. Compare the cost-effectiveness of nusinersen versus OA based on equal efficacy - **PS and T1 model.**
2. Explore changes in the total number of caregivers for all health states with values of 1 and 3 caregivers applied – **all models.**
3. Remove stopping rules with nusinersen related to the permanent ventilation (PV) state, see further details below –**T1 model**.
4. Remove health state costs for the period of extended survival vs BSC with nusinersen and OA – **T1 model**.
5. Apply alternative severity modifiers for the PS (1.2) and T2/3 (1.7) model (**versus BSC only, not relevant versus OA**).
6. Remove social care costs – **all models.**
7. Apply carer utility decrements, rather than increments – **all models.**
8. Remove nusinersen discontinuation - **PS and T1 model.**

In terms of point 3, in the original base case of the type 1 models, it was assumed that once a person entered the permanent ventilation health state they discontinued from nusinersen and this aligned with the stopping criteria of the managed access agreement. This assumption is maintained in the updated base case presented in this addendum. However, during the Appraisal Committee meeting it was noted that a proportion of the SMA population would likely receive some clinical benefit from treatment even if receiving permanent ventilation. Therefore, this has been explored within a series of scenario analyses within type 1 models (although this is also considered in the presymptomatic model, no patients were recorded as requiring permanent ventilation in NURTURE and transitions to this state do not occur in the treatment arm of the model). This scenario is not relevant for the type 2/3 model as a negligible proportion of patients require PV as per the original Biogen submission (as reported by Trucco et al.[1]).

[1] Trucco F, Ridout D, Scoto M et al., Respiratory Trajectories in Type 2 and 3 Spinal Muscular Atrophy in the iSMAC Cohort Study. Neurology. 2021 Jan 26;96 (4): e587-e599.

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Initially, a scenario was completed whereby it was assumed that 100% of people receiving nusinersen would remain on treatment when in the permanent ventilation state. The outputs from this scenario are presented in the results section. However, this approach is associated with two major limitations. Firstly, it is understood that this approach does not reflect the true clinical experience of nusinersen usage in NHS clinical practice (hence the approach adopted in the base case). As per the updated 2025 paediatric registry report for nusinersen (p31, section 5.9), only 6 cases of permanent ventilation were recorded with nusinersen use. 100% of these cases were in type 1 patients originally enrolled in the expanded access program, where patients received compassionate use of nusinersen prior to the managed access agreement being established. The EAP cohort had noticeably more severe progression than the non-EAP cohort prior to treatment (mean age at treatment initiation, 3.59 years [range 0.52- 13.28]vs 0.52 years [range 0.03-2.91], respectively). In the final MAA cohort, 3 patients were recorded as receiving any ventilation type for ≥ 16 hours/day continuously for > 21 days and a further 2 patients had a tracheostomy (at baseline). One further patient was recorded as requiring permanent ventilation but was not included in the final MAA cohort due to missing baseline information. These patients represent a very small number (and a cohort unlikely to be as prevalent in the future) compared with the expected natural history of SMA type 1 where approximately 90% of children are either deceased or require permanent ventilation by the age of 2 years.

Secondly, when this approach is implemented in the type 1 model it leads to substantial life year gains with nusinersen (versus BSC). This is because, as described in Section B.3.3.2.4 of Document B from the Company submission, in the type 1 model the mortality of people in the following health states was based on the same overall survival curve from ENDEAR/SHINE: permanent ventilation, not sitting and sitting with support. Additionally, the overall survival data from ENDEAR/SHINE indicated that nusinersen was associated with significantly lower mortality than sham control in the type 1 sub-population. Therefore, the rate of mortality is substantially lower in the permanent ventilation state when 100% of the population remain on nusinersen and this leads to these people remaining in this state for many years.

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This is not expected to reflect the true experience of people with type 1 SMA even with continued treatment due to other comorbidities.

Due to these issues, two alternative scenarios have been implemented related to the permanent ventilation state. In these scenarios it has been assumed that 50% and 20%, respectively, of people in the nusinersen arm remain on this intervention when they enter the permanent ventilation state and they remain on this intervention until death. Therefore, in these scenarios, 50% and 80% of the nusinersen cohort, respectively, are assumed to discontinue the intervention at the point they enter the permanent ventilation state (if they hadn't discontinued previously). It should be noted that all scenarios related to permanent ventilation are expected to overestimate both the usage of nusinersen and the survival of people within this state. The chosen methods could not be improved due to time constraints and a paucity of data on the use of disease-modifying treatment in the PV state. Therefore, all analyses related to the PV state should be considered as exploratory.

In terms of point 8 (discontinuations), when a comparison of nusinersen and OA is undertaken this results in [redacted] for OA (see Results section for more information). These [redacted] are largely driven by two major factors. Firstly, as OA is a one-off gene therapy there is no discontinuation implemented in the models with this intervention. Therefore, it is explicitly assumed that everyone who receives treatment at baseline will experience a treatment effect for the full model time horizon. Alternatively, an ongoing discontinuation rate is applied to people receiving nusinersen, which means that in the long term the majority of people stop nusinersen and, therefore, experience the effectiveness estimates for BSC. This approach is necessary in the absence of long-term data related to OA but is highly likely to overestimate the effectiveness (and hence QALY gains) associated with OA. The issue of overestimating QALYs with OA is exacerbated by the fact that an on-treatment utility of 0.15 is applied and, as no one receiving OA can discontinue, this means this utility increment is applied for the full-time horizon for those receiving OA (until they die).

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It is not feasible to capture OA discontinuation within the models. However, it is possible to explore the impact of this parameter on the models by removing discontinuation with nusinersen, which essentially means that the two treatments have equivalent rates of discontinuation. Therefore, a scenario has been completed related to this.

Results

For ease of interpretation (i.e. to avoid negative ICERs), results are presented based on net monetary benefit (NMB) values, alongside the ICERs. A cost-effectiveness threshold of £30,000 per QALY was used for the NMB calculations. All comparisons against OA are based on the nusinersen PAS price and OA list price and therefore should be interpreted with caution. In addition, the EAG base case is an assumed one based on the latest EAG report as Biogen were not provided with unredacted outcomes in order to validate.

Section 2.1 Updated base case analysis results

A series of updates have been made to the previous EAG base case. These updates have been summarised in Table 7 to Table 11. The results of the final updated base case show that the ICERs for nusinersen versus BSC were [redacted] in the pre-symptomatic, type 1 and type 2/3 sub-populations, respectively. When compared against OA (at list price), nusinersen was [redacted] and this means it is more intuitive to report NMB values (rather than ICERs). In the updated base case, the NMB was [redacted] in the pre-symptomatic and type 1 populations, respectively.

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Table 7. Updates to the deterministic base case for the pre-symptomatic SMA model - nusinersen vs BSC

Model updates	Nusinersen total costs	Nusinersen total QALYs	BSC total costs	BSC total QALYs	Incremental costs	Incremental QALYs	ICER	NMB at £30,000 per QALY gained
EAG base case (assumed)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Initial corrections*	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Update severity modifier to 1.7	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Increase on-treatment utility to 0.15	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Apply 2 carers for each health state	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Reduce health state costs for DMT	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
New base case (all combined)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

*Change utility increments to 0.10 rather than 10%, use carer utility data from Tappenden et al 2021, cap utilities based on the general pop. & apply severity modifier of 1.7 to patient QALYs only.

Table 8. Updates to the deterministic base case for the pre-symptomatic SMA model - nusinersen vs OA

Model updates	Nusinersen total costs	Nusinersen total QALYs	OA total costs	OA total QALYs	Incremental costs	Incremental QALYs	ICER	NMB at £30,000 per QALY gained
EAG base case (assumed)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Initial corrections*	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Increase on-treatment utility to 0.15	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Apply 2 carers for each health state	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Reduce health state costs for DMT	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
New base case (all combined)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

*Adjust application of MAIC data, change utility increments to 0.10 rather than 10%, use carer utility data from Tappenden et al 2021, cap utilities based on the general pop.

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Table 9. Updates to the deterministic base case for the type 1 SMA model - nusinersen vs BSC

Model updates	Nusinersen total costs (£)	Nusinersen total QALYs	BSC total costs (£)	BSC total QALYs	Incremental costs (£)	Incremental QALYs	ICER	NMB at £30,000 per QALY gained
EAG base case (assumed)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Initial corrections*	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Increase on-treatment utility to 0.15	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Apply 2 carers for each health state	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Reduce health state costs for DMT	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
New base case (all combined)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

*Change utility increments to 0.10 rather than 10%, use carer utility data from Tappenden et al 2021, cap utilities based on the general pop. & apply severity modifier of 1.7 to patient QALYs only.

Table 10. Updates to the deterministic base case for the type 1 SMA model - nusinersen vs OA

Model updates	Nusinersen total costs	Nusinersen total QALYs	OA total costs	OA total QALYs	Incremental costs	Incremental QALYs	ICER	NMB at £30,000 per QALY gained
EAG base case (assumed)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Initial corrections*	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Increase on-treatment utility to 0.15	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Apply 2 carers for each health state	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Reduce health state costs for DMT	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
New base case (all combined)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

*Adjust application of MAIC data, change utility increments to 0.10 rather than 10%, use carer utility data from Tappenden et al 2021, cap utilities based on the general pop.

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Table 11. Updates to the deterministic base case for the type 2/3 SMA model - nusinersen vs BSC

Model updates	Nusinersen total costs	Nusinersen total QALYs	BSC total costs	BSC total QALYs	Incremental costs	Incremental QALYs	ICER	NMB at £30,000 per QALY gained
EAG base case (assumed)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Initial corrections*	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Increase on-treatment utility to 0.15	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Apply 2 carers for each health state	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Reduce health state costs for DMT	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
New base case (all combined)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

*Change utility increments to 0.10 rather than 10%, use carer utility data from Tappenden et al 2021, cap utilities based on the general pop. & apply severity modifier of 1.2 to patient QALYs only.

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Section 2.2 Updated scenario analysis results

Nusinersen remained [redacted] versus BSC in all pre-symptomatic scenarios. In the type 1 sub-population, the ICER varied from [redacted] (when health state costs were removed in the period of extended survival) to [redacted] (when 100% of nusinersen patients remained on treatment in the PV scenario). In the type 2/3 sub-population, the ICERs varied from [redacted].

When compared against OA (at list price), nusinersen was [redacted] and this means it is more intuitive to report NMB values (rather than ICERs). In the pre-symptomatic sub-population, the NMB improved to [redacted] when a carer disutility (rather than a carer utility increment) was applied. Also, one scenario was undertaken in which a large increase in the NMB was recorded – this is described in more detail below. In the type 1 sub-population, the NMB was greater than [redacted] in all scenarios analysed.

In all scenarios comparing nusinersen and OA (except one), a large incremental QALY gain was estimated with OA. For example, in the updated base case for the type 1 sub-population, the incremental QALY gains with OA was [redacted]. As described previously, this is expected to be a substantial overestimate of the effectiveness of OA and this level of QALY gain would not reflect the true experience of people with type 1 SMA. To explore this issue, a scenario was completed in which discontinuations were removed for nusinersen (as explained in the previous section). In this scenario, the incremental QALYs reduced substantially to [redacted] and [redacted] for the PS and type 1 sub-populations, respectively. The impact is particularly noteworthy in the PS sub-population as the overall NMB changed from [redacted] in the updated base case to [redacted] in this scenario.

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Table 12. Deterministic scenario results from the pre-symptomatic SMA model - nusinersen vs BSC

Scenarios	Nusinersen total costs	Nusinersen total QALYs	BSC total costs	BSC total QALYs	Incremental costs	Incremental QALYs	ICER	NMB at £30,000 per QALY gained
New base case	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
1: Change total number of caregivers to 1 for all health states.	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
2: Change total number of caregivers to 3 for all health states.	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
3: Apply alternative severity modifiers (1.2 for PS)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
4. Removal of social care costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
5. Apply a carer disutility	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

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Table 13. Deterministic scenario results from the pre-symptomatic SMA model - nusinersen vs OA

Scenarios	Nusinersen total costs	Nusinersen total QALYs	OA total costs	OA total QALYs	Incremental costs	Incremental QALYs	ICER	NMB at £30,000 per QALY gained
New base case	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
1: Change total number of caregivers to 1 for all health states.	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
2: Change total number of caregivers to 3 for all health states.	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
3: Equal efficacy between NUS and OA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
4. Removal of social care costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
5. Apply a carer disutility	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
6. Remove nusinersen discontinuations	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

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Table 14. Deterministic scenario results from the T1 SMA model - nusinersen vs BSC

Scenarios	Nusinersen total costs	Nusinersen total QALYs	BSC total costs	BSC total QALYs	Incremental costs	Incremental QALYs	ICER	NMB at £30,000 per QALY gained
New base case	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
1: Change total number of caregivers to 1 for all health states.	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
2: Change total number of caregivers to 3 for all health states.	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
3: Remove PV state stopping rules – 100% NUS remain on treatment	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
4: Remove PV state stopping rules – 50% NUS remain on treatment	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
5: Remove PV state stopping rules – 20% NUS remain on treatment	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
6: Remove health state costs for the period of extended survival with NUS.	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
7. Removal of social care costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
8. Apply a carer disutility	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

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Table 15. Deterministic scenario results from the T1 SMA model - nusinersen vs OA

Scenarios	Nusinersen total costs	Nusinersen total QALYs	OA total costs	OA total QALYs	Incremental costs	Incremental QALYs	ICER	NMB at £30,000 per QALY gained
New base case	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
1: Change total number of caregivers to 1 for all health states.	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
2: Change total number of caregivers to 3 for all health states.	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
3: Remove PV state stopping rules – 100% NUS remain on treatment	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
4: Remove PV state stopping rules – 50% NUS remain on treatment	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
5: Remove PV state stopping rules – 20% NUS remain on treatment	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
6: Remove health state costs for the period of extended survival with NUS and OA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
7: Equal efficacy between NUS and OA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
8. Removal of social care costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
9. Apply a carer disutility	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
10. Remove nusinersen discontinuations	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

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Table 16. Deterministic scenario results from the T2/3 SMA model - nusinersen vs BSC

Scenarios	Nusinersen total costs	Nusinersen total QALYs	BSC total costs	BSC total QALYs	Incremental costs	Incremental QALYs	ICER	NMB at £30,000 per QALY gained
New base case	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
1: Change total number of caregivers to 1 for all health states.	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
2: Change total number of caregivers to 3 for all health states.	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
3: Apply alternative severity modifiers (1.7 for T2/3)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
4. Removal of social care costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
5. Apply a carer disutility	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

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ID6195 Roche post-ACM1 analyses

1. Starting and stopping rules from MAA

No change

2. Type 0 and 4 SMA

No change

3. Equality issues

- Base case
    - Use absolute utility increment approach (see point 5)

4. Comparators

- Base case
    - Compare to BSC (Type 1 and Types 2/3)
- Scenario analyses
    - Compare to other DMTs
    - Compare to 'standard of care' blend accounting for expected treatment rates in clinical practice
        - Standard of care comprises of 99% DMT and 1% BSC in the Type 1 population and 95% DMT and 5% BSC in the Type 2/3 population, informed by REACH estimates and Roche data gathering from key prescribing centres (previously shared)

5. Capturing functional changes in utility values

- Base case
    - Considers absolute utility increment of 0.16, informed by DMD preserved upper limb to mildly impaired upper limb or moderately impaired upper limb decrement from Audhya et al [2023]
        - Committee considered that the most appropriate approach was to consider an absolute increment rather than the original proportional increase. This avoids the model valuing better health states more and ensures the model captures these important benefits in all health states.
        - Allows the model to capture the nuanced motor function benefits patients consider are important, such as lifting the head, holding an object or using a computer, which are currently not captured as well as possible in the original analyses.

        - Existing utility value estimates in SMA and other neuromuscular conditions are limited as they are derived from a small number of studies and are based on relatively small samples. These utility values are also limited as they primarily consider major mobility motor function health states, and miss capturing the value associated with more nuanced motor function improvements that are equally (and often more) important to patients and their carers. This was flagged as a concern of the clinical and patient representatives at ACM1.
        - Audhya et al considers this issue in Duchenne Muscular Dystrophy (DMD). The study highlights that utility values in DMD are also limited in that they predominantly characterise health states by focusing on ambulatory status and fail to address other potentially important aspects of function and HRQoL across the course of the disease. These include upper limb and hand function, mobility, the ability to transfer (into and out of bed, or from the wheelchair to the toilet), and respiratory insufficiency requiring ventilation, which are all important domains contributing to functional status and HRQoL in DMD. The aim of the study was to estimate EQ-5D-5L and HUI utility values, based on patient-reported health status, for a range of health states representing varied clinical and functional states in DMD, including investigating minor motor functions such as upper limb movement within health state utility values.
        - Audhya et al presented EQ-5D utility values that look to support the importance of upper limb movement as a proxy for nuanced motor function improvements for patients with SMA. The study showed that, in the early non-ambulatory health state, mild impairment of upper limb function reduced EQ-5D utility values from 0.46 to 0.30. This trend is also mirrored in the HUI-2 which shows a drop in patient utility of 0.12.
        - The decline in upper limb function directly correlates with impairments in specific domain scores of the various utility measures relevant to upper limb movement. Such as “sensation” and “self-care” of the HUI-2, "dexterity" of the HUI-3 and “self-care” and "usual activities” of the EQ-5D, which all increase with worsening upper limb function. The study notes that deficits in dexterity drive deficits in the ability to perform usual activities, creating a large loss of quality of life.
        - These utility values should be interpreted with caution due to small sample sizes, but serve to highlight alternative utility increments which aim to capture the importance of minor motor functions such as upper limb movement to patients with SMA. The importance of these motor functions have been highlighted by the patient and clinical community and Roche has attempted to consider flexibility and pragmatism in its selection of the most appropriate increment to best capture this importance.
    - Application of disease-related complication decrements less the period of extended survival in addition to base case absolute utility increment approach
        - The utility increment proposed by the committee to consider nuanced improvements of motor function still does not adequately capture all important aspects of living with SMA. In previous iterations of the model, the company analyses included options to consider the health-related

quality of life and cost implications of disease related complications, such as scoliosis, bulbar function, and respiratory complications. The company proposes that the base case should capture the impact of disease-related complications for the period of expected BSC survival in addition to greater utility increment to capture nuanced improvements in minor motor functions. This approach would avoid a similar issue to the 'carer QALY trap', where DMTs would be penalised by improving patient survival.

        - Scenario analyses test the exclusion of healthcare resource use and health-related quality of life impacts of disease-related complications and alternative approaches, such as applying for the full time horizon and applying as increments.

    - Application of a cap to avoid health state utilities (including the absolute increment) to exceed general population norms

- Scenarios
    - Alternative absolute utility increment greater than the original 0.1, informed by relevant literature in similar disease areas
        - Alternative utility values have been sourced from a Motor Neuron Disease cost-effectiveness modelling publication (Alan Moore [2021]). The paper reports health state utility values by King's Staging and MiToS to capture the deterioration in function.
        - King's Staging for Motor Neuron Disease tracks disease progression by the number of central nervous system regions affected (bulbar, upper limbs, lower limbs, respiratory), moving from Stage 1 (one region) to Stage 5 (death).
            - Stage 1: Disease in one CNS region (e.g., just limbs or bulbar area).
            - Stage 2: Disease in two CNS regions.
            - Stage 3: Disease in all three CNS regions (bulbar, upper limbs, lower limbs).
            - Stage 4: Progression to significant functional impairment.
                - 4A: Requires gastrostomy (feeding tube).
                - 4B: Requires non-invasive ventilation (NIV).
            - Stage 5: Death.
        - MiToS, or the Milano-Torino Staging System (MiToS), is a clinical tool used to stage the progression of Motor Neuron Disease by assessing functional loss in walking, self-care, swallowing, communication, and breathing, where Stage 0 is no loss of function in any key domain (normal function) and Stage 5 is Death.
            - Stage 0: No loss of function in any key domain (normal function).
            - Stage 1: Loss of function in one domain.
            - Stage 2: Loss of function in two domains.
            - Stage 3: Loss of function in three domains.

        - Stage 4: Loss of function in all four domains.
        - Stage 5: Death.
    - For this scenario an assumption has been made that the first King's Staging domain lost for patients with MND is lower limbs, so a transition from Stage 1 and Stage 2 is most likely to reflect a loss of upper limb movement.
        - 0.16, EQ-5D-5L Kings Stage 1 to Stage 2, from Alan Moore [2021] Table 4.3
    - Considering MiToS, a similar assumption is made where the Stage 1 is likely to be related to the walking domain so an average of the difference between Stage 1 and Stages 2-4 are taken for the 'loss of non-motor function' impact.
        - 0.17, MiToS Stage 1 to average of Stage 2-4, from Alan Moore [2021] Table 4.3
    - As with base case DMD derived inputs, these utility impacts should be taken with caution, but every attempt has been made to ensure that concerns raised at ACM1 over the models being unable to capture benefits that are important to patients and carers are addressed.
- Test greater absolute utility increments to account for nuanced motor function gains **and** avoidance of disease complications, e.g.
    - base case value, informed by Audhya et al 2023, plus the average of disease-related complication increments to pragmatically account for the impact of all aspects of SMA important to patients - capped by general population utility.
    - base case value, informed by Audhya et al 2023, plus SMA REACH-UK caregiver survey gain of 0.15 when a child moves from total feeding dependence to independent self-feeding, to pragmatically account for the impact of all aspects of SMA important to patients - capped by general population utility.
        - *We suggest that when these scenarios are investigated, disease-related decrements are excluded to avoid double counting.*
- Test application of 0.1 utility increment previously rejected by committee, as stress test scenario
    - The committee considered that the 10% utility increase used by the EAG was inappropriate. The committee concluded that an absolute utility increment was more appropriate but that a value of 0.1 or 10% used by the EAG was likely to underestimate the true impact nuanced improvements have on patients with SMA. However, for the interest of completeness, the company has provided a scenario with the 0.1 increment applied to all health states, capped by general population utility.

6. Common inputs and assumptions across Biogen / Roche models

No change from the previously aligned approach, but any additional updates presented at this stage, around utility benefits (Point 5) and health state costs (Point 10) in particular, are likely to lead again to divergence from Biogen's work presumably being done in parallel

7. Patient utility values

Biogen values used for consistency.

8. Carer utility values

- Base case
    - Use increment approach (as per original Biogen approach).
    - Assume the same values for all types, in alignment with patient utilities.
    - Include original Roche submitted 2.2 carers (and 3 for permanently ventilated health state) from Burden of Illness study
        - Committee considered that 1 carer was likely underestimating the true impact to caregivers. The committee requested a higher average number of carers across all health states.
        - The originally submitted Roche approach considered a greater number of carers across all health states, informed by the company conducted burden of illness study (Appendix R). The burden of illness study was conducted at the time of TA755 to generate robust real-world data from patients with SMA and their carers in the UK where a total of 122 patient surveys and 80 carer surveys were completed. This study estimated a value of 2.2 carers for the majority of health states, with the exception of 3 carers for the permanently ventilated health state.
        - An additional health-related quality of life study was conducted during the managed access period (Health-Related Quality of Life Study (HRQoL) in Spinal Muscular Atrophy Roche report on file 2024 provided in the reference pack). The primary objective of this study was to primarily generate utility data quantifying HRQoL associated with the risdiplam cost-effectiveness model. However, secondary objectives included collecting supplementary HRQoL information to further inform the impact of SMA on people with SMA and their caregivers, such as caregiver demographics and numbers. The mean (SD) number of informal caregivers for the analysis set was 2.5 (1.1), which was similar across all grouped SMA health states (Not sitting/sitting with support: 2.6 [0.7]; sitting without support: 2.5 [1.4]; standing/walking: 2.3 [0.5]). The mean (SD) number of professional carers for the overall set was 2.6 (3.1). Whereas when stratified by SMA health state group, the number more than doubled for the not sitting/sitting with support group (5.3 [3.6]), decreasing progressively for sitting without support (1.5 [1.5]) and standing/walking (0.3 [0.5]). However, for consistency, Roche utilised the previous 2.2 carer number from TA755.

- Scenarios
    - Test exclusion of greater number of carers
        - Committee considered 1 carer was likely underestimating the true impact to caregivers. For completeness, the company has provided a scenario of the original 1 carer per health state value. However, the company strongly believes this underestimates the impact of caregiving.
    - Test inclusion of family and caregiving effect modifiers from Pennington et al (2025)
    - Test a decrement approach to account for carer quality of life.
        - However, the company believes that the increment approach is more appropriate for this specific decision problem, given the substantial 'carer QALY trap' that can be observed for DMTs extending the survival of people with SMA.

9. Treatment discontinuation

- Base case
    - No permanently ventilated stopping rule for risdiplam or nusinersen
    - Considers treatment discontinuation data from SUNFISH and FIREFISH and REACH registry data for nusinersen
        - Company consider the impact discontinuation has on treatment costs and efficacy. Upon discontinuation, the proportion of discontinued patients switch to BSC transitions.
        - Company argue that longer-term FIREFISH and SUNFISH data are more robust and more appropriate to capture the impact of discontinuation on costs and outcomes. The clinical trials have longer-term follow up so observe discontinuation events over a longer period of time.
        - The presymptomatic analysis considers treatment discontinuation from the Type 2/3 model, in line with the original Biogen approach. Therefore, the analysis considers SUNFISH discontinuation in the company base case and REACH data in scenario analyses / the simulated committee base case. An assumption of no discontinuation can be used to simulate using more Type 1-like discontinuation, in line with the paediatric REACH dataset.
        - However, Roche would like to flag the discontinuation rates from the FISH trials or the REACH registry data as a whole are likely not a true reflection of expected administration rates over the longer term. There are a number of reasons why patients may discontinue treatment for a short period of time, but there is often the expectation that these patients will resume treatment following this period. These may include stopping risdiplam for fertility considerations and subsequent pregnancy or breastfeeding, or resolving short term gastro-intestinal adverse reactions. We are aware of a small number of individuals who have not been able to travel with the oral liquid formulation of risdiplam which has led to a short duration off treatment; however with the recently approved tablet

formulation of risdiplam that does not require refrigerated storage, this is likely to occur less frequently.

        - Roche argue that the proportion of patients discontinuing in the REACH and SUNFISH/FIREFISH datasets may only tell part of the story. We still maintain the position that the pragmatic health state related stopping rules provided in scenario analysis are a sensible, pragmatic approach to capturing the long-term reasons for stopping treatment i.e., when benefit is deemed to be lost on worse health states.
        - Newly diagnosed infants are typically started on risdiplam treatment (and less commonly nusinersen) immediately after diagnosis/confirmation of SMA while the baby is being considered for onasemnogene abeparvovec. Guidance was shared by the SMA REACH clinical network advocating for immediate *SMN2* targeted treatment initiation in this clinical scenario in February 2025; given the latest REACH data cut submitted to NICE/the EAG was April 2025 this cohort may not be fully represented in the risdiplam discontinuation rates reported.
        - Regarding nusinersen, the discontinuation rate is directly based on the per-cycle rates reported in the Biogen company submission (within the committee papers). This is based on Biogen's interpretation/calculation of their REACH data and including any assumptions they have made here, which we have limited visibility over and therefore have to trust has been modelled appropriately. Any changes in this approach as part of this additional analysis step could lead to differences in company approaches (and relates to Point 6 around common inputs/assumptions).

- Scenarios
    - Test original treatment discontinuation assumptions i.e. health state dependent stopping criteria (pragmatic scenario already provided in previous EAG models)
        - As explained above, we believe this provides a pragmatic estimation of the likely reasons for long-term discontinuation (e.g. clinical decision of loss of benefit in worse health states) without relying on short-term discontinuation events where patients would expect to return to treatment as soon as possible (e.g. travel, fertility, resolution of adverse reactions)
    - Test the inclusion of treatment discontinuation data from REACH registry and equivalent data for nusinersen
        - As explained above, OLE data is generally more robust (combination of follow-up duration and higher patient numbers) so Roche advocates for the use of FISH clinical trial data in the base case. However, we have provided a scenario for the use of REACH registry data for completeness. REACH registry data was collected in the managed access period and provides a UK-specific dataset of real-world use of DMTs. As with the FIREFISH and SUNFISH datasets described above, we would like to flag that the reasons for discontinuation are important. We would expect a significant proportion of those who discontinued in the REACH datasets to return to treatment as soon as possible to continue to receive clinical benefit. Regardless of data source used, we argue that none of the available data tells the whole story regarding long-term patient administration rates and the reasons for discontinuation and/or whether

patients return to treatment. We believe that REACH discontinuation rates, specifically for the adult population, could potentially overestimate the real discontinuation rates / underestimate the real long-term administration rates expected in clinical practice over the long term.

10. Health state costs

- Base case
    - This base case uses relevant data for on- and off-treatment healthcare resource use to capture the reduction in healthcare resource use highlighted by the clinical and patient representatives at ACM1. Adjusting health state costs better reflects the true value of DMTs to patients, carers and the healthcare system by reducing frequent and burdensome healthcare visits.
    - The company base case method for adjustment considers an alternative version of the HST24 costs as used in the EAG base case. The aggregate HST24 health state costs were replaced with more granular estimates available from the HST24 appendix. The disaggregated granular HST24 estimates allowed for an adjustment to account for the expected reduction in specific health state cost components expected while patients are being treated with DMTs (compared to BSC).
    - The disaggregated costs were adjusted using estimates from Zhu et al 2024. This study demonstrates that nusinersen treatment is associated with substantial reductions in healthcare resource utilisation and medical costs compared to the pre-treatment period (i.e. BSC). These savings are primarily driven by significant decreases in inpatient admissions and respiratory-related care. Paediatric patients saw cost reductions across both inpatient and emergency settings, adult patients saw massive inpatient savings but an increase in emergency department costs due to non-SMA-related factors.
        - **Inpatient admissions:** Overall Cohort: Total inpatient admission costs decreased by 68% (from ~$1.97 million to ~$627,000). Paediatric (<18 years): Average cost per patient: Dropped from $22,903 to $8,466 (a 63% reduction). Adult (≥18 years): Average cost per patient: Dropped from $13,997 to $2,899 (a 79% reduction).
        - **Emergency department visits:** Paediatric: Total costs decreased by 56% (from ~$100,700 to ~$44,700) and the number of ED visits dropped by 21%. Adult Patients: Total costs increased by 72% (from ~$19,300 to ~$33,200) and the number of ED visits increased by 47%. However, the study notes that this increase in adult ED visits was likely unrelated to SMA. Visits for common SMA comorbidities (respiratory, gastrointestinal, musculoskeletal) remained low or stable, suggesting the cost increase was due to other medical issues. Nevertheless, we have included this increase in our base case and estimates for the adult population could be considered conservative.
    - The study shows that DMTs provide a clear economic benefit by lowering the burden of severe SMA complications that typically require expensive hospital care. The reduction in inpatient admissions, emergency department visits and respiratory costs suggests that DMTs stabilises disease progression, moving

patients away from resource intensive and therefore high cost BSC resources such as mechanical ventilation and prolonged hospitalisations.

- Health state costs expected with DMTs were adjusted using outcomes from Zhu et al consistently for patients being treated with risdiplam and nusinersen, to specifically reduce the relevant HST24-derived cost components (i.e. Hospitalisations and 'GP and Emergency') by 47% (i.e. the overall relative difference in the number of inpatient admissions following DMT) and 8% (i.e. the overall relative difference in total ED visits), respectively.
- Off-treatment (i.e. BSC and discontinued patients in the other treatment arms) health state costs are based on the unadjusted granular HST24 costs.

NB: Breakdown of costs from Roche HCRU (micro-costing) study are already provided in the model and the Roche Health Care Resource Use (HCRU) in Spinal Muscular Atrophy (SMA) report on file provided in the reference pack, with information for the aggregate costs derived from TA588 or HST24 naturally being limited to what had been reported in the respective submissions

- Scenarios
  - Test the impact of no adjustment, i.e. the original base case (all health state costs based on aggregate HST24 data, as per EAG implementation)
  - Include separate health state costs estimates for patients being treated with DMTs vs patients on BSC, based on
    - Separate micro-costing, where on- and off-treatment health state costs based on the Roche HCRU micro-costing study instead of the HST24 disaggregated costs. Then on-treatment costs were further adjusted using hospitalisation data from Zhu et al. 2024 (for paediatric and adult SMA patients pre- and post-DMT based on US claims analyses); applying the reported relative change in proportions of patients with inpatient/ED admissions and number of admissions per year to the hospitalisation and specialist visit cost items (resulting in correspondingly lower health state costs for on-tx patients)
  - Relative reduction from off-treatment (BSC) costs
    - Applying a single percentage reduction (same across all health states) to calculate on-treatment (DMT) health state costs from the HST24-based base case costs. Relative reduction uses the 68% from Zhu et al. (based on the observed reduction in average cost of inpatient admissions following DMT)
  - Relative reduction applied to base case costs
    - Applying the health state-specific relative difference between the micro-costed off–treatment and on-treatment health state costs (as calculated using the *separate health state costs estimates for patients being treated with DMTs vs patients on BSC* option) to the base case HST24 costs to derive corresponding on-treatment health state costs (still anchored to the original base case values from HST24 but accounting for the expected relative reduction in costs as reported by Zhu et al.)

11. Background care costs

- Base case
    - No change
- Scenarios
    - Removal of background care costs (i.e. all health state/HCRU costs) for the period of extended survival with RSD
        - Scenario considers capturing background care costs only for median BSC life years, which removes the costs of the period of extended survival with risdiplam

12. Severity weights vs BSC

- Base case
    - Use most appropriate severity weight dependent on predicted QALYs
- Scenarios
    - Use consistent 1.7 severity weight across all SMA Types

13. Acceptable ICER threshold

- Following relevant considerations identified to date:
    - uncaptured benefits of treatment
    - difficulty assessing utility values in children
    - rarity of the condition
    - high background care costs
    - equality issues
    - unmet patient need (if treatments withdrawn)
    - uncertainty in long-term and comparative clinical benefit of treatment

Timing of treatment initiation is a variable which has a significant impact on the outcomes of individuals with SMA. The awareness of SMA has increased in the UK, thanks to collaborative efforts of patient advocacy groups and clinical teams working with their community colleagues to educate on the early symptoms of the condition. However, there are still sadly too many children who are diagnosed after symptoms have been present for weeks or even months. A UK government funded In-Service Evaluation (ISE) of newborn screening for SMA was announced in the summer 2025. The research component of the ISE is being commissioned via the NIHR's Health Technology Assessment (HTA) and a recent update confirmed that an application had been received in response to the advertised funding opportunity. The application is progressing through the funding process, and the HTA funding committee decision is anticipated in March 2026. Supporters anticipate that this will lead to newborn screening being implemented across England and Wales in the coming years.

As reported in the European nonrandomised controlled trial (Schwartz O et al. 2024) treatment with a disease modifying therapy earlier in individuals with SMA will result in improved outcomes, which will have a positive effect on the individuals and families as well as reducing the cost and burden on the NHS and society (Weidlich D et al. 2023; Servais L et al. 2025). This earlier diagnosis will improve clinical and health-related quality of life outcomes while reducing high-cost high burden healthcare resource use. We raised the point that earlier diagnosis for incident patients will lead to much better clinical and cost-effectiveness outcomes for the overall evolving cohort of SMA patients who receive DMTs at ACM1 and would like to reiterate this here for the committee to consider at ACM2.

Cost effectiveness results

Table 1: Impact of alternative assumptions on simulated committee base case

	Type 1		Type 2/3		Presymptomatic	
Scenario	**ICER vs BSC**	**ICER vs standard of care (weighted)**	**ICER vs BSC**	**ICER vs standard of care (weighted)**	**ICER vs BSC**	**ICER vs standard of care (weighted)**
Simulated committee base case	**£51,740**	**Dominant**	**£89,736**	**Dominant**	**£22,402**	**Dominant**
Discontinuation: FIREFISH or SUNFISH OLE	£47,904	Dominant	£85,435	Dominant	£21,522	Dominant
Health state costs: On-treatment costs informed by adjusted granular HST24 costs	£40,228	Dominant	£58,565	Dominant	£19,084	Dominant
Company base case (including both of the above changes)	**£34,112**	**Dominant**	**£56,032**	**Dominant**	**£18,835**	Dominant

Table 2: Deterministic cost-effectiveness results – company Type 1 base case

Discounted results				**Incremental - Risdiplam versus comparator**			
Treatment	**Costs**	**LYs**	**QALYs**	**Costs**	**LYs**	**QALYs**	**ICER per QALY**
Risdiplam	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-
Nusinersen	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominant
Onasemnogene abeparvovec	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Less effective at lower costs
BSC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£34,112

Standard of care (weighted)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominant

Table 3: Deterministic cost-effectiveness results – company Type 2/3 base case

Discounted results				**Incremental - Risdiplam versus comparator**			
Treatment	**Costs**	**LYs**	**QALYs**	**Costs**	**LYs**	**QALYs**	**ICER per QALY**
Risdiplam	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-
Nusinersen	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominant
BSC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£56,032
Standard of care (weighted)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominant

Table 4: Deterministic cost-effectiveness results – company presymptomatic base case

Discounted results				**Incremental - Risdiplam versus comparator**			
Treatment	**Costs**	**LYs**	**QALYs**	**Costs**	**LYs**	**QALYs**	**ICER per QALY**
Risdiplam	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-
Nusinersen	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	NA (B)*
Onasemnogene abeparvovec	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	NA (A)*
BSC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£18,835
Standard of care (weighted)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	NA (B)*

Scenario analysis

Table 5: Scenario analysis – Type 1 company base case

Description	**ICER vs BSC**	**ICER vs SoC (weighted)**
Company base case	**£34,112**	**Dominant**

1	Treatment utility increment value: 0.10	£36,324	Dominant
2	Treatment utility increment value: 0.15	£34,462	Dominant
3	Treatment utility increment value: 0.27	£30,844	Dominant
4	Treatment utility increment value: 0.27 without disease-related complication decrements	£30,521	Dominant
5	Exclusion of disease-related complication decrements	£33,717	Dominant
6	Exclusion of disease-related complication decrements and costs	£33,490	Dominant
7	Inclusion of disease-related complication decrements and costs, for the entire time horizon	£41,737	Dominant
8	Limit to one carer	£40,066	Dominant
9	Inclusion of family and care giving effect modifiers from Pennington et al. (2025)	£50,794	Dominant
10	Carer utility decrement approach	£61,102	Dominant
11	Exclude per cycle discontinuation	£40,228	Dominant
12	Exclude per cycle discontinuation and include health state stopping rules	£40,913	Dominant
13	Change risdiplam discontinuation to REACH data	£40,228	Dominant
14	Inclusion of separate health state costs when on DMT: alternative Roche HCRU study microcosting	£45,459	Dominant
15	Inclusion of separate health state costs when on DMT: relative decrease for DMTs (based on Zhu 2024)	£12,952	Dominant
16	Inclusion of separate health state costs when on DMT: relative decrease for DMTs (based on Patel 2024)	£1,035	Dominant
17	Inclusion of separate health state costs when on DMT: relative reduction to base case costs	£37,733	Dominant
18	Exclusion of separate health state costs when on DMT (original base case)	£47,904	Dominant
19	Removal of background care costs for the period of extended survival compared to BSC	£28,705	Dominant
20	Use 1.7x severity threshold	£34,112	Dominant

Table 6: Scenario analysis – Type 2/3 company base case

Description	**ICER vs BSC**	**ICER vs SoC (weighted)**
Company base case	**£56,032**	**Dominant**

1	Treatment utility increment value: 0.10	£64,356	Dominant
2	Treatment utility increment value: 0.15	£57,267	Dominant
3	Treatment utility increment value: 0.27	£45,514	Dominant
4	Treatment utility increment value: 0.27 without disease-related complication decrements	£60,478	Dominant
5	Exclusion of disease-related complication decrements	£73,402	Dominant
6	Exclusion of disease-related complication decrements and costs	£73,882	Dominant
7	Inclusion of disease-related complication decrements and costs, for the entire time horizon	£56,122	Dominant
8	Limit to one carer	£63,318	Dominant
9	Inclusion of family and care giving effect modifiers from Pennington et al. (2025)	£55,958	Dominant
10	Carer utility decrement approach	£55,882	Dominant
11	Exclude per cycle discontinuation	£39,899	Dominant
12	Exclude per cycle discontinuation and include health state stopping rules	£30,155	Dominant
13	Change risdiplam discontinuation to REACH data	£58,565	Dominant
14	Inclusion of separate health state costs when on DMT: alternative Roche HCRU study microcosting	£91,435	Dominant
15	Inclusion of separate health state costs when on DMT: relative decrease for DMTs (based on Zhu 2024)	£1,092	Dominant
16	Inclusion of separate health state costs when on DMT: relative decrease for DMTs (based on Patel 2024)	Dominant	Dominant
17	Inclusion of separate health state costs when on DMT: relative reduction to base case costs	£35,609	Dominant
18	Exclusion of separate health state costs when on DMT (original base case)	£85,435	Dominant
19	Removal of background care costs for the period of extended survival compared to BSC	£57,589	Dominant
20	Use 1.7x severity threshold	£56,032	Dominant

Table 7: Scenario analysis – Presymptomatic company base case

Description	**ICER vs BSC**	**ICER vs SoC (weighted)**
Company base case	**£18,835**	**Dominant**

1	Treatment utility increment value: 0.10	£19,484	Dominant
2	Treatment utility increment value: 0.15	£18,940	Dominant
3	Treatment utility increment value: 0.27	£17,943	Dominant
4	Treatment utility increment value: 0.27 without disease-related complication decrements	£18,923	Dominant
5	Exclusion of disease-related complication decrements	£21,187	Dominant
6	Exclusion of disease-related complication decrements and costs	£19,520	Dominant
7	Inclusion of disease-related complication decrements and costs, for the entire time horizon	£19,372	Dominant
8	Limit to one carer	£23,097	Dominant
9	Inclusion of family and care giving effect modifiers from Pennington et al. (2025)	£23,049	Dominant
10	Carer utility decrement approach	£25,070	Dominant
11	Exclude per cycle discontinuation	£11,668	Dominant
12	Exclude per cycle discontinuation and include health state stopping rules	£11,631	Dominant
13	Change risdiplam discontinuation to REACH data	£19,084	Dominant
14	Inclusion of separate health state costs when on DMT: alternative Roche HCRU study microcosting	£34,882	Dominant
15	Inclusion of separate health state costs when on DMT: relative decrease for DMTs (based on Zhu 2024)	£6,084	Dominant
16	Inclusion of separate health state costs when on DMT: relative decrease for DMTs (based on Patel 2024)	£821	Dominant
17	Inclusion of separate health state costs when on DMT: relative reduction to base case costs	£14,743	Dominant
18	Exclusion of separate health state costs when on DMT (original base case)	£21,522	Dominant
19	Removal of background care costs for the period of extended survival compared to BSC	£14,056	Dominant
20	Use 1.7x severity threshold	£18,835	Dominant

CONFIDENTIAL

Spinal muscular atrophy: nusinersen (MAA review of TA588) and risdiplam (MAA review of TA755) [ID6195]

Confidential addendum to the EAG report including confidential discounted prices

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Date completed 02/02/2026

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1 Introduction

On the 11th of November 2025, NICE held the first appraisal committee meeting on therapies for spinal muscular atrophy (SMA) focusing on nusinersen (TA 588) and risdiplam (TA 755). This analysis included the NICE committee, and representatives from: the Newcastle EAG, the SMA patient community, the MAA registry, Biogen to support the evidence for nusinersen, and Roche to support the evidence for risdiplam. The outcome of this meeting was a pause of the appraisal to consider additional analyses focused on the committee preferences agreed during the meeting.

This addendum reports the updated analyses from Biogen, Roche, and the EAG respectively. A summary of the committee preferences is presented below:

1. Risdiplam / nusinersen should not be used concurrently, or after previous successful treatment with intravenous OA (as defined in MAA). Treatment should be stopped if the patient shows sustained deterioration across a range of outcome measures

2. If eventually recommended for presymptomatic and types 1-3, recommend the treatments within their marketing authorisations. Mention in narrative that people with type 4 may benefit from treatment, but committee has not seen clinical and cost-effectiveness evidence.

3. Use absolute utility increment rather than % to capture treatment benefit in severe health states, see item 5.

4. In practice, decision-making comparators are:

    a. Presymptomatic: Intravenous OA, BSC (for small number not able to have OA)

b. T1 SMA: Intravenous OA, BSC (for cohort who were too old/heavy for intravenous OA when it became available, or not able to have OA due to contraindications)

c. T2/3 SMA: BSC

5. Utility increment of 0.1 is a conservative adjustment; ask companies to explore higher increments and/or function-specific increments in scenarios (e.g. capturing disutility for scoliosis/respiratory support). Utility should be capped at general population norm.

6. Common inputs and assumptions aligned between Biogen and Roche models.

7. Use Biogen & EAG-preferred utility values for all types as no negative values, higher utilities in severe health states and consistent with HST24.

8. Carer QoL should be added to base cases using increment approach. Assume same values for all types, in alignment with patient utilities. Would also like to see scenarios with higher average number of carers across all health states, and scenario using decrement approach. (Companies to provide)

9. Remove permanent ventilation stopping rules for both treatments and include treatment discontinuation for both treatments -propose using MAA data for Roche for consistency with Biogen. (Companies to provide)

10. Breakdown of HST24/Biogen costs and Roche costs separate estimates for health state costs on/off DMTs, and supporting evidence around lower admission rates etc. (Companies to provide)

11. Committee will consider scenario which removes background care costs for period of extended survival on DMTs. (Companies to provide)

12. Use 1.7 for presymptomatic, with scenario considering 1.2 for BSC comparison. Use x1.7 weight for type 1 BSC comparison; Use x1.2 for types 2/3, with scenario considering 1.7. (Companies to provide)

Table 1. Summary of treatments with a discounted price used in the model

Technologies	Pharmaceutical Form	Price source	List price quoted by NICE	PAS/CMU price quoted by NICE	Price % reduction quoted by NICE	List price used in company model	PAS % reduction implemented in model
Nusinersen	12m/5ml	PAS	£75,000	[redacted]	[redacted]	£75,000	[redacted]
Risdiplam	0.75mg/ml	PAS	£7,900	[redacted]	[redacted]	£7,900	[redacted]
Onasemnogene abeparvovec - OA	2 × 10^13 vector genomes/ml	PAS	£1,795,000	[redacted]	[redacted]	£1,600,081 (£1,798,139 used in the Biogen model with inflation adjusted)	[redacted]

Abbreviations: CMU = commercial medicines unit; NICE = National Institute for Health and Care Excellence; PAS = Patient Access Scheme

2 Biogen's cost-effectiveness results for nusinersen

2.1 Biogen base-case Pre-symptomatic SMA

Table 2. Biogen base-case model assumptions: Pre-symptomatic SMA

SMA type	Presym
Starting model	Biogen Dec 25
Carer QALY inclusion	Included (increment approach)
Number of carers	2 in base-case, 1 or 3 in scenarios
Utility increment for uncaptured benefits for patients	0.15 increments for DMTs in base-case
Health State Costs - BSC	Biogen HST 24
Health State Costs - DMT	[redacted] reduction of hospitalisation costs in base-case
Background care cost inclusions	Included
Severity modifier	1.7
Disease related impact (scoliosis, respiratory & bulbar disutility)	None included
Treatment stopping rule for PV patients	No treatment when PV
Other treatment discontinuation	Scenarios where 100%/80%/50% patients receive nusinersen at PV

Prices used for intervention and comparators	PAS price for all treatments
Patient utility values	HST 24 (no difference by type)
Carer utility values	Biogen approach (Bastida et al. No difference by type).
Other relevant assumptions:	Discontinuation rates based on the 2023 cut-off of the paediatric MAA registry data, rather than the more recent 2025 cut-off. Relative efficacy of nusinersen compared to OA assumed equivalent for 18 months, then MAIC estimates applied as absolute differences until month 60, patients are assumed only to maintain or lose motor ability after 60 months. Any excess in the proportion of patients above 100% were adjusted down in the health states with lower motor ability.

Table 3. Deterministic pairwise results

Technologies	Total costs (£)	Total LYG	Patient QALYs	Carer QALYs	Total QALYs	Incr. costs (£)	Incr. LYG	Incr. Patient QALYs (without severity)	Incr. Patient QALYs (with severity)	Incr. QALYs	ICER (£/QALY)
Nusinersen	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Onasemnogene abeparvovec	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
BSC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Abbreviations: ICER: incremental cost effectiveness ratio; LYG: life years gained; QALYs: quality-adjusted life years											

Table 4. Deterministic incremental results

Technologies	Total costs (£)	Patient QALYs	Carer QALYs	Total QALYs	Incr. costs (£)	Incr. Patient QALYs (without severity)	Incr. Patient QALYs (with severity)	Incr. QALYs	ICER (£/QALY)
BSC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Nusinersen	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Onasemnogene abeparvovec	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Abbreviations: ICER: incremental cost effectiveness ratio; QALYs: quality-adjusted life years									

Table 5. Deterministic scenario analyses: nusinersen vs BSC (1.7 severity modifier)

Scenarios	Incremental costs	Incremental QALYs	ICER	NMB at £30,000 per QALY gained
New base case	[redacted]	[redacted]	[redacted]	[redacted]
1: Change total number of caregivers to 1 for all health states.	[redacted]	[redacted]	[redacted]	[redacted]
2: Change total number of caregivers to 3 for all health states.	[redacted]	[redacted]	[redacted]	[redacted]
3: Apply alternative severity modifiers (1.2 for PS)	[redacted]	[redacted]	[redacted]	[redacted]
4. Removal of social care costs	[redacted]	[redacted]	[redacted]	[redacted]
5. Apply a carer disutility	[redacted]	[redacted]	[redacted]	[redacted]
Abbreviations: ICER: incremental cost effectiveness ratio; QALYs: quality-adjusted life years; NMB: net monetary benefit				

Table 6. Deterministic scenario analyses: nusinersen vs OA (no severity modifier)

Scenarios	Incremental costs	Incremental QALYs	ICER	NMB at £30,000 per QALY gained
New base case	[redacted]	[redacted]	[redacted]	[redacted]
1: Change total number of caregivers to 1 for all health states.	[redacted]	[redacted]	[redacted]	[redacted]
2: Change total number of caregivers to 3 for all health states.	[redacted]	[redacted]	[redacted]	[redacted]
3: Equal efficacy between NUS and OA	[redacted]	[redacted]	[redacted]	[redacted]
4. Removal of social care costs	[redacted]	[redacted]	[redacted]	[redacted]
5. Apply a carer disutility	[redacted]	[redacted]	[redacted]	[redacted]
6. Remove nusinersen discontinuations	[redacted]	[redacted]	[redacted]	[redacted]
Abbreviations: ICER: incremental cost effectiveness ratio; QALYs: quality-adjusted life years; NMB: net monetary benefit				

2.2 Biogen base-case Type 1 SMA

Table 7. Biogen base-case model assumptions: Type 1 SMA

SMA type	Type 1
Starting model	Biogen Dec 25
Carer QALY inclusion	Included (increment approach)
Number of carers	2 in base-case, 1 or 3 in scenarios
Utility increment for uncaptured benefits for patients	0.15 increments for DMTs in base-case
Health State Costs - BSC	Biogen HST 24
Health State Costs - DMT	[redacted] reduction of hospitalisation costs in base-case
Background care cost inclusions	Included
Severity modifier	1.7
Disease related impact (scoliosis, respiratory & bulbar disutility)	None included
Treatment stopping rule for PV patients	No treatment when PV
Other treatment discontinuation	Scenarios where 100%/80%/50% patients receive nusinersen at PV
Prices used for intervention and comparators	PAS price for all treatments

Patient utility values	HST 24 (no difference by type)
Carer utility values	Biogen approach (Bastida et al. No difference by type).
Other relevant assumptions:	Discontinuation rates based on the 2023 cut-off of the paediatric MAA registry data, rather than the more recent 2025 cut-off. Relative efficacy of nusinersen compared to OA assumed equivalent for 18 months, then MAIC estimates applied as absolute differences until month 60, patients are assumed only to maintain or lose motor ability after 60 months. Any excess in the proportion of patients above 100% were adjusted down in the health states with lower motor ability.

Table 8. Deterministic pairwise results

Technologies	Total costs (£)	Total LYG	Patient QALYs	Carer QALYs	Total QALYs	Incr. costs (£)	Incr. LYG	Incr. Patient QALYs (without severity)	Incr. Patient QALYs (with severity)	Incr. QALYs	ICER (£/QALY)
Nusinersen	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Onasemnogene abeparvovec	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
BSC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
*ICER for onasemnogene abeparvovec versus nusinersen as the incr. costs and incr. QALYs lie in South-West quadrant of the CE plane. Abbreviations: ICER: incremental cost effectiveness ratio; LYG: life years gained; QALYs: quality-adjusted life years											

Table 9. Deterministic incremental results

Technologies	Total costs (£)	Patient QALYs	Carer QALYs	Total QALYs	Incr. costs (£)	Incr. Patient QALYs (without severity)	Incr. Patient QALYs (with severity)	Incr. QALYs	ICER (£/QALY)
BSC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Nusinersen	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Onasemnogene abeparvovec	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Abbreviations: ICER: incremental cost effectiveness ratio; QALYs: quality-adjusted life years									

Table 10. Deterministic scenario analyses: nusinersen vs BSC (1.7 severity modifier)

Scenarios	Incremental costs	Incremental QALYs	ICER	NMB at £30,000 per QALY gained
New base case	[redacted]	[redacted]	[redacted]	[redacted]
1: Change total number of caregivers to 1 for all health states.	[redacted]	[redacted]	[redacted]	[redacted]
2: Change total number of caregivers to 3 for all health states.	[redacted]	[redacted]	[redacted]	[redacted]
3: Remove PV state stopping rules – 100% NUS remain on treatment	[redacted]	[redacted]	[redacted]	[redacted]
4: Remove PV state stopping rules – 50% NUS remain on treatment	[redacted]	[redacted]	[redacted]	[redacted]
5: Remove PV state stopping rules – 20% NUS remain on treatment	[redacted]	[redacted]	[redacted]	[redacted]
6: Remove health state costs for the period of extended survival with NUS.	[redacted]	[redacted]	[redacted]	[redacted]
7. Removal of social care costs	[redacted]	[redacted]	[redacted]	[redacted]
8. Apply a carer disutility	[redacted]	[redacted]	[redacted]	[redacted]
Abbreviations: ICER: incremental cost effectiveness ratio; QALYs: quality-adjusted life years, NMB: net monetary benefit				

Table 11. Deterministic scenario analyses: nusinersen vs OA (no severity modifier)

Scenarios	Incremental costs	Incremental QALYs	ICER	NMB at £30,000 per QALY gained
New base case	[redacted]	[redacted]	[redacted]	[redacted]
1: Change total number of caregivers to 1 for all health states.	[redacted]	[redacted]	[redacted]	[redacted]
2: Change total number of caregivers to 3 for all health states.	[redacted]	[redacted]	[redacted]	[redacted]
3: Remove PV state stopping rules – 100% NUS remain on treatment	[redacted]	[redacted]	[redacted]	[redacted]
4: Remove PV state stopping rules – 50% NUS remain on treatment	[redacted]	[redacted]	[redacted]	[redacted]
5: Remove PV state stopping rules – 20% NUS remain on treatment	[redacted]	[redacted]	[redacted]	[redacted]
6: Remove health state costs for the period of extended survival with NUS and OA	[redacted]	[redacted]	[redacted]	[redacted]
7: Equal efficacy between NUS and OA	[redacted]	[redacted]	[redacted]	[redacted]
8. Removal of social care costs	[redacted]	[redacted]	[redacted]	[redacted]
9. Apply a carer disutility	[redacted]	[redacted]	[redacted]	[redacted]
10. Remove nusinersen discontinuations	[redacted]	[redacted]	[redacted]	[redacted]

*ICER for onasemnogene abeparvovec versus nusinersen as the incr. costs and incr. QALYs lie in South-West quadrant of the CE plane.
Abbreviations: ICER: incremental cost effectiveness ratio; QALYs: quality-adjusted life years, NMB: net monetary benefit

2.3 Biogen base-case Type 2/3 SMA

Table 12. Biogen base-case model assumptions: Pre-symptomatic SMA

SMA type	Type 2/3
Starting model	Biogen Dec 25
Carer QALY inclusion	Included (increment approach)
Number of carers	2 in base-case, 1 or 3 in scenarios
Utility increment for uncaptured benefits for patients	0.15 increments for DMTs in base-case
Health State Costs - BSC	Biogen HST 24
Health State Costs - DMT	[redacted] reduction of hospitalisation costs in base-case
Background care cost inclusions	Included
Severity modifier	1.2
Disease related impact (scoliosis, respiratory & bulbar disutility)	None included
Treatment stopping rule for PV patients	No treatment when PV
Other treatment discontinuation	PV assumptions not applicable to this model
Prices used for intervention and comparators	PAS price for all treatments
Patient utility values	HST 24 (no difference by type)

Carer utility values	Biogen approach (Bastida et al. No difference by type).
Other relevant assumptions:	Discontinuation rates based on the 2023 cut-off of the paediatric MAA registry data, rather than the more recent 2025 cut-off.

Table 13. Deterministic pairwise results

Technologies	Total costs (£)	Total LYG	Patient QALYs	Carer QALYs	Total QALYs	Incr. costs (£)	Incr. LYG	Incr. Patient QALYs (without severity)	Incr. Patient QALYs (with severity)	Incr. QALYs	ICER (£/QALY)
Nusinersen	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
BSC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Abbreviations: ICER: incremental cost effectiveness ratio; LYG: life years gained; QALYs: quality-adjusted life years											

Table 14. Deterministic scenario analyses: nusinersen vs BSC (1.2 severity modifier)

Scenarios	Incremental costs	Incremental QALYs	ICER	NMB at £30,000 per QALY gained
New base case	[redacted]	[redacted]	[redacted]	[redacted]
1: Change total number of caregivers to 1 for all health states.	[redacted]	[redacted]	[redacted]	[redacted]
2: Change total number of caregivers to 3 for all health states.	[redacted]	[redacted]	[redacted]	[redacted]
3: Apply alternative severity modifiers (1.7 for T2/3)	[redacted]	[redacted]	[redacted]	[redacted]
4. Removal of social care costs	[redacted]	[redacted]	[redacted]	[redacted]
5. Apply a carer disutility	[redacted]	[redacted]	[redacted]	[redacted]
Abbreviations: ICER: incremental cost effectiveness ratio; QALYs: quality-adjusted life years; NMB: net monetary benefit				

3 Roche's cost-effectiveness results for risdiplam

3.1 Roche base-case Pre-symptomatic SMA

Table 15. Roche base-case model assumptions: Pre-symptomatic SMA

SMA type	Presym
Starting model	Roche Jan 26
Carer QALY inclusion	Included (increment approach)
Number of carers	2.2 in base-case, 1 or 3 in scenarios
Utility increment for uncaptured benefits for patients	0.16 increments for DMTs in base-case
Health State Costs - BSC	Biogen HST 24
Health State Costs - DMT	Base-case: 47% reduction in hospitalisation costs, 8% reduction in GP and Emergency Department visits.
Background care cost inclusions	Included
Severity modifier	1.7
Disease related impact (scoliosis, respiratory & bulbar disutility)	Application of disease-related complication disutilities for a period of survival equivalent to BSC in the base-case.
Treatment stopping rule for PV patients	100% on treatment when PV
Other treatment discontinuation	Discontinuation rates based on SUNFISH and FIREFISH

Prices used for intervention and comparators	PAS price for all treatments
Patient utility values	HST 24 (no difference by type)
Carer utility values	From Bastida et al (originally used by Biogen). No difference between presymptomatic and type 1. Assumes additional caregiver on treatment utility of 0.05 for “not sitting” and “sitting” health states.
Other relevant assumptions:	Health state costs used from HST24 not inflated to 2024

Table 16. Deterministic pairwise results

Technologies	Total costs (£)	Total LYG	Patient QALYs	Carer QALYs	Total QALYs	Incr. costs (£)	Incr. LYG	Incr. Patient QALYs (without severity)	Incr. Patient QALYs (with severity)	Incr. QALYs	ICER (£/QALY)
Risdiplam	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Onasemnogene abeparvovec	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
BSC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Abbreviations: ICER: incremental cost effectiveness ratio; LYG: life years gained; QALYs: quality-adjusted life years											

Table 17. Deterministic incremental results

Technologies	Total costs (£)	Patient QALYs	Carer QALYs	Total QALYs	Incr. costs (£)	Incr. Patient QALYs (without severity)	Incr. Patient QALYs (with severity)	Incr. QALYs	ICER (£/QALY)
BSC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Risdiplam	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Onasemnogene abeparvovec	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Abbreviations: ICER: incremental cost effectiveness ratio; QALYs: quality-adjusted life years; OA: Onasemnogene abeparvovec									

Table 18. Deterministic scenario analyses: risdiplam vs BSC (1.7 severity modifier)

#	Description	Incremental costs	Incremental QALYs	ICER	NMB at £30,000 per QALY gained
	Company base case	[redacted]	[redacted]	[redacted]	[redacted]
1	Treatment utility increment value: 0.10	[redacted]	[redacted]	[redacted]	[redacted]
2	Treatment utility increment value: 0.15	[redacted]	[redacted]	[redacted]	[redacted]
3	Treatment utility increment value: 0.27	[redacted]	[redacted]	[redacted]	[redacted]
4	Treatment utility increment value: 0.27 without disease-related complication decrements	[redacted]	[redacted]	[redacted]	[redacted]
5	Exclusion of disease-related complication decrements	[redacted]	[redacted]	[redacted]	[redacted]
6	Exclusion of disease-related complication decrements and costs	[redacted]	[redacted]	[redacted]	[redacted]
7	Inclusion of disease-related complication decrements and costs, for the entire time horizon	[redacted]	[redacted]	[redacted]	[redacted]
8	Limit to one carer	[redacted]	[redacted]	[redacted]	[redacted]
9	Inclusion of family and care giving effect modifiers from Pennington et al. (2025)	[redacted]	[redacted]	[redacted]	[redacted]
10	Carer utility decrement approach	[redacted]	[redacted]	[redacted]	[redacted]
11	Exclude per cycle discontinuation	[redacted]	[redacted]	[redacted]	[redacted]
12	Exclude per cycle discontinuation and include health state stopping rules	[redacted]	[redacted]	[redacted]	[redacted]
13	Change risdiplam discontinuation to REACH data	[redacted]	[redacted]	[redacted]	[redacted]
14	Inclusion of separate health state costs when on DMT: alternative Roche HCRU study microcosting	[redacted]	[redacted]	[redacted]	[redacted]
15	Inclusion of separate health state costs when on DMT: relative decrease for DMTs (based on Zhu 2024)	[redacted]	[redacted]	[redacted]	[redacted]

16	Inclusion of separate health state costs when on DMT: relative decrease for DMTs (based on Patel 2024)	[redacted]	[redacted]	[redacted]	[redacted]
17	Inclusion of separate health state costs when on DMT: relative reduction to base case costs	[redacted]	[redacted]	[redacted]	[redacted]
18	Exclusion of separate health state costs when on DMT (original base case)	[redacted]	[redacted]	[redacted]	[redacted]
19	Removal of background care costs for the period of extended survival compared to BSC	[redacted]	[redacted]	[redacted]	[redacted]
20	Use 1.7x severity threshold	[redacted]	[redacted]	[redacted]	[redacted]
Abbreviations: ICER: incremental cost effectiveness ratio; QALYs: quality-adjusted life years					

Table 19. Deterministic scenario analyses: risdiplam vs OA (no severity modifier)

#	Description	Incremental costs	Incremental QALYs	ICER	NMB at £30,000 per QALY gained
	Company base case	[redacted]	[redacted]	[redacted]	[redacted]
1	Treatment utility increment value: 0.10	[redacted]	[redacted]	[redacted]	[redacted]
2	Treatment utility increment value: 0.15	[redacted]	[redacted]	[redacted]	[redacted]
3	Treatment utility increment value: 0.27	[redacted]	[redacted]	[redacted]	[redacted]
4	Treatment utility increment value: 0.27 without disease-related complication decrements	[redacted]	[redacted]	[redacted]	[redacted]
5	Exclusion of disease-related complication decrements	[redacted]	[redacted]	[redacted]	[redacted]
6	Exclusion of disease-related complication decrements and costs	[redacted]	[redacted]	[redacted]	[redacted]
7	Inclusion of disease-related complication decrements and costs, for the entire time horizon	[redacted]	[redacted]	[redacted]	[redacted]
8	Limit to one carer	[redacted]	[redacted]	[redacted]	[redacted]

9	Inclusion of family and care giving effect modifiers from Pennington et al. (2025)	[redacted]	[redacted]	[redacted]	[redacted]
10	Carer utility decrement approach	[redacted]	[redacted]	[redacted]	[redacted]
11	Exclude per cycle discontinuation	[redacted]	[redacted]	[redacted]	[redacted]
12	Exclude per cycle discontinuation and include health state stopping rules	[redacted]	[redacted]	[redacted]	[redacted]
13	Change risdiplam discontinuation to REACH data	[redacted]	[redacted]	[redacted]	[redacted]
14	Inclusion of separate health state costs when on DMT: alternative Roche HCRU study microcosting	[redacted]	[redacted]	[redacted]	[redacted]
15	Inclusion of separate health state costs when on DMT: relative decrease for DMTs (based on Zhu 2024)	[redacted]	[redacted]	[redacted]	[redacted]
16	Inclusion of separate health state costs when on DMT: relative decrease for DMTs (based on Patel 2024)	[redacted]	[redacted]	[redacted]	[redacted]
17	Inclusion of separate health state costs when on DMT: relative reduction to base case costs	[redacted]	[redacted]	[redacted]	[redacted]
18	Exclusion of separate health state costs when on DMT (original base case)	[redacted]	[redacted]	[redacted]	[redacted]
19	Removal of background care costs for the period of extended survival compared to BSC	[redacted]	[redacted]	[redacted]	[redacted]
20	Use 1.7x severity threshold	[redacted]	[redacted]	[redacted]	[redacted]
Abbreviations: ICER: incremental cost effectiveness ratio; QALYs: quality-adjusted life years					

3.2 Roche base-case Type 1 SMA

Table 20. Roche base-case assumptions: Type 1 SMA

SMA type	Type 1
Starting model	Roche Jan 26
Carer QALY inclusion	Included (increment approach)
Number of carers	2.2 in base-case, 1 or 3 in scenarios
Utility increment for uncaptured benefits for patients	0.16 increments for DMTs in base-case
Health State Costs - BSC	Biogen HST 24
Health State Costs - DMT	Base-case: 47% reduction in hospitalisation costs, 8% reduction in GP and Emergency Department visits.
Background care cost inclusions	Included
Severity modifier	1.7
Disease related impact (scoliosis, respiratory & bulbar disutility)	Application of disease-related complication disutilities for a period of survival equivalent to BSC in the base-case.
Treatment stopping rule for PV patients	100% on treatment when PV
Other treatment discontinuation	Discontinuation rates based on SUNFISH and FIREFISH

Prices used for intervention and comparators	PAS price for all treatments
Patient utility values	HST 24 (no difference by type)
Carer utility values	From Bastida et al (originally used by Biogen).No difference between presymptomatic and type 1. Assumes additional caregiver on treatment utility of 0.05 for “not sitting” and “sitting” health states.
Other relevant assumptions:	Health state costs used from HST24 not inflated to 2024

Table 21. Deterministic pairwise results

Technologies	Total costs (£)	Total LYG	Patient QALYs	Carer QALYs	Total QALYs	Incr. costs (£)	Incr. LYG	Incr. Patient QALYs (without severity)	Incr. Patient QALYs (with severity)	Incr. QALYs	ICER (£/QALY)
Risdiplam	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Onasemnogene abeparvovec	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
BSC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
*ICER for onasemnogene abeparvovec versus risdiplam as the incr. costs and incr. QALYs lie in South-West quadrant of the CE plane. Abbreviations ICER: incremental cost effectiveness ratio; LYG: life years gained; QALYs: quality-adjusted life years											

Table 22. Deterministic incremental results

Technologies	Total costs (£)	Patient QALYs	Carer QALYs	Total QALYs	Incr. costs (£)	Incr. Patient QALYs (without severity)	Incr. Patient QALYs (with severity)	Incr. QALYs	ICER (£/QALY)
BSC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Risdiplam	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Onasemnogene abeparvovec	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Abbreviations: ICER: incremental cost effectiveness ratio; QALYs: quality-adjusted life years									

Table 23. Deterministic scenario analyses: risdiplam vs BSC (1.7 severity modifier)

#	Description	Incremental costs	Incremental QALYs	ICER	NMB at £30,000 per QALY gained
	Company base case	[redacted]	[redacted]	[redacted]	[redacted]
1	Treatment utility increment value: 0.10	[redacted]	[redacted]	[redacted]	[redacted]
2	Treatment utility increment value: 0.15	[redacted]	[redacted]	[redacted]	[redacted]
3	Treatment utility increment value: 0.27	[redacted]	[redacted]	[redacted]	[redacted]
4	Treatment utility increment value: 0.27 without disease-related complication decrements	[redacted]	[redacted]	[redacted]	[redacted]
5	Exclusion of disease-related complication decrements	[redacted]	[redacted]	[redacted]	[redacted]
6	Exclusion of disease-related complication decrements and costs	[redacted]	[redacted]	[redacted]	[redacted]
7	Inclusion of disease-related complication decrements and costs, for the entire time horizon	[redacted]	[redacted]	[redacted]	[redacted]
8	Limit to one carer	[redacted]	[redacted]	[redacted]	[redacted]
9	Inclusion of family and care giving effect modifiers from Pennington et al. (2025)	[redacted]	[redacted]	[redacted]	[redacted]
10	Carer utility decrement approach	[redacted]	[redacted]	[redacted]	[redacted]
11	Exclude per cycle discontinuation	[redacted]	[redacted]	[redacted]	[redacted]
12	Exclude per cycle discontinuation and include health state stopping rules	[redacted]	[redacted]	[redacted]	[redacted]
13	Change risdiplam discontinuation to REACH data	[redacted]	[redacted]	[redacted]	[redacted]
14	Inclusion of separate health state costs when on DMT: alternative Roche HCRU study microcosting	[redacted]	[redacted]	[redacted]	[redacted]
15	Inclusion of separate health state costs when on DMT: relative decrease for DMTs (based on Zhu 2024)	[redacted]	[redacted]	[redacted]	[redacted]
16	Inclusion of separate health state costs when on DMT: relative decrease for DMTs (based on Patel 2024)	[redacted]	[redacted]	[redacted]	[redacted]
17	Inclusion of separate health state costs when on DMT: relative reduction to base case costs	[redacted]	[redacted]	[redacted]	[redacted]

18	Exclusion of separate health state costs when on DMT (original base case)	[redacted]	[redacted]	[redacted]	[redacted]
19	Removal of background care costs for the period of extended survival compared to BSC	[redacted]	[redacted]	[redacted]	[redacted]
20	Use 1.7x severity threshold	[redacted]	[redacted]	[redacted]	[redacted]
Abbreviations: ICER: incremental cost effectiveness ratio; QALYs: quality-adjusted life years					

Table 24. Deterministic scenario analyses: risdiplam vs OA (no severity modifier)

#	Description	Incremental costs	Incremental QALYs	ICER	NMB at £30,000 per QALY gained
	Company base case	[redacted]	[redacted]	[redacted]	[redacted]
1	Treatment utility increment value: 0.10	[redacted]	[redacted]	[redacted]	[redacted]
2	Treatment utility increment value: 0.15	[redacted]	[redacted]	[redacted]	[redacted]
3	Treatment utility increment value: 0.27	[redacted]	[redacted]	[redacted]	[redacted]
4	Treatment utility increment value: 0.27 without disease-related complication decrements	[redacted]	[redacted]	[redacted]	[redacted]
5	Exclusion of disease-related complication decrements	[redacted]	[redacted]	[redacted]	[redacted]
6	Exclusion of disease-related complication decrements and costs	[redacted]	[redacted]	[redacted]	[redacted]
7	Inclusion of disease-related complication decrements and costs, for the entire time horizon	[redacted]	[redacted]	[redacted]	[redacted]
8	Limit to one carer	[redacted]	[redacted]	[redacted]	[redacted]
9	Inclusion of family and care giving effect modifiers from Pennington et al. (2025)	[redacted]	[redacted]	[redacted]	[redacted]
10	Carer utility decrement approach	[redacted]	[redacted]	[redacted]	[redacted]
11	Exclude per cycle discontinuation	[redacted]	[redacted]	[redacted]	[redacted]

12	Exclude per cycle discontinuation and include health state stopping rules	[redacted]	[redacted]	[redacted]	[redacted]
13	Change risdiplam discontinuation to REACH data	[redacted]	[redacted]	[redacted]	[redacted]
14	Inclusion of separate health state costs when on DMT: alternative Roche HCRU study microcosting	[redacted]	[redacted]	[redacted]	[redacted]
15	Inclusion of separate health state costs when on DMT: relative decrease for DMTs (based on Zhu 2024)	[redacted]	[redacted]	[redacted]	[redacted]
16	Inclusion of separate health state costs when on DMT: relative decrease for DMTs (based on Patel 2024)	[redacted]	[redacted]	[redacted]	[redacted]
17	Inclusion of separate health state costs when on DMT: relative reduction to base case costs	[redacted]	[redacted]	[redacted]	[redacted]
18	Exclusion of separate health state costs when on DMT (original base case)	[redacted]	[redacted]	[redacted]	[redacted]
19	Removal of background care costs for the period of extended survival compared to BSC	[redacted]	[redacted]	[redacted]	[redacted]
20	Use 1.7x severity threshold	[redacted]	[redacted]	[redacted]	[redacted]

*ICER for onasemnogene abeparvovec versus risdiplam, as the incr. costs and incr. QALYs lie in South-West quadrant of the CE plane.
Abbreviations: ICER: incremental cost effectiveness ratio; QALYs: quality-adjusted life years

3.3 Roche base-case Type 2/3 SMA

Table 25. Roche base-case assumptions: Type 2/3 SMA

SMA type	Type 2/3
Starting model	Roche Jan 26
Carer QALY inclusion	Included (increment approach)
Number of carers	3 for not sitting, 2.2 for other health states in base-case, 1 or 3 in scenarios
Utility increment for uncaptured benefits for patients	0.16 increments for DMTs in base-case
Health State Costs - BSC	Biogen HST 24
Health State Costs - DMT	Base-case: 47% reduction in hospitalisation costs, 8% reduction in GP and Emergency Department visits.
Background care cost inclusions	Included
Severity modifier	1.7
Disease related impact (scoliosis, respiratory & bulbar disutility)	Application of disease-related complication disutilities for a period of survival equivalent to BSC in the base-case.
Treatment stopping rule for PV patients	100% on treatment when PV
Other treatment discontinuation	Discontinuation rates based on SUNFISH and FIREFISH

Prices used for intervention and comparators	PAS price for all treatments
Patient utility values	HST 24 (no difference by type)
Carer utility values	The source of carer utility values was not clear; these values did not match with Bastida et al (originally used by Biogen). Assumes additional caregiver on treatment utility of 0.05 for “not sitting” and “sitting” health states.
Other relevant assumptions:	Health state costs used from HST24 not inflated to 2024

Table 26. Deterministic pairwise results

Technologies	Total costs (£)	Total LYG	Patient QALYs	Carer QALYs	Total QALYs	Incr. costs (£)	Incr. LYG	Incr. Patient QALYs (without severity)	Incr. Patient QALYs (with severity)	Incr. QALYs	ICER (£/QALY)
Risdiplam	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
BSC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Abbreviations: ICER: incremental cost effectiveness ratio; LYG: life years gained; QALYs: quality-adjusted life years											

Table 27. Deterministic scenario analyses: risdiplam vs BSC (1.7 severity modifier)

#	Description	Incremental costs	Incremental QALYs	ICER	NMB at £30,000 per QALY gained
	Company base case	[redacted]	[redacted]	[redacted]	[redacted]
1	Treatment utility increment value: 0.10	[redacted]	[redacted]	[redacted]	[redacted]
2	Treatment utility increment value: 0.15	[redacted]	[redacted]	[redacted]	[redacted]
3	Treatment utility increment value: 0.27	[redacted]	[redacted]	[redacted]	[redacted]
4	Treatment utility increment value: 0.27 without disease-related complication decrements	[redacted]	[redacted]	[redacted]	[redacted]
5	Exclusion of disease-related complication decrements	[redacted]	[redacted]	[redacted]	[redacted]
6	Exclusion of disease-related complication decrements and costs	[redacted]	[redacted]	[redacted]	[redacted]
7	Inclusion of disease-related complication decrements and costs, for the entire time horizon	[redacted]	[redacted]	[redacted]	[redacted]
8	Limit to one carer	[redacted]	[redacted]	[redacted]	[redacted]
9	Inclusion of family and care giving effect modifiers from Pennington et al. (2025)	[redacted]	[redacted]	[redacted]	[redacted]

10	Carer utility decrement approach	[redacted]	[redacted]	[redacted]	[redacted]
11	Exclude per cycle discontinuation	[redacted]	[redacted]	[redacted]	[redacted]
12	Exclude per cycle discontinuation and include health state stopping rules	[redacted]	[redacted]	[redacted]	[redacted]
13	Change risdiplam discontinuation to REACH data	[redacted]	[redacted]	[redacted]	[redacted]
14	Inclusion of separate health state costs when on DMT: alternative Roche HCRU study microcosting	[redacted]	[redacted]	[redacted]	[redacted]
15	Inclusion of separate health state costs when on DMT: relative decrease for DMTs (based on Zhu 2024)	[redacted]	[redacted]	[redacted]	[redacted]
16	Inclusion of separate health state costs when on DMT: relative decrease for DMTs (based on Patel 2024)	[redacted]	[redacted]	[redacted]	[redacted]
17	Inclusion of separate health state costs when on DMT: relative reduction to base case costs	[redacted]	[redacted]	[redacted]	[redacted]
18	Exclusion of separate health state costs when on DMT (original base case)	[redacted]	[redacted]	[redacted]	[redacted]
19	Removal of background care costs for the period of extended survival compared to BSC	[redacted]	[redacted]	[redacted]	[redacted]
20	Use 1.7x severity threshold	[redacted]	[redacted]	[redacted]	[redacted]
Abbreviations: ICER: incremental cost effectiveness ratio; QALYs: quality-adjusted life years					

4 EAG's implementation of committee preferences into the economic models

The EAG's implementation compared against committee preferences are presented below and the EAG's base-case assumptions for each of the SMA models are also summarised later in section 9. The points considered in the EAG base-case assumptions and any additional scenarios are highlighted in bold below.

1. Risdiplam / nusinersen should not be used concurrently, or after previous successful treatment with intravenous OA (as defined in MAA). Treatment should be stopped if the patient shows sustained deterioration across a range of outcome measures.

Biogen and Roche model: Patients assumed to receive BSC only after discontinuation. No additional changes required.

2. If eventually recommended for presymptomatic and types 1-3, recommend the treatments within their marketing authorisations. Mention in narrative that people with type 4 may benefit from treatment, but committee has not seen clinical and cost-effectiveness evidence.

No changes required to the economic models.

3. Use absolute utility increment rather than % to capture treatment benefit in severe health states, see point 5.

Biogen and Roche model, treatment-related utilities applied as an absolute increment.

4. In practice, decision-making comparators are:

    a. Presymptomatic: Intravenous OA, BSC (for small number not able to have OA)

b. T1 SMA: Intravenous OA, BSC (for cohort who were too old/heavy for intravenous OA when it became available, or not able to have OA due to contraindications)

c. T2/3 SMA: BSC

Biogen and Roche models: BSC and intravenous OA used as the comparator intervention when appropriate.

5. Utility increment of 0.1 is a conservative adjustment; ask companies to explore higher increments and/or function-specific increments in scenarios (e.g. capturing disutility for scoliosis/respiratory support). Utility should be capped at general population norm.

Biogen and Roche model: utility increment of 0.16 implemented as the base-case capped at population norm based on Audhya et al [2023]. Scenario with 0.1

6. Common inputs and assumptions aligned between Biogen and Roche models.

No additional changes required in the economic models.

7. Use Biogen & EAG-preferred utility values for all types as no negative values, higher utilities in severe health states and consistent with HST24.

No additional changes required in the economic models.

8. Carer QoL should be added to base cases using increment approach. Assume same values for all types, in alignment with patient utilities. Would also like to see scenarios with higher average number of carers across all health states, and scenario using decrement approach.

Biogen and Roche models: carer utilities added to the base-case using the Biogen base-case values and assuming only 1 carer. Scenarios with decremental utilities, and either 1.5 or 2.2 carers.

9. Remove permanent ventilation stopping rules for both treatments and include treatment discontinuation for both treatments -propose using MAA data for Roche for consistency with Biogen.

Biogen and Roche models: removed permanent ventilation stopping rules. Assume that patients at PV can discontinue treatment based on discontinuation at non-sitting states.

Roche model: assume patients can discontinue to BSC

10. Breakdown of HST24/Biogen costs and Roche costs separate estimates for health state costs on/off DMTs, and supporting evidence around lower admission rates etc.

Biogen and Roche models: use HST24 cost estimates for BSC, assumed a reduction on relevant HST24-derived cost components of 47% for Hospitalisations and 'GP and Emergency', and 8% for inpatient admissions and ED visits for DMTs based on Zhu et al 2024.

Scenario: No health state cost difference between DMTs and BSC; assumed and [redacted] reduction in hospitalisation costs for DMTs.

11. Committee will consider scenario which removes background care costs for period of extended survival on DMTs.

Scenario: removing background care costs for extended survival.

12. Use 1.7 for presymptomatic, with scenario considering 1.2 for BSC comparison. Use x1.7 weight for type 1 BSC comparison; Use x1.2 for types 2/3, with scenario considering 1.7.

Biogen and Roche models: Base-case multipliers of 1.7 for pre-symptomatic; 1.7 for type 1 SMA; and 1.2 for type 2/3 SMA for comparisons with BSC.

Scenario: 1.2 weight for pre-symptomatic SMA; 1.7 weight for type 2/3 SMA.

5 EAG's patient QALY assumptions

Committee preference point 3: Use absolute utility increment rather than % to capture treatment benefit in severe health states, see point 5.

Committee preference point 5: Utility increment of 0.1 is a conservative adjustment; ask companies to explore higher increments and/or function-specific increments in scenarios (e.g. capturing disutility for scoliosis/respiratory support). Utility should be capped at general population norm.

Biogen and Roche model: utility increment of 0.16 for nusinersen, risdiplam, and OA implemented as the base-case capped at population norm based on Audhya et al [2023] based on the evidence presented by Roche. This utility increment was applied additively and capped at the UK population norms.

The impact of further disease-related events such as scoliosis, bulbar function, and respiratory complications was not included in the patient utility values due to the risk of generating negative utilities and the lack of evidence of impact from disease modifying therapies. Instead, the EAG base-case assumes the potential impact on complications is captured in the reduction of hospitalisation and health resource use costs.

6 EAG's treatment discontinuation assumptions

Committee preference point 9: Remove permanent ventilation stopping rules for both treatments and include treatment discontinuation for both treatments -propose using MAA data for Roche for consistency with Biogen.

Biogen and Roche models: removed permanent ventilation stopping rules. Assume that patients at PV can discontinue treatment based on discontinuation at non-sitting states.

Roche model: assume patients can discontinue to BSC

The EAG's discontinuation assumptions were primarily informed by the results of the managed access agreement (MAA) reports for nusinersen and risdiplam respectively, specifically the paediatric reports for the data cut of April 2025.

The EAG's base-case of nusinersen was informed by Table 4 of the MAA report: nusinersen treatment (at latest visit) using type II/III non-sitters, sitters, and walkers results for patients discontinuing nusinersen treatment for any reason. Data for type 2/3 SMA patients was applied to the pre-symptomatic and type 1 population, to the health-states closely aligned to the motor milestones in Table 4 of the MAA report. Discontinuation at permanent ventilation was assumed equivalent to non-sitters. The probability of discontinuation was assumed to be constant over time.

The EAG's base-case of risdiplam was informed by Table 4 of the MAA report: risdiplam treatment (at latest visit) using type II/III non-sitters, and sitters/walkers results for patients discontinuing risdiplam treatment for any reason. Data for type 2/3 SMA patients was applied to the pre-symptomatic and type 1 population, to the health-states closely aligned to the motor milestones in Table 4 of the MAA report. Discontinuation at permanent ventilation was assumed equivalent to non-sitters. The probability of discontinuation was assumed to be constant over time.

7 EAG's carer QALY assumptions

Committee preference point 8: Carer QoL should be added to base cases using increment approach. Assume same values for all types, in alignment with patient utilities. Would also like to see scenarios with higher average number of carers across all health states, and scenario using decrement approach.

Biogen and Roche models: carer utilities added to the base-case using the Biogen base-case values and assuming only 1 carer. Scenarios with decremental utilities, and either 1.5 or 2.2 carers.

The QALYs in the EAG base-case models (for both nusinersen and risdiplam) were informed by the utility estimates taken from Bastida et al (used in the Company's Biogen models and previously used in TA588), and no difference between SMA types was assumed.

8 EAG's health state costs assumptions

Committee preference point 10: Breakdown of HST24/Biogen costs and Roche costs separate estimates for health state costs on/off DMTs, and supporting evidence around lower admission rates etc.

Biogen and Roche models: use HST24 cost estimates for BSC, assumed a reduction on relevant HST24-derived cost components of 47% for Hospitalisations and 'GP and Emergency', and 8% for inpatient admissions and ED visits for DMTs based on Zhu et al 2024. This was based on the evidence provided by Roche

Scenario: No health state cost difference between DMTs and BSC; assumed and [redacted] reduction in hospitalisation costs for DMTs based on the approach submitted by Biogen.

9 Difference in approach between companies and the EAG

Issue- 1	Reduction of health state costs on DMT
Recap of what company did	**Biogen:** [redacted] reduction of hospitalisation costs in base-case across all models; taken from HST24, inflated to 2024 **Roche:** 47% reduction in hospitalisation costs, 8% reduction in GP and Emergency Department visits, across all models. Health state costs taken from HST24 but not inflated to 2024.
EAG view on what was done, what are the strengths, what are the limitations	Biogen assumed an [redacted] reduction in hospitalisation costs for presymptomatic population based on the outputs observed in ENDEAR/SHINE and CHERISH/SHINE in type 1 and type 2/3 SMA subpopulations. These costs contributed to a substantial percentage of the total health state costs. These costs were primarily driven by decrease in hospitalisation from serious respiratory events in the nusinersen arm, which is a generalisation based on a specific outcome. Whilst the EAG acknowledges such a high reduction in hospitalisation costs may be plausible in the trial population, it may overestimate the reductions in the NHS practice.

	Roche assumption on reduction of hospitalisation costs were informed by Zhu et al 2024, which demonstrates reductions in healthcare resource utilisations from nusinersen using real world data (claims data in the US). The reductions in costs were driven by reduction in inpatient admissions, emergency department visits, and respiratory treatments. Roche assumed same % reductions across DMTs and adjusted the outcomes from Zhu et al consistently. The EAG acknowledges that the data used is informed by the US claims data, however, may better reflect routine health care resource utilisation than trial-based evidence. In addition, the EAG is uncertain to what extent the Biogen's approach may be double counting cost-savings, as the model already includes the impact of reduced costs from avoiding permanent ventilation.
EAG preference for this assumption	For both nusinersen and risdiplam models preferred the following assumptions for base-case and scenario analysis. **Base-case**: 47% reduction in hospitalisation costs, 8% reduction in GP and Emergency Department visits.; taken from HST24, inflated to 2024

	Scenarios: No difference in DMT costs/[redacted]% reduction in hospitalisation costs; taken from HST24, inflated to 2024
Rationale for EAG preference	The EAG considers Biogen's data on reductions in hospitalisation costs too optimistic and is likely to overestimate costs reductions in NHS practice. Data informed by the real-world evidence used by Roche are considered to better reflect routine health care resource utilisation. Nevertheless, the EAG conducted a scenario analysis using the Biogen's data to assess the impact of high reductions in hospitalisation costs on the ICER. In addition, this also ensured consistency across company models.
Issue-2	**Treatment while on PV**
Recap of what company did	**Biogen:** Base-case- No treatment when PV Scenarios: where 100%/80%/50% patients receive nusinersen at PV **Roche:** 100% treatment when PV
EAG view on what was done, what are the strengths, what are the limitations	Biogen continued with their original base-case assumptions of no treatment in PV health state. However, several scenario analyses where not all PV patients received treatment were conducted.

	Nevertheless, this was not what the committee suggested. Roche followed what the committee suggested, and all received treatment when in PV state.
EAG preference for this assumption	100% treatment when PV
Rationale for EAG preference	The EAG considered that 100% treatment assumption when on PV health state aligned with the committee's suggestion. In addition, it ensured consistency across company models.
Issue-3	**On treatment utility increment**
Recap of what company did	**Biogen:** 0.15 increments for DMTs in base-case **Roche**: 0.16 increments for DMTs in base-case
EAG view on what was done, what are the strengths, what are the limitations	Biogen based their on-treatment utility increment value for DMTs on proposal of SMA UK in their comments on the EAG report. Roche used on treatment utility increment informed by Audhya et al 2023
EAG preference for this assumption	Base-case: 0.16 increments for DMTs implemented as the base-case capped at

	population norm based on Audhya et al [2023]. Scenario: with 0.1 increment
Rationale for EAG preference	The EAG considered that the value informed by Audhya et al [2023]. Better reflected the on-treatment utilities from the DMTs as it considered improvement in upper limb functions (a proxy for nuanced motor function improvements for patients with SMA). Audhya et al is based on Duchenne Muscular Dystrophy population and is the only evidence available. Nevertheless, the scenario analysis with the value of 0.1 assess the impact of uncertainties in on treatment utility increments.
Issue-4	**Utility decrement for complications**
Recap of what company did	**Biogen:** Disutility from disease related complication (scoliosis, respiratory & bulbar) was not included **Roche:** Disutility from disease related complication (scoliosis, respiratory & bulbar) was included for a period of survival equivalent to BSC in the base-case.

EAG view on what was done, what are the strengths, what are the limitations	Biogen does not incorporate disease related complication and associated utility decrements in its models whereas Roche does. The EAG considers the utility decrement data to be highly uncertain and notes a risk of double counting if the health state utility values already capture these effects. In addition, the Roche approach also leads to negative utility values which was not acceptable to the patients.
EAG preference for this assumption	Disutility from disease related complication (scoliosis, respiratory & bulbar) was not included
Rationale for EAG preference	The impact of further disease-related events such as scoliosis, bulbar function, and respiratory complications was not included in the patient utility values due to the risk of generating negative utilities and the lack of evidence of impact from disease modifying therapies. Instead, the EAG base-case assumes the potential impact on complications is captured in the reduction of hospitalisation and health resource use costs. The EAG considers the utility decrement data to be highly uncertain and notes a risk of double counting if the health state utility values already capture these effects.

	Therefore, the EAG does not consider these utility decrements.
Issue-5	**Carer utility increment**
Recap of what company did	**Biogen:** Taken from Bastida et al, and no difference by SMA type **Roche:** Taken from Bastida et al and no difference by SMA type, for presymptomatic and type 1 SMA. However, the carer utility values used for type 2/3 SMA do not match with those from Bastida et al (EAG cannot say for sure where Roche took these values from). In addition, assumes additional caregiver on treatment utility of 0.05 for “not sitting” and “sitting” health states.
EAG view on what was done, what are the strengths, what are the limitations	Biogen used the carer utilities originally used in their original submission prior to the committee meeting. Roche utilised the values from Bastida et al (used originally by Biogen) for pre-symptomatic and type 1 SMA models. The source of carer utility values used in Type 2/3 SMA models was not clear. In addition, the company has not provided any justification for additional caregiver on treatment utility of 0.05 for “not sitting” and “sitting” health states used in their model.

	The EAG considers this in appropriately used.
EAG preference for this assumption	Same as the Biogen approach (Taken from Bastida et al and no difference by SMA type.
Rationale for EAG preference	Considering the available evidence, the EAG considers the utility values used by Biogen, which were accepted in a previous NICE TA 588, to be appropriate
Issue-6	**Number of carers**
Recap of what company did	**Biogen:** Base case: 2; Scenarios: 1 or 3 **Roche:** Base case: 2.2, Scenarios: 1 or 3 For type 2/3 SMA: Basecase: 3 for not sitting, 2.2 for other health states; Scenarios: 1 or 3 in scenarios
EAG view on what was done, what are the strengths, what are the limitations	The EAG acknowledges the uncertainty in the number of carers, and consider the data used and the scenario analysis undertaken by both the companies to be informative. However, the committee recommended increasing the number of carers from the base-case originally presented.
EAG preference for this assumption	Base case: 1; Scenarios: 1.5 or 2.2

Rationale for EAG preference	The EAG followed the committee's recommendation and used the minimum number of carers in the basecase, with higher numbers explored in scenario analysis. This ensured consistency across company models.
Issue-7	**Severity modifier**
Recap of what company did	**Biogen**: 1.7 for presymptomatic and type 1; 1.2 for type 2/3 **Roche:** 1.7 for presymptomatic, type 1, and type 2/3
EAG view on what was done, what are the strengths, what are the limitations	Both the companies applied severity weights according to the QALY shortfall in their respective models. The EAG considers this approach to be appropriate.
EAG preference for this assumption	Base-case: 1.7 for presymptomatic and type 1; 1.2 for type 2/3 Scenarios: 1.2 and 1.7
Rationale for EAG preference	The EAG acknowledges that the severity weights used by the companies were appropriate, however the EAG applied a weight of 1.2 for type 2/3 models to align with the committee's recommendation and to ensure consistency across both treatments. Nevertheless, the EAG

	assessed the impact of varying severity weights in its models.
Issue-8	**Treatment discontinuation**
Recap of what company did	**Biogen**: Discontinuation rates based on the 2023 cut-off of the paediatric MAA registry data, rather than the more recent 2025 cut-off. **Roche:** Discontinuation rates based on SUNFISH and FIREFISH
EAG view on what was done, what are the strengths, what are the limitations	The EAG considers the discontinuation rates from MAA registry data more representative of the real-world NHS practice than the trial data under controlled conditions.
EAG preference for this assumption	Discontinuation rates based on the 2025 cut of the paediatric MAA registry data.
Rationale for EAG preference	The EAG applied discontinuation rates based on the most recent available MAA registry. In addition, the EAG conducted scenarios with no discontinuations from treatments.
Issue-9	**Efficacy for OA**
Recap of what company did	**Biogen**: Relative efficacy of nusinersen compared to OA assumed equivalent for 18 months, then MAIC estimates applied as absolute differences until month 60,

	patients are assumed only to maintain or lose motor ability after 60 months. **Roche:** OA effectiveness assumed equivalent to risdiplam for presymptomatic only/ and used MAIC estimates
EAG view on what was done, what are the strengths, what are the limitations	The EAG considers that the MAIC estimates are based on a small sample size and are associated with a high risk of bias. Therefore, they are not considered appropriate for use in the base-case models (presymptomatic), should instead be applied in the exploratory analysis. Considering the limitations of the available data, the EAG considers Roche's approach of assuming equal effectiveness between OA and risdiplam (for presymptomatic) to be appropriate.
EAG preference for this assumption	Base-case: OA effectiveness assumed equivalent to nusinersen or risdiplam for presymptomatic population, whereas for type 1, MAIC estimates were used for risdiplam and nusinersen. Scenario: For symptomatic, OA effectiveness equivalent for 18 months, then MAIC estimates applied as absolute differences until month 60, patients are assumed only to maintain or lose motor ability after 60 months.

	For type 1, OA effectiveness assumed equivalent to risdiplam/nusinersen
Rationale for EAG preference	Considering the limitations of the available data, the EAG assumed equal effectiveness between OA and Nusinersen/Risdiplam in the base-case (for type 1, only for 18 months). Difference in effectiveness were explored only in scenario analysis.

10 Table showing the health state costs (on and off treatment) used in the EAG models

Health state costs-BSC

Health state	Cost (annual)	Cost per 4 monthly cycle (nusinersen)	Cost per monthly cycle (risdiplam)
Permanent ventilation	£328,245	£109,415	£27,354
Not sitting	£130,451	£43,484	£10,871
Sitting without support	£78,441	£26,147	£6,537
Standing with support	£9,680	£3,227	£807
Walking independently	£9,680	£3,227	£807

Health state costs DMTs

Health state	Cost (annual)	Cost per 4 monthly cycle (nusinersen)	Cost per monthly cycle (risdiplam)
Permanent ventilation	£210,175	£70,058	£17,515
Not sitting	£92,231	£30,744	£7,686
Sitting without support	£56,552	£18,851	£4,713

Standing with support	£9,524	£3,175	£794
Walking independently	£9,524	£3,175	£794

11 Table showing updated QALY shortfall calculations (to inform severity modifier)

Roche submission- (Risdiplam vs BSC)

	Presymptomatic	Type1	Type 2/3
QALY for general population	25.29	25.28	24.21
Total QALYs for this population	[redacted]	[redacted]	[redacted]
Absolute Shortfall	[redacted]	[redacted]	[redacted]
Proportional Shortfall	[redacted]	[redacted]	[redacted]
Severity modifier	1.7	1.7	1.7

Biogen submission- (Nusinersen vs BSC)

	Presymptomatic	Type1	Type 2/3
QALY for general population	24.27	24.26	23.94
Total QALYs for this population	[redacted]	[redacted]	[redacted]
Absolute Shortfall	[redacted]	[redacted]	[redacted]
Proportional Shortfall	[redacted]	[redacted]	[redacted]
Severity modifier	1.7	1.7	1.20

The EAG used the severity modifier weights recommended by the committee for both the nusinersen and risdiplam models and are the same ones as used by the Biogen in their revised submission. This ensured consistency across company models. However, the EAG also conducted scenario analyses using alternative severity weights.

12 EAG's cost-effectiveness results for nusinersen

12.1 EAG base-case Pre-symptomatic SMA

Table 28. EAG's base-case assumptions: Pre-symptomatic SMA

SMA type	Presym
Starting model	EAG-Biogen
Carer QALY inclusion	Included (increment approach)
Number of carers	1 in base-case, 1.5 or 2.2 in scenarios
Utility increment for uncaptured benefits for patients	0.16 increments for DMTs in base-case. Scenario with 0.1 increment
Health State Costs - BSC	Biogen HST 24
Health State Costs - DMT	Base-case: 47% reduction in hospitalisation costs, 8% reduction in GP and Emergency Department visits. Scenarios: No difference in DMT costs/[redacted]% reduction in hospitalisation costs
Background care cost inclusions	Included
Severity modifier	1.7

Disease related impact (scoliosis, respiratory & bulbar disutility)	None included
Treatment stopping rule for PV patients	100% on treatment when PV
Other treatment discontinuation	Discontinuation rates for PV assumed equal to “non-sitting” health states. Discontinuation rates based on the 2025 cut of the paediatric MAA registry data.
Prices used for intervention and comparators	PAS price for all treatments
Patient utility values	HST 24 (no difference by type)
Carer utility values	Biogen approach (Bastida et al. No difference by type).
Other relevant assumptions:	Base-case: OA effectiveness assumed equivalent to nusinersen. Scenario: Relative efficacy of nusinersen compared to OA assumed equivalent for 18 months, then MAIC estimates applied as absolute differences until month 60, patients are assumed only to maintain or lose motor ability after 60 months.

	Any excess in the proportion of patients above 100% were adjusted down in the health states with lower motor ability.

Table 29. Deterministic pairwise results

Technologies	Total costs (£)	Total LYG	Patient QALYs	Carer QALYs	Total QALYs	Incr. costs (£)	Incr. LYG	Incr. Patient QALYs (without severity)	Incr. Patient QALYs (with severity)	Incr. QALYs	ICER (£/QALY)
Nusinersen	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Onasemnogene abeparvovec	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
BSC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Abbreviations: ICER: incremental cost effectiveness ratio; LYG: life years gained; QALYs: quality-adjusted life years											

Table 30. Deterministic incremental results

Technologies	Total costs (£)	Patient QALYs	Carer QALYs	Total QALYs	Incr. costs (£)	Incr. Patient QALYs (without severity)	Incr. Patient QALYs (with severity)	Incr. QALYs	ICER (£/QALY)
BSC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Nusinersen	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Onasemnogene abeparvovec	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Abbreviations: ICER: incremental cost effectiveness ratio; QALYs: quality-adjusted life years									

Table 31. Deterministic scenario analyses: nusinersen vs BSC (1.7 severity modifier)

Scenarios	Incremental costs	Incremental QALYs	ICER	NMB at £30,000 per QALY gained
New base case	[redacted]	[redacted]	[redacted]	[redacted]
1: Change total number of caregivers to 1.5 for all health states.	[redacted]	[redacted]	[redacted]	[redacted]
2: Change total number of caregivers to 2.2 for all health states.	[redacted]	[redacted]	[redacted]	[redacted]
3: Utility increment for DMTs switched to 0.1	[redacted]	[redacted]	[redacted]	[redacted]
4: No difference in DMT health costs	[redacted]	[redacted]	[redacted]	[redacted]
5: [redacted]% reduction in hospitalisation costs for DMT	[redacted]	[redacted]	[redacted]	[redacted]
6: Removal of social care costs	[redacted]	[redacted]	[redacted]	[redacted]
7: Apply alternative severity modifiers (1.2 for PS)	[redacted]	[redacted]	[redacted]	[redacted]
8: Decremental approach for carer utilities	[redacted]	[redacted]	[redacted]	[redacted]
10: No discontinuation for nusinersen	[redacted]	[redacted]	[redacted]	[redacted]
11: Remove health state costs for the period of extended survival with NUS and OA	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: ICER: incremental cost effectiveness ratio; QALYs: quality-adjusted life years; NMB: net monetary benefit; DMT: disease modifying treatment

Table 32. Deterministic scenario analyses: nusinersen vs OA (no severity modifier)

Scenarios	Incremental costs	Incremental QALYs	ICER	NMB at £30,000 per QALY gained
New base case	[redacted]	[redacted]	[redacted]	[redacted]
1: Change total number of caregivers to 1.5 for all health states.	[redacted]	[redacted]	[redacted]	[redacted]
2: Change total number of caregivers to 2.2 for all health states.	[redacted]	[redacted]	[redacted]	[redacted]
3: Utility increment for DMTs switched to 0.1	[redacted]	[redacted]	[redacted]	[redacted]
4: No difference in DMT health costs	[redacted]	[redacted]	[redacted]	[redacted]
5: [redacted]% reduction in hospitalisation costs for DMT	[redacted]	[redacted]	[redacted]	[redacted]
6: Removal of social care costs	[redacted]	[redacted]	[redacted]	[redacted]
7: Apply alternative severity modifiers (1.2 for BSC)	[redacted]	[redacted]	[redacted]	[redacted]
8: Decremental approach for carer utilities	[redacted]	[redacted]	[redacted]	[redacted]
9: OA effectiveness based on MAIC estimates	[redacted]	[redacted]	[redacted]	[redacted]
10: No discontinuation for nusinersen	[redacted]	[redacted]	[redacted]	[redacted]
11: Remove health state costs for the period of extended survival with NUS and OA	[redacted]	[redacted]	[redacted]	[redacted]

*ICER for onasemnogene abeparvovec versus nusinersen as the incr. costs and incr. QALYs lie in South-West quadrant of the CE plane. Abbreviations: ICER: incremental cost effectiveness ratio; QALYs: quality-adjusted life years; NMB: net monetary benefit; DMT: disease modifying treatment; OA: Onasemnogene abeparvovec

12.2 EAG base-case Type 1 SMA

Table 33. EAG's base-case assumptions: Type 1 SMA

SMA type	Type 1
Starting model	EAG-Biogen
Carer QALY inclusion	Included (increment approach)
Number of carers	1 in base-case, 1.5 or 2.2 in scenarios
Utility increment for uncaptured benefits for patients	0.16 increments for DMTs in base-case. Scenario with 0.1 increment
Health State Costs - BSC	Biogen HST 24
Health State Costs - DMT	Base-case: 47% reduction in hospitalisation costs, 8% reduction in GP and Emergency visits. Scenarios: No difference in DMT costs/[redacted]% reduction in hospitalisation costs
Background care cost inclusions	Included
Severity modifier	1.7
Disease related impact (scoliosis, respiratory & bulbar disutility)	None included
Treatment stopping rule for PV patients	100% on treatment when PV

Other treatment discontinuation	Discontinuation rates for PV assumed equal to “non-sitting” health states. Discontinuation rates based on the 2025 cut of the paediatric MAA registry data.
Prices used for intervention and comparators	PAS price for all treatments
Patient utility values	HST 24 (no difference by type)
Carer utility values	Biogen approach (Bastida et al. No difference by type).
Other relevant assumptions:	Discontinuation rates based on the 2023 cut-off of the paediatric MAA registry data, rather than the more recent 2025 cut-off. Relative efficacy of nusinersen compared to OA assumed equivalent for 18 months, then MAIC estimates applied as absolute differences until month 60, patients are assumed only to maintain or lose motor ability after 60 months. Any excess in the proportion of patients above 100% were

	adjusted down in the health states with lower motor ability. Scenario: OA effectiveness equivalent to Nusinersen

Table 34. Deterministic pairwise results

Technologies	Total costs (£)	Total LYG	Patient QALYs	Carer QALYs	Total QALYs	Incr. costs (£)	Incr. LYG	Incr. Patient QALYs (without severity)	Incr. Patient QALYs (with severity)	Incr. QALYs	ICER (£/QALY)
Nusinersen	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Onasemnogene abeparvovec	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
BSC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
*ICER for onasemnogene abeparvovec versus nusinersen as the incr. costs and incr. QALYs lie in South-West quadrant of the CE plane. Abbreviations: ICER: incremental cost effectiveness ratio; LYG: life years gained; QALYs: quality-adjusted life years											

Table 35. Deterministic incremental results

Technologies	Total costs (£)	Patient QALYs	Carer QALYs	Total QALYs	Incr. costs (£)	Incr. Patient QALYs (without severity)	Incr. Patient QALYs (with severity)	Incr. QALYs	ICER (£/QALY)
BSC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Nusinersen	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Onasemnogene abeparvovec	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Abbreviations: ICER: incremental cost effectiveness ratio; LYG: life years gained; QALYs: quality-adjusted life years									

Table 36. Deterministic scenario analyses: nusinersen vs BSC (1.7 severity modifier)

Scenarios	Incremental costs	Incremental QALYs	ICER	NMB at £30,000 per QALY gained
New base case	[redacted]	[redacted]	[redacted]	[redacted]
1: Change total number of caregivers to 1.5 for all health states.	[redacted]	[redacted]	[redacted]	[redacted]
2: Change total number of caregivers to 2.2 for all health states.	[redacted]	[redacted]	[redacted]	[redacted]
3: Utility increment for DMTs switched to 0.1	[redacted]	[redacted]	[redacted]	[redacted]
4: No difference in DMT health costs	[redacted]	[redacted]	[redacted]	[redacted]
5: [redacted]% reduction in hospitalisation costs for DMT	[redacted]	[redacted]	[redacted]	[redacted]
6: Removal of social care costs	[redacted]	[redacted]	[redacted]	[redacted]
7: Decremental approach for carer utilities	[redacted]	[redacted]	[redacted]	[redacted]
8: OA effectiveness equal	[redacted]	[redacted]	[redacted]	[redacted]
9: Remove health state costs for the period of extended survival with NUS and OA	[redacted]	[redacted]	[redacted]	[redacted]
10: Remove nusinersen discontinuation	[redacted]	[redacted]	[redacted]	[redacted]
Abbreviations: ICER: incremental cost effectiveness ratio; QALYs: quality-adjusted life years; NMB: net monetary benefit; DMT: disease modifying treatment; OA: Onasemnogene abeparvovec				

Table 37. Deterministic scenario analyses: nusinersen vs OA (no severity modifier)

Scenarios	Incremental costs	Incremental QALYs	ICER	NMB at £30,000 per QALY gained
New base case	[redacted]	[redacted]	[redacted]	[redacted]
1: Change total number of caregivers to 1.5 for all health states.	[redacted]	[redacted]	[redacted]	[redacted]
2: Change total number of caregivers to 2.2 for all health states.	[redacted]	[redacted]	[redacted]	[redacted]
3: Utility increment for DMTs switched to 0.1	[redacted]	[redacted]	[redacted]	[redacted]
4: No difference in DMT health costs	[redacted]	[redacted]	[redacted]	[redacted]
5: [redacted]% reduction in hospitalisation costs for DMT	[redacted]	[redacted]	[redacted]	[redacted]
6: Removal of social care costs	[redacted]	[redacted]	[redacted]	[redacted]
7: Decremental approach for carer utilities	[redacted]	[redacted]	[redacted]	[redacted]
8: OA effectiveness equal to nusinersen	[redacted]	[redacted]	[redacted]	[redacted]
9: Remove health state costs for the period of extended survival with NUS and OA	[redacted]	[redacted]	[redacted]	[redacted]
10: Remove nusinersen discontinuation	[redacted]	[redacted]	[redacted]	[redacted]

*ICER for onasemnogene abeparvovec versus nusinersen as the incr. costs and incr. QALYs lie in South-West quadrant of the CE plane.
Abbreviations: ICER: incremental cost effectiveness ratio; QALYs: quality-adjusted life years; NMB: net monetary benefit; DMT: disease modifying treatment; OA: Onasemnogene abeparvovec

12.3 EAG base-case Type 2/3 SMA

Table 38. EAG's base-case assumptions: Type 2/3 SMA

SMA type	Type 2/3
Starting model	EAG-Biogen
Carer QALY inclusion	Included (increment approach)
Number of carers	1 in base-case, 1.5 or 2.2 in scenarios
Utility increment for uncaptured benefits for patients	0.16 increments for DMTs in base-case. Scenario with 0.1 increment
Health State Costs - BSC	Biogen HST 24
Health State Costs - DMT	Base-case: 47% reduction in hospitalisation costs, 8% reduction in GP and Emergency visits. Scenarios: No difference in DMT costs/[redacted]% reduction in hospitalisation costs
Background care cost inclusions	Included
Severity modifier	1.2
Disease related impact (scoliosis, respiratory & bulbar disutility)	None included
Treatment stopping rule for PV patients	100% on treatment when PV

Other treatment discontinuation	Discontinuation rates for PV assumed equal to “non-sitting” health states. Discontinuation rates based on the 2025 cut of the paediatric MAA registry data.
Prices used for intervention and comparators	PAS price for all treatments
Patient utility values	HST 24 (no difference by type)
Carer utility values	Biogen approach (Bastida et al. No difference by type).
Other relevant assumptions:	Discontinuation rates based on the 2023 cut-off of the paediatric MAA registry data, rather than the more recent 2025 cut-off.

Table 39. Deterministic pairwise results

Technologies	Total costs (£)	Total LYG	Patient QALYs	Carer QALYs	Total QALYs	Incr. costs (£)	Incr. LYG	Incr. Patient QALYs (without severity)	Incr. Patient QALYs (with severity)	Incr. QALYs	ICER (£/QALY)
Nusinersen	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
BSC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Abbreviations: ICER: incremental cost effectiveness ratio; LYG: life years gained; QALYs: quality-adjusted life years											

Table 40. Deterministic scenario analyses: nusinersen vs BSC (1.2 severity modifier)

Scenarios	Incremental costs	Incremental QALYs	ICER	NMB at £30,000 per QALY gained
New base case	[redacted]	[redacted]	[redacted]	[redacted]
1: Change total number of caregivers to 1.5 for all health states.	[redacted]	[redacted]	[redacted]	[redacted]
2: Change total number of caregivers to 2.2 for all health states.	[redacted]	[redacted]	[redacted]	[redacted]
3: Utility increment for DMTs switched to 0.1	[redacted]	[redacted]	[redacted]	[redacted]
4: No difference in DMT health costs	[redacted]	[redacted]	[redacted]	[redacted]
5: [redacted]% reduction in hospitalisation costs for DMT	[redacted]	[redacted]	[redacted]	[redacted]
6: Removal of social care costs	[redacted]	[redacted]	[redacted]	[redacted]
7: Apply alternative severity modifiers (1.7 for PS)	[redacted]	[redacted]	[redacted]	[redacted]
8: Decremental approach for carer utilities	[redacted]	[redacted]	[redacted]	[redacted]

9: Remove nusinersen discontinuation	[redacted]	[redacted]	[redacted]	[redacted]
10: Remove health state costs for the period of extended survival with NUS	[redacted]	[redacted]	[redacted]	[redacted]
Abbreviations: DMT = Disease Modifying Treatment; ICER: incremental cost effectiveness ratio; QALYs: quality-adjusted life years; NMB: net monetary benefit				

13 EAG's cost-effectiveness results for risdiplam

13.1 EAG base-case Pre-symptomatic SMA

Table 41. EAG's base-case assumptions: Pre-symptomatic SMA

SMA type	Presym
Starting model	EAG-Roche
Carer QALY inclusion	Included (increment approach)
Number of carers	1 in base-case, 1.5 or 2.2 in scenarios
Utility increment for uncaptured benefits for patients	0.16 increments for DMTs in base-case. Scenario with 0.1 increment
Health State Costs - BSC	Biogen HST 24
Health State Costs - DMT	Base-case: 47% reduction in hospitalisation costs, 8% reduction in GP and Emergency Department visits. Scenarios: No difference in DMT costs/[redacted]% reduction in hospitalisation costs
Background care cost inclusions	Included
Severity modifier	1.7
Disease related impact (scoliosis, respiratory & bulbar disutility)	None included

Treatment stopping rule for PV patients	100% on treatment when PV
Other treatment discontinuation	Discontinuation rates for PV assumed equal to “non-sitting” health states. Discontinuation rates based on the 2025 cut of the paediatric MAA registry data.
Prices used for intervention and comparators	PAS price for all treatments
Patient utility values	HST 24 (no difference by type)
Carer utility values	Biogen approach (Bastida et al. No difference by type).
Other relevant assumptions:	Base-case: OA effectiveness assumed equivalent to risdiplam.

Table 42. Deterministic pairwise results

Technologies	Total costs (£)	Total LYG	Patient QALYs	Carer QALYs	Total QALYs	Incr. costs (£)	Incr. LYG	Incr. Patient QALYs (without severity)	Incr. Patient QALYs (with severity)	Incr. QALYs	ICER (£/QALY)
Risdiplam	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Onasemnogene abeparvovec	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
BSC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Abbreviations: ICER: incremental cost effectiveness ratio; LYG: life years gained; QALYs: quality-adjusted life years											

Table 43. Deterministic incremental results

Technologies	Total costs (£)	Patient QALYs	Carer QALYs	Total QALYs	Incr. costs (£)	Incr. Patient QALYs (without severity)	Incr. Patient QALYs (with severity)	Incr. QALYs	ICER (£/QALY)
BSC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Risdiplam	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Onasemnogene abeparvovec	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Abbreviations: ICER: incremental cost effectiveness ratio; LYG: life years gained; QALYs: quality-adjusted life years									

Table 44. Deterministic scenario analyses: risdiplam vs BSC (1.7 severity modifier)

Scenarios	Incremental costs	Incremental QALYs	ICER	NMB at £30,000 per QALY gained
New base case	[redacted]	[redacted]	[redacted]	[redacted]
1: Change total number of caregivers to 1.5 for all health states.	[redacted]	[redacted]	[redacted]	[redacted]
2: Change total number of caregivers to 2.2 for all health states.	[redacted]	[redacted]	[redacted]	[redacted]
3: Utility increment for DMTs switched to 0.1	[redacted]	[redacted]	[redacted]	[redacted]
4: No difference in DMT health costs	[redacted]	[redacted]	[redacted]	[redacted]
5: [redacted]% reduction in hospitalisation costs for DMT	[redacted]	[redacted]	[redacted]	[redacted]
6: Removal of social care costs	[redacted]	[redacted]	[redacted]	[redacted]
7: Apply alternative severity modifiers (1.2 for PS)	[redacted]	[redacted]	[redacted]	[redacted]
8: Decremental approach for carer utilities	[redacted]	[redacted]	[redacted]	[redacted]
10: No discontinuation for risdiplam	[redacted]	[redacted]	[redacted]	[redacted]
11: Remove health state costs for the period of extended survival with RIS and OA	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: ICER: incremental cost effectiveness ratio; NMB: net monetary benefit; QALYs: quality-adjusted life years; DMT: disease modifying treatment

Table 45. Deterministic scenario analyses: risdiplam vs OA (no severity modifier)

Scenarios	Incremental costs	Incremental QALYs	ICER	NMB at £30,000 per QALY gained
New base case	[redacted]	[redacted]	[redacted]	[redacted]
1: Change total number of caregivers to 1.5 for all health states.	[redacted]	[redacted]	[redacted]	[redacted]
2: Change total number of caregivers to 2.2 for all health states.	[redacted]	[redacted]	[redacted]	[redacted]
3: Utility increment for DMTs switched to 0.1	[redacted]	[redacted]	[redacted]	[redacted]
4: No difference in DMT health costs	[redacted]	[redacted]	[redacted]	[redacted]
5: [redacted]% reduction in hospitalisation costs for DMT	[redacted]	[redacted]	[redacted]	[redacted]
6: Removal of social care costs	[redacted]	[redacted]	[redacted]	[redacted]
7: Apply alternative severity modifiers (1.2 for PS, Ris Vs BSC)	[redacted]	[redacted]	[redacted]	[redacted]
8: Decremental approach for carer utilities	[redacted]	[redacted]	[redacted]	[redacted]
10: No discontinuation for risdiplam	[redacted]	[redacted]	[redacted]	[redacted]
11: Remove health state costs for the period of extended survival with RIS and OA	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: ICER: incremental cost effectiveness ratio; NMB: net monetary benefit; QALYs: quality-adjusted life years; DMT: disease modifying treatment

13.2 EAG base-case Type 1 SMA

Table 46. EAG's base-case assumptions: Type 1 SMA

SMA type	Type 1
Starting model	EAG-Roche
Carer QALY inclusion	Included (increment approach)
Number of carers	1 in base-case, 1.5 or 2.2 in scenarios
Utility increment for uncaptured benefits for patients	0.16 increments for DMTs in base-case. Scenario with 0.1 increment
Health State Costs - BSC	Biogen HST 24
Health State Costs - DMT	Base-case: 47% reduction in hospitalisation costs, 8% reduction in GP and Emergency visits. Scenarios: No difference in DMT costs/[redacted]% reduction in hospitalisation costs
Background care cost inclusions	Included
Severity modifier	1.7
Disease related impact (scoliosis, respiratory & bulbar disutility)	None included
Treatment stopping rule for PV patients	100% on treatment when PV

Other treatment discontinuation	Discontinuation rates for PV assumed equal to “non-sitting” health states. Discontinuation rates based on the 2025 cut of the paediatric MAA registry data.
Prices used for intervention and comparators	PAS price for all treatments
Patient utility values	HST 24 (no difference by type)
Carer utility values	Biogen approach (Bastida et al. No difference by type).
Other relevant assumptions:	Discontinuation rates based on the 2023 cut-off of the paediatric MAA registry data, rather than the more recent 2025 cut-off. MAIC estimates used to calculate the relative effectiveness of OA compared to risdiplam. Scenario: effectiveness of OA assumed equivalent to risdiplam

Table 47. Deterministic pairwise results

Technologies	Total costs (£)	Total LYG	Patient QALYs	Carer QALYs	Total QALYs	Incr. costs (£)	Incr. LYG	Incr. Patient QALYs (without severity)	Incr. Patient QALYs (with severity)	Incr. QALYs	ICER (£/QALY)
Risdiplam	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Onasemnogene abeparvovec	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
BSC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

*ICER for onasemnogene abeparvovec versus risdiplam as the incr. costs and incr. QALYs lie in South-West quadrant of the CE plane.
Abbreviations: ICER: incremental cost effectiveness ratio; LYG: life years gained; QALYs: quality-adjusted life years

Table 48. Deterministic incremental results

Technologies	Total costs (£)	Patient QALYs	Carer QALYs	Total QALYs	Incr. costs (£)	Incr. Patient QALYs (without severity)	Incr. Patient QALYs (with severity)	Incr. QALYs	ICER (£/QALY)
BSC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Risdiplam	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Onasemnogene abeparvovec	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: ICER: incremental cost effectiveness ratio; QALYs: quality-adjusted life years

Table 49. Deterministic scenario analyses: risdiplam vs BSC (1.7 severity modifier)

Scenarios	Incremental costs	Incremental QALYs	ICER	NMB at £30,000 per QALY gained
New base case	[redacted]	[redacted]	[redacted]	[redacted]
1: Change total number of caregivers to 1.5 for all health states.	[redacted]	[redacted]	[redacted]	[redacted]
2: Change total number of caregivers to 2.2 for all health states.	[redacted]	[redacted]	[redacted]	[redacted]
3: Utility increment for DMTs switched to 0.1	[redacted]	[redacted]	[redacted]	[redacted]
4: No difference in DMT health costs	[redacted]	[redacted]	[redacted]	[redacted]
5: [redacted]% reduction in hospitalisation costs for DMT	[redacted]	[redacted]	[redacted]	[redacted]
6: Removal of social care costs	[redacted]	[redacted]	[redacted]	[redacted]
7: Decremental approach for carer utilities	[redacted]	[redacted]	[redacted]	[redacted]
8: OA effectiveness equivalent to risdiplam	[redacted]	[redacted]	[redacted]	[redacted]
9: Remove health state costs for the period of extended survival with RIS and OA	[redacted]	[redacted]	[redacted]	[redacted]
10: Remove risdiplam discontinuation	[redacted]	[redacted]	[redacted]	[redacted]
Abbreviations: ICER: incremental cost effectiveness ratio; QALYs: quality-adjusted life years; OA: Onasemnogene abeparvovec; DMT: disease modifying treatment; NMB: net monetary benefit				

Table 50. Deterministic scenario analyses: risdiplam vs OA (no severity modifier)

Scenarios	Incremental costs	Incremental QALYs	ICER	NMB at £30,000 per QALY gained
New base case	[redacted]	[redacted]	[redacted]	[redacted]
1: Change total number of caregivers to 1.5 for all health states.	[redacted]	[redacted]	[redacted]	[redacted]
2: Change total number of caregivers to 2.2 for all health states.	[redacted]	[redacted]	[redacted]	[redacted]
3: Utility increment for DMTs switched to 0.1	[redacted]	[redacted]	[redacted]	[redacted]
4: No difference in DMT health costs	[redacted]	[redacted]	[redacted]	[redacted]
5: [redacted]% reduction in hospitalisation costs for DMT	[redacted]	[redacted]	[redacted]	[redacted]
6: Removal of social care costs	[redacted]	[redacted]	[redacted]	[redacted]
7: Decremental approach for carer utilities	[redacted]	[redacted]	[redacted]	[redacted]
8: OA effectiveness equivalent to risdiplam	[redacted]	[redacted]	[redacted]	[redacted]
9: Remove health state costs for the period of extended survival with RIS and OA	[redacted]	[redacted]	[redacted]	[redacted]
10: Remove risdiplam discontinuation	[redacted]	[redacted]	[redacted]	[redacted]

*ICER for onasemnogene abeparvovec versus risdiplam as the incr. costs and incr. QALYs lie in South-West quadrant of the CE plane.

Abbreviations: ICER: incremental cost effectiveness ratio; QALYs: quality-adjusted life years; OA: Onasemnogene abeparvovec; DMT: disease modifying treatment; NMB: net monetary benefit

13.3 EAG base-case Type 2/3 SMA

Table 51. EAG's base-case assumptions: Type 2/3 SMA

SMA type	Type 2/3
Starting model	EAG-Roche
Carer QALY inclusion	Included (increment approach)
Number of carers	1 in base-case, 1.5 or 2.2 in scenarios
Utility increment for uncaptured benefits for patients	0.16 increments for DMTs in base-case. Scenario with 0.1 increment
Health State Costs - BSC	Biogen HST 24
Health State Costs - DMT	Base-case: 47% reduction in hospitalisation costs, 8% reduction in GP and Emergency visits. Scenarios: No difference in DMT costs/[redacted]% reduction in hospitalisation costs
Background care cost inclusions	Included
Severity modifier	1.2
Disease related impact (scoliosis, respiratory & bulbar disutility)	None included
Treatment stopping rule for PV patients	100% on treatment when PV

Other treatment discontinuation	Discontinuation rates for PV assumed equal to “non-sitting” health states. Discontinuation rates based on the 2025 cut of the paediatric MAA registry data.
Prices used for intervention and comparators	PAS price for all treatments
Patient utility values	HST 24 (no difference by type)
Carer utility values	Biogen approach (Bastida et al. No difference by type).
Other relevant assumptions:	Discontinuation rates based on the 2023 cut-off of the paediatric MAA registry data, rather than the more recent 2025 cut-off.

Table 52. Deterministic pairwise results

Technologies	Total costs (£)	Total LYG	Patient QALYs	Carer QALYs	Total QALYs	Incr. costs (£)	Incr. LYG	Incr. Patient QALYs (without severity)	Incr. Patient QALYs (with severity)	Incr. QALYs	ICER (£/QALY)
Risdiplam	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
BSC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Abbreviations: ICER: incremental cost effectiveness ratio; LYG: life years gained; QALYs: quality-adjusted life years											

Table 53. Deterministic scenario analyses: risdiplam vs BSC (1.2 severity modifier)

Scenarios	Incremental costs	Incremental QALYs	ICER	NMB at £30,000 per QALY gained
New base case	[redacted]	[redacted]	[redacted]	[redacted]
1: Change total number of caregivers to 1.5 for all health states.	[redacted]	[redacted]	[redacted]	[redacted]
2: Change total number of caregivers to 2.2 for all health states.	[redacted]	[redacted]	[redacted]	[redacted]
3: Utility increment for DMTs switched to 0.1	[redacted]	[redacted]	[redacted]	[redacted]
4: No difference in DMT health costs	[redacted]	[redacted]	[redacted]	[redacted]
5: [redacted]% reduction in hospitalisation costs for DMT	[redacted]	[redacted]	[redacted]	[redacted]
6: Removal of social care costs	[redacted]	[redacted]	[redacted]	[redacted]
7: Apply alternative severity modifiers (1.7 for PS)	[redacted]	[redacted]	[redacted]	[redacted]
8: Decremental approach for carer utilities	[redacted]	[redacted]	[redacted]	[redacted]

9: Remove risdiplam discontinuation	[redacted]	[redacted]	[redacted]	[redacted]
10: Remove health state costs for the period of extended survival with RIS	[redacted]	[redacted]	[redacted]	[redacted]
Abbreviations: ICER: incremental cost effectiveness ratio; DMT: disease modifying treatment; QALYs: quality-adjusted life years				

EAG summary report (Date: 08/04/2026) – Produced by Newcastle University TAR Group

1. DEVOTE study notes

Phase II/III study:

Part A assessed initial safety and tolerability of 28/28mg nusinersen. Included patients aged 2 to 15 years with onset of ≥6 months and an estimated life expectancy >2 years; naïve to treatment.

Part B was an RCT, double blind, of efficacy and safety of 50/28mg nusinersen in treatment naïve participants with infantile onset SMA. A smaller cohort of later onset treatment naïve patients was also included.

Part C was open label assessing 50/28mg nusinersen in patients who transitioned from 12/12mg nusinersen regimen.

Patient characteristics are similar to those presented in the original data (e.g. registry data) for key characteristics such as age at symptom onset.

Section	Part	EAG comments
Methods	A (n = 6)	- Small sample size
	B (Infantile: 50/28mg n = 50 12/12mg n = 25 Matched sham n = 20 Later onset: 50/28mg n = 16 12/12mg n = 8 Matched sham n = 16 Matched 12/12mg n = 32)	- Dosing for 12/12mg included loading dose of 12mg on days 1, 15, 29 and 64, followed by maintenance doses on days 183 and 279. - Dosing for 50/28mg included loading dose of 50mg on days 1 and 15, followed by 28mg doses on days 135 and 279. - Both groups received sham procedure as required to ensure blinded was maintained. - Imbalance of randomisation (2:1) leads to an increase in sample size to obtain same precision of the estimated treatment comparison (12.5%). Given this is a rare disease and already suffers from small patient numbers, this could add further uncertainty to the results. - Randomisation procedure is not reported in detail, clinical trial record states sequential assignment. Unclear regarding treatment allocation, which could introduce selection bias. - Clinical trial record states only participants and carers were blinded, outcome assessors therefore not blinded. - For infantile comparison to sham group (ENDEAR) states pre-specified match group based on disease duration and baseline CHOP-INTEND. However, no statistical results posted to suggest

		how similar these groups are. Disease duration is longer and CHOP -INTEND score is higher in the SHAM group than the 50/28 and 12/12mg groups (table 1 of study). Additionally, age at first dose and age at symptom onset are both higher in the SHAM group. For comparison of 50/28 vs 12/12mg there are also some variations in baseline characteristics, 50/28mg appear slightly older at first dose and symptom onset. CHOP-INTEND and HINE scores are similar though. - For late onset comparison, propensity matching is mentioned and it is noted that the matched SHAM group and 50/28mg group have remaining imbalances. Again, no statistics appear to be reported for comparison of key factors which makes judging the accuracy of the propensity matching for any groups difficult. For 50/28mg vs 12/12mg there are noticeable differences in HFMSE (20.3 vs 13.8, respectively) and RULM (20.2 vs 14.9) scores. This suggests the patients in the 12/12mg group may have a higher severity level. - Small sample size for late onset patients.
	C (overall n = 40 Infantile onset n = 2 Later onset <18yrs n = 14 Later onset 18yrs+ n = 24)	- Open label study assessing impact of changing dose from 12/12mg to 50/28mg - Dosing: patients received 50mg 4 months (±14 days) from last 12mg dose followed by two maintenance doses on days 121 and 241. - Only two infantile patients makes any generalisation difficult.
Results	A	- 4 of 6 patients reported adverse events. Serious events were not related to drug (a fall and leg fracture was experienced by 1 patient). - Not powered to detect changes in measures (i.e. RULM and HFMSE) but does show improvement and maintenance for 5 of 6 patients. Patient with leg injury showed decline, which is likely attributed to this instant.
	B	- For motor outcomes: No statistically significant differences noted for infant or late onset SMA when comparing 50/28mg and 12/12mg regimes. - Adverse event profile appears similar between 50/28 and 12/12mg.
	C	- Results suggest improvement of motor skills in line with other findings - Adverse events don't appear to be reported for this cohort.
Interpretation	A	The EAG believe this small cohort shows the increased dose has similar adverse event profile to the lower dose. However, caution is required given the very small sample size.

	B	The EAG note that the sample size is small, there are uncertainty around the results. Some sources of bias exist, including randomisation process with allocation concealment unclear. Outcome assessment not being blind also introduces potential risk of bias. Results appear to be consistent and safety profile appears similar between the two dose groups.
	C	Limited data, especially in infantile onset patients. Results suggest moving to the increased dose may be feasible and lead to improvement in motor function, although results are highly uncertain (wide confidence intervals: Figure 1 in supplementary material). Also, adverse event data does not appear to be reported and needs to be considered.

2. Economic evaluation models - EAG Summary

Model	Checks	EAG comments
Presymptomatic	The models incorporate updated drug cost calculations and enable cost comparisons across different dosage levels.	The calculation and cost comparison functionalities are fully embedded and appropriately executed with the models resulting in logically consistent results.
Type 1 SMA		
Type 2/3 SMA		

2026



Spinal Muscular Atrophy uk

SUPPORTING • INFORMING • ADVOCATING

Impact of Disease-Modifying Therapies on SMA Patient Outcomes and Resource Utilisation

PORTIA THORMAN

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Executive Summary

1. Caregiver Burden and Reliance on Support

The data reveals a significant shift in care requirements following the initiation of treatment (Nusinersen or Risdiplam).

- **Reduction in Care Hours:** There is a clear trend of patients moving from high-dependency care categories (e.g., 24-hour professional or family care) to more autonomous states. Multiple respondents reported that their need for constant supervision has decreased, allowing family members to return to work or education.
- **Unpaid Carer Integration:** The majority of respondents rely on a "support team" of 1–3 unpaid family carers. Treatment has not only reduced the *number* of hours required but has fundamentally changed the *nature* of the care, moving from "survival-critical" support (breathing/suctioning/lifting) to "facilitatory" support (driving/social integration).
- **Autonomy and Social Inclusion:** Qualitative evidence highlights that treatment allows for "full and active social lives". Examples include more independent travel and the ability for people living with SMA to act as supporters (e.g., tutoring) rather than just recipients of care.

2. Changes in Functional and Motor Grouping

The survey data provides critical evidence on how treatment affects "Motor Function Groups" and "Respiratory Function Groups."

- **Stability as a Key Metric:** While not every patient "jumped" to a higher functional group, (non-sitter, sitter, stander, walker) the data strongly supports the **value of stabilisation**. In a progressive disease, "no change" in a functional group is a positive clinical outcome, as it represents a halt in what would otherwise be a steady decline.
- **Functional Gains:** Where changes were reported, they included significant milestones such as improved head control, increased stamina for manual wheelchair use, and enhanced ability to perform activities of daily living (ADLs).
- **Respiratory Stability:** In the respiratory function groups, respondents noted a marked decrease in the frequency of chest infections and a reduced need for intensive respiratory support (like frequent nebulisation or suctioning), which keeps patients in "stable" functional brackets for longer periods.

3. Impact on Healthcare Resource Use (HCRU)

A primary benefit captured in the data is the **stabilisation of health**, which directly correlates to a reduction in unplanned healthcare interventions.

- **Planned vs. Emergency Care:** Respondents reported that their hospital interactions have become largely "planned and routine," typically occurring approximately three times per year. This is a significant departure from the natural history of SMA, which often involves frequent emergency admissions for respiratory crises.
- **Reduced Clinical Demand:** By maintaining respiratory and physical stability, patients are avoiding the "frequent medical interventions or excessive healthcare demands" characteristic of untreated SMA. This stability allows patients to manage their health with confidence and minimal disruption to their education or professional lives.

- **Avoidance of Degeneration:** Treatment is described as a "barrier" against the severe disability and reliance on carers that would otherwise necessitate intensive social and medical care packages.

Conclusion

The data confirms that nusinersen and risdiplam provide benefits that extend far beyond simple motor scores. They deliver **meaningful economic and social value** by reducing the lifelong burden on the NHS and social care systems, while allowing both patients and their carers to lead independent, productive lives with improved mental wellbeing.

1.0 Demographics of respondents

This report summarises data collected from 113 people living with SMA in the UK who are currently prescribed either risdiplam (Evrysdi) or nusinersen (Spinraza).

Date collection period 18/12/25 – 09/01/2026

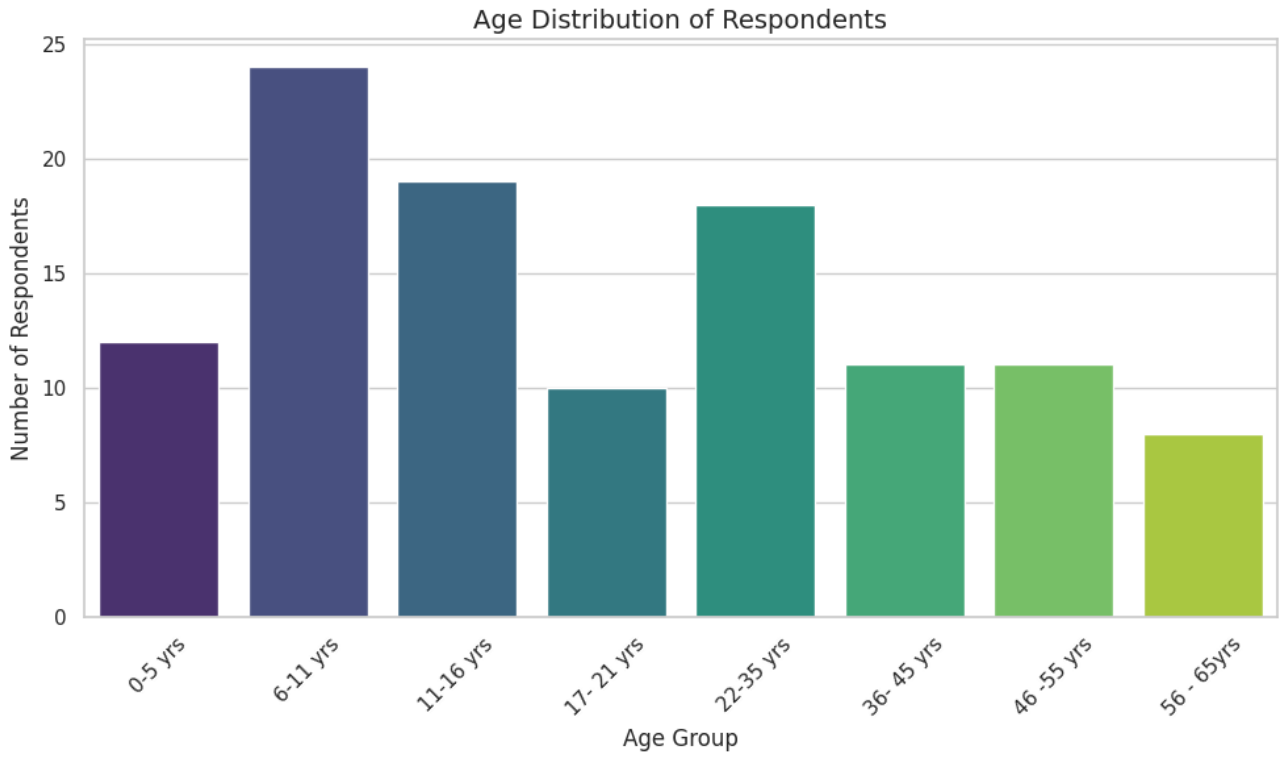


Fig.1

fig. 2a

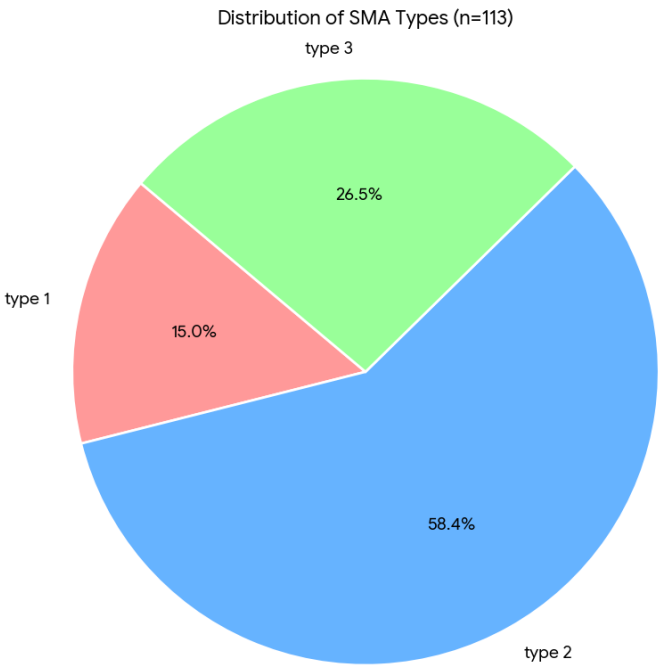
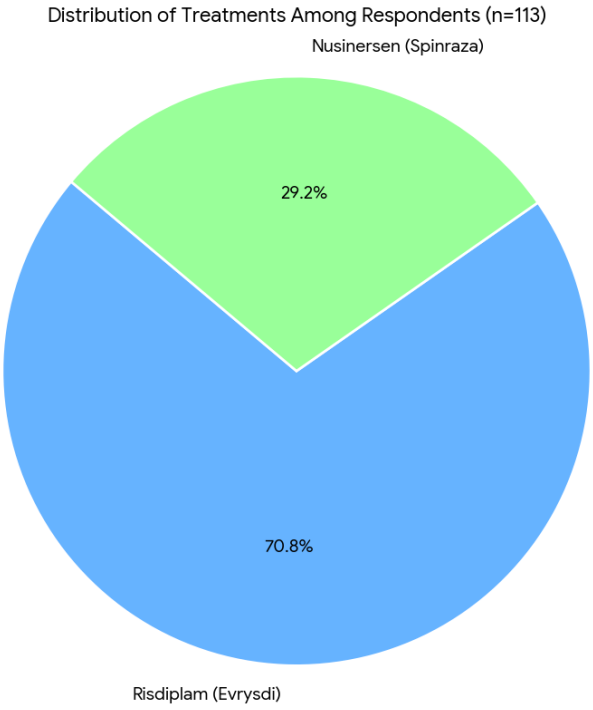

Distribution of SMA Types (n=113)
type 3
26.5%
type 1
15.0%
58.4%
type 2

fig 2b.


Distribution of Treatments Among Respondents (n=113)
Nusinersen (Spinraza)
29.2%
70.8%
Risdiplam (Evrysdi)

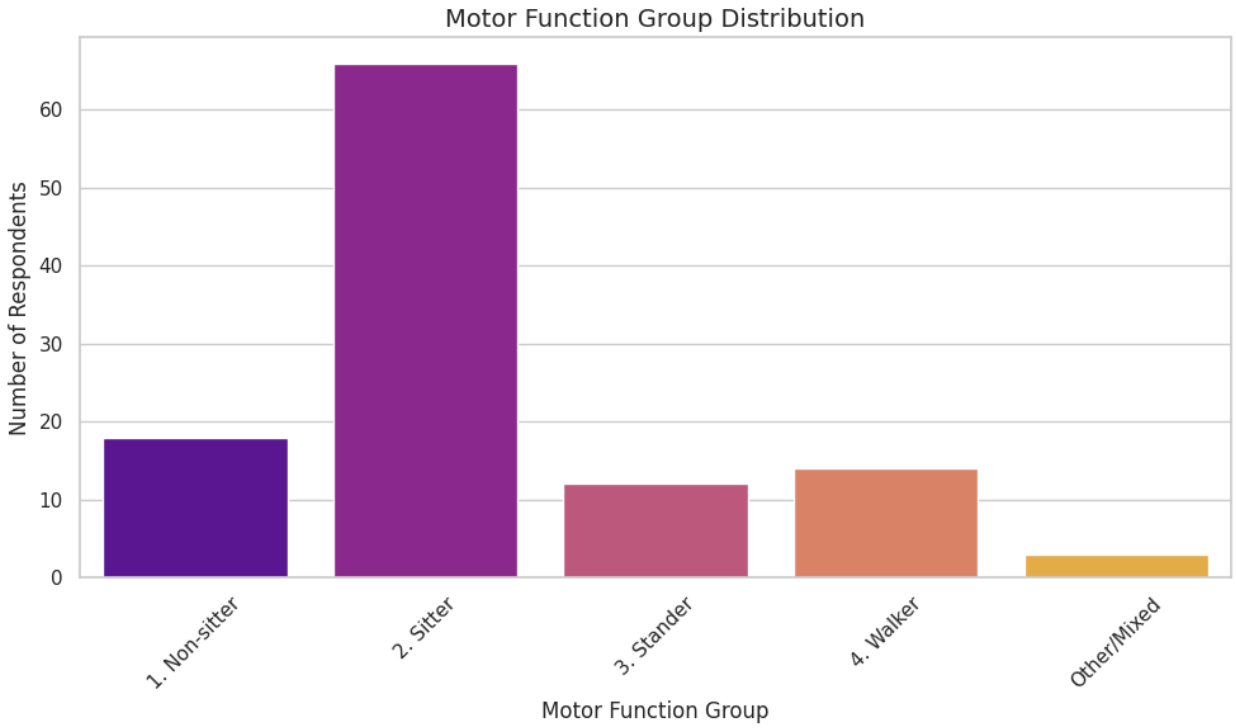
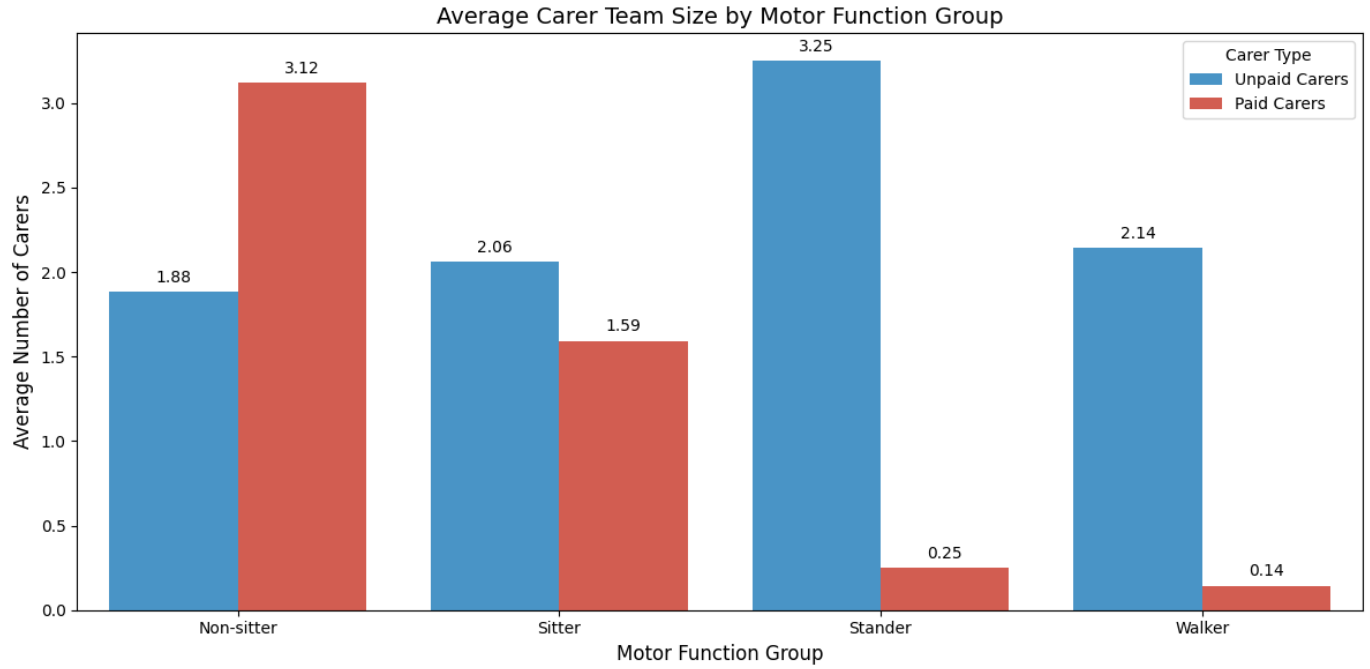


Fig.3

2.0 Number of carers in a support team.

A support team represents a "pool" of people (family, friends, or professionals) who rotate to provide coverage. For individuals requiring high levels of support, a larger team is necessary to manage shifts, prevent burnout, and ensure 24-hour safety. For example, a team of four paid carers does not mean four people are providing care simultaneously; rather, it means four people share the responsibility across different days or night shifts.

Fig.4



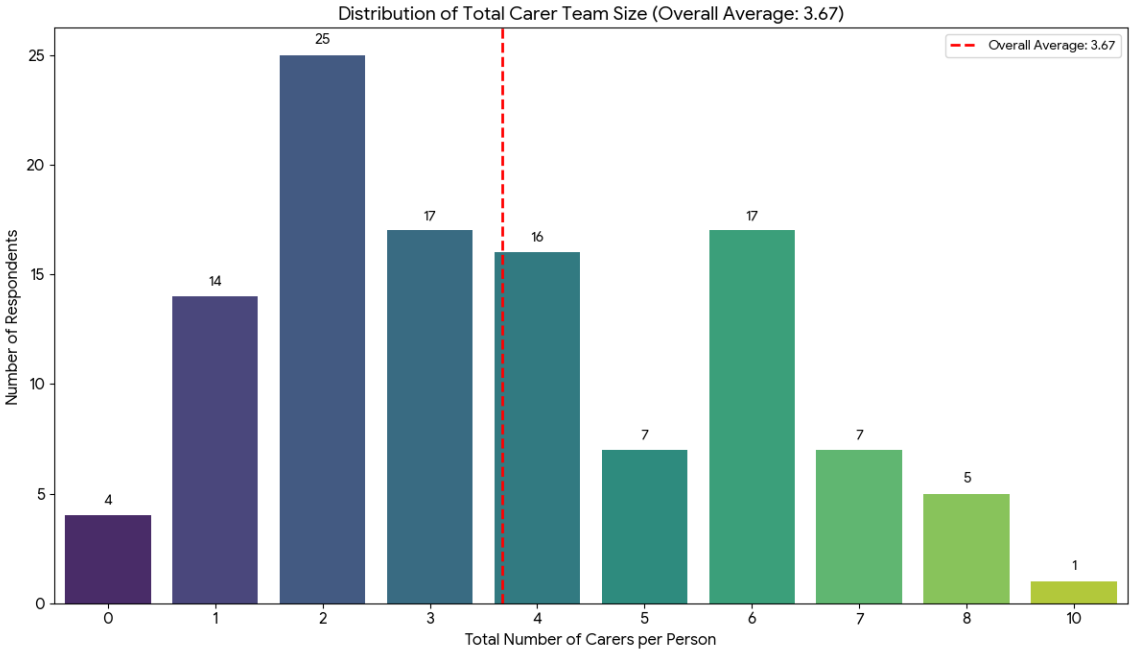


Fig. 5

2.1 Variation within the data set

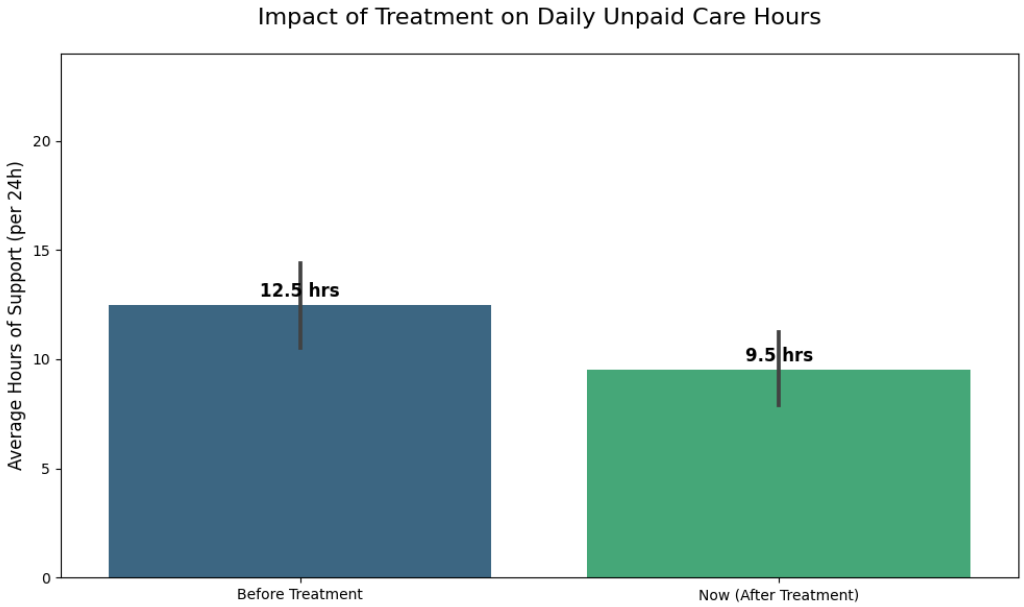
- **Small Teams:** Approximately 16% of respondents (18 people) operate with very minimal support, having either 0 or 1 carer.
- **Large Teams:** There is a significant tail of high-intensity support needs. **30 respondents (26.5%)** manage a complex support structure of **6 or more carers**, with one respondent reporting a team of 10 carers.
- **Average Support:** While the team sizes range from 0 to 10, the "typical" experience falls between 2 and 4 carers, at 3.67 carers per person.

For future cohorts of people living with SMA, newborn screening and early treatment will significantly reduce or eliminate the need for care and support of this nature.

3.0 Impact of treatment on hours of unpaid (family and friends) support received.

The introduction of treatment has led to a measurable reduction in both the physical burden and the emotional strain placed on the families of those living with SMA.

fig.6



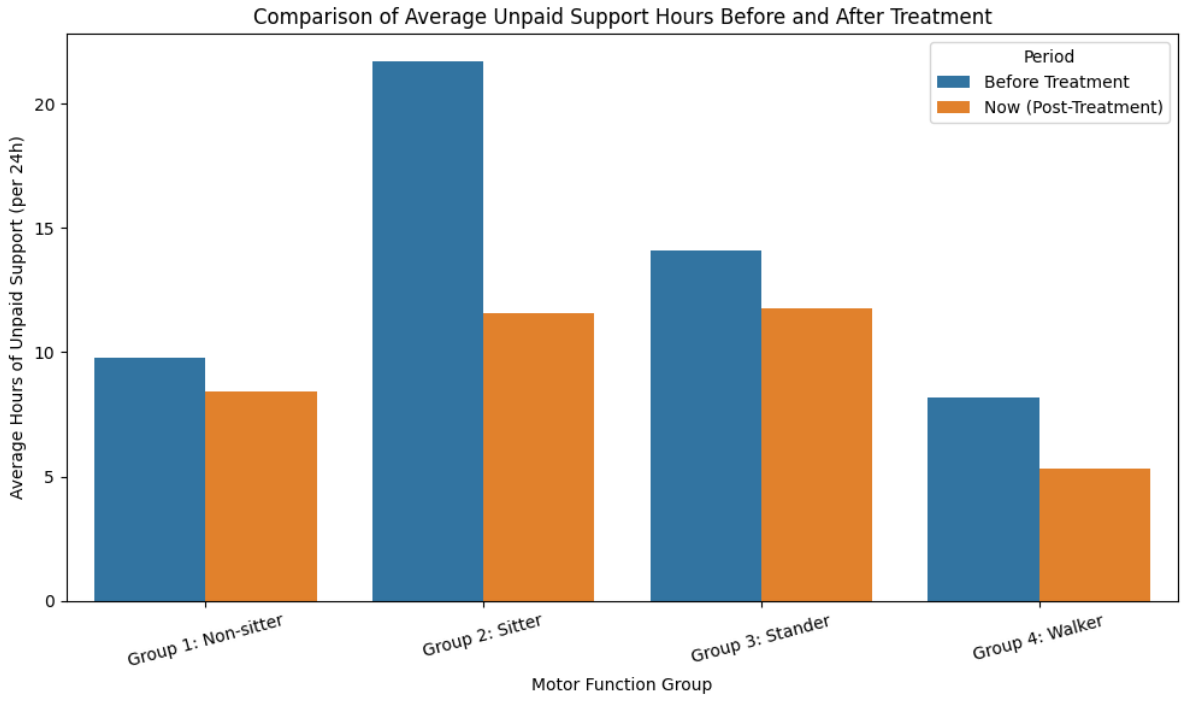


Fig.7

3.1 Reduction in Care Hours

Responses show a significant decrease in the daily hours of unpaid care required after starting treatment:

- **Average Daily Hours:** The average unpaid care support required dropped from **12.6 hours** before treatment to **9.7 hours** now.
- **Overall Reduction:** This represents a **23% reduction** in the care burden, freeing up nearly **3 hours per day** for carers to focus on work, other family members, or their own wellbeing.
- **Shift in High-Need Care:** The number of respondents who reported being "fully reliant" (10/10 on the survey's reliance scale) on unpaid care dropped from **67 to 49**, indicating that treatment is helping patients move toward greater independence.

3.2 Qualitative Impact on Carer Wellbeing and Mental Health.

The open-text responses highlight three primary areas of improvement for carers:

- **Mental Health and Anxiety:** Carers report feeling "less worried" and "more hopeful about the future." One respondent noted that the stability of the patient allows the family to go out "knowing [the person with SMA] feels safe."
- **Sleep and Physical Health:** Improvements in patient stability (especially respiratory) lead to better sleep for carers. One carer noted, *"I sleep better, I feel more hopeful about her future."*
- **Economic Participation:** Several respondents highlighted that the reduction in care needs has allowed carers to **return to work or increase their hours**, directly impacting the family's financial stability. One respondent noted that their carer can now *"do things they like doing" and "work more hours."*

4.0 Impact of treatment on reliance on paid personal assistants (PAs) / carers

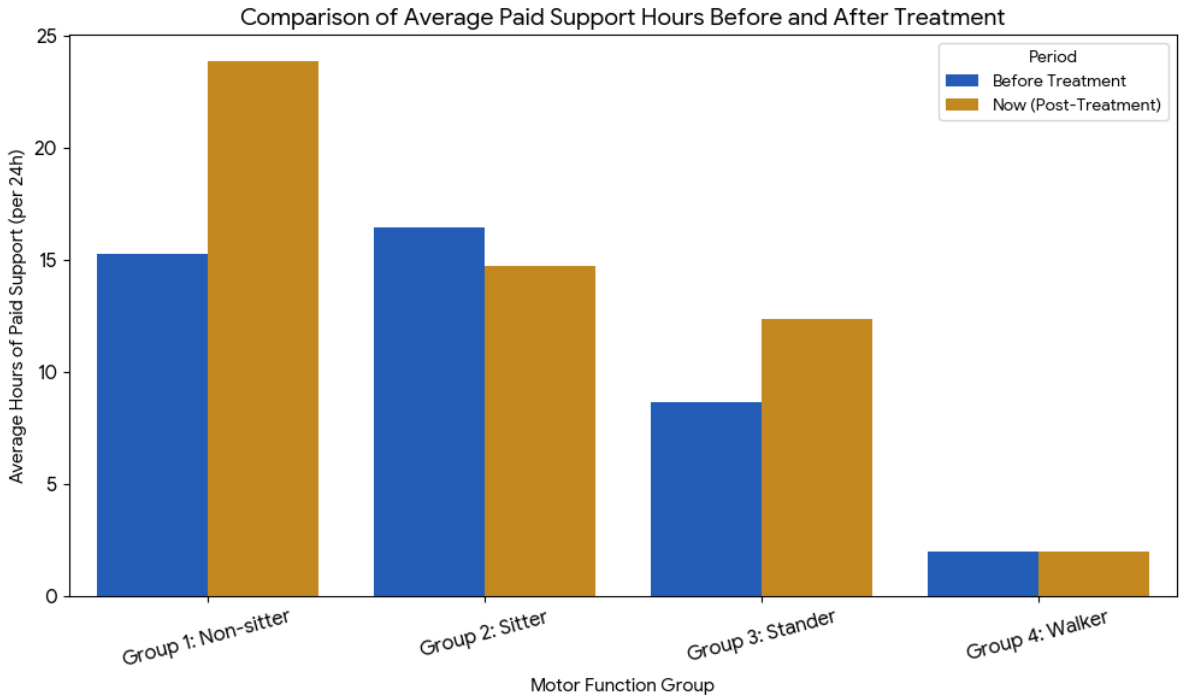


Fig.8

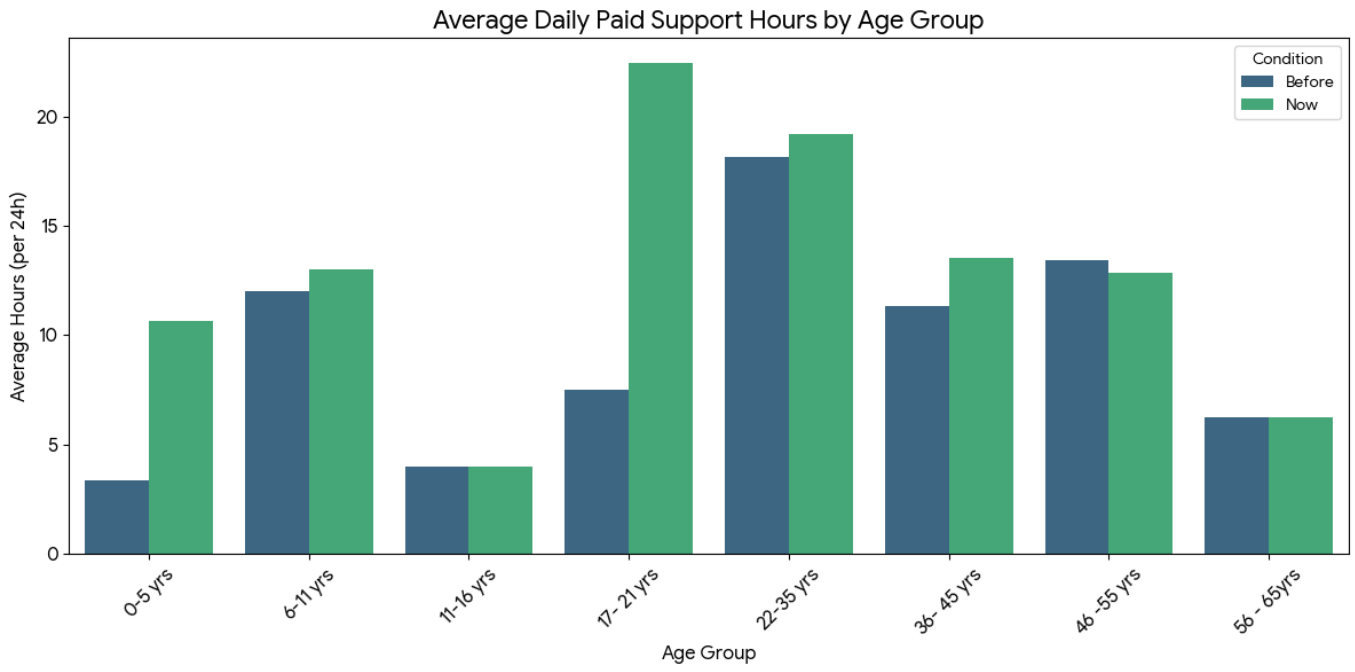


Fig.9

The impact of treatment on paid support reliance varies significantly across age groups, reflecting the changing life stages of individuals with SMA.

4.1 Analysis by Life Stage

Infants and Young Children (0–5 years)

- **Trend:** Significant increase in paid support hours (from an average of **3.3** to **10.7 hours**).
- **Why?** Qualitative feedback indicates that many of these children were "too young" for formal social care before treatment. As treatment has allowed them to survive and reach school age, families are now accessing paid support to enable their children to attend nursery or to provide parents with necessary respite. Early diagnosis and treatment through newborn screening has been proven to significantly reduce this trend.

Transition to Adulthood (17–21 years)

- **Trend:** The most dramatic increase in paid support (from **7.5** to **22.5 hours**).
- **Why?** This reflects a major "success" of treatment. As young adults gain clinical stability, they are moving into higher education or independent living. The surge in paid hours is not due to a health decline, but rather a **shift from family-provided care (unpaid) to professional PA support** to facilitate further education or work attendance and personal autonomy.

Established Adults (22–45 years)

- **Trend:** Slight increase or stability in hours.

- **Why?** For adults, treatment is primarily about **stabilisation**. While the number of hours remains high (average **13–19 hours**), the quality of that time changes. Respondents in this age bracket noted that they are now "more independent" and can use their PAs to help with university, workplace tasks or cooking, rather than just basic physical care.

Older Adults (46–65 years)

- **Trend:** Stability or slight decrease in paid hours.
- **Why?** This group represents long-term survivors for whom treatment has provided the stability to maintain their current living arrangements and prevent the need for more intensive institutional care.

5.0 Impact of Treatment on Functional Groups

5.1 Motor Function Groups

These categories describe the individual's maximum physical mobility and core strength:

Functional group	Definition
1.Non-sitter	unable to sit or roll independently
2.Sitter	able to sit with support but not stand
3.Stander	able to sit and stand but not walk independently
4.Walker	able to walk with or without equipment

Treatments have demonstrated a profound impact on motor function, with the majority of respondents experiencing either a clinical group improvement or significant functional gains within their existing group.

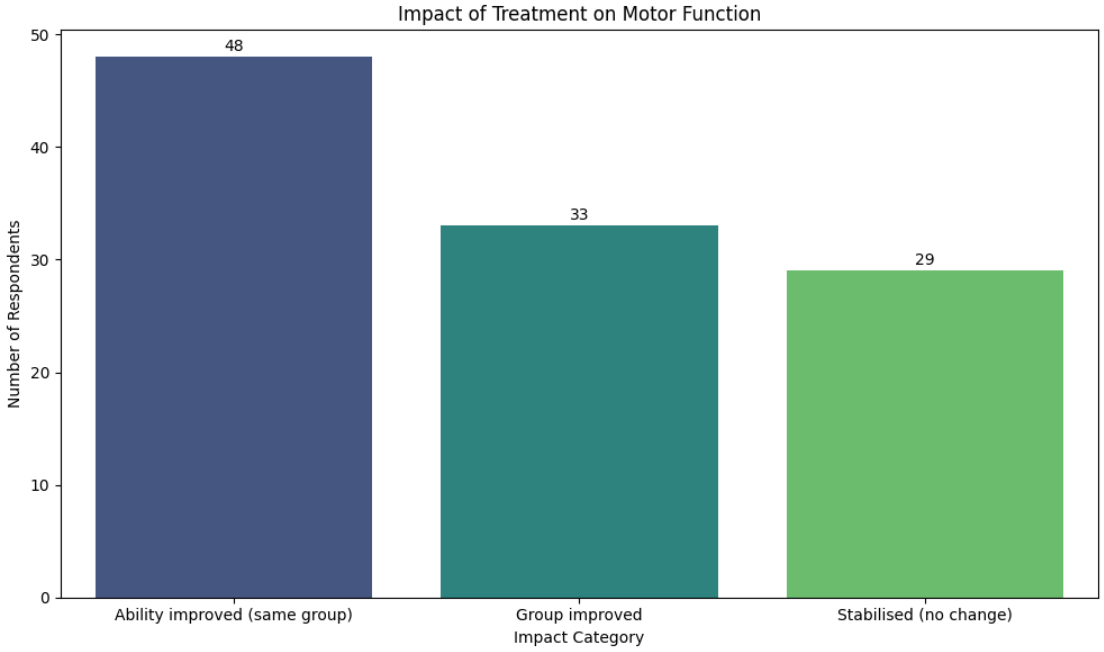


Fig.10

5.2 Qualitative insights

30% of respondents to these questions did not move to a higher functional group but have experienced improvements within the same functional group.

Themes were captured from each functional group within the free text responses:

Group 1: Non-Sitters (Unable to sit or roll independently)

For those in the most restricted motor group, improvements are often focused on fine motor skills, head control, and energy levels.

- **Fine Motor Control:** Increased ability to move forearms and fingers, allowing for tasks like feeding oneself, using a pen at school for longer periods, and drawing on an iPad.
- **Core & Neck Stability:** Some reported gaining the ability to sit up for short periods without support or having a "stronger neck" to hold their head up for longer.
- **Physical Stamina:** Significant increases in "physical energy," which allows for more productivity throughout the day.
- **Milestones:** One respondent noted they could now "lift my legs to play with my toes" and "roll over" since starting treatment.

Group 2: Sitters (Able to sit with support but not stand)

In this group, the primary benefits are related to increased core stability and the maintenance of current abilities (prevention of deterioration).

- **Core Strength:** Improved ability to bend down from a wheelchair to pick items up from the floor and return to an upright seated position independently.
- **Upper Body Mobility:** Moving arms faster and for longer periods. Improved grip strength has allowed some to open "twist top lids" and type more efficiently for university degrees or work.
- **Independence in Transit:** Better core and back engagement helps patients stay stable when traveling over "bumpy and cobbled ground," which previously would have "thrown the body from side to side."
- **Fatigue Management:** A noticeable reduction in fatigue, with many Spinraza patients noting they can "feel" the medicine wearing off when they are due for a "top-up."

Group 3: Standers (Able to sit and stand but not walk independently)

This group highlights a transition toward greater weight-bearing activities and significant independence in self-care.

- **Weight Bearing:** Gaining the ability to stand with support or orthotics, and in some cases, standing independently for short durations.
- **Advanced Mobility:** Transitioning from "just sitting unaided" to taking steps in a hydrotherapy pool or using a walker. Some have regained the ability to crawl.
- **Self-Care Independence:** Significant gains in being able to:

- Dress and undress independently.
- Wash their own hair and clean their body.
- Transfer in and out of a wheelchair or onto a commode independently.

- **Range of Motion:** Being able to "reach arms higher" and move the head "faster and more smoothly."

Group 4: Walkers (Able to walk with or without equipment)

For those who can walk, the treatment focus is on endurance, safety, and recovery from surgery.

- **Walking Quality:** Improved balance and the ability to walk further and for longer durations.
- **Safety and Resilience:** Increased stamina and balance allow patients to "save themselves from falling" or "get up from the floor after a fall" independently.
- **Post-Surgical Support:** One respondent noted that the treatment was likely the only reason they were still walking following major spinal surgery.
- **General Capability:** An overall feeling of being "stronger" and able to "push self more" during physical activities.

5.3 Respiratory Function groups

Functional group	Definition
1.Permanently ventilated	Have a tracheostomy
2.Semi-permanently ventilated	Permanently ventilated (for more than 16 hours/day for 21 consecutive days and this is not because of an acute reversible chest infection)
3,Ventilated	Ventilated for less than 16 hrs / day and at night time
4.Nocturnal ventilation	Night time ventilation only
5. Flexible ventilation	Ventilated only when poorly or tired
6.Not ventilated	No ventilation required at any time

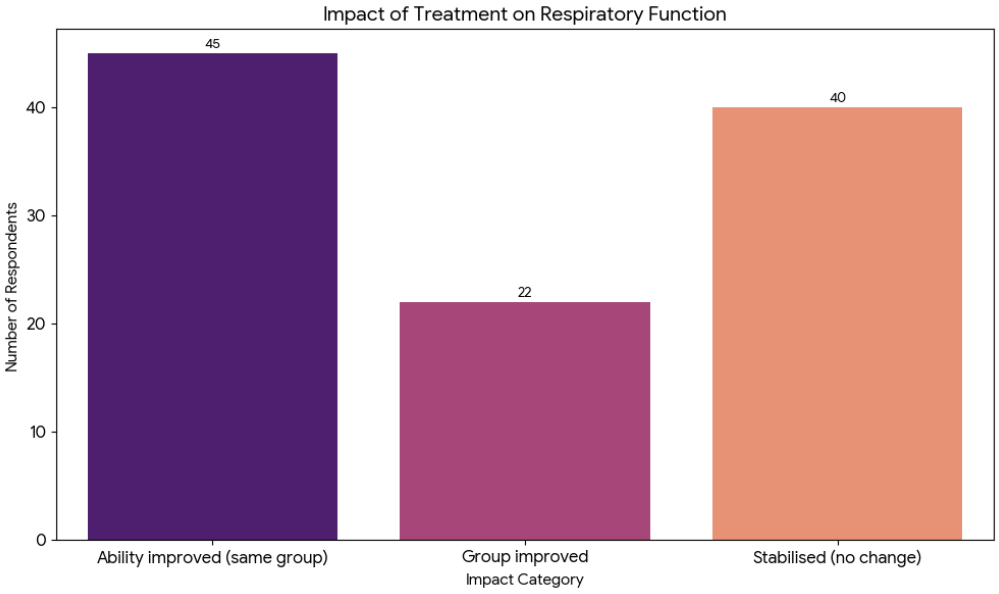


fig. 11

5.4 Qualitative insights

Treatments have had a transformative effect on the respiratory health of participants, with the vast majority experiencing either a formal improvement in their clinical functional group, a noticeable improvement in breathing ability within their current group, or a critical stabilisation of their condition.

1. Ability Improved (Same Group)

This category represents the largest group of respondents at **39.8%.** While these patients remain in the same clinical respiratory category, they report significant "quality of life" breathing improvements:

- **Airway Clearance:** Many reported a "stronger cough," which is vital for preventing the buildup of mucus.
- **Respiratory Volume:** Patients noted "stronger, deeper breaths" and measurable improvements in lung capacity.
- **Health Resilience:** A reduction in susceptibility to chest infections and improved recovery times from common illnesses (like colds) were frequently cited.

2. Group Improved

19.5% of respondents experienced a significant enough change in their respiratory health to move into a better functional group:

- **Life-Changing Stability:** One respondent noted that prior to treatment, they had regular hospital admissions and required intubation; since starting, they have had only one chest infection, describing the change as "nothing short of life-changing."
- **Ease of Breathing:** Patients reported that it has become "easier to breathe unassisted" and that their lungs feel "clearer" and less "chesty."

3. Stabilised (No Change)

For **35.4% of respondents**, their respiratory function remained the same. In the context of a progressive condition like SMA, stabilisation is viewed as a major clinical success:

- **Prevention of Decline:** Participants noted that at their age, "no change is a fantastic result," especially when clinicians had previously told them to expect significant deterioration.
- **Ongoing Protection:** Even those who reported that it "feels the same" often mentioned that they have avoided chest infections and hospital stays that were regular occurrences before the treatment.

6.0 Impact of treatment on Healthcare Resource Use (HCRU)

Treatments have had a significant positive impact on healthcare utilisation, with the majority of respondents reporting either a decrease or stability in their reliance on emergency care, GP visits, and specialist medical equipment.

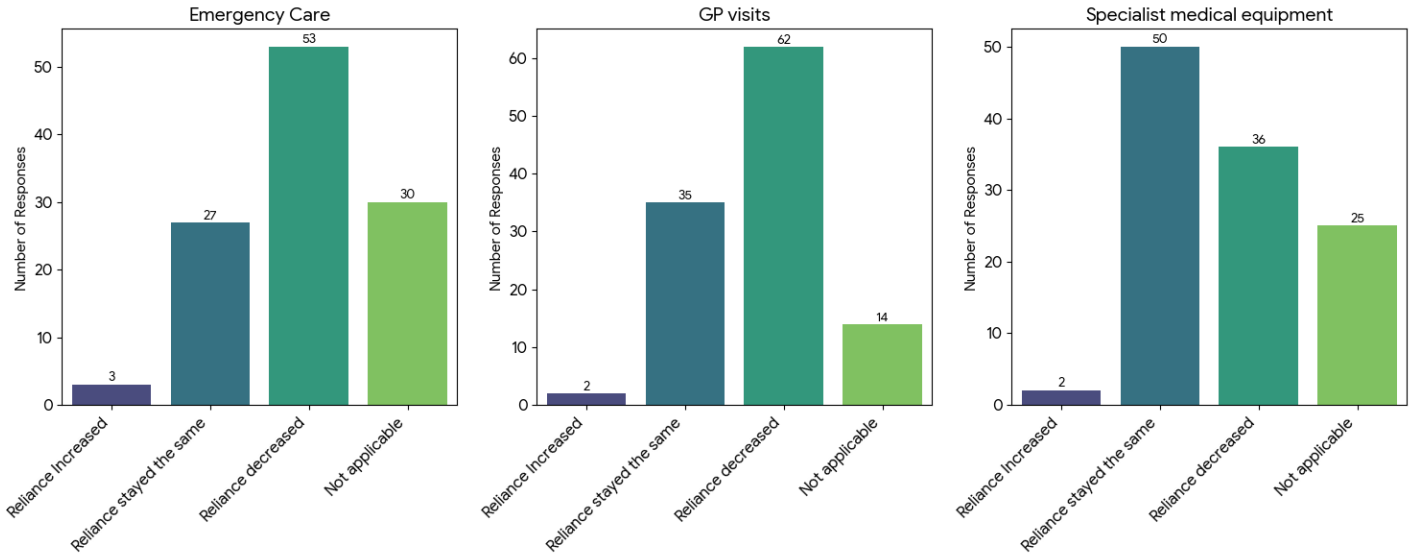


fig.12

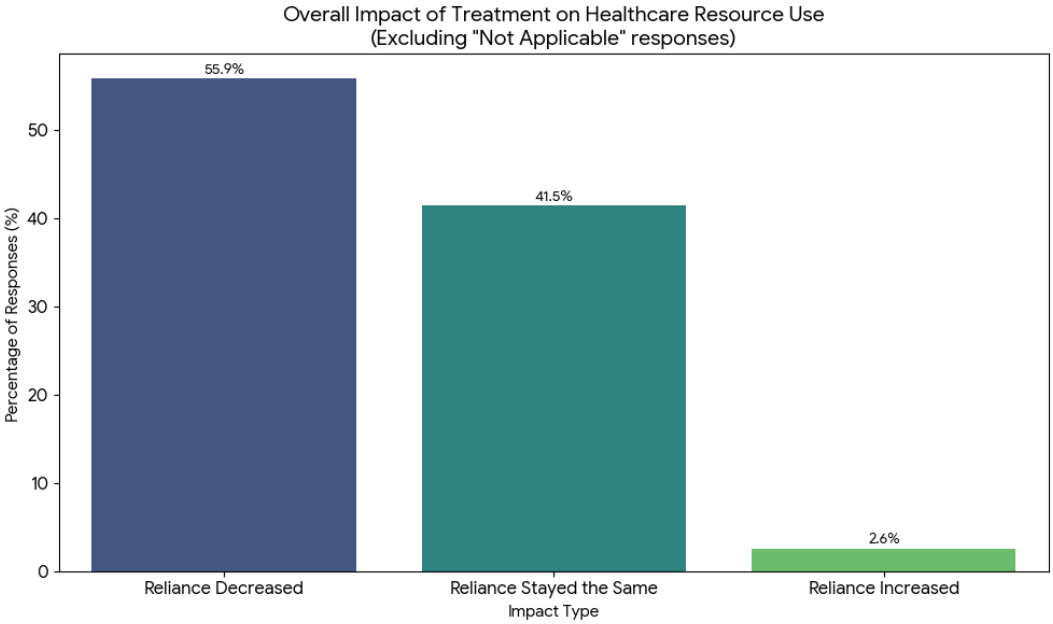


Fig.13

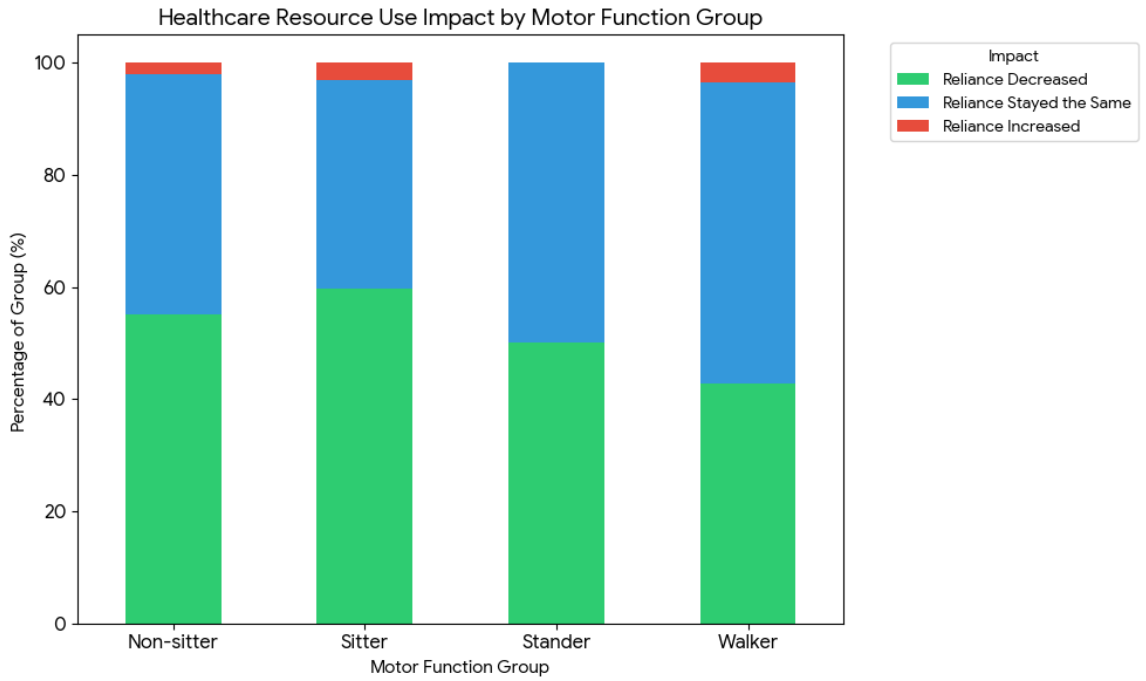


fig.14

The overall impact of treatment on healthcare resource utilisation is overwhelmingly positive, characterised by a significant reduction in the need for acute and routine medical services. Across all tracked metrics, the majority of patients reported that their reliance on the healthcare system has either decreased or stabilised.

Key Findings in Healthcare Resource Use

1. Reduction in Acute and Routine Care

The most significant impact was seen in **GP visits** and **Emergency Care**:

- **GP Visits: 55%** of respondents reported a decrease in reliance on their GP. This suggests that the treatment has improved overall health stability, reducing the frequency of illness-related consultations.
- **Emergency Care: 47%** of respondents saw a decrease in their need for emergency services. This is a critical indicator of reduced crisis events, such as acute respiratory failures or injury-related emergencies.

2. Specialist Equipment & Stabilisation

For **Specialist Medical Equipment** (such as cough assist or suction machines):

- **32%** reported a decreased need, often linked to improved respiratory strength and a "stronger cough."
- **44%** reported that their reliance stayed the same. In a progressive condition like SMA, stabilisation—preventing the need for *more* or more complex equipment—is a significant clinical achievement

6.1 Qualitative insights

Respondents noted that the reduction in resource use directly translates to:

- **Fewer Hospital Admissions:** Many patients highlighted that they have avoided hospital stays for over a year, a marked change from their pre-treatment history.
- **Reduced Caregiver Burden:** As medical needs decrease, the pressure on both paid and unpaid carers to manage medical crises or transport patients to appointments is lessened.
- **Financial Impact:** While the treatment itself is a major cost, the data shows a "trickle-down" saving in secondary healthcare costs, including fewer emergency call-outs and reduced use of consumable medical supplies.

7.0 Impact of treatment on Quality of Life and Wellbeing

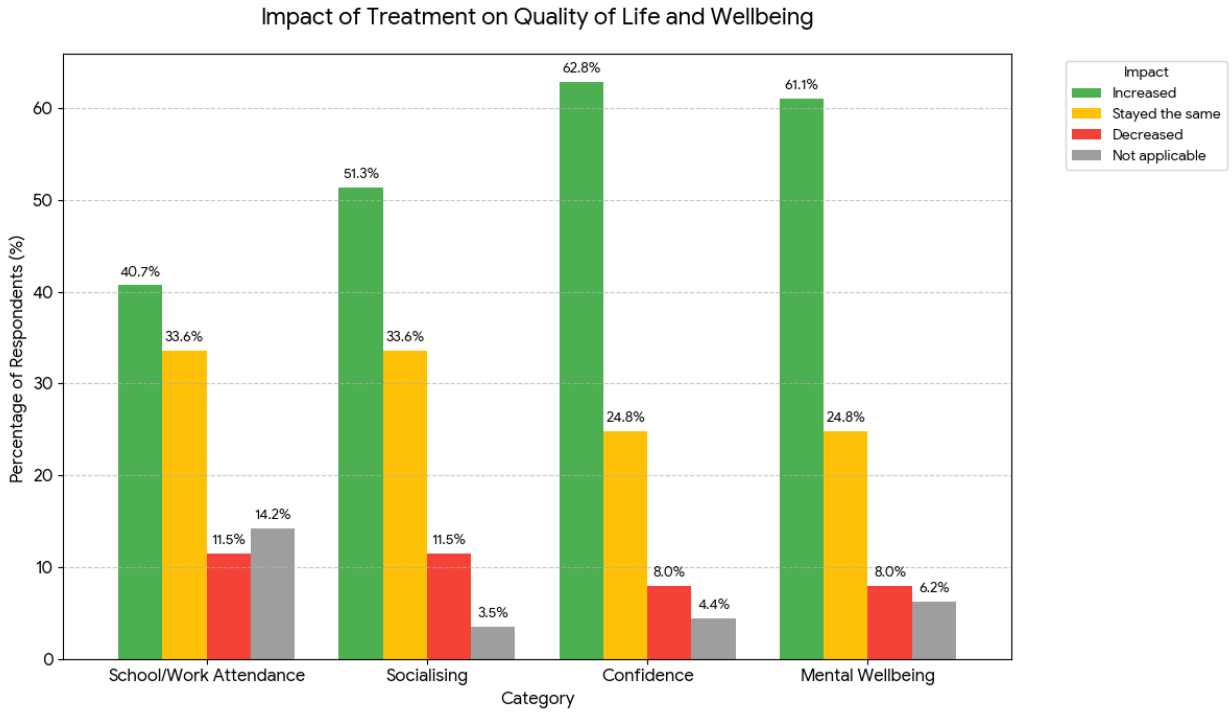


fig. 15

The impact of treatment on the psychosocial wellbeing and daily lives of respondents is overwhelmingly positive. Across all four categories; School/Work attendance, Socialising, Confidence, and Mental Wellbeing. The majority of participants reported significant improvements.

The data suggests that where a "decrease" was reported, it was almost universally linked to the **burden of living with a complex disability** (surgery, care systems, hospital travel) rather than a failure of the disease-modifying therapy to stabilise the condition.

7.1 Qualitative Insights

1. Confidence & Mental Wellbeing

These areas saw the most substantial gains, with greater academic & professional autonomy. For students and working adults, the treatment has reduced the "cognitive load" of managing SMA. Increased stamina means less time spent recovering from the physical toll of a school or work day.

- **Reduced Absence:** *"Attendance has improved as there are fewer hospital stays and less fatigue. He can now focus on his studies rather than just trying to get through the day."*
- **Future Ambition:** *"Without treatment, I would face severe disability and a negative impact on my future prospects. Now, I am well integrated into university and plan for my career with confidence."*
- **Productivity:** *"I can work longer hours at my desk without the back pain and exhaustion I used to feel by midday."*

2. Social Integration & Spontaneity

Socialising was previously a "high-cost activity that required days of planning and recovery. Treatment has made social interaction more accessible and frequent.

- **The "Social Battery":** *"I have more energy for socialising in the evenings. Previously, I was too tired after work to do anything but go to bed."*
- **Inclusion:** *"My child can now attend birthday parties and play dates without me worrying they will be too exhausted to function the next day. They feel like 'one of the kids' now."*
- **Community Engagement:** *"I travel independently across London on my own, confidently managing public transport to meet friends, something I wouldn't have dared before"*

3.The "Psychological Safety" of Stability

A significant number of respondents highlighted that confidence comes not just from new physical gains, but from the removal of the fear of decline.

- **Mental Relief:** *"The constant fear of 'what will I lose next year?' has been replaced by a sense of security. That peace of mind is worth as much as the physical strength."*
- **Self-Image:** *"I feel more confident in my body. I'm not just 'the person with SMA'—I'm a person who can hold a conversation without getting breathless."*
- **Resilience:** *"My mental wellbeing has improved knowing that I have a 'buffer' against common colds that used to lead to pneumonia."*

4. Challenges Beyond Treatment

Those who did not report improvements often pointed to **systemic failures** rather than medical ones.

- **The Care Barrier:** *"My confidence is high because of the drug, but my mental health suffers because I cannot find reliable PAs. The medicine is working, but the care system is broken."*
- **Surgical Interruptions:** *"Post-surgery recovery was hard. It felt like a step back socially, even though the medication kept my lungs strong enough to survive the operation."*

8. Conclusion

In conclusion, the patient reported data confirms that Disease-Modifying Therapies (DMTs) nusinersen (Spinraza) and risdiplam (Evrysdi) have fundamentally altered the clinical trajectory of SMA. By shifting the disease course from one of inevitable decline to a state of stability or functional gain, these treatments deliver a triple-benefit:

- **Clinical Efficacy**: 95% of patients achieved respiratory stability or improvement, and 72% saw meaningful motor function gains. This stability directly prevents the high-intensity medical crises historically associated with SMA.
- **Systemic Resource Savings**: Improved patient health has triggered a significant reduction in healthcare demand, with 55% of patients requiring fewer GP visits and 47% reducing their reliance on emergency care.
- **Socio-Economic Value:** Enhanced physical function has led to a 60%+ increase in confidence and mental wellbeing, greater participation in work and education, and a dramatic reduction in the need for professional paid care teams as patients move toward greater independence.

Ultimately, these therapies transition SMA from a condition requiring constant crisis management to a manageable state that allows for long-term independence, social contribution, and a drastically reduced burden on the healthcare system.