NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Nusinersen for treating Spinal Muscular Atrophy [TA588]

Managed Access Agreement treatment criteria evidence review:

Non-ambulant type III Spinal Muscular Atrophy population

Company evidence submission

December 2020

File name	Version	Contains confidential information	Date
TA588_MAA extension non-ambulant type III SMA	**FINAL**	**No**	**07 December 2020**

Instructions for companies

This is the template for submission of evidence to the National Institute for Health and Care Excellence (NICE) as part of the nusinersen Managed Access Agreement (MAA) treatment criteria review concerning the non-ambulant type III Spinal Muscular Atrophy (SMA) population.

This submission should not be longer than 75 pages, excluding appendices and the pages covered by this template. If it is too long it may not be accepted.

This submission should be a stand-alone document, and not require scrutiny of documents submitted and produced during the original appraisal. Where cross referring is necessary to any evidence or guidance produced during the original appraisal, please use the following format: Document, heading, subheading (page X).

In this template any information that should be provided in an appendix is listed in a box.

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- https://understandingpatientdata.org.uk/sites/default/files/2017-07/Identifiability%20briefing%205%20April.pdf
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1. Full redacted version (AIC/CIC/ DPD shown as [redacted])
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NICE will provide the company with an opportunity to review the final documents for confidentiality marking ahead of the final publication of the evidence review documents on the NICE website.

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Contents

Tables and figures

Abbreviations

6MWT	6-minute walk test
AE	Adverse events
ALS-FRS	Amyotrophic Lateral Sclerosis Functional Rating Scale
ASO	antisense oligonucleotides
BSC	best supportive care
CHOP INTEND	Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders
CMAP	compound muscle action potential
DMT	disease-modifying treatment
EMA	European Medicines Agency
FVC	forced vital capacity
HFMSE	Hammersmith Functional Motor Scale Expanded
HRQoL	health-related quality of life
KAFOs	Knee-Ankle-Foot Orthoses
MAA	Managed Access Agreement
MUNE	Motor Unit Number Estimation
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
PK	pharmacokinetic
QoL	quality of life
RULM	Revised Upper Limb Module
SAE	serious adverse event
SE	standard error
SLR	systematic literature review
SMA	spinal muscular atrophy
SMN	survival motor neuron
SPC	Summary of Product Characteristics
ULM	Upper Limb Module

A.1. Outline of review objectives

A.1.1. Review objectives

To review new evidence demonstrating the comparable clinical effectiveness of nusinersen for treating non-ambulant type III spinal muscular atrophy (SMA) patients compared to the population described by the company as 'later-onset SMA' in the original appraisal (those who were able to sit independently but never had the ability to walk independently).

Subject to the outcome of the evidence review, consider whether the eligibility criteria of the Managed Access Agreement (MAA) should be amended to expand access to type III SMA patients who no longer have independent ambulation.

Background

Spinal muscular atrophy, or SMA, is a rare genetic disorder that causes muscle weakness and progressive loss of movement. It is most commonly caused by defects in the gene *survival motor neuron-1* (*SMN1)*, which leads to degeneration of motor neurones in the spinal cord (this is termed '5q SMA'). The motor neurones most affected by this condition are those that allow walking, crawling, arm movement, head and neck movement, swallowing and breathing. SMA causes substantial disability and may lead to increased mortality and reduced life expectancy. The most severe forms of SMA typically cause death before age two years, although people with later-onset types of SMA usually live into adolescence or adulthood. SMA also has substantial effects on families and carers, including the impact of caring for the patient, the need for specialist equipment and ongoing emotional, financial and social impacts.

SMA is a heterogeneous condition, which is clinically classified and often grouped into four main types, based on the age of onset of symptoms and the impact of the resulting muscle weakness on the person's ability to sit, and walk. The types of SMA decrease in severity from type I, in which symptoms arise before age six months, to type IV (adult-onset). Babies with SMA type I have low muscle tone (hypotonia) and severe muscle weakness which affects movement, swallowing and breathing. In type II SMA, the onset of symptoms is between seven and 18 months of age, and people with this condition are often severely disabled and unable to walk unaided. Type III SMA is a

heterogeneous condition, with a varying degree of muscle weakness appearing between age 18 months and 18 years; people with type III SMA can walk or sit unaided at some point, but many lose mobility over time.

In July 2019 National Institute for Health and Care Excellence (NICE) recommended nusinersen as an option for treating 5q SMA only if:

- people have pre-symptomatic SMA, or SMA types I, II or III and
- the conditions in the MAA are followed.
    - Access to treatment is conditional on a five-year MAA, with data collection to address the significant uncertainties about the clinical benefits of nusinersen.
    - The MAA includes the following eligibility criteria:

    'If gained independent ambulation prior to initiation of therapy must still be independently ambulant, with the exception paediatric patients who have lost independent ambulation in the previous 12 months' (defined as prior to 28 July 2019)

    'Independent ambulation is defined as per the WHO definition: patient takes at least five steps independently in upright position with the back straight. One leg moves forward while the other supports most of the body weight. There is no contact with a person or object'

    - Patients with type III SMA who had lost independent ambulation over 12 months prior to the MAA publication are not eligible to start treatment with nusinersen as part of the MAA.

The NICE health technology appraisal committee was unable to make a recommendation for all patients with type III SMA who had lost the ability to walk because this population was not included in the key clinical trial (CHERISH) used to inform the economic model for those with 'later-onset' SMA. CHERISH recruited 126 patients who developed SMA symptoms between six months and 12 years and who were able to sit independently but never had the ability to walk independently.

Exceptionally for an MAA, following a request from NHS England and NHS Improvement and Biogen arising out of commercial negotiations, an evidence review clause was included in the agreement as follows:

> MAA clause 4.2: *The MAA Oversight Committee will consider any significant new evidence made available by Biogen in relation to the non-ambulant Type III SMA patients that may impact the eligibility criteria of the MAA. This does not commit any stakeholder to making an amendment to the MAA unless justified*.

In line with this clause, NICE will facilitate the Managed Access Oversight Committee (MAOC) to undertake a review of new evidence concerning non-ambulant SMA type III patients, as outlined below and in Appendix A1-A.

The technology

Nusinersen (Spinraza, Biogen) is a 2'-O-methoxyethyl antisense oligonucleotide which stimulates the *SMN-2* gene to increase SMN protein levels. It is administered by intrathecal injection.

Nusinersen has a marketing authorisation in the UK for treating 5q SMA. It has been studied in clinical trials compared with placebo (sham procedure) in infants and children with SMA.

Intervention(s)	Nusinersen
Population(s)	People with type III 5q spinal muscular atrophy who no longer have independent ambulation
Comparators	• Best supportive care • Comparable clinical benefit to those who were able to sit independently but never had the ability to walk independently.
Outcomes	The outcome measures to be considered include: • motor function (including, where applicable, age-appropriate motor milestones and evidence of retention of fine motor skills) • 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 (if available).

Clinical Analysis	An External Assessment Centre will be appointed by NICE to assess the new evidence and address the following questions for presentation to the Managed Access Oversight Committee to support the decision-making process: 1. Is the new evidence of sufficient quality for decision making concerning the existing eligibility criteria with respect to non-ambulant type III SMA patients? 2. Does the new evidence demonstrate a comparable clinical benefit for non-ambulant type III paediatric and adult patients, as with those patients who were able to sit independently but never had the ability to walk independently, compared to best standard of care for all of the following outcomes collectively: o motor function (including, where applicable, age-appropriate motor milestones and evidence of retention of fine motor skills) o respiratory function o complications of spinal muscular atrophy (including, for example, scoliosis and muscle contractures) o need for non-invasive or invasive ventilation o stamina and fatigue o mortality o adverse effects of treatment o health-related quality of life (if available) 3. Does the new evidence provide sufficient new information and demonstrate a comparable clinical benefit for non-ambulant patients to support a recommendation to amend the MAA eligibility criteria to expand access to non-ambulant type III SMA patients?
Economic analysis	No economic analysis will be undertaken
Other considerations	In the event of a final decision to amend the MAA eligibility criteria to expand access to type III SMA patients who no longer have independent ambulation, stakeholders will be asked (during the 7-day stakeholder engagement stage) to consider the impact of this change on the starting and stopping criteria in the MAA and their continued appropriateness.

Appendix A1-A: Nusinersen MAA treatment criteria review process

No.	Step	Detail
1	**Outline of evidence review objectives**	MA team prepares an outline of objectives for the External Assessment Centre (EAC), company and MAOC and set out the scope of the evidence review.
2	**Review initiation: notification of deadline for new evidence submission**	The company and MAOC members are given formal notice of the need to submit data within 28-days to initiate the evidence review process. All new evidence is shared with the company in the first instance.
3	**External evidence review**	The EAC assess the new evidence and deliver recommendations in line with the Outline of Objectives document
4	**Clarification questions and responses**	During the review, the EAC sends any clarification questions to the company. The company have seven days to respond to clarification questions.
5	**Managed Access Oversight Committee (MAOC) review**	The MAOC reviews the recommendations from the external evidence review and indicates whether they support the recommendations of the EAC.
6	**Stakeholder engagement**	The MA Team prepares a brief concerning the outcome of the MAOC review for circulation to the MAOC. The MAOC are invited to submit any comments or requests for clarifications during a 7-day consultation period. Points of clarification are reviewed by the MA Team and updated details are incorporated into the final briefing stage that follows. A further meeting with stakeholders will be held if required.
7	**Final briefing**	MA team produce a brief summarising the evidence submitted and a short statement concerning the outcome for the MAOC for information only, prior to publication.
8	**Final recommendation publication**	The evidence submitted and a short statement concerning the outcome (and an amended, executed MAA, if applicable) are published on the NICE website.

Membership of the MAOC

The MAOC is a group of key stakeholders (including the agreement signatories) convened by the NICE MA team to monitor the progress of the MAA throughout the agreement term. The nusinersen MAOC membership is as follows:

Voting members

- A representative from NHS England (who will also provide updates on behalf of the clinical panel)
- Two paediatric clinical experts in the treatment of children with spinal muscular atrophy

- One clinical expert in the treatment of adults with spinal muscular atrophy
- One physiotherapist involved in the treatment of spinal muscular atrophy
- A representative from SMA UK (patient organisation)
- A representative from Treat SMA (patient organisation)
- A representative from MDUK (patient organisation).

Non-voting members

- NICE Managed Access Associate Director
- NICE Technical Advisor or Analyst
- NICE Senior Manager Evidence Generation and Oversight
- SMA-REACH Clinical/Academic representative
- SMA-REACH (Global) Trial Manager
- A representative from the adult SMA data network
- Two standing representatives from Biogen (company) and 1 substitute representative. **Note:** Biogen representatives will be present for the first part of the MAOC review meeting only (during presentation of the evidence). The MAOC will deliberate and make their decision in private.

Observers/advisors

- NICE Technology Appraisals Committee C Chair (MAOC review meeting chair)
- NICE Technology Appraisals Committee C member
- Representatives from the External Assessment Centre.

A.1.2. Description of the technology being appraised

Table 1. Technology being appraised

UK approved name and brand name	Nusinersen (Spinraza®)
Mechanism of action	Nusinersen is an antisense ASO that increases the level of functional SMN protein by binding to a splice silencing site on intron 7 of the SMN2 pre-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. (Biogen SPC 2020).

	Healthy individuals have two SMN genes, *SMN1* and *SMN2*, located on chromosome 5q. *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 patients with SMA have a loss or mutation of both copies of *SMN1*, but retain at least 1 copy of *SMN2*, which is able to 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* (Arnold et al 2015; Arkblad et al 2009).
Marketing authorisation/CE mark status	Nusinersen has marketing authorisation from the EMA (granted on 30 May 2017) (EMA 2017) for the treatment of 5q SMA (Biogen SPC 2020).
Indications and any restriction(s) as described in the summary of product characteristics (SPC)	The indication in the UK is for the treatment of 5q SMA, as per the marketing authorisation from the EMA (Biogen SPC 2020).
Indications and restrictions as per current MAA	All patients entering the current MAA must fulfil the following entry requirement (this aligns to type I, II, III and pre-symptomatic): • no permanent ventilation/tracheostomy requirement at baseline • intrathecal injection must be technically feasible • must not have spinal fusion surgery following a diagnosis of scoliosis that may prohibit safe administration of nusinersen • must not have severe contractures that prohibit motor milestones • if gained ambulation prior to initiation of therapy must still be independently ambulant, with the exception of paediatric patients who have lost independent ambulation in the previous 12 months, these paediatric patients need to regain ambulation within 12 months in order to still be eligible • must not be a type IV patient • must not be a type 0 SMA patient (NICE 2019).
Method of administration and dosage	Treatment with nusinersen should be initiated 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 four months thereafter. The recommended, licensed dose is 12 mg (5 ml) per administration for the loading dose and the maintenance dose (Biogen SPC 2020). Nusinersen is administered as an intrathecal bolus injection over 1–3 minutes, via lumbar puncture, directly into the CSF (Biogen SPC 2020).
Additional tests or investigations	*Genetic testing* A diagnosis is confirmed through genetic tests which is a quantitative analysis of both *SMN1* and *SMN2* using MLPA, qPCR or NGS, and through physical examination, regardless of treatment choice (Mercuri et al 2018b). *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 (Biogen SPC 2020). *Thrombocytopaenia and coagulation abnormalities*

	Other ASOs which are administrated systemically have caused coagulation abnormalities. Nusinersen is administered intrathecally and not systemically. No adverse events of this type with a confirmed causal link to nusinersen have been observed in the clinical trials or post marketing surveillance. Based on this the marketing authorisation only suggests to perform platelet and coagulation laboratory testing if clinically indicated (Biogen SPC 2020). *Renal toxicity* Renal toxicity has been observed after administration of other systemically administered ASOs, although not with intrathecal nusinersen to date. Based on this the marketing authorisation suggests 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 (Biogen SPC 2020).
Abbreviations: ASO, antisense oligonucleotides; EMA; European Medicines Agency; MAA, managed access agreement; MLPA, multiplex ligation-dependent probe amplification; mRNA, messenger ribonucleic acid; NGS, next-generation sequencing; qPCR, quantitative polymerase chain reaction; SMA, spinal muscular atrophy; SMN, survival motor neuron.	

A.1.3. Overall summary of submission

Burden of SMA

- SMA is a rare, genetic, neuromuscular disease, which is debilitating for all patients and fatal for the worst affected (EMA 2017). The disease affects all systems involving voluntary muscle function, including the musculoskeletal, respiratory and gastrointestinal systems, leading to muscle wasting and weakness (Wang et al 2007).
- Without a disease-modifying treatment, disease progression will persist. Following loss of ambulation, patients continue to experience deterioration of motor function, muscle weakness and the prospective loss of upper limb function and fine motor skills (Mercuri et al 2016; Wang et al. 2007). Additionally, decline in respiratory and bulbar function may occur, increasing the likelihood of respiratory infections and need for ventilation (van der Heul et al 2019; Schroth 2009; Wang et al. 2007).
- The loss of upper limb function drastically impacts an individual's independence and quality of life (QoL); reducing their freedom and aptitude to undertake everyday tasks such as self-transferring in and out of a wheelchair, feeding

themselves, using a toilet independently, and engaging with digital devices (Belter et al 2020; Lamb and Peden 2008).

- Reduced independence necessitates a growing care package that provides round-the-clock professional care, posing a substantial economic burden to affected families and on the health and social care system (Armstrong et al 2016; Qian et al 2015).

Unmet need – non-ambulant type III SMA

- Nusinersen is currently reimbursed under a managed access agreement (MAA) in England, subject to the criteria specified for pre-symptomatic, type I, II and III 5q SMA, but not for non-ambulant adults with type III SMA and paediatric individuals with type III SMA who lost ambulation >12 months prior to treatment initiation (NICE 2019). The lack of access for type III sitters represents inequality compared with type II sitters that access nusinersen despite never having gained the ability to walk.
- In the absence of nusinersen, people with non-ambulant type III SMA do not have access to any disease-modifying treatment and therefore must be managed symptomatically (Kirschner et al 2018) – meaning their disease will continue to progress, gradually eroding their independence and QoL.

Evidence and benefits of nusinersen

- The improvement (vs. the natural history decline) in disease conferred with nusinersen would allow non-ambulant type III patients to continue their daily activities, maintain independence and retain their QoL (Appendix G).
- New evidence on the clinical benefits of nusinersen in non-ambulant adults and children with type III SMA is provided by clinical trials CS2, CS12 and the ongoing long-term follow-up SHINE (CS11) study; as well as two key sources of real-world evidence, an Italian registry (Maggi et al 2020) and an integrated European registries analysis (Biogen data on file - registries non-ambulant type III data 2020).
- Clinically significant improvements in Hammersmith Functional Motor Scale Expanded (HFMSE) score (≥3pt change) were achieved in 58% of people with

non-ambulant type III SMA (n=19), after 14 months of treatment with nusinersen (median 3pt change, p<0.05) (Maggi et al. 2020)

- When comparing the slopes (change in score over time) of the HFMSE and RULM scores (n=[redacted]) pre- vs. post-nusinersen initiation, a statistically significant difference was observed (p=0.002 HMFSE; p=0.019 RULM) (Biogen data on file - registries non-ambulant type III data 2020).
- Nusinersen-treated patients (n=159) showed an improvement in the slope of HFMSE (mean 0.015 ± 0.01 pts/week) and RULM (mean 0.018 ± 0.01 pts/week) scores, whereas untreated patients (best supportive care [BSC] alone, n=9) showed a decline in the slopes of both scores (−0.109 ± 0.02 pts/week [HFMSE] and −0.009 ± 0.02 pts/week [RULM]) (Biogen data on file - registries non-ambulant type III data 2020).
- Nusinersen has already unequivocally demonstrated benefit in SMA non-sitters, sitters and walkers, enabling the achievement of motor milestones beyond those expected based on the known natural history of the disease, as evidenced from clinical trials and observational data, with over 11,000 patients treated globally (by Q3 2020) (Biogen 2020).
- The evidence presented in this submission further confirms the clinical benefit of nusinersen in a broad populatione with non-ambulant type III, with significant increases in HFMSE scores compared with pre-nusinersen treatment and patients that do not receive nusinersen. Additionally, the results presented are comparable to people with SMA who are able to sit independently but never had the ability to walk (type II) (Maggi et al. 2020; Mercuri et al 2018a). Therefore, people with non-ambulant type III should be allowed access to nusinersen with the opportunity to collect further data under the MAA before re-appraisal of nusinersen for the treatment of 5q SMA by the end of July 2024.

A.1.4. Health condition

Previous NICE submission and managed access agreement

Nusinersen has marketing authorisation from the European Medicines Agency (EMA) for the treatment of 5q SMA. It is currently reimbursed in England subject to the criteria specified in the managed access agreement (MAA) for pre-symptomatic, type I, II and III SMA (NICE 2019). According to the MAA criteria, for patients with type III SMA to be eligible for treatment they must be independently ambulant prior to the initiation of nusinersen therapy, with the exception of paediatric patients, who are also eligible if they have lost independent ambulation in the previous 12 months prior to initiating nusinersen (NICE 2019).

Ambulation is defined by the World Health Organization (WHO) as when a patient can take at least five steps independently in an upright position with their back straight, one leg moves forward while the other supports most of the body weight, and there is no contact with another person or object – as reflected in the MAA (NICE 2019).

At the time of appraisal, in 2019, nusinersen was broadly recommended in SMA types I and II based on established evidence of benefit in these patient populations (NICE 2019). The lack of specific clinical evidence of benefit in non-ambulant adults with type III SMA and paediatric individuals with type III SMA who lost ambulation >12 months prior to treatment initiation (hereafter referred to collectively as people with non-ambulant type III SMA), resulted in these populations being ineligible to receive nusinersen reimbursement. However, no biological rationale was provided to support this decision. The original MAA recognised the potential for supporting evidence to become available with clause 4.2 allowing for a re-review once sufficient evidence was available to support use in these non-reimbursed patient groups (NICE 2019).

People with non-ambulant type III SMA currently have no access to any disease-modifying treatment and represent a population of high unmet need. This submission presents additional clinical evidence demonstrating the benefits of nusinersen in people with non-ambulant type III SMA with the aim being to expand access to this subgroup. As will be presented below, nusinersen provides clinical benefits in the non-ambulant population with type III SMA, which are consistent with the clinical benefits

seen in the non-ambulant ‘later-onset’ SMA (akin to SMA type II) population, in which nusinersen reimbursement is already granted.

Spinal muscular atrophy background

SMA is a rare, genetic, neuromuscular disease, which is debilitating for all patients and fatal for the worst affected (EMA 2017). The disease affects all systems involving voluntary muscle function, including the musculoskeletal, respiratory and gastrointestinal systems, leading to muscle wasting and weakness (Wang et al. 2007). SMA, which is recognised by the EMA as an orphan disease, is the leading genetic cause of infant mortality (Darras 2015). There are two genes that code for the survival of motor neuron (SMN) protein, *SMN1* and *SMN2.* SMA results when *SMN1* expression is disrupted, either through homozygous mutation of *SMN1* or *SMN1*-to-*SMN2* gene conversion (Feldkotter et al 2002). *SMN2* gene expression only partially compensates for the absence of *SMN1.* In addition to *SMN2* copy number, variables that may impact an individual’s phenotype are sequence variation in the *SMN2* gene, trans-regulatory splicing factors acting on *SMN2*, epigenetic modifiers acting on *SMN2* and lower expression of plastin 3 ubiquitin (Wirth et al 2013 ; Prior et al 2000). Over time, this leads to progressive loss of motor function and respiratory decline, due to denervation of muscles (Szabo et al 2020; Arnold et al. 2015).

Despite the monogenetic cause of SMA, the disease presents as a continuum of severity. For the purpose of prognostication and research clarity, SMA has traditionally been divided into five subtypes (0–IV) (Table 2) (Farrar et al 2017; Wadman 2017; Butchbach 2016). However, due to the wide spectrum of disease phenotypes, there is considerable overlap between types: a ‘mild’ type II has the same experience of the disease as a ‘severe’ type III. Regardless of SMA type, the natural deterioration of motor function and muscle weakness is consistent across all individuals, with disease progression continuing over a patient’s lifetime (Wadman 2017). This is illustrated in Figure 1, as people with SMA type IIIa in their third and fourth decade have similar low upper limb muscle strength and HFMSE scores to people with SMA type IIb.

Table 2. The classification and spectrum of characteristics associated with spinal muscular atrophy

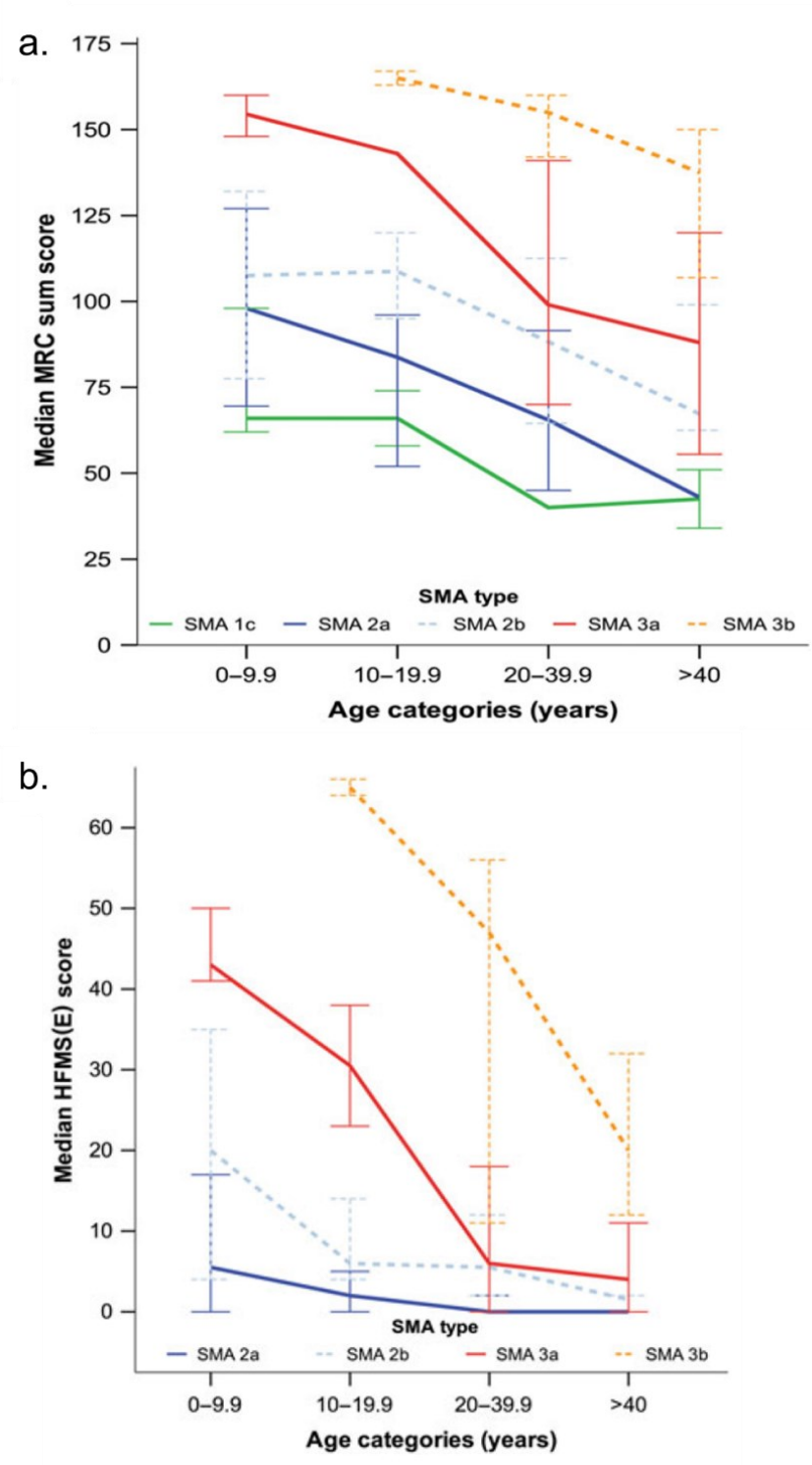
Age of onset	Maximal motor milestone	Motor ability and additional features	Type
Before birth	None	Severe hypotonia; unable to sit and roll [a]	SMA 0
<6 months	None	Severe hypotonia; unable to sit and roll [b]	SMA I
6–18 months	Sitting	Proximal weakness: unable to walk independently [c]	SMA II
>18 months	Walking	May lose ability to walk [d]	SMA III
>18 years	Normal	Mild motor impairment	SMA IV

Abbreviations: SMA, spinal muscular atrophy; SMN2, survival of motor neuron 2.

Notes: [a] Need for respiratory support at birth; contractures at birth, reduced foetal movements. [b] Ia joint contractures present at birth; Ic may achieve head control. [c] IIa: able to sit unsupported, no ability to stand or walk with help; IIb: able to sit unsupported and in addition, the ability to stand or walk with help. [d] IIIa: onset at 18−36 months, able to walk independently; type IIIb: onset at >36 months, able to walk independently.

Source: (Hassan et al 2020; Farrar et al. 2017)

Figure 1. Muscle weakness in relation to age in SMA types Ic–IIIb. (a) MRC scores for total upper limb strength. (b) HFMSE scores



Abbreviations: MRC, Medical Research Council; HFMSE, Hammersmith Functional Motor Scale Expanded; SMA, spinal muscular atrophy.
Source: (Wadman et al 2018)

Consequently, the international community is now moving away from categorising patients by maximum function gained, towards categorising patients by their current

gross motor function; when categorised as such, patients are either non-sitters, sitters or walkers (Mercuri et al. 2018b). This classification is also used in rehabilitation assessment (Table 3) and clinical management. As type III patients who have lost ambulation share many aspects with type II patients, the two groups are collectively indicated as 'sitters' (Mercuri et al. 2018b). The appeal of this categorisation is due to an individual's gross motor function often being associated with global muscular dysfunction levels, such as those related to respiratory and bulbar function (Trucco et al 2020; Mercuri et al. 2018b).

Table 3. SMA classification based on current gross motor function

	Non-sitters	Sitters	Walkers
Definition	Patients that are unable to sit without aid	Patients that are able to sit independently but not walk independently	Independently ambulant patients
Rehabilitation goals	To optimise function, minimise impairment, and optimise tolerance to various positions	To prevent contractures and scoliosis. To maintain, restore or promote function and mobility	To maintain, restore or promote function, mobility, and adequate joint range, and improve balance and endurance
Motor function scales	CHOP INTEND, HINE	HFMSE (RHS), RULM, MFM, EK2	HFMSE (RHS), RULM, 6MWT, EK2

Abbreviations: 6MWT, 6-Minute Walk Test; CHOP INTEND, The Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders; EK2, Egen Klassifikation Scale; HFMSE, Hammersmith Functional Motor Scale Expanded; HINE, Hammersmith Infant Neurological Examination; MFM, Motor Function Measure; RHS, Revised Hammersmith Scale; RULM, Revised Upper Limb Module
Source: (Mercuri et al. 2018b; Wang et al. 2007)

Non-ambulant type III SMA

Natural disease progression

In general, muscle deterioration starts in the lower limbs, followed by progressive decline of strength in the upper limbs. Type III SMA is characterised by reaching the ability to walk independently; however, as the disease progresses – and typically by the age of five years – onset of muscle strength deterioration starts to cause both gait impairments and fatigue (Mercuri et al. 2016; Darras 2015). On average by the age of 12 years, patients start to lose the ability to walk without support and by the age of 15 years they typically lose the ability to walk altogether (Wadman et al. 2018). This loss of ambulation has a drastic impact on independence and QoL.

'when I started my undergraduate degree in [redacted], I didn't use a wheelchair at all and could live independently. By the time I finished my Masters in [redacted] I was heavily reliant on a wheelchair and am now sourcing an electric wheelchair to use in conjunction with a wheelchair accessible vehicle as, whilst I can still walk several steps unaided, I am unable to go out without assistance to get me to and from the wheelchair to my current car. My dad currently has to take me to and from work each day' **Person A with type III SMA (Appendix G)**

Patients with the most severe form of type III SMA, type IIIa, can lose the ability to stand with support by the age of 15 years, and even lose the ability to sit without support (at 25 years of age, on average) (Table 4) (Wadman et al. 2018). These motor milestone achievements vary between individuals with type III SMA on a spectrum so wide that functional abilities and respiratory patterns of individuals with a less severe form (IIIa) closely resemble type II individuals (Finkel et al 2015; Sansone et al 2015). This is reinforced by the experience of patients:

'I am so close to being able to be eligible [for nusinersen] as I needed aids all my life to help me walk and [I am] now more like a type 2 rather than type 3, I can't walk since eight years.' **Person B with type III SMA, [redacted] (Appendix G).**

Table 4. Loss of motor skills in SMA type II and III (natural history study)

	Type IIa (n = 44)	**Type IIb (n = 36)**	**Type IIIa (n = 40)**	**Type IIIb (n = 36)**
Sit without support (n, %)	16 (38)	3 (9)	7 (20)	0 (0)
Age at losing ability to sit, mean (range)	8.7 (0.7-29.1)	16.5 (13-16.5)	25 (15.5-40.5)	NA
Stand with support (n, %)	NA	31 (89)	20 (59)	8 (24)
Age at losing ability to stand with support	NA	6.5 (1.1-46)	15.3 (3.5-49.5)	34.3 (6.5-60.5)
Walk with support (n, %)	NA	21 (84)	22 (65)	10 (30)
Age at losing ability to walk with support	NA	5.9 (0.8-14)	15 (3.5-45.5)	32.7 (6.5-58.5)
Walk without support (n, %)	NA	NA	23 (68)	16 (47)
Age at losing ability to walk without support	NA	NA	11.8 (2.5-34.5)	34.1 (6.5-65.7)
Abbreviations: NA, not applicable; SMA, spinal muscular atrophy Source: (Wadman et al. 2018)				

In addition to loss of ambulation, continued deterioration of muscle strength can result in the loss of upper limb function and fine motor skills, which are crucial components

of an individual's independence, further reducing QoL. (Janssen et al 2020). This deterioration of upper limb function was determined in a UK study where a statistically ($p<0.05$) and clinically significant decline in RULM score (baseline median score: 30) in the 24 months following loss of ambulation in children with type III SMA was recorded (n=16, mean score change: −3pt [± 3pt]) (Wolfe et al 2020).

'The changes of strength in my arms, has significantly affected my independence in multiple ways and has affected my quality of life much more, than when I stopped walking. I now need assistance with all forms of personal care. Home and social life and my career are all now becoming affected. I am losing my independence.'
Person C with type III SMA, [redacted] (Appendix G).

'Our grandchild [redacted] is losing upper body strength weekly and her only hope of continuing using her arms to write, draw, cake decorate, hold a drink, feed herself, dress, wash etc.is to have treatment, she is well aware of this.' **Grandparent of Person D with type III SMA,[redacted] (Appendix G) January 2020**

As the disease progresses, people with type III SMA also have an increased susceptibility for respiratory disease resulting from impaired mobility and scoliosis. Respiratory susceptibility is found in both type II and type IIIa, highlighting the comparable disease characteristics and unmet need in these non-ambulant 'sitter' populations (Wan et al 2020; NICE 2019). A UK study, in children with non-ambulant type III SMA, showed a statistically ($p<0.05$) and clinically significant decline in percentage forced expiratory volume (FEV%) (baseline median score: 95%) in the 24 months following loss of ambulation (n=23, mean decrease: −17.2% ± 15.3%) (Wolfe et al. 2020).

Respiratory muscle weakness and decreased cough capacity are the main causes of pulmonary complications that result in morbidity and mortality in patients with neuromuscular disorders (Park et al 2010). The occurrence of respiratory muscle weakness during times of illness and after surgery (e.g. for scoliosis), can increase the need for non-invasive ventilation (NIV), airway-secretion mobilisation and clearance techniques (Darras 2015; Schroth 2009; Wang et al. 2007). In addition, those individuals with type III SMA who do not receive disease-modifying treatment are at an increased likelihood of developing jaw, mastication and swallowing problems,

which has extreme consequences on daily activities and living (van der Heul et al. 2019; van Bruggen et al 2016).

'My swallow is even weaker; I cannot drink normal water without choking, I have to drink fizzy water if I don't want to swallow it the wrong way. Chewing is much harder, my jaw burns when I eat and I often have to stop intermittently. I cannot cough at all. All of this and I'm still not eligible!' **Person D with type III SMA [redacted] (Appendix G) October 2020**

Quality of life and economic burden

For patients who have lost ambulation, retention of upper limb function and fine motor skills are crucial. The ability to retain the use of even a single finger is considered to be a meaningful QoL treatment goal for some SMA patients, enabling them to use an electric wheelchair or engage with digital devices (Rouault et al 2017). Without reimbursement of a disease-modifying treatment, the freedom and aptitude to undertake everyday tasks such as self-transfer in and out of a wheelchair, feeding oneself, using a toilet independently, and engaging with digital devices will decline and eventually be lost (Belter et al. 2020; Lamb and Peden 2008). This may have knock-on effects on their ability to work/study, leading to reduced hours or even the loss of employment entirely, with lifelong impacts on health-related quality of life (HRQoL). Individuals experience considerable anxiety regarding their declining functional state.

'As I have progressed my anxiety/panic attacks have become more, in the time since nusinersen has been approved by NICE, I have lost the ability to transfer by myself from my wheelchair/toilet/bed and car! I am fast losing the ability to do any weight bearing at all. This has caused me extreme anxiety; I'm losing any independence that could have been saved.' **Person E with type III SMA, [redacted] not on nusinersen (Appendix G) January 2020**

'Despite now needing to use an electric wheelchair, I have continued to live independently and work professionally through this time. The changes of strength in my arms, has significantly affected my independence in multiple ways and has affected my quality of life much more, than when I stopped walking. I now need assistance with all forms of personal care, I cannot transfer from my wheelchair, open doors, lift items, such as a cup of drink and a knife and fork. Home and social life and my career are all now becoming affected. I am losing my independence. Costs for personal assistance have multiplied massively. I am not embarrassed to

say that I am terrified each day by the thought of losing all arm strength and ability.'
Person C with type III SMA, [redacted] (Appendix G)

An ever-increasing demand for care, both in terms of frequency and intensity, accompanies the continued natural deterioration in an individual's condition (Qian et al. 2015). The required care package quickly escalates to round-the-clock professional caregiving, as seen in the 2018 CURE SMA membership survey, where more than two-thirds of people with SMA type III had a paid caregiver that assisted for more than 20 hours per week (Belter et al. 2020). This poses a substantial economic burden to affected individuals and family members providing informal care (a high proportion of working parents of children with SMA have to reduce work hours or even leave their jobs), leading to financial strain and further impact on their HRQoL (Klug et al 2016), and on wider society (Qian et al. 2015).

The unrelenting disease progression also presents an economic burden to the healthcare system, with an increased demand for healthcare resources such as inpatient and intensive care stays, outpatient visits, rehabilitation and physiotherapy, psychological support, and durable medical equipment (Armstrong et al. 2016). The overall societal and economic burden will only continue to increase in the absence of reimbursement for disease-modifying treatment in people with non-ambulant type III SMA (Armstrong et al. 2016; Klug et al. 2016).

The lack of a disease-modifying treatment

Without disease-modifying treatment, people with non-ambulant type III SMA must be managed symptomatically. This means that the underlying processes of disease progression at the cellular level are not tackled, resulting in further motor neurone deterioration and the eventual and devastating loss of other muscle function, such as that of the upper limb. Access to symptomatic management strategies are variable and dependent on patient functional status and on the geographic variation in access to multidisciplinary teams within specialist centres (Kirschner 2018). The international community agrees that patients with type III SMA who can sit but not walk have similar medical needs to patients with type II and should receive similar holistic medical care irrespective of the age at which their symptoms started, or the maximal function previously gained (Mercuri et al. 2016; Finkel et al. 2015) – highlighting the unmet

need for the non-ambulant type III SMA population and inequality compared with the type II population who do have access to nusinersen.

'At age 21, [redacted] I lost the ability to walk completely, had I had access to [nusinersen], I very much doubt I would have lost that ability & would have been able to maintain some strength in my legs to be able to transfer independently. I now, at the [redacted], have to rely on a carer (my mum) to hoist me to & from, my bed, wheelchair & commode (I can no longer use the toilet independently). Why am I, like other type 3 non ambulant people, being left to become as weak, if not weaker, than those who are in receipt of treatment. It is devastating to me & my family. There is a hospital providing [nusinersen] a five miles away from me but because I can no longer take five steps, I am denied treatment & being left to face an uncertain life, in which I will continue to deteriorate & become weaker.' **Person F with type III SMA, [redacted] (Appendix G)**

Clinical stabilisation, enabling the maintenance of residual function, is considered by patients as therapeutic progress: In 2019, 96.7% of 1,327 validated responses to Europe's SMA Community survey stated they would 'consider it to be progress if there was a drug to stabilise their current clinical state' (Appendix G). Patients express how this would provide them with hope for an independent future.

I am getting weaker and want to have treatment to maintain what strength I have left and for an independent future.' **Person G with type III SMA, [redacted] (Appendix G) January 2020**

'I'm not looking for major improvements, just a sense of stability so I can carry out my future how I want to live it. My arms are already getting weaker and weaker and so is my breathing and my swallow. It's said there isn't enough benefit to me having the treatment as I wouldn't regain or maintain the ability to walk. But that's not what's important to me! I just want to be able to not choke on my packet of crisps and to be able to lift my cup of tea to my mouth!!!' **Person H with type III SMA, [redacted] (Appendix G)**

Equality considerations

The therapeutic indication of nusinersen includes the entire spectrum of patients with 5q SMA. This is based on the broad efficacy and safety of nusinersen shown across different populations, the common underlying pathophysiology of SMA across phenotypes, and its established mechanism of action that is relevant to all types of SMA (EMA 2017). Therefore, in addition to type I, II and ambulant type III, reimbursed

access to treatment should evidently include non-ambulant type III as well. This ineligibility to access in England is not consistent with technology assessments in other countries (NICE 2019; SMC 2018). Countries such as Scotland do not limit access to therapy on the arbitrary status of walking, and do not include stopping rules that apply solely to patients with type III SMA, such as the requirement to re-gain ambulation within 12 months of treatment initiation. Individuals with type II SMA who are also unable to walk are not restricted to reimbursement with this criteria (NICE 2019; SMC 2018).

In addition, type III SMA patients who are ambulant and thus exhibit a less severe phenotype of SMA than those who are non-ambulant have access to nusinersen, highlighting that this inequity in access discriminates on the basis of disability. This is due to the decision-making process basing the evaluation of treatment benefit on an individual's maximal motor milestones previously achieved and not on current need and the potential benefit of nusinersen on future outcomes.

'[Nusinersen's] benefits have been measured through tests of leg strength which just isn't what is important in daily practical life. I would still use a wheelchair even if I could walk a few paces.' **Person H with type III SMA, [redacted] (Appendix G) January 2020**

This inequality is demonstrated in a real-world example in Appendix H. Case studies (of two siblings) are presented, where one sibling is receiving nusinersen and the other is not. Both children have the same number of *SMN2* copies (3) and exhibit disease progression; however, one of the siblings is not currently eligible for treatment due to being older and therefore further along the disease progression continuum. The difference in eligibility of treatment for siblings is deeply unfair as one child has experienced disease stabilisation whereas the other is progressing. Effects on the individual child (and family) who are 'unable' to start treatment given current limitations is significant and damaging.

Given the lack of disease-modifying treatments and the evidence showing that all SMA types have the potential to benefit from nusinersen treatment, it is important that all patients are given an equal opportunity to stabilise their disease, irrespective of their age, current level of disability or geography.

A.2. Clinical effectiveness

Summary of evidence in the non-ambulant type III SMA population

- New evidence on the clinical benefits of nusinersen in non-ambulant adults and children with type III SMA is provided by clinical trials CS2, CS12 and the ongoing long-term follow-up SHINE (CS11) study; as well as two key sources of real-world evidence, an Italian registry (Maggi et al. 2020) and an integrated European registry analysis (Biogen data on file - registries non-ambulant type III data 2020).
- Nusinersen was generally well tolerated across all newly identified studies, with laboratory safety tests being unremarkable. No new types of adverse events (AEs) were identified and Biogen's assessment of nusinersen's benefit-risk profile has not changed (Biogen SPC 2020).
- A decline in motor function is a key feature of the documented natural history of SMA. A 3pt decline per year in HMFSE score was observed in a real-world setting (registry data – untreated patients) (Biogen data on file - registries non-ambulant type III data 2020). A statistically ($p<0.05$) and clinically significant decline in RULM score (baseline median score: 30) in the 24 months following loss of ambulation (n=16, mean score change: −3pt ± 3pt) was observed in a UK study, in children with non-ambulant type III SMA (Wolfe et al. 2020) – Therefore, disease stabilisation is a clinically meaningful deviation from prognosis and represents therapeutic progress.
- Clinically significant improvements in HFMSE score (≥3pt change) were achieved in 58% of people with non-ambulant type III SMA (n=19), after 14 months of treatment with nusinersen (median 3pt change, $p<0.05$) (Maggi et al. 2020)
- Clinically significant improvements in RULM score (≥2pt change) were achieved in 53% of people with non-ambulant type III SMA (n=19), after 14 months of treatment with nusinersen (median 2pt change, $p<0.05$) (Maggi et al. 2020)

- Overall, up to 79% of people with non-ambulant type III SMA (n=19) showed improvement in function (in HFMSE and/or RULM score) with nusinersen treatment (51%, 60% and 79% at 6, 10 and 14 months, respectively) (Maggi et al. 2020)
- Nusinersen-treated patients (n=159) showed an improvement in the slope of HFMSE (mean 0.015 ± 0.01 pts/week) and RULM (mean 0.018 ± 0.01 pts/week) scores, whereas untreated patients (BSC alone, n=9) showed a decline in the slopes of both scores (−0.109 ± 0.02 pts/week [HFMSE] and −0.009 ± 0.02 pts/week [RULM]) (Biogen data on file - registries non-ambulant type III data 2020).
- When comparing the slopes (change in score over time) of the HFMSE and RULM scores (n=[redacted]) pre- vs post-nusinersen initiation a statistically significant difference was observed (p=0.002 HMFSE; p=0.019 RULM) (Biogen data on file - registries non-ambulant type III data 2020).
- The maximum Upper Limb Module (ULM) score of 18pts was achieved by 100% (n=4) of patients by day 350 (CS12) and maintained until Day 1,530 (last measurement, n=3) in CS11
- Regaining ambulation after nusinersen treatment was achieved in 50% (n=2) of patients during CS12. This reversal in disease progression is never observed without treatment (Darras et al 2019).
- Improvements in muscle strength, upper body strength, and stamina have been subjectively reported by treated patients (case series).
- Disappearance of tremors and contractures have been reported in case studies of patients after initiating nusinersen.
- Disease stabilisation is observed in both the non-ambulant type III and type II populations – improvements and/or stabilisation in HFMSE and RULM scores are observed in both populations (in adults and children), in the clinical trial setting (Biogen data on file - NCT02594124 2018; Mercuri et al. 2018a) as well as in the real-world (Biogen data on file - registries non-ambulant type III data 2020; Maggi et al. 2020), demonstrating the comparable benefits of nusinersen

in non-ambulant patients regardless of type. These results are not unexpected as the natural disease progression without a disease-modifying treatment (DMT) is similar in both populations – highlighting the comparable benefit of nusinersen treatment to both populations in terms of disease stabilisation and QoL.

A.2.1. Identification and selection of relevant studies

Two systematic literature reviews (SLRs) were undertaken, which identified relevant studies from October 2017 onwards. The first SLR identified all studies that presented data on the clinical outcomes of people with non-ambulant type III SMA who were treated with nusinersen. The second SLR focused on identifying studies that presented HRQoL data in the type III SMA population.

See appendix B (clinical SLR) and appendix E (HRQoL SLR) for full details of the process and methods used to identify and select studies.

The objectives of this submission are:

1. Present evidence of the clinical effectiveness of nusinersen in individuals with non-ambulant type III SMA (Sections A2.1–A2.10).
2. Compare evidence of the clinical effectiveness of nusinersen in the non-ambulant type III SMA population with the type II SMA population (those who were able to sit independently but never had the ability to walk independently) (Section 2.11).

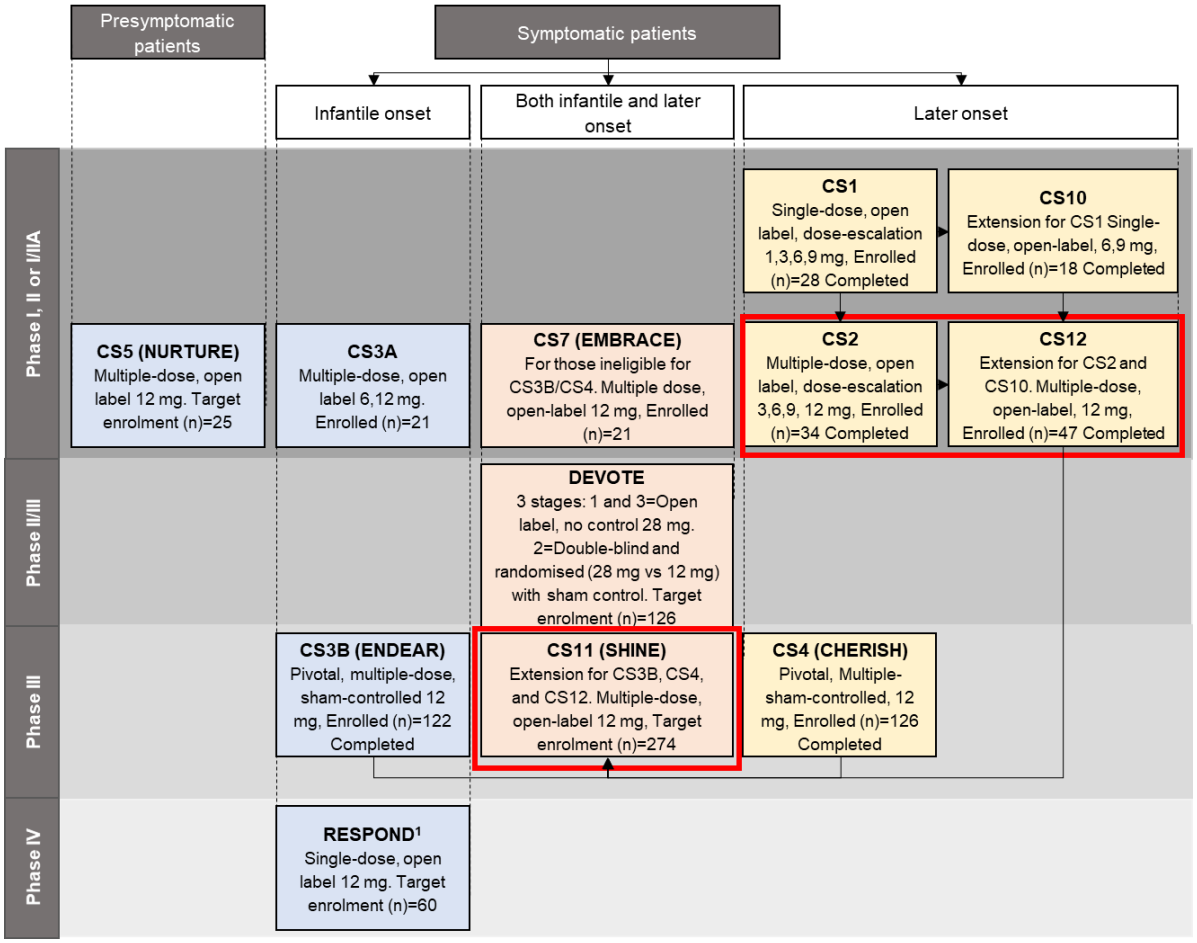
A.2.2. List of relevant clinical effectiveness evidence

Evidence of the clinical benefits of nusinersen in people with non-ambulant type III SMA is provided by the clinical trials CS2 and CS12 (studies in symptomatic later-onset [type II and type III] SMA), and CS11 (a study in symptomatic infantile and later-onset SMA). All three aforementioned studies are part of the wider nusinersen clinical development programme designed to evaluate treatment across a range of SMA phenotypes (Figure 2).

Additional real-world evidence is provided from two key sources, which have become available since the original NICE MAA decision:

1. An Italian registry database study, which included 51 people (adult) with non-ambulant type III SMA and 13 people with type II SMA (Maggi et al. 2020).
2. A European registries analysis (commissioned by Biogen), which enrolled 168 people (paediatric and adult) with non-ambulatory type III SMA, of whom 159 were nusinersen-treated and nine were untreated, from Germany, Italy and Spain (Biogen data on file - registries non-ambulant type III data). Additional supportive data from SMArtCARE were also published (Walter et al 2019).

Figure 2. Overview of the nusinersen clinical development programme (CS2, CS12 and CS11/SHINE) are relevant to support this submission)



Notes: Spinal muscular atrophy type refers to enrolment ages. Infantile onset: symptom onset prior to or equal to six months. Later onset: symptom onset after or equal to seven months. Pre-symptomatic patients are those genetically destined to develop SMA but do not currently have symptoms. [1] RESPOND: the study population consists of patients who have previously been treated with Onasemnogene Abeparvovec-xioi.
Source: (EMA 2017)

The Phase I single-arm extension studies and double-blind Phase III trial include people with non-ambulant type III SMA – relevant to this submission (clinical efficacy):

- Later-onset patients (CS2 and CS12): Extensions of Phase I, open-label, single arm studies CS1 and CS10, respectively, to assess the efficacy and safety of

nusinersen administered intrathecally in symptomatic, later-onset patients (i.e. those who have or are most likely to develop SMA type II or III).

- Infantile and later-onset patients (CS11 [SHINE]): A Phase III, open-label extension study in patients who previously participated in ENDEAR, CHERISH, CS12 or CS3A to assess long-term efficacy and safety of nusinersen administered intrathecally in symptomatic, later-onset patients (i.e. those who have or are most likely to develop SMA type II or III). This is an Ongoing study; data presented in this submission are from a data-cut of 15 October 2018.
- In Section 2.11, comparable clinical benefit is demonstrated for individuals with non-ambulant type III, as with those individuals who were able to sit independently but never had the ability to walk independently (type II), compared to best standard of care; the key evidence for the latter population is derived from both the CHERISH (CS4) study as well as the Italian registry (Maggi et al. 2020).

An overview of the key studies providing evidence for this submission (non-ambulant type III SMA) is shown in Table 5. An overview of relevant supportive evidence for this submission can be found in Table 6.

Table 5. Key studies

Study type	Study name/location	Reference(s)	Clinical effectiveness evidence
Clinical trial	CS2 (NCT01703988) [a]	(Darras et al. 2019), (Deconinck 2019) (case series) [b, c]	Table 7
	CS12 (NCT01494701) [a]	(Darras et al. 2019), (Deconinck 2019) (case series) [b, c]	
	CS11 (NCT02594124) SHINE	(Muntoni et al 2020) (case series) [c]	
European registry data	Data from Italian secondary and tertiary care centres for SMA (adults)	(Maggi et al. 2020)	Table **8**
	Registry data commissioned by Biogen (include patients from Germany [SMArtCARE], Italy [ISMAR] and Spain [CuidAME])	(Biogen data on file - registries non-ambulant type III data ; Walter et al. 2019)	Table 9

Abbreviations: ISMAR, International SMA Consortium Spinal Muscular Atrophy Patient Registry (Italy, UK, US); SMA, spinal muscular atrophy
Notes: [a] One additional study was identified (Kirschner et al. 2018), however, only 3 non-ambulatory patients were mentioned with the note that they all had a ULM score of 18 (max) at all study visits. For this reason Kirschner et al, 2018 is not specifically reported throughout this submission. [b] (Deconinck 2019)(conference proceeding) describes five patients that are included in CS11 (SHINE); however, they do not present any data as part of SHINE. [c] One patient (out of five reported) has non-ambulant type III SMA in both (Deconinck 2019) and (Muntoni et al. 2020) – there is a likelihood that this is the same patient.

Table 6. Supportive studies

Study type	Study name/location	Reference(s)	Section
Retrospective database	Technical University Munich, Germany	(Cordts et al 2020) (n=5)	As these are all case series/studies, no methods have been listed separately. All case series/studies have been summarised in Section 2.6
Prospective database	Hospital data records (Massachusetts General, US)	(Yeo et al 2020) (n=2)	
Case series	Neurorehabilitation Unit, NEMO Clinical Center, Italy	(Barp et al 2020) (n=2)	
	Neurology and Physical Medicine and Rehabilitation, Mayo Clinic, US	(Shah et al 2020) (n=1)	
	Shikoku (131 hospitals)	(Okamoto et al 2020) (n=1)	
	Case series UK clinician (Leeds)	Appendix H	

A summary of the key clinical studies providing evidence on the clinical effectiveness of nusinersen in the non-ambulant type III SMA population is provided in Table 7.

Table 7. Clinical effectiveness evidence: CS2, C12 and CS11

	CS2 (NCT01703988)	CS12 (NCT01494701)	CS11 SHINE
Study design	Phase I/IIa, open-label, multicentre, multiple-dose, dose-escalation study	Phase I, multicentre, open-label, multiple-dose extension study	Open-label extension study (ongoing)
Population	Symptomatic later-onset SMA (Non-ambulant type III SMA: n=4)	Symptomatic later-onset SMA: patients from CS2 and CS10 (Non-ambulant type III SMA: n=5)	Infantile and later-onset SMA from ENDEAR, CHERISH, CS12 and CS3A (non-ambulant type III SMA: n=7)
Intervention	Nusinersen (N=34)	Nusinersen (N=47)	Nusinersen (N=279)
Supported marketing authorisation	Yes: supportive	Yes: supportive	No
Reported outcomes specified in the decision problem	• Motor function (HFMSE, MUNE, ULM, 6MWT) • AEs	• Motor function (HFMSE, MUNE, ULM) • HRQoL • CMAP • AEs	

Abbreviations: 6MWT, 6minute walk test; ACEND, Assessment of Caregiver Experience with Neuromuscular Disease; AE, adverse event; CMAP, compound muscle action potential; HFMSE, Hammersmith Functional Motor Scale Expanded; HRQoL, health-related quality of life; MUNE, Motor Unit Number Estimation; PedsQL, Paediatric Quality of Life Inventory; SMA, spinal muscular atrophy; ULM, Upper Limb Module.

An overview of the key registry studies providing evidence on the clinical effectiveness of nusinersen in the non-ambulant type III SMA population is provided in Table 8 and Table 9.

Table 8. Clinical effectiveness evidence: Italian registry

Study	Italian registry data from secondary and tertiary care centres for SMA
Reference	(Maggi et al. 2020)
Study design	Retrospective
Population	Adults (>18yrs) with ambulant or non-ambulant type III or type II SMA (non-ambulant type III: n=51)
Intervention	Nusinersen (N=116)
Reported outcomes specified in the decision problem	Primary outcomes: HFMSE and RULM Secondary outcomes: Respiratory function tests (FVC% and FEV1%)

Abbreviations: FVC, forced vital capacity; FEV1, forced expiratory volume in 1sec; HFMSE, Hammersmith Functional Motor Scale Expanded; RULM, Revised Upper Limb Module; SMA, spinal muscular atrophy

Table 9. Clinical effectiveness evidence: European registries data

Study	SMArtCARE, ISMAR, CuidAME
Reference	(Biogen data on file - registries non-ambulant type III data 2020); (Walter et al. 2019)
Study design	Observational registry
Population	Children and adults (any age) with either type III or type IV SMA. (non-ambulant type III: n=[redacted])
Intervention/comparator	Nusinersen (N=382)
Reported outcomes specified in the decision problem	• HFMSE • RULM
Abbreviations: ALS-FRS, Amyotrophic Lateral Sclerosis Functional Rating Scale; HFMSE, Hammersmith Functional Motor Scale Expanded; MRC, Medical Research Council; RULM, Revised Upper Limb Module; SMA, spinal muscular atrophy; VC, vital capacity.	

A.2.3. Summary of methodology of relevant clinical effectiveness evidence

Methodology

CS2 (NCT01703988), CS12 (NCT01494701) and CS11 (NCT02594124/SHINE) methodologies are summarised in Table 10.

Table 10. Comparative summary of trial methodology for CS2, CS12 and CS11.

Trial number (acronym)	CS2 (NCT01703988)	CS12 (NCT01494701)	CS11 (NCT02594124/SHINE)
Location	4 US study centres	4 US study centres	14 study centres: US, AU, BE, CA, DE, HK, IT, JP, KR, ES, SE, TR, UK and FR
Trial design	Phase I/IIa, open-label, multicentre, multiple-dose, dose-escalation	Phase I, multicentre, open-label, multiple-dose extension	Open-label extension
Nusinersen treatment (via intrathecal injection)[a]	Four treatment arms, receiving nusinersen on Days 1, 29 and 85: Cohort 1: 3mg Cohort 2: 6mg Cohort 3: 9mg Cohort 4: 12mg followed by enrolment into CS12	Four doses of 12mg nusinersen administered at 6-month intervals on Days 1, 169, 351, and 533	Intrathecal nusinersen injections Maintenance treatment Q4M
Setting	Secondary care	Secondary care	Secondary care
Primary outcomes	AEs SAEs Discontinuations due to AEs Highest severity of AEs	AEs SAEs Neurological examinations Vital signs Physical examinations and weight Clinical laboratory tests (serum chemistry, haematology, urinalysis, and coagulation) CSF laboratory tests (cell count, protein, and glucose) ECGs Use of concomitant medications	AEs SAEs Clinically significant abnormalities: neurological examination vital sign weight laboratory parameters coagulation parameter ECG (12-lead) Concomitant medications (change from baseline)

Trial number (acronym)	CS2 (NCT01703988)	CS12 (NCT01494701)	CS11 (NCT02594124/SHINE)
Secondary outcomes	PK parameters of nusinersen (Cmax, Tmax, AUCinf, CSF drug concentrations, renal clearance [cohort 4 only])	PK parameters of nusinersen in plasma and CSF	Motor milestones attained (WHO, HINE) (%) Time to death or permanent ventilation Not requiring ventilation Change from baseline: CHOP-INTEND, HFMSE, RULM, 6MWT, CMAP, body measurements (length/height, head, chest and arm circumference), Cobb-angle (X-ray), QoL CMAP responders (%) Achievement standing alone or walking with assistance Serious respiratory events Hospitalisations (and duration) Disease-related AEs and hospitalisations OS

Abbreviations: 6MWT, 6-minute walk test; AE, adverse event; AUCinf, area under the plasma concentrations time curve from the time of the intrathecal dose to the last collected sample; CHOP-INTEND, Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders; CMAP, compound motor action potentials; Cmax, maximum concentration; CSF, cerebrospinal fluid; ECG, electrocardiogram; HFMSE, Hammersmith Functional Motor Scale Expanded; HINE, Hammersmith Infant Neurological Examination; OS, overall survival; QoL, quality of life; SAE, serious adverse event; Tmax, time to maximum concentration; WHO, World Health Organization.

Notes: [a] Dosing in these clinical trials is different to the marketing authorisation (loading doses on Days 0, 14, 28 and 63. Followed by maintenance dose Q4M. Efficacy assessments conducted during the course of CS2 and CS12 studies included the Hammersmith Functional Motor Scale–Expanded (HFMSE), Upper Limb Module (ULM) test, 6-Minute Walk Test (6MWT), compound muscle action potential (CMAP), and quantitative multipoint incremental motor unit number estimation (MUNE).

Sources: (Biogen data on file - NCT02594124 2018; Biogen data on file - NCT01494701 2017; Biogen data on file - NCT01703988 2015)

CS2 (NCT01703988), CS12 (NCT01494701) and CS11 (NCT02594124/SHINE) eligibility criteria are summarised in Table 11.

Table 11. Eligibility criteria for CS2, CS12 and CS11

Trial	Inclusion criteria	Exclusion criteria
CS2	• 2–15 years of age • Signed informed consent of parent or guardian • Genetic documentation of 5q SMA (homozygous gene deletion or mutation) • Clinical signs attributable to SMA • Able to complete all study procedures, measurements, visits and parent/patient has adequately supportive psychosocial circumstances, in the opinion of the Investigator • Estimated life expectancy >2 years from Screening • Meets age-appropriate institutional criteria for use of anaesthesia/sedation if use is planned for study procedure • For patients of reproductive age: females to have adequate birth control or be abstinent (after negative pregnancy test at Screening) and males be abstinent	• Respiratory insufficiency (invasive or non-invasive ventilation) • Medical necessity for a gastric feeding tube, where the majority of feeds are given by this route • Previous scoliosis surgery that would interfere with the LP injection procedure • Hospitalisation for surgery or pulmonary event within two months of screening or planned during the duration of the study • Presence of an untreated or inadequately treated active infection requiring systemic antiviral or antimicrobial therapy at any time during the screening period • History of brain or spinal cord disease that would interfere with 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 ISIS 396443 in clinical study ISIS 396443-CS1 Cohorts 2, 3, or 4 • Dosing with ISIS 396443 in clinical study ISIS 396443-CS10 • Clinically significant abnormalities in haematology or clinical chemistry parameters or ECG at the Screening visit • Treatment with investigational drug, biological agent, or device within one month of Screening or five half-lives of study agent, whichever is longer. • Treatment with valproate or hydroxyurea within three months of screening. • Any history of gene therapy or cell transplantation • Ongoing medical condition (e.g. wasting or cachexia, severe anaemia) that would interfere with the conduct and assessments of the study (incl. safety) or would compromise the ability of the participant to undergo study procedures

Trial	Inclusion criteria	Exclusion criteria
CS12	• Signed informed consent of parent or guardian and signed informed consent of participant, if indicated per participant's age and institutional guidelines • Satisfactory completion of dosing and all study visits in Study CS2 or CS10 with an acceptable safety profile, per Investigator judgment • Able to complete all study procedures, measurements, visits and parent/participant has adequately supportive psychosocial circumstances, in the opinion of the investigator • Estimated life expectancy > two years from Screening • Meets age-appropriate institutional criteria for use of anaesthesia/sedation if use is planned for study procedure • For patients of reproductive age: females to have adequate birth control or be abstinent (after negative pregnancy test at Screening) and males be abstinent	• Had any new condition or worsening of existing condition which, in the opinion of the Investigator, would have made the subject unsuitable for enrolment or could have interfered with the subject participating in or completing the study • Dosing in Study CS2 or CS10 within 180 days or longer than 396 days from Screening • Hospitalisation for surgery or pulmonary event within two months of Screening or planned during the study • Presence of an untreated or inadequately treated active infection requiring systemic antiviral or antimicrobial therapy • Clinically significant abnormalities in haematology or clinical chemistry parameters or ECG, as assessed by the Site Investigator, at the Screening Visit that would have rendered the subject unsuitable for inclusion • Treatment with another investigational drug (e.g., valproate, riluzole, carnitine, creatine, sodium phenylbutyrate, hydroxyurea, salbutamol, etc.), biological agent, or device within one month of Screening or five half-lives of study agent, whichever was longer. Any history of gene therapy or cell transplantation.
CS11/ SHINE	• Signed informed consent of parent or guardian and signed informed consent of participant, if indicated per participant'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. early termination of the index study) within the preceding 16 weeks • Able to complete all study procedures, measurements, visits and parent/participant has adequately supportive psychosocial circumstances, in the opinion of the investigator • For patients of reproductive age: females to have adequate birth control or be abstinent (after negative pregnancy test at Screening) and males be abstinent	• Have any condition or worsening condition which in the opinion of the Investigator would make the participant unsuitable for enrolment, or could interfere with participating in or completing the study • Clinically significant abnormalities in haematology or clinical chemistry parameters or ECG, as assessed by the Site Investigator, at the Screening visit that would render the participant unsuitable for participation in the study • The participant'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 • Participant's parent or legal guardian is not willing or able to meet standard of care guidelines (including vaccinations and respiratory syncytial virus prophylaxis if available), nor provide nutritional and respiratory support throughout the study • Treatment with another investigational agent, biological agent, or device within one month of Screening, or five half-lives of study agent, whichever was longer
Abbreviations: CNS, central nervous system; CSF, cerebrospinal fluid; ECG, electrocardiogram; LP, lumbar puncture; SMA, spinal muscular atrophy; SMN, survival motor neuron protein. Sources: CSRs CS2, CS12, CS11 (Biogen data on file)		

The registry studies' methodology is summarised in Table 12.

Table 12. Comparative summary of study methodology for European registries

Study ID	Italian registry	European registries	SMArtCARE
Reference(s)	(Maggi et al. 2020)	(Biogen data on file - registries non-ambulant type III data)	(Walter et al. 2019)
Location	Italy	Germany, Italy, Spain	Germany, Austria and Switzerland
Trial design	Retrospective cohort study	Prospective registries (observational)	Prospective observational
Nusinersen treatment	• Loading doses of 12mg nusinersen at Days 0, 14, 28 and 63 • Maintenance doses every four months in accordance with standard protocol	• Loading doses of 12mg nusinersen at Days 0, 14, 28 and 63 • Maintenance doses every four months in accordance with local protocol	• Loading doses of 12mg nusinersen at Days 0, 14, 28 and 63 • Maintenance doses every four months up to 300 days
Settings and locations where the data were collected	18 secondary or tertiary care centres for SMA in Italy	Germany (SMArtCARE), Italy (ISMAR), Spain (CuidAME)	Online platform for SMA patients seen by health-care providers in Germany, Austria and Switzerland
Primary outcomes	• HFMSE • RULM • 6MWT	• HFMSE • RULM • 6MWT	• MRC sum score • VC and VC %predicted in sitting position • ALS-FRS • RULM • HFMSE • 6MWT • Safety • (Biomarkers in the spinal fluid)
Secondary outcomes	• FVC (%of predicted) • FEV1(% of predicted)		

Abbreviations: 6MWT, 6-metre walking test; ALS-FRS, Amyotrophic Lateral Sclerosis Functional Rating Scale; FEV1, forced expired volume in 1sec; FVC, forced vital capacity; HFMSE, Hammersmith Functional Motor Scale Expanded; MRC, Medical Research Council; RULM, Revised Upper Limb Module SMA, spinal muscular atrophy; VC, vital capacity.

The registry studies' eligibility criteria are summarised in Table 13.

Table 13. Eligibility criteria for European registries

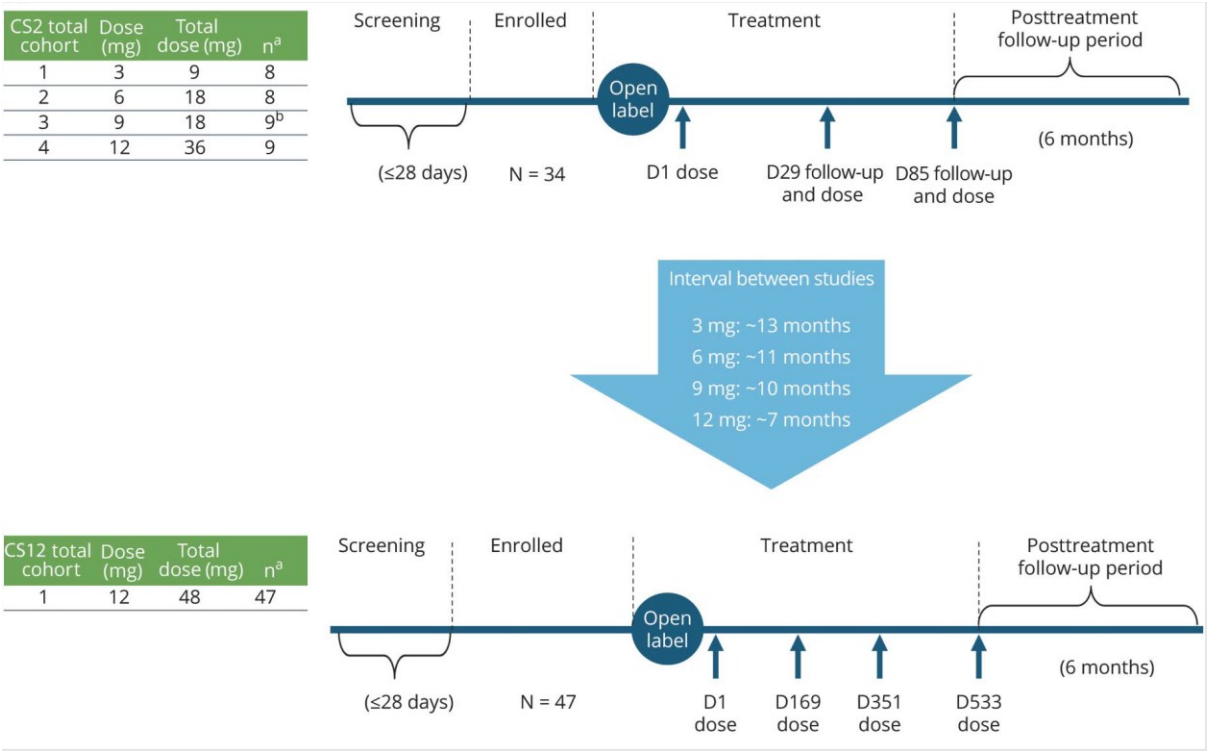
Study ID	Italian registry	European registries	SMArtCARE
Reference(s)	(Maggi et al. 2020)	(Biogen data on file - registries non-ambulant type III data)	(Walter et al. 2019)
Inclusion criteria	• Clinical and molecular diagnosis of type II or type III SMA • Nusinersen treatment started in adult (age >18 years) • Clinical data available at least at baseline (T0– beginning of treatment) and six months (T6).	• Genetically confirmed 5q SMA Analysis specific: • Type III or IV SMA • Treated with nusinersen • ≥1 visit prior to nusinersen initiation • ≥6 months follow-up post-nusinersen initiation	• Confirmed genetic diagnosis of type III 5q SMA • Treated with nusinersen between October 2017 and May 2019.
Exclusion criteria	n/a	• Participation in an RCT • Not able to receive nusinersen due to scoliosis • Follow-up <6months post-treatment initiation	n/a
Abbreviations: RCT, randomised controlled trial; SMA, spinal muscular atrophy.			

Study design

CS2/12/11

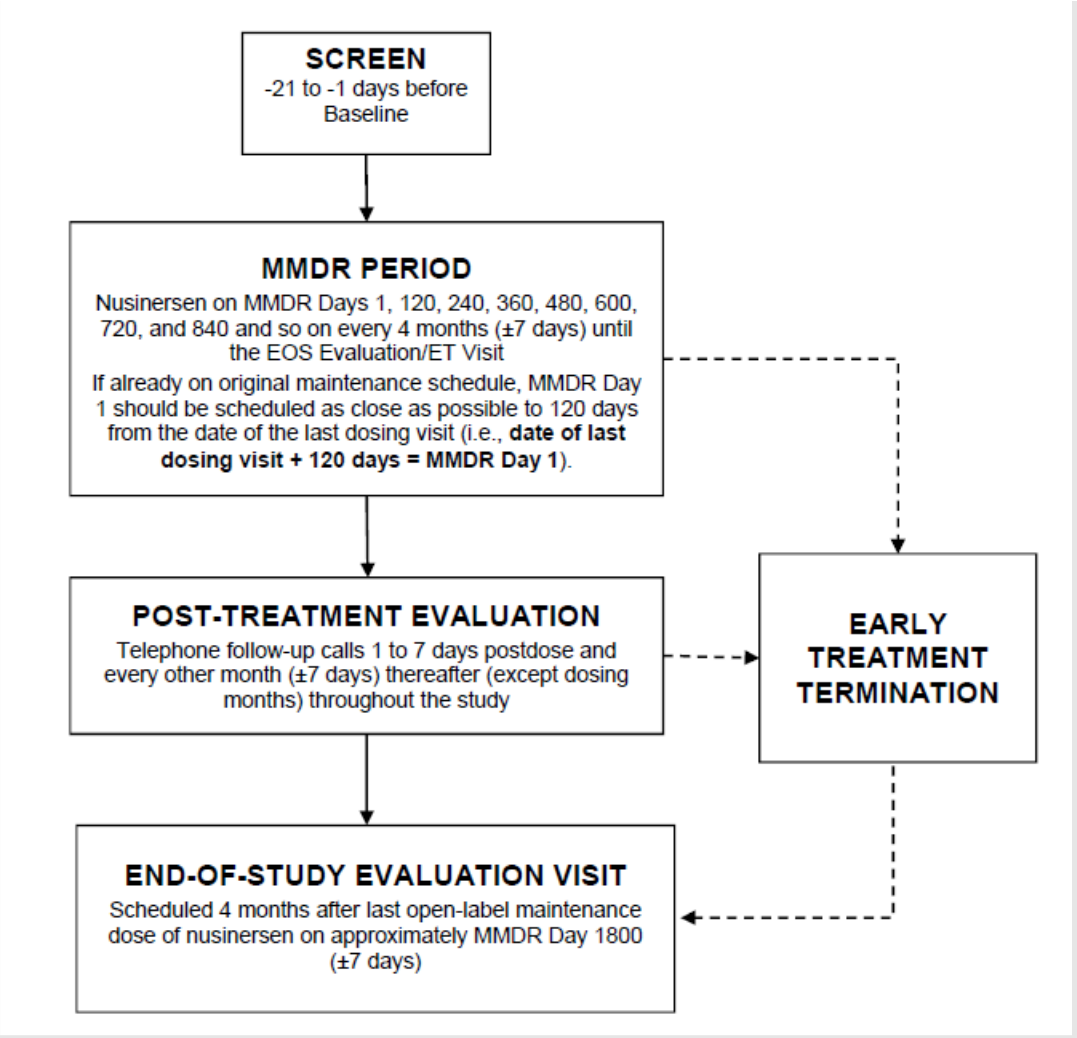
CS2 comprised four cohorts of paediatric (2–15 years) patients (non-ambulant type III SMA: n=4), all received different doses of nusinersen (Figure 3) as per the protocol loading schedule (Day 1, 29 and 85 [this is not the label dosing]) before continuing onto CS12. C12 was an extension study (non-ambulant type III SMA: n=5), including patients from CS2 (and CS10), where Q6M (treatment every six months) nusinersen administration was continued – patients were followed up for six months post Day 533.

Figure 3. CS2 (Phase 1b/2a open label) and CS12 (extension) study designs and patient disposition



CS11 is a long-term follow-up study, including patients from CS3b, CS4 and CS12 evaluating the long-term efficacy and safety of nusinersen. Patients received maintenance treatment Q6M, with last follow-up scheduled at Day 1,800 (study is ongoing) (Figure 4).

Figure 4. Study design CS11 – participants from CS12



European registries

Data from three registries were combined to conduct the analyses described in this submission. For an overview of all three registries see Figure 5, more detailed information per registry is provided in the sections that follow.

Figure 5. Overview European registries

SMArtCARE	CuidAME	ISMAR
▪ German-speaking countries ▪ Prospective non-randomised registry ▪ Standardised validated instruments ▪ Data collected during routine visits (4 months for nusinersen-treated, 6 months for untreated) ▪ E.g. assessed patient relevant endpoint: deaths, ventilation, HINE-2, CHOP INTEND, HFMSE, RULM, 6-MWT, scoliosis, AEs, AES due to therapy discontinuation, SAEs	▪ Spain ▪ Under development ▪ 6 participating clinics ▪ Standardised validated instruments ▪ Retrospective and prospective monitoring of all SMA patients to evaluate drug influence and natural course of the disease	▪ 3 separate registries: Italy, UK and USA ▪ 16 clinics ▪ Do not share one protocol ▪ Share harmonised data collection ▪ Evaluate influence of treatment

Abbreviations: 6-MWT, 6-metre walking test; AE, adverse event; CHOP-INTEND, Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders; HINE, Hammersmith Infant Neurological Examination; HFMSE, Hammersmith Functional Motor Scale Expanded; RULM, Revised Upper Limb Module; SAE, serious adverse event.

SMArtCARE (Germany)

The main objective of the SMArtCARE registry (German Clinical Study ID: DRKS00012699) (SMArtCARE 2020) was the evaluation of all people with 5q-SMA, regardless of their current treatment, as well as the planning and monitoring of therapeutic interventions in German-speaking countries. It is therefore an indication-specific clinical registry.

The data collection was based on an international consensus for SMA registries (TREAT-NMD Neuromuscular Network, iSMAC) and took place as part of regular, clinically recommended routine visits of patients depending on their current treatment regimen. This also determined the time and frequency of the follow-up examinations. The standardised results were collected during routine visits at regular intervals of four (nusinersen treatment) or six months (max time frame recommended by guidelines). Case report forms (CRFs) were available for standardised follow-up. Electronic data were used for data capture with the aid of an electronic data capture (EDC) system. This system is a web-based data entry system administered by the Freiburg University Medical Center. SMArtCARE OPEN app platform was used and an OPEN app software called Clinical Insight. This software complies with the highest international standards for data protection and quality management (GDPR). OPEN App has developed several registries for rare and chronic diseases and is the official provider of European reference networks (Clinical Patient Management System, ERN-CPMS). The data can be linked between different projects and registers.

The SMArtCARE registry was initiated prior to nusinersen approval in Europe but it did not start enrolment until the launch of nusinersen. Most patients in the registry were treated with nusinersen, as it is deemed to provide significant benefit.

ISMAR (Italy)

The development of the registry of the International Consortium for Spinal Muscular Atrophy (iSMAC), a prospective cohort study entitled ISMAR (Register number: MER-SMA-18-00 ISMAC (FPG ID 1894, no website available) (Mercuri et al 2019), was the result of an ongoing collaboration between three large national networks in the US, Italy and UK in 16 locations. ISMAR prospectively collected harmonised data from patients with genetically confirmed 5q-SMA. The main purpose was to gain increased understanding of the disease and response to treatments. The data for the registry were collected as part of regular, clinically recommended, routine visits – depending on their current treatment regimen.

The three locations operated according to a common electronic CRF (eCRF) with a common data dictionary. The data presented in this submission were derived from the Italian part of the register. The US registry surveys were excluded because the transferability to the English/Welsh healthcare context could not be ensured. The data from the UK part of the registry could not be included due to the limited availability of appropriate data (i.e. data on the paediatric type III SMA population, who lost ambulation in the 12 months prior to initiation of nusinersen treatment [as per MAA criteria] with sufficient follow-up, and there were delays in centre setup/service delivery).

CuidAME (Spain)

This registry collected data from six clinics relevant to the care of people diagnosed with 5q-SMA (CuidAME 2020). The SMArtCARE registry served as a model for its structure and organisation, with data collection aligned to the TREAT-NMD core minimum dataset. The orientation towards SMArtCARE ensured that comparable criteria were used across institutions. All people with SMA, regardless of their current treatment, were monitored within CuidAME; it is therefore also an indication registry. This registry contained standardised and validated evaluations for documenting motor function in people with SMA. Data for the registry was collected as part of regular,

clinically recommended, routine visits, depending on their current treatment regimen. The main purpose of the registry was to provide retrospective and prospective monitoring of all people with SMA to gain a better understanding of the natural course of SMA and the influence of drug treatment.

Key tools used for assessments of study outcomes

HFMSE

The HFMSE is a tool used to assess motor function and has been validated for use in SMA (Glanzman et al 2011). The scale has 20 scored activities for use in later-onset SMA (types II and III) and limited ambulation, as well as an additional module of 13 items to allow evaluation of ambulatory patients (Schneider et al 2017; Mercuri et al. 2016). Each motor skill item was scored on a three-point Likert scale from zero (no response) to two (full response), with a total score range of 0–66 (Table 14). The scale provides objective information on motor ability and clinical progression and is therefore a clinically relevant measure of treatment efficacy in later-onset SMA patients. A Phase I study of nusinersen reaffirmed that the HFMSE is sensitive to change with a three-point score change considered clinically meaningful (O'Hagen et al 2007).

Table 14. HMFSE activities and their relationship to activities of daily living

HMFSE Item	HMFSE activities	Activities of daily living
Non-ambulatory patients (incl. limited ambulation)		
1	Able to sit on chair or with legs off bed with or without hand support	Sitting on normal school chair or public spaces (stools in restaurant); sitting on toilet; sitting in car; independence out of the house; dress by herself/himself
2	Able to sit on floor cross legged or legs stretched in front	Play on floor with siblings; sit on lounge chair, deckchair; picnic; travel with less equipment; inclusion in activities
3	Able to bring hands to face at eye level	Wash face; brush and style; eat; put on eyeglasses; answer telephone; blow nose
4	Able to bring hands to head	Scratch head; wash, brush, style hair; put on hat; dress upper body
5	Roll to side	Sleep by myself in my own room; caregiver does not have to wake up to turn him/her; help during dressing lying down; not having to turn head to see
6-7-8-9	Roll	Play; sleep well; sunbathe; experience space; reach for something at sides when lying down
10	Able to lie down from sitting	Independence: lie down and rest when tired; fun movement when falling; rest on the back; safety: fall in a controlled way (avoid head trauma)

HMFSE Item	HMFSE activities	Activities of daily living
11	Able to raise head when lying prone	Turn head react to stimulus, visual exploration of surroundings; read a book; not be afraid of choking; watch tv; on beach not get sand in face
12-13	Able to prop on forearms or extend arms	Read a book; watch tv; stretch back; sunbathe
14	Able to sit up from lying	No need for assistant; wake up and not have to wait for someone to sit me up; independence; sit up and drink at night
15	Able to four-point knee	Play like an animal in school; hiding; be able to fit under small spaces
16	Able to craw	Move around; experience space; go get objects; play on floor
17	Lift head from supine	Change head position; drink at night; read; watch tv; check the clock or alarm
18	Stand with support	Use toilet standing (boy); use full length mirror, perceive body dimensions and proportions; shower properly; climb in car; use kitchen burners, cook
19	Stand without support	Public spaces: wait for bus, stand in queue; cook; use normal sink; dress; reach something on a shelf
Ambulatory patients		
20	Able to walk	Freedom; go where and when you please; get to places; not to have to rely on wheelchair batteries
21-22	Able to flex hip from supine	Dress (pants, socks); scratch legs; change position
23-24-25-26	Able to half knee	Pick up object on floor; tie shoelaces; put away object on low surfaces; pet a dog; play; kneel in church; talk with a kid
27	Able to go from standing to sitting	Not get hurt when falling or not fall in an embarrassing way; sit on grass or sand; pet a dog; sit beside a friend in same position/play on floor; pick up something from floor
28	Able to squat	Sit when needed; pick up objects on floor; pee; tie shoes; pull up trousers
29	Able to jump	Have fun, play; dance, gymnastics; avoid obstacles; normality; go to friends' home regardless of where they live; stay and live in my own home
30-31-32-33	Go up and down stairs	Absence of barriers; normality; go to friends' home regardless of where they live; stay and live in my own home
Source: (Pera et al 2017)		

RULM and ULM

The (R)ULM is a validated SMA-specific outcome measure that assesses upper limb functional abilities in individuals with SMA (Mazzone et al 2017). The original test (ULM) consisted of nine items, which measured motor function using common equipment (e.g. drawing a continuous line with a pencil, picking up a coin and placing in a cup, pressing a button to turn on a lamp, lifting a beverage can to drink, removing

the lid from a plastic container, lifting a weight and moving it from circle to circle on pre-printed paper). The maximum score possible is 18 (Mazzone et al 2011).

The revised version (RULM) consisted of 19 scorable items: 18 items scored from zero (unable) to two (full achievement) scale, as with the HFMSE, and one item that was scored as zero (unable) or one (able). The total score therefore ranged from 0–37 points with lower scores reflecting poorer ability (Pera et al. 2017).

Baseline characteristics

CS2/12/11

The demographic and baseline characteristics of the people with type III SMA in CS2/CS12 (Table 15) were consistent with a standard population of type III SMA (Farrar et al. 2017). CS2/CS12 data reported by (Darras et al. 2019) are presented in Table 26. An additional case series was identified in the SLR (Deconinck 2019), no baseline data were reported. No baseline data were reported for the CS11 (SHINE) study.

Table 15. Baseline characteristics CS2/C12

Characteristic	Values (SMA type III) (n=17)
Male, n (%)	7 (41)
Mean age at screening in CS2, years ± SD (range)	8.9 ± 4.4 (3–15)
Mean age at symptom onset, months ± SD (range)	22.0 ± 13.5 (6–60)
Mean age at SMA diagnosis, months ± SD	43.6 (32.4; 15–144)
SMN2 copy number, n 2 3 4	 1 10 6
Non-ambulatory, n (%)	4 (24)
HFMSE score, mean ± SE (range) – non-ambulatory	29.5 ± 3.5 (20–37)
ULM score, mean ± SE (range) [a]	16.0 ± 1.2 (14–18)
CMAP amplitude, mean mV ± SE (range)	5.4 ± 0.6 (1–10)
CMAP area, mean mV/ms ± SE (range)	14.5 ± 2.1 (2–33)
MUNE, mean ± SE (range)	108.3 ± 12.6 (21–206)

Abbreviations: CMAP, compound muscle action potential; HFMSE, Hammersmith Functional Motor Scale–Expanded; MUNE, motor unit number estimation; SD, standard deviation; SE, standard error; SMA, spinal muscular atrophy; *SMN*, survival motor neuron; ULM, Upper Limb Module.
Notes: [a] Only assessed in non-ambulant children: SMA type II, n=11; SMA type III, n=4.
Source: (Darras et al. 2019)

Italian registry

Baseline characteristics of the non-ambulant type III SMA population are presented in Table 16 (Maggi et al. 2020).

Table 16. Baseline characteristics, Italian registry – non-ambulant type III SMA

Variable, median (min–max)		non-ambulant type III (n=51)
Age at onset (years)		3 (0.3–15)
Age at T0 (years)		40 (18–72)
Disease duration at T0 (years)		37 (14–63)
Gender (F/M)		15/36
SMN2 copies, n (%)	*two*	2 (3.9)
	three	16 (31.4)
	four	21 (41.2)
	unknown	12 (23.5)
Salbutamol, n (%)		9 (17.8)
Ventilatory support at T0 (%)		8 (15.7) [a]
Surgery for scoliosis (%)		7 (13.7)
HFMSE score		9 (0–40)
RULM score		20 (0–34)
FVC (% of predicted)		83 (30–128) (n=40)
FEV1 (% of predicted)		84.3 (35–120) (n=35)

Abbreviations: FEV1, forced expired volume in 1sec; FVC, forced vital capacity; HFMSE, Hammersmith Functional Motor Scale Expanded; RULM, Revised Upper Limb Module; SMA, spinal muscular atrophy; SMN, survival motor neuron.
Notes: [a] Two patients used ventilatory support due to obstructive sleep apnoea and a further patient refused ventilatory support although indicated
Source: (Maggi et al. 2020)

European registries

Due to the availability of data and requirements for the analysis we have presented baseline data for the overall cohort and a sub-cohort. The overall cohort included all enrolled individuals with non-ambulatory type III SMA (n=168; nusinersen-treated n=159), baseline characteristics are presented in Table 17. The sub-cohort included all enrolled individuals with non-ambulatory type III SMA, who were treated with nusinersen and had ≥1 visit prior to nusinersen initiation and ≥6 months follow-up ([redacted]). Baseline characteristics of the sub-cohort is presented in Table 18.

Table 17. Baseline characteristics, European registries – non-ambulant type III SMA (overall cohort)

Baseline characteristics	All (n=168)	Treated (n=159)	Untreated (n=9)
Gender, M/F n (%)	[redacted]	[redacted]	[redacted]
Registry, n (%)			
German	[redacted]	[redacted]	[redacted]
Italian	[redacted]	[redacted]	[redacted]
Spain	[redacted]	[redacted]	[redacted]
***SMN2* copies, n (%)**			
1	0 (0)	0 (0)	0 (0)
2	14 (8)	14 (9)	0 (0)
3	67 (40)	62 (39)	5 (56)
4	53 (32)	52 (33)	1 (11)
> 4	1 (0.6)	1 (0.6)	0 (0)
Unknown	33 (20)	30 (19)	3 (33)
Adult patients at V0, n (%)	[redacted]	[redacted]	[redacted]
Age at symptom onset, n (%)			
< 3 years	106 (64)	101 (64)	5 (56)
≥ 3 years	60 (36)	56 (36)	4 (44)
Disease duration, years, mean ± SD; median (min–max)	[redacted]	[redacted]	[redacted]
Age at first dose of treatment, years, mean ± SD; median (min–max)	[redacted]	[redacted]	NA
Age at last dose of treatment, years, mean ± SD; median (min–max)	[redacted]	[redacted]	NA
Age at last follow-up, years, mean ± SD; median (min–max)	[redacted]	[redacted]	[redacted]
Number of doses, mean ± SD; Median (min–max)	7.16 ± 2.70 8.00 (1.00–12.00) N=159	7.16 ± 2.70 8.00 (1.00–12.00)	NA
Feeding			
Unsupported	11 (6)	11 (7)	-
Oral, no supplements needed	13 (8)	8 (5)	5 (56)
Oral intake solids	47 (28)	43 (27)	4 (44)
No feeding tube	97 (58)	97 (61)	-

Baseline characteristics	All (n=168)	Treated (n=159)	Untreated (n=9)
Motor function			
HFMSE score, mean ± SD; Median (min–max)	17.93 ± 13.48 16.00 (0.00–59.00) N=121	17.32 ± 13.15 15.00 (0.00–59.00) N=117	35.75 ± 11.79 33.50 (24.00–52.00) N=4
RULM score mean ± SD; Median (min–max)	22.83 ± 8.58 24.00 (0.00–37.00) N=115	22.68 ± 8.67 24.00 (0.00–37.00) N=111	27.25 ± 3.50 29.00 (22.00–29.00) N=4
Number of subjects who use a wheelchair	N=155	N=151	N=4
Yes (full-time/part-time), n(%)	81/11 (92.9/7.1)	81/11 (89.8/7.2)	4 (100)
No	11 (7.1)	11 (7.2)	0 (0)
Non-invasive ventilation	20 (11.90)	18 (11.32)	2 (22.22)
Ventilator support	N=14	N=12	N=2
Daily/weekly	4 (29)	3 (25)	1 (50)
Night	6 (43)	5 (42)	1 (50)
Yes (8h)	2 (14)	2 (17)	-
Other	2 (14)	2 (17)	-
Scoliosis			
Yes	62 (36.91)	62 (38.99)	0 (0.00)
No	106 (63.09)	97 (61.01)	9 (100.00)
Serious respiratory events[1]			
n (%)	1/144 (0.69)	1/140 (0.71)	0/4 (0.00)
Events	1	1	0
Total subject months (in registry)	1728	1680	48

Abbreviations: HFMSE, Hammersmith Functional Motor Scale Expanded; Max, maximum; Min, minimum; SD, standard deviation; SMA, spinal muscular atrophy; SMN, spinal motor neuron; RULM, Revised Upper Limb Module; V0, start treatment.
Notes: [1] in the 12 months before baseline (V0) based on medical records. If data was not available in all patients the number of patients it was available in is listed (per item).

Table 18. Baseline characteristics, European registries – non-ambulant type III SMA (sub-cohort) [c]

Category	n (%)	Mean ± SD	Median (min–max)
Gender, M/F	[redacted]	-	-
Registry			
German	[redacted]	-	-
Italian	[redacted]	-	-
Spain	[redacted]	-	-
Number of *SMN2* copies			
2 copies	[redacted]	-	-
3 copies	[redacted]	-	-
4 copies	[redacted]	-	-
Unknown	[redacted]	-	-

Category	n (%)	Mean ± SD	Median (min–max)
Adult patients at V0	[redacted]	-	-
Age at symptom onset		[redacted]	[redacted]
< 3 years	[redacted]		
≥ 3 years	[redacted]		
Disease duration, years (n=50)	-	[redacted]	[redacted]
Age at first dose of treatment, years	-	[redacted]	[redacted]
Age at last dose of treatment, years	-	[redacted]	[redacted]
Age at last follow-up, years	-	[redacted]	[redacted]
Number of doses	-	[redacted]	[redacted]
Feeding			
Unsupported	[redacted]	-	-
Oral, no supplements needed	[redacted]	-	-
Oral intake solids	[redacted]	-	-
Feeding tube	[redacted]	-	-
Motor function			
HFMSE score (n=32)	-	[redacted]	[redacted]
RULM score (n=30)	-	[redacted]	[redacted]
Number of subjects who use a wheelchair	[redacted]	-	-
Yes	[redacted]	-	-
No [a]	[redacted]	-	-
Non-invasive ventilation	[redacted]	-	-
Ventilator support	[redacted]	-	-
Daily/weekly	[redacted]	-	-
Night	[redacted]	-	-
Yes (8h)	[redacted]	-	-
Other	[redacted]	-	-
Missing	[redacted]	-	-
Scoliosis, Yes/No	[redacted]	-	-
Serious respiratory events [b] **(n=45)**	[redacted]	-	-
events	[redacted]	-	-
Total subject months (in registry)	[redacted]	-	-

Abbreviations: HFMSE, Hammersmith Functional Motor Scale Expanded; Max, maximum; Min, minimum; SD, standard deviation; SMA, spinal muscular atrophy; SMN, spinal motor neuron; RULM, Revised Upper Limb Module; V0, start treatment.
Notes: [a] no details available in the database. [b] in the 12 months prior to V0. [c] Only included patients with at least one visit before treatment and six months of follow-up after treatment initiations.

A.2.4. Statistical analysis and definition of study groups in the relevant clinical effectiveness evidence

An overview of the statistical analyses across the clinical trials (CS2/CS12/CS11 (SHINE) is presented in Table 19. More detailed descriptions per study can be found in the sections that follow.

Table 19. Summary of statistical analyses – clinical trials

Study name	CS2 (NCT01703988)	CS12 (NCT01494701)	CS11/SHINE (NCT02594124)
Hypothesis objective	No hypothesis presented in CSR	No hypothesis presented in CSR	There was no hypothesis presented for this long-term follow-up study
Statistical analysis	• In view of the exploratory nature of this study, adjustments for multiplicity of testing were generally not used • multiple records within the same visit were averaged • Simple descriptive summary statistics, such as n, mean, SD, median, IQR, minimum, and maximum for continuous variables, and counts and percentages for categorical variables were used to summarise most data. • Where appropriate, p-values were reported. • Hypotheses were tested using 2-sided tests whose Type I error rates are controlled at alpha = 0.05	• Baseline was defined as the last non-missing value prior to the first dose of ISIS 396443 • Missing values were not imputed • Simple descriptive summary statistics, such as n, mean, SD, SEM, median, IQR, minimum and maximum for continuous variables, and counts and percentages for categorical variables were used to summarise most data	• individual sites in this multicentre study were pooled • For the analysis of efficacy, the approach was to preserve the index study groupings
Sample size, power calculations	Sample size was selected based on prior experience with Phase 1 multiple-dose studies of ASOs to ensure that the safety and tolerability of ISIS 396443 would be adequately assessed while minimising unnecessary subject exposure	Based on the number of participants in Study CS2 and CS10	Based solely on number of participants enrolled in Studies CS3A/B, CS4, CS12, and 232SM202, who may have been eligible for participation in this study

Study name	CS2 (NCT01703988)	CS12 (NCT01494701)	CS11/SHINE (NCT02594124)
Data management, patient withdrawals	Data were single entered into the EDC system by the Investigator Site Staff. Programmed edit checks (computer logic checking the validity of the data entered and also prompting for missing data that was expected to be entered) were run, and automatic queries were generated. Sponsor reviewed all data for accuracy and validity and generated additional queries in the EDC system when necessary	Clinical data management review was performed on the subject data received by the Sponsor. Subject data were checked for consistency, omissions, and any apparent discrepancies. In addition, the data were reviewed for adherence to the protocol and GCP.	Study site personnel entered the participants' clinical data into EDC. If the data did not meet predetermined parameters, a discrepancy was displayed and corrections were made by study site personnel. Discrepancy responses were reviewed by data management and closed. Quality control data reviews were performed prior to database lock.

Abbreviations: ASO, antisense nucleotide; CSR, clinical study report; EDC, electronic data capture; GCP, Good Clinical Practice; IQR, interquartile range; SD, standard deviations; SEM, standard error of the mean.

An overview of the statistical analyses across the European registry studies is presented in Table 20. More detailed descriptions per study can be found in the sections that follow.

Table 20. Summary of statistical analyses – registries

Study name	Italian registry[1]	European registries[2]
Hypothesis objective	No hypothesis presented	• H0: nusinersen treatment = no DMT • H1: nusinersen treatment ≠ no DMT
Statistical analysis	• Wilcoxon-Mann-Whitney or Student's t test: distributions of quantitative and ordinal values • Spearman method: correlations between quantitative and/or ordinal variables • χ2 test: distributions of categorical variables • Logistic regression: identify effects of predictor variables (age, sex, *SMN2* copy number) on treatment response • No formal correction for multiple testing was adopted – reporting nominal (0.05>p>0.01) or strong (p<0.01) statistical significance.	• Mixed-effects model (nusinersen vs DMT-untreated) • Piece-wise linear analysis (HFMSE and RULM scores)
Data management, patient withdrawals	• Responders: improved from baseline by ≥3 HFMSE points, ≥2 RULM points • Overall responders: responder in at least one of the outcomes	• The completeness of the data for each survey time (loss-to-follow-up, drop-outs) and the completeness of the survey times are ensured by using the mixed effect model. • The implementation and maintenance of quality assurance and quality control systems is carried out through written SOPs and in accordance with GCP. • The data is checked for completeness, consistency and plausibility

Abbreviations: DMT, disease-modifying treatment; GCP, Good Clinical Practice; HFMSE, Hammersmith Functional Motor Scale–Expanded; RULM, Revised Upper Limb Module; SMN, survival motor neuron; SOP, standard operating procedure.
Notes: due to the nature of registries, no official sample size or power calculations were conducted.
Sources: [1] (Maggi et al. 2020). [2] (Biogen data on file - full registries report 2020)

CS2/12 and CS11/SHINE

Analysis set

For CS2 and CS12, see Table 21 and Table 22 for an overview of the analysis set, respectively. All safety analyses (primary outcome) were conducted on the safety population, pharmacokinetic (PK) analyses were conducted on the PK population, and efficacy and biomarker analyses were conducted on the evaluable population. In addition to these populations, some data displays were provided for 'all screened', 'all enrolled' and 'screening failures' subjects, but no data analyses were performed for these populations (Biogen data on file - NCT01494701 2017; Biogen data on file - NCT01703988 2015).

Table 21. CS2 analysis set

Analysis population	Description
Safety population	All enrolled participants who received at least one dose of study drug
PK population	All enrolled participants who had evaluable PK data
Evaluable population	All participants who were registered, received all scheduled doses of study drug, and completed the Day 92 visit
Abbreviations: PK, pharmacokinetic.	

Table 22. CS12 analysis set

Analysis population	Description
Safety population	All enrolled participants who received at least one dose of study drug
PK population	All enrolled participants who received at least one dose of study drug
Evaluable population	All participants who received at least one dose of study treatment and completed follow-up visits through at least Day 85
Abbreviations: PK, pharmacokinetic	

For CS11, see Table 23 for an overview of the analysis set. All safety analyses were conducted on both safety sets and efficacy analyses were conducted on the efficacy population for each visit. Presentations of immunogenicity data were based on all dosed participants (Biogen data on file - NCT02594124 2018).

Table 23. CS11 analysis set

Analysis population	Description
First safety population	All participants who received at least one dose of study drug (as per index studies CS2/12)
Second safety population	All participants who were enrolled and received at least one dose of nusinersen or underwent sham procedure during Study CS11
Efficacy population (per visit)	The subset of participants in the Safety Set who had the opportunity to be assessed at that visit
PK population	all participants who were enrolled and for whom there was at least one evaluable post-dose/post-sham procedure PK sample
Abbreviations: PK, pharmacokinetic.	

Imputation CS11

As CS11 was a follow-up study for participants from several index studies, therefore several things were taken into consideration, including the handling of any missing data.

For participants randomised to nusinersen in the index studies, the index studies and CS11 are considered as one period (nusinersen period) and all data available were used for imputation. However, for participants who were randomised to receive sham in the index studies, the sham period and nusinersen period were considered completely separated and no imputation was allowed between the two periods. The exception was for the combined analyses (i.e. baseline characteristics and safety analysis), where sham and nusinersen were presented as one treatment arm.

The imputation for HFMSE and upper limb was based on the total score, while the imputation for WHO, Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders (CHOP INTEND), and HINE was based on item level/motor milestone level. The imputation of missing data followed these rules:

1. Any missing baseline was imputed using median within stratum considering non-missing baseline records.
    a. For WHO and HINE motor milestones, in any cases when the calculated median was not an integer, it was rounded to be an integer
2. For post baseline visits flanked by non-missing visits, missing values were imputed using linear interpolation using an imputed baseline, if necessary. Only actual visits with a non-missing date were imputed for each participant.
    a. For HFMSE, if six or more item scores were missing, then the total score was imputed as if all the 33 items were missing
    b. For RULM, if three or more items were missing, then the total score was imputed as if all the 19 items were missing
    c. For ULM, if more than two items were missing, then the total score was imputed as if all the nine items were missing
    d. For WHO motor milestones, if for a milestone either 'No (refusal)' or 'Unable to test' were observed at a visit, then the result was first set to missing
3. If it was the last assessment, date was present, and at least one item was non-missing, the following approaches were followed:
    a. For the HFMSE and (R)ULM limb, the value was imputed using the last observed total score.

b. For the other assessments, the lowest observed value for an item assigned to the analysis visit within the stratum was used for the imputation.

The stratum for the imputation of baseline and last assessment, mentioned in points one and three were as follows:

- Type II (first nusinersen dose in Study CS1/CS2)
- Type III (first nusinersen dose in Study CS1/CS2)
- Previous control (first sham procedure in Study CS3B or CS4)
- Previous control in CS11/Part 2 (first nusinersen dose in Study CS11)
- Previous ISIS (first nusinersen dose in Study CS3B, CS4, or CS3A)

The median value calculated was within the stratum defined by the median disease duration at first dose. Disease duration at first dose is age at first dose or sham procedure minus age of SMA onset.

Patient disposition

Patient disposition, including diagrams showing the flow of participants through each stage of the trials for CS2, CS12 and CS11 are presented in Appendix B.

Registries

Analysis set

The Italian registry analysis set is presented in Table 24. The analysis set for the European registries is shown in Table 25.

Table 24. Italian registry analysis set

Analysis population	Description
Responders	Improved from baseline by ≥3 HFMSE points, ≥2 RULM points
Overall responders	Responder in at least one of the outcomes
Abbreviations: HFMSE, Hammersmith Functional Motor Scale Expanded; RULM, Revised Upper Limb Module	

Table 25. European registries analysis set

Analysis population	Description
FAS	All participants with baseline (V0) data available
Abbreviations: FAS, full analysis set	

Potential confounding factors

For the European registries data (Biogen data on file - full registries report 2020), the background covariates were assessed as potential confounders: V0-variables related to the patient population in terms of demographics and clinical history, such as patient, age at symptom onset, age at onset of treatment, age at baseline, type of SMA, ambulatory status, *SMN2* copy number, gender, disease duration at baseline, feeding difficulty, race/ethnicity and registry (Spain/Italy/Germany).

Patient disposition

Patient disposition, including diagrams showing the flow of participants through each registry are presented in Appendix B.

A.2.5. Quality assessment of the relevant clinical effectiveness evidence

A summary of the studies (publications) that underwent quality assessment is presented in Table 26. Please see Appendix B for the detailed quality assessments of the clinical studies and Appendix E for the detailed quality assessments of the HRQoL studies.

Table 26. Summary of studies that underwent quality assessment

Trials	Observational studies	RWE case series
(Darras et al. 2019)	Italian registry (Maggi et al. 2020)	(Barp et al. 2020)
(Muntoni et al. 2020)	SMArtCARE (Walter et al. 2019)	(Shah et al. 2020)
(Deconinck 2019)	European registries (Biogen data on file - registries non-ambulant type III data 2020)	(Okamoto et al. 2020)
(Kirschner et al. 2018)	(Gunther et al 2019)	(Cordts et al. 2020)
	(Belter et al. 2020)	(Yeo et al. 2020)
	(van der Heul et al. 2019)	(Stam et al 2018)
	(Darba 2020)	
	(Love et al 2019)	
	(Weaver et al 2020)	

For clinical, non-randomised studies, the QuEENS (Quality of Effectiveness Estimates from Non-randomised Studies) checklist was used to assess the quality of the studies. Tools from the National Institute of Health (NIH) were used for other study types (as

relevant) to determine the quality in terms of being either good, fair or poor. (The European registries also have an additional QA completed, based on the criteria set out in the Transparent Reporting of studies Conducted using Observational Routinely-collected Data [RECORD].)

A.2.6. Clinical effectiveness results of the relevant trials

CS2/12 and CS11 (SHINE)

Primary endpoints (safety and tolerability of nusinersen)

The results on safety and tolerability are presented in Section 2.10 (adverse events).

Secondary endpoints (efficacy of nusinersen)

Motor function

Improvements in motor function were observed in people with non-ambulant type III SMA treated with nusinersen (Table 27). Maximum ULM scores, which are particularly relevant to assess disease progression after the loss of ambulation, were reached in 100% (n=4) of the people with non-ambulant type III SMA by Day 350 and maintained to the latest endpoint in CS12; Day 1,150. Of particular note, 50% (n=2) of these patients regained the ability to walk independently during the course of the study (they had lost this ability before treatment with nusinersen was started).

Only three individuals with non-ambulatory type III SMA from the CS2/12 study[1] progressed to the CS11/SHINE long-term extension study (ongoing),at Day 1,530 (latest follow-up time point reported in CSR) no change in ULM score was observed compared with baseline – indicating a maintained stabilisation of disease (Biogen data on file - NCT02594124 2018).

Compound muscle action potential (CMAP) and Motor Unit Number Estimation (MUNE) scores were only reported in the overall type III SMA population without a breakdown specific for the non-ambulant population – they are therefore not reported in this submission (Darras et al. 2019).

[1] The assumption is made that Muntoni et al, 2020 and Deconinck et al, 2019 reported on the same five patients, including one with non-ambulant type III SMA and that this patient is also reported in the CSR for CS11/SHINE.

Table 27. Clinical efficacy outcomes CS2/12 – non-ambulant type III SMA

	Baseline (CS2)	Follow-up				
		No specific time reported	Day 253	Day 350	Day 1,150	Day 1,530
HFMSE score	mean (SE, range) 29.5 (3.5; 20–37)	--	≥3-point change[a]: n=1	NR	NR	NR
ULM score	mean (SE, range) 16.0 (1.2; 14–18)	--	NR	n=4 (100%) max score (18pts)	n=4 (100%) max score (18pts)	n=3 (100%) max score (18pts)
Ambulation, n (%)	*Non-ambulant:* 4 (100)	*Non-ambulant:* 2 (50) *Ambulant:* 2 (50)	--	--	--	
Abbreviations: HFMSE, Hammersmith Functional Motor Scale–Expanded; NR, not reported; SE, standard error; SMA, spinal muscular atrophy; ULM, Upper Limb Module. Notes: [a] clinically meaningful change Sources: (Darras et al. 2019) (Biogen data on file - NCT02594124 2018)						

Italian registry (adults with non-ambulant type III SMA)

Adults with SMA were eligible for inclusion, the reported groups were split into type II SMA, non-ambulant type III SMA (type III 'sitters') and ambulant type III SMA (type III 'walkers') (Maggi et al. 2020; Biogen data on file - NCT02594124 2018). As the focus of the submission is on the non-ambulant type III SMA population, this section only summarises the results from this population – for a comparison of non-ambulant type III SMA with type II SMA, see Section 2.11.

Primary outcomes (motor function)

Motor function (reflected by HFMSE and RULM scores) was assessed at baseline (T0) and following the start of nusinersen treatment at six months (T6), 10 months (T10) and 14 months (T14). Significant changes from baseline in HFMSE scores, across the non-ambulant type III SMA population, were observed at all time points ($p<0.05$) and increased over time – demonstrating benefit of continued treatment. The largest changes from baseline in RULM scores were observed at T10 and T14 ($p<0.05$) (Table 28 and Figure 6).

Clinically meaningful improvements in HFMSE (≥3-point change) and RULM (≥2 point change) were observed in up to 58% and 53% of people with non-ambulant type III

SMA after 14 months of nusinersen treatment (compared with baseline: p<0.05). Overall, 79% of patients had a clinically meaningful response in at least one of these two measures after 14 months of nusinersen treatment (Table 29). This in contrast to the decline in motor function observed in natural history cohorts of SMA; (Wijngaarde et al 2020) studied motor function in a cohort of adult SMA patients (not treated with nusinersen), showing a yearly decline of 0.7pts (type IIIa) or 0.6pts (type IIIb) in HFMSE scores.

Table 28. Motor function changes at T6, T10 and T14 – non-ambulant type III SMA

Timeframe	Variable	N	Mean ± SD	Median (min–max)	Paired Wilcoxon p-value
T0–T6 change	HFMSE	51	1.37 ± 2.02	1 (−4 to 6)	**<0.0001**
	RULM	51	0.63 ± 2.48	0 (−8 to 6)	0.056
T0–T10 change	HFMSE	35	2.51 ± 2.94	1 (−3 to 9)	**<0.0001**
	RULM	33	1 ± 2.45	1 (−6 to 5)	**0.021**
T0–T14 change	HFMSE	19	3.53 ± 3.67	3 (−3 to 11)	**0.0014**
	RULM	19	1.47 ± 2.5	2 (−6 to 5)	**0.018**

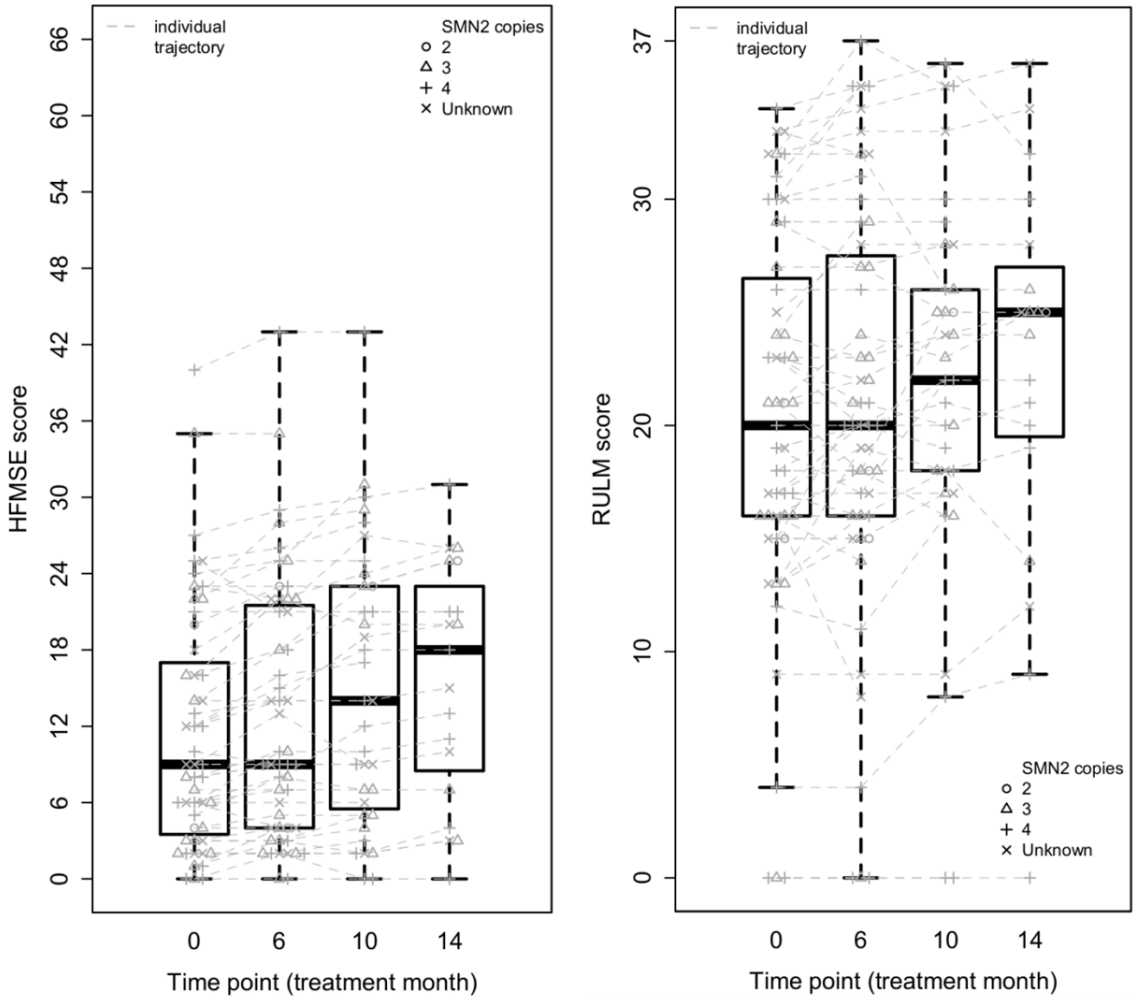
Abbreviations: HFMSE, Hammersmith Functional Motor Scale Expanded; RULM, Revised Upper Limb Module; SD, standard deviation; SMA, Spinal Muscular Atrophy; T0-6-10-14, baseline, six months, 10 months and 14 months.
Notes: Significant p-values are highlighted in bold.

Table 29. Clinically meaningful functional improvement during nusinersen treatment

Score	N	T6	T10	T14
HFMSE	Total N	51	35	19
	Responders, n (%)	14 (27)	14 (40)	11 (58)
RULM	Total N	51	33	19
	Responders, n (%)	15 (29)	13 (39)	10 (53)
Overall	Total N	51	35	19
	Responders, n (%)	26 (51)	21 (60)	15 (79)

Abbreviations: HFMSE, Hammersmith Functional Motor Scale Expanded; RULM, Revised Upper Limb Module; SMA, spinal muscular atrophy.
Notes: Responders are defined as ≥3-point HFMSE score change from T0, ≥2-point RULM score change from T0. 'Overall' response is defined as clinically meaningful response in at least one measure.

Figure 6. Box-Whisker-Beeswarm plots of HFMSE scores and RULM scores across time points – non-ambulant type III SMA



Abbreviations: HFMSE, Hammersmith Functional Motor Scale Expanded; IQR, interquartile range; RULM, Revised Upper Limb Module; SMA, spinal muscular atrophy.
Notes: Boxes identify first to third quartile range in the distribution, thick horizontal lines indicate median values, and whiskers indicate minimum/maximum values or first/third quartile ± 1.5 * the IQR, whichever is the least extreme. 'Beeswarms', superimposed in grey, indicate all individual values for the 51 patients with longitudinal data. Different dot types identify *SMN2* copy number. Dashed lines describe individual patient trajectories.

Secondary outcomes (lung function)

People with type III SMA can have a decline in lung function as disease progression continues. From a retrospective cohort study, it was seen that percent predicted forced vital capacity (FVC %pred), steadily declines from 10 years of age in patients with type III SMA who are not receiving disease-modifying treatment. In all individuals with type III, FVC %pred declined by 6.3% per year between eight and 13 years, followed by a slower decline (0.9% per year). It is important to consider that decline in respiratory function may be less reversible than motor function in patients with SMA. Parenchymal

damage will occur with recurrent previous aspiration and prolonged chest infection without sufficient cough function. Subsequent motor improvement will have a blunted effect on improving lung function. Thus stabilisation would be considered a significant therapeutic benefit from nusinersen (Trucco et al. 2020).

Within the Italian registry, FVC% showed no significant changes over 14 months of nusinersen treatment in the non-ambulant type III SMA population (Table 30). This diminution in decline in respiratory function is noteworthy.

Table 30. Pulmonary function (FVC%) changes at T6, T10 and T14 – non-ambulant type III SMA

Timeframe	N	Mean ± SD	Median (min–max)	Paired Wilcoxon p-value
T0–T6 change	19	0 ± 9.04	1 (−19 to 28)	n.s.
T0–T10 change	7	3.3 ± 7.83	4.1 (−10 to 16)	n.s.
T0–T14 change	8	4.25 ± 8.55	1 (−4 to 19)	n.s.
Abbreviations: FVC%, percent-predicted forced vital capacity; n.s., not significant; SD, standard deviation; SMA, Spinal Muscular Atrophy; T0-6-10-14, baseline, six months, 10 months and 14 months.				

European registries data (adults and children with non-ambulatory type III SMA)

The population of interest within the registries included people with non-ambulant type III SMA from Germany (n=97), Italy (n=47) and Spain (n=24). As the focus of this submission is on the non-ambulant type III SMA population, this section only summarises the results from this population. A comparison of nusinersen-treated (n=159) with untreated patients (BSC alone; n=9) will be presented in the overall cohort. Additional analyses presented were conducted on the sub-cohort, which included all enrolled individuals with non-ambulatory type III SMA, who were treated with nusinersen and had ≥1 visit prior to nusinersen initiation and ≥6 months follow-up (n=[redacted]). Both paediatric (n=[redacted]) and adults (n=[redacted]) with non-ambulant type III SMA were included in the analysis.

Outcomes (motor function)

Nusinersen-treated versus untreated patients

In the analysis (data cut-off: August 2020) HFMSE and RULM scores were assessed using a standard mixed model. The standard linear mixed model was fit among both treated and untreated patients using outcome data collected after treatment initiation

(for treated patients) or after the assigned index date (for untreated patients). The model estimated slopes of change over time separately in each treatment group, thus permitting assessment of whether the trajectory of the outcome over time differed between treated and untreated patients. Results were expressed as estimated change in pts/week (95% CI) and slopes were adjusted for important covariates. For HFMSE score, there was a statistically significant difference (p<0.001) observed between the slopes of nusinersen-treated patients (0.015 pts/week; 95% CI: 0.003–0.027) versus the untreated patients (−0.109 pts/week; 95% CI: −0.144 to −0.074). For RULM score, a trend was observed in the increasing slope in the nusinersen-treated patients (0.018 pts/week; 95% CI: 0.007–0.028) vs. untreated patients (−0.009 pts/week; 95% CI: −0.039–0.021).

Sub-cohort ([redacted]) analyses

In the analysis (data cut-off: August 2020) HFSME and RULM were assessed prior and post-initiation of nusinersen. Table 31 shows the average number of visits and follow-up, pre-and post-initiation of treatment, in the non-ambulant type III SMA analysis population.

Table 31. Visit and follow-up of patients – pre- and post-nusinersen initiation

	Pre-treatment initiation	Post-initiation
Visits, n (median; range)	[redacted]	[redacted]
Time between visits, days (median; range)	[redacted]	[redacted]
Follow-up, weeks (mean, ± SD)	[redacted]	[redacted]
Abbreviations: SD, standard deviation.		

The piecewise linear mixed model was restricted to treated patients with data on outcomes both before and after treatment. The model estimated a pre-treatment slope as well as a change in that slope at the time of treatment initiation, thus permitting assessment of whether treatment impacted the trajectory of the outcome over time.

The HFMSE results showed that before the start of nusinersen treatment the score decreased (calculated to be an average of 0.06 points per week [2.9pts per year]) – which was statistically significant [p<0.0001]), with a stabilising effect seen after nusinersen treatment was initiated. This change in slope, indicating stabilisation of disease, from pre- to post-treatment was statistically significant (p=0.002) (Table 32).

The RULM scores showed a significant decrease in slope before initiation of nusinersen treatment (p<0.0001), with a halting of this decline observed after the initiation of nusinersen, which stayed constant over time, this change of slope between pre- and post-treatment initiation was significant (p=0.019) (Table 32). The same trend was seen when patients (n=2) with a ceiling effect were excluded from the analysis (analysis not shown).

Table 32. HFMSE and RULM score slopes – pre- and post-nusinersen initiation

	HFMSE	RULM
Slope before initiation of nusinersen		
Estimated change pts/week ± SE	−0.056 ± 0.004	−0.021 ± 0.004
95% CI	(−0.064 to −0.048)	(−0.029 to −0.013)
P-value	<0.001	<0.0001
Slope after initiation of nusinersen		
Estimated change pts/week ± SE	−0.010 ± 0.013	−0.002 ± 0.005
95% CI	(−0.035 to 0.014)	(−0.013 to 0.008)
P-value	n.s	n.s
Change in slope, p-value	p=0.002	p=0.019

Abbreviations: CI, confidence interval; HFMSE, Hammersmith Functional Motor Scale Expanded; RULM, Revised Upper Limb Module; SE, standard error.

Supportive RWE case series: clinical outcomes

SLR-identified case series

The clinical SLR identified five relevant studies that presented supplementary evidence to support the key findings from the clinical trials (CS2, CS12 and CS11 SHINE) and European registries. Of these five studies, one was a retrospective database study (Cordts et al. 2020), one was a prospective database study (Yeo et al. 2020) and three were case series (Barp et al. 2020; Okamoto et al. 2020; Shah et al. 2020).

The retrospective database study (Cordts et al. 2020) presented HFMSE, Amyotrophic Lateral Sclerosis Functional Rating Scale (ALS-FRS-R) and RULM score data on patients with SMA type III (n=5) who were all non-ambulant and treated with nusinersen. The mean HFMSE and ALS-FRS-R scores were not evaluable, as data was not available for four out of five patients at the 14 months follow-up.

(Yeo et al. 2020), a prospective database study presented HFMSE and RULM scores in six participants treated with nusinersen, of whom two were non-ambulant type III. In

both individuals, the HMSFE scores remained stable over a 14-month follow-up period. Meanwhile, one patient had a clinically meaningful improvement in RULM score due to an increase in two points over a 15–18-month follow-up. While the RULM score remained stable for the other patient over a 14-month follow-up.

Within (Barp et al. 2020) two non-ambulant participants with type III SMA underwent clinical assessments at baseline (T0) and after 10 and 24 months from beginning nusinersen treatment. One patient reported a subjective improvement regarding their muscular endurance, while their RULM and HFMSE scores remained stable over time. In the second subject, their RULM scores remained stable, while their HFMSE score decreased between the first (26/66) and the second (21/66) follow up (the patient had to interrupt physiotherapy due to the COVID-19 pandemic).

(Shah et al. 2020) reported data for one non-ambulant individual with type III SMA who received a loading dose of nusinersen and eight maintenance infusions over an 8-month period. Grip and pinch strength measured at baseline and in six to 12-month intervals improved over a 24-month period. Additionally, in the subject's dominant hand there was a 2- and 3-fold increase in grip and pinch strength, respectively -— indicating a change in strength of smaller muscle groups. The subject also reported multiple other subjective improvements in function. This return of fine motor skills after treatment with nusinersen leads to improved patient independence.

(Okamoto et al. 2020) reported findings from 21 SMA patients, of whom one was non-ambulant with type III. No functional scales were used to quantitatively report findings, although the patient reported improvements in fine movement of their hands and fingers after 10 months of nusinersen treatment.

Clinician and SMA UK-provided case studies

For full details, please see Appendix G (SMA UK case series and survey) and Appendix H (clinician case studies).

Supportive evidence is presented in the form of case studies/series, including survey results, in patients that are currently receiving nusinersen treatment, which report motor function improvements (in several patients to the extent that they can now walk [further] with Knee-Ankle-Foot Orthoses [KAFOs]), improved core strength, and the disappearance of tremors and contractures in some individuals.

The activity of nusinersen in preventing and even reversing disease progression is demonstrated in two separate siblings case series. [redacted]

(Appendix H2)

In patients initiating nusinersen after losing ambulation in the previous 12 months, positive outcomes were reported as they achieve more independence and are able to perform actions they were not able to do previously. However, they and their caregivers still have anxiety around the possibility of the treatment being stopped, even though it is proving beneficial, as they/their child may fall within the current MAA stopping criterion of inability to regain ambulation within 12 months of nusinersen initiation. Biogen therefore ask the committee to review whether the stopping criteria are appropriate.

'The way in which [Person I] is progressing is having a big impact on Person I's mental wellbeing as well as Person I's physical health. The stability and improvements have provided [Person I] with more self-confidence and independence. Now that Person I has started to get oneself out of their wheelchair and is starting to learn to transfer it gives us hope that they could one day take themselves to the bathroom. The possibility of losing treatment when [Person I] is making such gains is devastating. ***The type 3a criteria is discriminating as those who are a weaker Type and those that are a stronger Type only have to prove that they are maintaining strength.*** *We live in fear that [Person I] could potentially*

have treatment stop and start to deteriorate again. The loss of treatment would reverse all [Person I's] hard work and gains which could possibly leave [Person I] at risk of health problems they does not currently have e.g. scoliosis. This treatment is not just about [Person I]. Our entire family unit is doing better because we have hope. We see stabilisation in [Person I] condition and improvements that we thought we would never see. We have hope in our hearts and have a genuine belief that if this treatment continues [Person I] will have an independent life, with work, relationships and a future. I have definitely seen improvements in my own mental health since commencing treatment.' **Parent of Person I with type III SMA (Appendix G)**

Additional data are presented in patients who are not receiving treatment currently (due to the restrictions in the MAA), showing the impact this is having on both their disease progression and QoL. As the disease is progressive, patients live with constant anxiety and stress as they lose upper body strength and independence.

'I am not embarrassed to say that I am terrified each day by the thought of losing all arm strength and ability. My life will change completely and the constant stress of waiting for this moment to happen is difficult to bear, when you know that there are drugs now available that could potentially help me. I can accept that I will probably not be able to walk again....I can live with that, but please recognise the huge importance of upper mobility and how devastating it can be to lose ability in this area. [nusinersen] could help massively in enabling people with SMA type 3 to sustain upper strength and therefore some independence within their lives.' **Person C with type III SMA, [redacted] (Appendix G)**

Thus, the well-being of patients could be improved through stabilisation of the disease.

The survey also noted how the arbitrary criteria for defining 'ambulation' have created a barrier to access for those who were clinically classified prior to the availability of nusinersen.

'Person B may have stepped more than five steps but never alone or unaided. Person B may have walked a few minutes back when [Person B] was diagnosed unaided not never with a straight back or one foot in front of the other! Person B's back swayed and walked side to side steps.' **Parent of Person B with type III SMA, [redacted] (Appendix G)**

'We want to again point out that we are perplexed at the way NICE has selected to use a definition of walking ability - taking five steps unaided - as an outcome Patient J has to achieve to continue treatment yet Patient J was never able to attain this at any stage of Patient J's life.' **Parent of Person J with type III SMA, [redacted] (Appendix G)**

Quality of life

The HRQoL systematic literature search identified 11 studies. These studies used a variety of tools to measure HRQoL, including Health Utilities Index Mark 3 (HUI3) system and various Paediatric Quality of Life Inventory questionnaires. Of these 11 studies, one presented a data breakdown specific to non-ambulant individuals with type III SMA (Belter et al. 2020) and four included nusinersen as an intervention (Weaver et al. 2020; Yeo et al. 2020; Montes et al 2019; Kirschner et al. 2018).

(Belter et al. 2020) presented HRQoL data from non-ambulant individuals with type III SMA (n=50), which were split into two subgroups, non-sitters (n=9) and sitters (n=41). To assess the overall HRQoL in patients with type III SMA, the HUI3 system was used, where scores can range from −0.36 (worst possible health state) through 0.00 (death) to 1.00 (perfect health), with scores lower than 0.70 corresponding to a severe disability. The mean HUI3 scores for the non-sitter and sitter subgroups were 0.14 and 0.23, respectively. Meanwhile, patients who had an increased functional status were associated with higher mean HUI3 scores, as those subgroups who could walk with support and walk independently had mean scores of 0.35 and 0.64, respectively. To put this in context, the mean HUI3 utility score for a range of neurological conditions across 776 individuals was 0.47 (95% CI 0.45–0.49) (Abel et al 2017).

Fatigue was assessed in (Belter et al. 2020), using the PROMIS Fatigue Short Form assessment tool where higher scores equate to greater levels of fatigue. The score of 50 represents the level of fatigue in the general population. Those individuals with type III SMA and categorised as sitters, reported a mean score of 58.4, compared to 57.7 for the type III subgroup who were classified as being able to walk independently.

The UK SMA community have provided HRQoL evidence regarding this sub population, highlighting the outcomes that are meaningful from the patients'/caregivers' perspectives (for full details see Appendix G). Specific patient and carer profiles from the PROMS survey were provided regarding non-ambulant children with type III SMA who are being treated with nusinersen in the UK (Appendix G), and similarly, adult patient profiles in this sub-population from across Europe (June 2020) (Appendix G). Additionally, results from two UK SMA community surveys, conducted between 10 January and 16 February 2020, were provided. One survey reported on individuals with type III SMA who are ineligible for access to nusinersen under the

current terms of the National Health Service (NHS) England MAA (n=25), and the other surveyed these individuals' caregivers (n=18) (Appendix G).

A case study (n=1) seen in Table 33 from the PROMS survey details a carer's reported outcomes for a non-ambulant child with type III SMA who has had access to nusinersen since 19 August 2020 (Appendix G). Although all the outcome improvements are overwhelmingly positive, with the caregiver reporting 'huge positive effects both mentally and physically' they also recognise the uncertainty surrounding the stopping criteria, by explaining that they

'live in fear that [their child] could potentially have treatment stopped and start to deteriorate again'. **Parent of Person H with type III SMA (Appendix G)**

Table 33. Caregiver reported outcomes (n=1) regarding their non-ambulant child with type III SMA

How has their treatment affected them?			
	9th Feb 2020	9th May 2020 (change since 9th Feb)	11th Sept 2020 (change since 9th May)
They seem happier than they did before	Strongly agree	Improved	Improved
They seem to like playing / socialising more with their friends at school / home than they did before	Strongly agree	Improved	Improved
They seem to be doing better at school / college	Agree	Improved	Improved
The family / their personal assistants need to do less to help them	Agree	Improved	Improved
The family needs less help from extended family (e.g. grandparents)	Neither agree nor disagree	Not applicable	Not applicable
They seem less stressed / worried about their SMA	Strongly agree	Improved	Improved
They seem less anxious about their future	Strongly agree	Improved	Improved
They have hope that continued treatment will mean they will have further improvements	Strongly agree	Improved	Improved
Notes: Nusinersen treatment was started on 19th August 2019 Source: Appendix G			

The use of nusinersen has enabled considerable improvements in the HRQoL of non-ambulant individuals with type III SMA across Europe. Individuals from Belgium, France and Serbia report an increased ease to undertake everyday tasks allowing a growing level of independence, with an individual explaining that their

'life is new since receiving this treatment' **Person K with type III SMA, [redacted] (Appendix G)**

and another describing that their

'days are fulfilled, with more activities' **Person K with type III SMA, [redacted] (Appendix G)**

as individuals report that they suffer less from fatigue and are able to relish in everyday life (Appendix G).

There is a very different narrative in those non-ambulant individuals with type III SMA who do not have access to nusinersen, as observed from the SMA UK community surveys (Appendix G). Although the loss of ambulation has led to challenges with undertaking everyday activities, this is being intensified with the deterioration of their upper limb function and strength resulting from the natural progression of SMA. This upper limb weakness threatens an individual's independence, with subjects commenting that tasks such as independently washing, writing, dressing, eating, and holding things are imperative to their HRQoL. One individual described her arm strength as

'the thing that affects me every minute of the day - I'm already in a wheelchair so it doesn't make much difference if nusinersen helps me stand up for a few seconds, I still couldn't go to the toilet independently. The creative activities that I'm most passionate about require arm strength, not leg strength (such as painting, drawing, cake decorating etc.) I can't imagine not being able to do these things anymore and yet soon I won't have to imagine it because it will be real.' **Person H with type III SMA, [redacted] (Appendix G) January 2020**

This subgroup of individuals is realistic that with nusinersen, major mobility improvements are unlikely, but are optimistic that with access to nusinersen, retention of upper limb function is feasible and an adequate quality of life can be maintained, as described by those individuals from across Belgium, France and Serbia (Appendix G).

'Any stabilisation of their condition would be a miracle. We are realistic and any sort of stabilisation or slowing of the effects would make such a difference in their lives.' **Aunt of Person L with type III SMA and Person M with type III SMA, [redacted] (Appendix G)**

Clinical stabilisation, enabling the maintenance of residual function, would be considered as therapeutic progress: In 2019, 96.7% of 1,327 validated responses to

SMA Europe's SMA Community survey stated they would 'consider it to be progress if there was a drug to stabilise their current clinical state'. Patients have expressed the importance of stabilisation in enabling them to continue with daily activities (Appendix G):

'I am getting weaker and want to have treatment to maintain what strength I have left and for an independent future. And do things myself, rather than asking for help all the time. I want to get stronger so I can use my hands and arms for day to day life activities like brushing my teeth, washing, writing, using cutlery, holding my computer controller.' ***Person G with type III SMA, [redacted] (Appendix G) January 2020***

'If a treatment is available to help me stay at or improve my ability slightly then it is worth it. I would rather stay the way I am now being able to do some things for myself rather than not be able to do anything at all which is the way it will end up going.' **Person N with type III SMA, [redacted] (Appendix G) January 2020**

'I'm not looking for major improvements, just a sense of stability so I can carry out my future how I want to live it. My arms are already getting weaker and weaker and so is my breathing and my swallow. It's said there isn't enough benefit to me having the treatment as I wouldn't regain or maintain the ability to walk. But that's not what's important to me! I just want to be able to not choke on my packet of crisps and to be able to lift my cup of tea to my mouth!!!' **Person H with type III SMA, [redacted] (Appendix G) January 2020**

With the current MAA entry and stopping criteria, patients' HRQoL has been affected in those who are not currently eligible for nusinersen. From the UK SMA community surveys, 79% (n=23/25) reported that they had been emotionally affected and that their day-to-day wellbeing had also been affected (Appendix G). Additionally, those who are not eligible for nusinersen reimbursement have described an increase in both the severity and frequency of anxiety with one individual stating that

'Not being eligible for treatment has had a severe impact on my mental health, I have been suffering from anxiety and panic attacks (something I've never experienced before) had trouble sleeping and have lost a considerable amount of weight.' **Person O with type III SMA, [redacted] (Appendix G)**

Relatives and caregivers of those individuals with type III SMA, are also greatly affected by the ineligibility of nusinersen for reimbursement, with 83% (n=15/18) of relatives strongly agreeing or agreeing that the lack of access to nusinersen has made

them stressed and that 61% (n=11/18) strongly agree or agree that it has affected their day-to-day wellbeing (Appendix G).

'Watching your child deteriorate over time is heart-breaking and we feel so desperately helpless. Knowing now the treatment is available makes me feel ill and desperately depressed.' **Parent of Person B with type III SMA, [redacted] (Appendix G)**

A.2.7. Subgroup analysis

The European registry data (Biogen data on file - registries non-ambulant type III data 2020) included both paediatric and adult patients. HFMSE and RULM scores in both populations, were aligned with the outcome (disease stabilisation post-nusinersen treatment) observed in the overall population, the changes in slopes of HFSME scores between pre- and post-nusinersen initiation were statistically significant in the overall group (p=0.002) and the paediatric subgroup (p=0.009). Statistically significant difference in RULM slopes between pre- and post-treatment initiation were observed in the overall population (p=0.019) and in the paediatric subpopulation (p=0.009), and a positive trend was observed in adults (p=0.31).

The full results for both sub-populations have been summarised in Appendix C.

A.2.8. Meta-analysis

No meta-analysis was carried out as there were no relevant comparators to nusinersen at the time of submission.

A.2.9. Indirect and mixed treatment comparisons

No indirect or mixed treatment comparisons were carried out as there were no relevant comparators to nusinersen at the time of submission.

A.2.10. Adverse reactions

The AEs and serious adverse events (SAEs) reported in the studies identified in Section A2.2 are summarised in Table 34 and Table 35. All AEs and SAEs were reported for the entire type III SMA population and not reported separately for the non-ambulant type III SMA population.

Table 34. Summary of AEs

N (%)	(Maggi et al. 2020) (N=116) All SMA3 patients	(Walter et al. 2019) (N=19) All SMA3 patients	(Yeo et al. 2020) (N=6) All SMA3 patients	(Cordts et al. 2020) (N=11) All SMA patients	(Darras et al. 2019) (N=28) All SMA3 patients
AEs leading to discontinuation	2 (1.9)	0 (0)	0 (0)	0 (0)	0 (0)
Common AEs reported					
No. of events No. of patients	NR 42 (40.7)	NR 11 (50.8)	12 6 (100)	11 NR	NR 28 (100)
AEs by preferred term					
Post procedure headache	NR	4 (21)	4 (67)	5 (9.4)	13 (46)
Hospitalisation due to headache	4 (3.9)	0 (0)	0 (0)	0 (0)	NR
Hospitalisation for an epidural blood patch	0 (0)	0 (0)	0 (0)	0 (0)	NR
Vertigo	0 (0)	0 (0)	2 (33.3)	0 (0)	NR
Lumbar/back pain	NR	7 (37)	0 (0)	3 (27.2)	9 (32)
Post LP complications	0 (0)	0 (0)	0 (0)	3 (27.2)	16 (57)
Worsening of existing hand tremor	2 (1.9)	0 (0)	0 (0)	0 (0)	NR
Renal colic requiring hospitalisation	0 (0)	0 (0)	0 (0)	0 (0)	NR
Fatigue	0 (0)	1 (5.3)	0 (0)	0 (0)	NR
Nasopharyngitis	NR	NR	NR	NR	12 (43)
Upper respiratory tract infection	NR	NR	NR	NR	12 (43)
Puncture site pain	NR	NR	NR	NR	11 (39)
Scoliosis	NR	NR	NR	NR	8 (29)
Pyrexia	NR	NR	NR	NR	7 (25)
Joint contracture	NR	NR	NR	NR	6 (21)
Rhinorrhoea	NR	NR	NR	NR	6 (21)
Vomiting	NR	NR	NR	NR	6 (21)

Abbreviations: AEs, adverse events

Table 35. Summary of reported SAEs

N (%)	(Darras et al. 2019)(N=28)
Summary of SAEs	5 (18)
Post-LP syndrome	2 (7.14)
Lower respiratory tract infection, respiratory distress, viral pneumonia	1 (3.6)
Respiratory failure and respiratory syncytial viral pneumonia	1 (3.6)
Vesicoureteral reflux and pyelonephritis	1 (3.6)

Abbreviations: AEs, adverse events; SAEs, serious adverse events

Across the five summarised studies, 180 individuals were treated with nusinersen and only one of these studies (Maggi et al. 2020) reported patient discontinuation (n=2) due to an AE. The most frequent AE was post-procedure headache. Nusinersen was generally well tolerated across all studies, with laboratory safety tests being unremarkable (when described). No safety information was detailed in the other publications (Barp et al. 2020; Okamoto et al. 2020; Shah et al. 2020).

The European registries reported safety events, specifically in the non-ambulant type III SMA population (Table 36). As in many other high-quality registries, AEs are not recorded in a standardised manner and the MedDRA classification is not used.

Table 36. European registries – safety

Category	Non-ambulant type III SMA (n=159)
Treatment discontinuations due to AE (inefficacy), n (%)	2 (1.3)
Abbreviations: AE, adverse event; SMA, spinal muscular atrophy.	

Additional safety issues

Communicating hydrocephalus not related to meningitis or bleeding has been reported in SMA patients, including children, treated with nusinersen in the post-marketing setting. A causal relationship with nusinersen has not been established. No cases of hydrocephalus were observed in the nusinersen clinical studies. A recent study from the US on the incidence of hydrocephalus in SMA patients not exposed to nusinersen showed a near 3-fold increased risk compared with non-SMA controls (Hall et al 2019). Data from the STR1VE trial (onasemnogene abeparvovec) in type I SMA (n=22) reported one case of hydrocephalus (Day et al).

Biogen's assessment of nusinersen's benefit-risk profile has not changed (Biogen SPC 2020). Although Biogen in conjunction with the EMA has not identified a causal link, it will continue to monitor the safety of nusinersen in the post-marketing setting.

Thrombocytopaenia and coagulation abnormalities, including acute severe thrombocytopaenia, have previously been observed after administration of other subcutaneous or intravenous antisense oligonucleotides (ASO) for other therapeutic indications. Nusinersen is administered intrathecally. In the integrated safety analysis of nusinersen, consisting of the eight studies described above, no cases of sustained

or severe thrombocytopaenia, nor bleeding-related AEs associated with decreased platelet counts were reported in the nusinersen-treated population (Mercuri et al 2017) . In view of the potential class effect, the Summary of Product Characteristics (SPC) states, as a precautionary measure that, platelet and coagulation laboratory testing is recommended prior to administration of nusinersen if clinically indicated (Biogen SPC 2020).

Renal toxicity has also previously been observed with other subcutaneous or intravenous ASOs for other therapeutic indications. Nusinersen is administered intrathecally. In the integrated safety analysis of nusinersen proteinuria was similar between nusinersen- and sham-control-treated patients (Mercuri et al. 2017). There is no indication that nusinersen causes renal toxicity. In view of the potential class effect, the SPC states, as a precautionary measure that, urine protein testing (preferably using a first morning urine specimen) is recommended, if clinically indicated. For persistent elevated urinary protein, further evaluation should be considered (Biogen SPC 2020).

Adverse reactions associated with the route of administration of nusinersen have been observed (Biogen SPC 2020). These adverse reactions are deemed to be due to the puncture of the meningeal layers during administration and not as an effect of the drug itself. The majority of these are reported within 72 hours of the procedure in keeping with classic post lumbar puncture syndrome, and Their incidence and severity were consistent with events expected to occur with lumbar punctures (Mercuri et al. 2017). No serious complications of lumbar puncture, such as serious infections, have been observed in the clinical trials of nusinersen.

Potential difficulties with lumbar puncture as a route of administration may be seen in very young patients and in those with scoliosis. The use of ultrasound or other imaging techniques to assist with intrathecal administration can be considered at the physician’s discretion (Biogen SPC 2020).

Adverse reactions have been identified during post-approval use of nusinersen (Biogen SPC 2020). Among patients treated with nusinersen, complications associated with lumbar puncture including subsequent serious meningeal infection have been observed. Meningeal infection is a risk whenever a procedure breeches the meningeal layers and can be minimised by appropriate sterile technique. The

frequency of these reactions is not known as they have been reported from the post-marketing setting, where there is no standardised manner of recording adverse reactions and the use of MedDRA classification.

A.2.11. Interpretation of clinical effectiveness and safety evidence

Treatment with nusinersen showed clinical benefit in non-ambulant type III patients comparable to those who were able to sit independently but never had the ability to walk independently (akin to type II SMA; who are currently eligible to receive nusinersen), as presented in this section.

Clinical and comparative effectiveness

Clinical trial evidence

CS11 (SHINE) included people with type II or type III SMA. Table 37 provides an overview of the included patients and HFMSE scores.

Table 37. SHINE HFMSE scores in type II and non-ambulant type III SMA

	n	Baseline	Last observed visit	mean change
Non-ambulant type III (CS2/12/11), mean (SE, range)	1	29.5 (3.5; 20–37)	NR	≥3-point
Type II (CS2/12), mean	11	21.3	28.6	+7.4pt
Type II (CS4 treated), mean	84	22.4	26.0	+3.6pt
Type II (CS4 untreated), mean	42	19.9	20.6	+0.7pt

A positive treatment effect of nusinersen was observed ([R]ULM scores) in non-ambulatory participants of Studies CS2/12 and Study CS11. Table 38 summarises the (R)ULM scores in CS11; at last observed visit, people with type II showed a median 3.0-point improvement from baseline (Figure 7), whereas people with non-ambulant type III remained stable at the ceiling score of 18 (as this score is the highest possible value on the scale it can only demonstrate a maintenance of effect) (Figure 8).

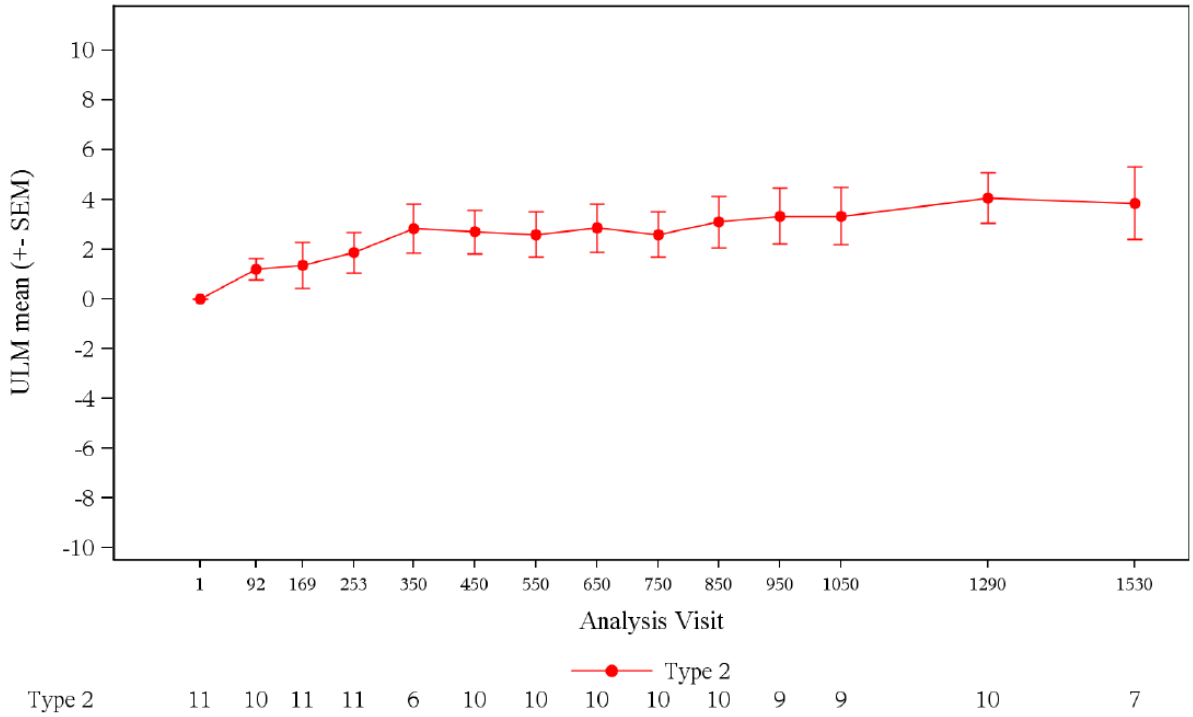
An increase of ≥2 points in the ULM is considered to represent a clinically meaningful improvement; however, the fact that most participants had ULM scores at the top of the dynamic range at baseline of Study CS11 limits the sensitivity of the ULM to assess continued improvement over the long term. When the total RULM score was mapped on the ULM scale to allow the participants from Study CS2 to be followed over time as

they transition to the RULM scale in Study CS11, results followed the same pattern as for the ULM scores.

Table 38. SHINE (R)ULM scores in type II and non-ambulant type III SMA

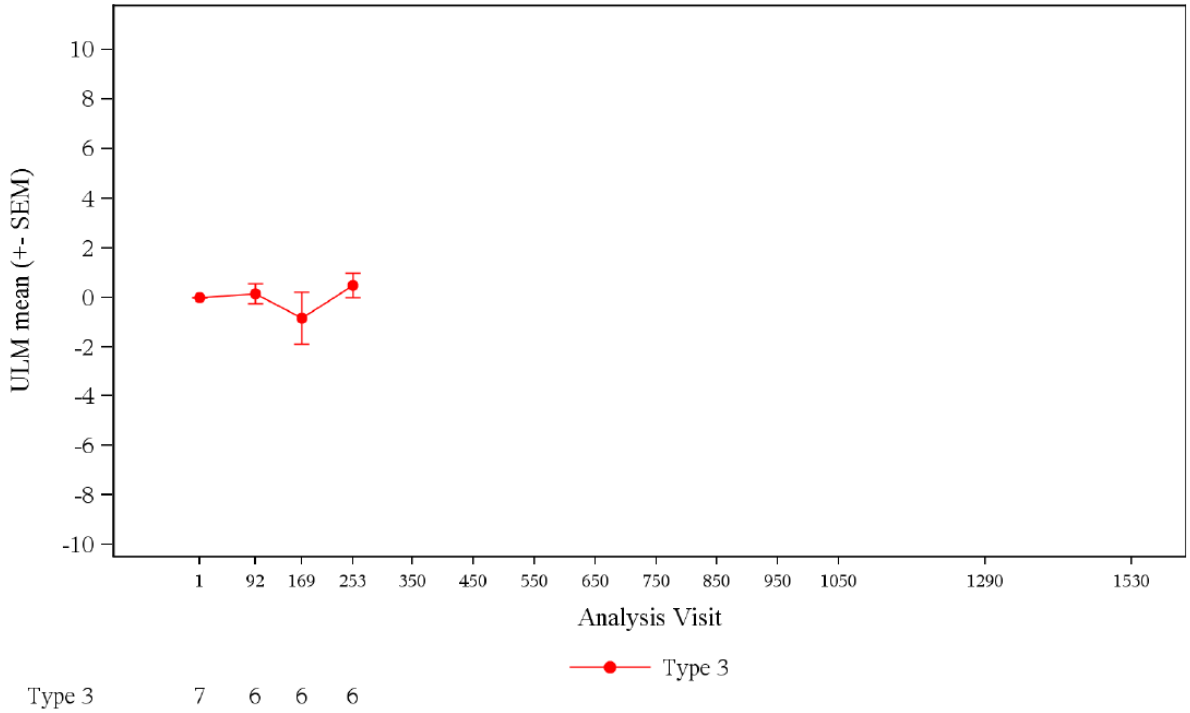
		Baseline	Last observed visit	median change
Non-ambulant type III, median	n=7	18.0 (max score)	18 (max score)	0 (stable)
Type II, median	n=11	11.0	16.0	+3.0pt
Abbreviations: (R)ULM, (Revised) Upper Limb Module; SMA, spinal muscular atrophy.				

Figure 7. ULM: mean change in total score from baseline by visit (CS2/12/11) – type II SMA



Notes: A visit is only presented if there are >5 subjects at that visit. Baseline presented at analysis visit 1. Only subjects with a non-missing value at baseline are presented.

Figure 8. ULM: mean change in total score from baseline by visit (CS2/12/11) – type III SMA



Notes: A visit is only presented if there are >5 subjects at that visit. Baseline presented at analysis visit 1. Only subjects with a non-missing value at baseline are presented.

Evidence from CS4 (CHERISH), which included individuals with genetically confirmed SMA who could sit independently, but never had the ability to walk independently (type II), was presented in the original submission – leading to this specific patient population (type II) to be included in the MAA.

CS4 data showed that nusinersen-treated patients (n=84) had a mean increase in RULM score of 4.2pt (95% CI: 3.4–5.0) at 15 months follow-up. A similar observation was made in the HFMSE score (4.0pt change [95% CI: 2.9–5.1]). The biggest changes were observed in children <6 years of age, indicating that the benefits are potentially greater the earlier in the disease course that treatment is initiated (Mercuri et al. 2018a).

In the clinical study data from people with non-ambulant type III, disease stabilisation could also be observed with HMFSE scores increasing and RULM scores remaining at the maximum score. The scores cannot be directly compared as CS4 included 84 patients, whereas in CS2/12 only four non-ambulant type III individuals were included (who were >6 years old); however, the results do indicate that nusinersen provides

disease stabilisation in both non-ambulant patient populations – providing a meaningful impact on patients' lives.

RWE (registries)

Registry data shows that nusinersen treatment is effective in stabilising disease in the non-ambulant type III population (Biogen data on file - registries non-ambulant type III data 2020). The slope of HFMSE score significantly declines before treatment with nusinersen (estimated at 0.06pts/week [equal to 3pts/year]), after treatment initiation the slope stabilises – showing a statistically significant difference pre- vs post-treatment. The same trend was observed for RUhavLM scores.

When considering the paediatric (n=[redacted]) and the adult (n=[redacted]) populations separately, similar patterns (although not statistically significant in adults) can be observed.

Observations from the Italian registry data (which included non-ambulant type III [n=51] and type II [n=13] patients) (Table 39) showed that nusinersen treatment led to improvements in HFMSE and RULM scores of both populations, although with higher responses for type III (Maggi et al. 2020).

Table 39. Motor function changes at T6, T10 and T14 – non-ambulant type III SMA

Timeframe	Variable	N	Mean ± SD	Median (min–max)	Paired Wilcoxon p-value
Type II SMA					
T0–T6 change	HFMSE	13	0.15 ± 2.08	0 (−5 to 5)	n.s.
	RULM	12	0.80 ± 1.95	0 (−1 to 6)	n.s.
T0–T10 change	HFMSE	9	1.00 ± 2.00	0 (0 to 6)	n.s.
	RULM	9	1.67 ± 1.80	2 (0 to 5)	**0.057**
T0–T14 change	HFMSE	5	1.20 ± 2.68	0 (0 to 6)	n.s
	RULM	5	1.60 ± 1.52	2 (0 to 3)	n.s
Non-ambulant type III					
T0–T6 change	HFMSE	51	1.37 ± 2.02	1 (−4 to 6)	**<0.0001**
	RULM	51	0.63 ± 2.48	0 (−8 to 6)	0.056
T0–T10 change	HFMSE	35	2.51 ± 2.94	1 (−3 to 9)	**<0.0001**
	RULM	33	1 ± 2.45	1 (−6 to 5)	**0.021**
T0–T14 change	HFMSE	19	3.53 ± 3.67	3 (−3 to 11)	**0.0014**
	RULM	19	1.47 ± 2.5	2 (−6 to 5)	**0.018**

Abbreviations: HFMSE, Hammersmith Functional Motor Scale Expanded; n.s., not significant; RULM, Revised Upper Limb Module; SD, standard deviation; SMA, Spinal Muscular Atrophy; T0-6-10-14, baseline, six months, 10 months and 14 months.
Notes: Significant p-values are highlighted in bold.

Thus, treatment with nusinersen leads to improvement or at least stabilisation of disease (as measured by HFMSE and/or RULM).

Safety evidence

No new types of AE, SAE, nusinersen-related (S)AE or other safety issues have been reported in the post-marketing setting. Even though in registries the AEs are not recorded in a standardised manner, the frequency and types of reported AEs are similar in the non-ambulant type III SMA population compared with the type II SMA population (Biogen data on file - registries non-ambulant type III data 2020; Maggi et al. 2020).

Strengths of the clinical evidence

The majority of data for the non-ambulant type III SMA population comes from registries – it shows that nusinersen is effective in stabilising disease in the real-world setting across a wide spectrum of severity and age, including patients living with non-ambulant type III SMA. The real-world nature of the data is even more pertinent as it shows that the treatment response is generalisable to the heterogenous populations seen in clinical practice. Case studies and series further support these findings – highlighting the stark difference in stabilising disease in patients who receive nusinersen treatment against the continued deterioration seen in those who currently do not, and the real-life impact that this has on improving the QoL of individuals and their caregivers.

Limitations of the clinical evidence

There are limited data available within a trial setting for this specific patient population; this is to be expected as 5q SMA is an orphan condition and the majority of patients have a diagnosis of type I or II. In addition, nusinersen has been available for the treatment of people with ambulant type III, stabilising their disease and preventing loss of ambulation – further limiting the size of the non-ambulant type III population.

Additional registry data showed similar patterns of disease stabilisation in large groups of non-ambulant type III patients, aligned with the outcomes seen in clinical trials. Low patient numbers are available in the untreated (BSC alone) cohort as nusinersen is reimbursed for all type III patients in the registry locations.

The limitations of motor scales are well-recognised, with floor and ceiling effects that may potentially lead to underestimation of the extent of decline or improvement (Vazquez-Costa 2020; Wadman et al. 2018). The scales also do not always capture what is most important to the patient such as finger dexterity required to control a wheelchair and thus gross mobility, which greatly impacts on QoL (Wan et al. 2020; McGraw et al 2017). Patient-reported outcomes enable inference of therapeutic benefit in relation to important symptoms that are not captured by motor measurements (e.g. less fatigue), which enable patients to perform activities of daily living (Vazquez-Costa 2020). Hence this submission additionally presented case studies (as mentioned above), which confirmed the treatment benefits of nusinersen beyond those demonstrated in the clinical studies and observational/registry studies.

Future considerations for this population

The size of the non-ambulant type III SMA population is expected to decrease over time as people with ambulant type III SMA have been eligible to receive nusinersen, which will ameliorate further deterioration of muscle function.

Overall conclusions

The evidence presented in this submission demonstrates the clinical and humanistic benefits of treatment with nusinersen in the non-ambulant type III SMA population, both adult and paediatric.

Nusinersen provides clinical benefits in people with non-ambulant type III SMA, as demonstrated by the clinical data and real-world evidence showing at least stabilisation, and improvement for some individuals, in motor function. Thus, treatment with nusinersen achieves meaningful outcomes as perceived by patients and caregivers, enabling maintenance or improvement of their current functional state. As the extent of motor function is correlated with bulbar and respiratory functions (Trucco et al. 2020), the benefits are expected to extend beyond motor function, reducing clinical decline over the long-term in these additional functional domains.

Halting progression in patients' current clinical and functional state is a major objective of treatment for people with non-ambulant type III SMA. Preventing progressive loss of independence has a tremendous impact on patients' and carers' QoL; it enables patients to continue to study/work and participate in leisure activities, thereby

contributing to society. This cannot be achieved through current standard of care alone. Nusinersen has been shown to be effective in stabilising disease progression, and in many cases achieving improvements, across all SMA populations, including the non-ambulant type III – both in clinical trials and in the real world (Section 2.6).

Currently the MAA states that paediatric non-ambulant type III individuals who lost the ability to walk in the last 12 months are eligible for treatment with nusinersen; however, the stopping rule states that if they do not regain ambulation within 12 months, nusinersen treatment must be stopped. As presented under the QoL heading of Section 2.6, this has a major impact not only on patients' anxiety but also their caregivers – they effectively exist in a state of uncertainty during that time. Ambulation should not be the sole goal of treatment for the non-ambulant population, especially as with the loss of ambulation and thus sitting in a wheelchair for extended periods of time, tendons shorten and contract, joints and bones remodel and muscles rebalance (Skalsky and McDonald 2012) – making the regain of ambulation progressively more difficult. Patients typically undergo a rigorous physical therapy plan alongside nusinersen treatment – but this has been impacted by the current COVID-19 pandemic. Instead, clinical stabilisation (focusing on outcomes such as upper body strength, upper limb function, fine motor function, and stamina) has a far greater impact on patients' independence and QoL and therefore also the value to society.

The comparison with type II SMA (achieved ability to sit but never achieved the ability to walk independently) shows that the clinical effectiveness (motor function) of nusinersen is comparable in both populations – i.e. at minimum stabilising the disease. This is expected as the documented natural history of the disease, regardless of the 'type' of SMA, shows that patients experience continued deterioration of motor skills and muscle weakness. This continued deterioration is consistent across all SMA 'sitters' (i.e. type II and non-ambulant type III) without disease-modifying treatment, regardless of their original condition on the SMA continuum. The international community is therefore moving away from the 'arbitrary' SMA typing, towards managing patients based on current gross motor function and, therefore, classifying them as non-sitters, sitters and walkers. The consistent deterioration of motor skills across the different types makes it difficult to apply the typing consistently in the 'real world' as there is much overlap in symptoms between, for example, people with either

type II or non-ambulant type III SMA. However, with the existing MAA criteria restricting nusinersen access for the latter, this distinction in treatment based on type of SMA has a major impact on patients as well as their caregivers, in terms of outcomes, disease progression and QoL.

The data presented in this submission showing comparable benefit of treatment in type II and non-ambulant type III patients is consistent with the expected categorisation of both populations as 'sitters' according to the above classification. The evidence presented in this submission (as well as nusinersen's mode of action) further emphasises the lack of clinical or biological plausibility as to why nusinersen treatment would not be as beneficial in people with non-ambulant type III as in those who are classified as type II.

Nusinersen has already unequivocally demonstrated benefit in SMA patients, enabling the achievement of motor milestones beyond expected based on the known natural history of the disease, as evidenced from clinical trials and observational data, with over 11,000 patients treated for durations of up to 6.5 years, globally (Biogen 2020). The evidence presented in this submission further confirms that clinical benefits are achieved in treated patients regardless of type. The current access inequality is not driven by patient need and the potential benefit of treatment, but instead by characteristics such as age and level of disability. People with non-ambulant type III SMA in Scotland, and much of Europe do have access to nusinersen (NICE 2019; SMC 2018). It is devastating that patients with SMA who could benefit from this therapy are being denied access, especially with the mounting evidence affirming the benefits of treatment in all populations, regardless of current in/ability to walk.

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A.4. Appendices

Appendix A : Appendix A: Summary of product characteristics (SmPC) and European public assessment report (EPAR)

Appendix B: Identification, selection and synthesis of clinical evidence

Appendix C: Subgroup analysis (not applicable)

Appendix D: Adverse reactions (not applicable)

Appendix E: Health-related quality-of-life studies

Appendix F: Checklist of confidential information

Appendix G: SMA UK case series and survey

Appendix H: Clinician case studies

Abbreviation list

HFMSE	Hammersmith Functional Motor Scale Expanded
HRQoL	health-related quality of life
MeSH	Medical Subject Headings
NICE	The National Institute for Health and Care Excellence
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
RULM	Revised Upper Limb Module
SLR	systematic literature review
SMA	spinal muscular atrophy

A.5. Appendix A: Summary of product characteristics (SmPC) and European public assessment report (EPAR)

Both documents have been separately added to the submission files.

A.5.1. A1.1 SmPC

Appendix A1. SPC Spinraza.pdf

A.5.2. A1.2 EPAR

Appendix A1. EPAR Spinraza.pdf

A.6. Appendix B: Identification, selection and synthesis of clinical evidence

A.6.1. B1.1 Identification and selection of relevant studies

A full systematic literature review (SLR) was undertaken to identify all studies that provide information on the clinical outcomes of treatment with nusinersen in the non-ambulant type III spinal muscular atrophy (SMA) population. This review was conducted in three stages, and followed Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) recommendations: a comprehensive and systematic search of the published literature to identify all potentially relevant studies; a systematic selection of relevant studies based on explicit inclusion and exclusion criteria; an extraction of relevant data from eligible studies to assess the clinical outcomes of nusinersen evidence.

Search strategy

Medline (Pubmed) and Embase (Elsevier) were used. Both search strategies were built using a variety of 'free text' and Medical Subject Headings (MeSH) terms (Table 40 and Table 41). These search terms included terms for non-ambulant patients with type III SMA and terms for various clinical outcomes. The timeframe for this SLR was 1 October 2017 to 21 October 2020, capturing new data since the 2017 National Institute for Health and Care Excellence (NICE) submission for nusinersen.

Table 40. Search strategy Medline – clinical nusinersen studies in the non-ambulant type III SMA

#	Search string	Hits
1	(((atrophy, spinal muscular[MeSH Terms]) OR (spinal muscular atrophy)) OR (SMA)) OR (Kugelberg-Welander)	29,013
2	((((Type 3) OR ("non-ambulant")) OR (SMA3)) OR (Type III)) OR (sitt*)	984,583
3	(nusinersen) OR (spinraza)	338
4	#1 AND #2 AND #3	**82**
5	("2017/10/01"[Date - Publication] : "3000"[Date - Publication])	3,979,885
6	#4 AND #5	**78**

Table 41. Search strategy Embase – clinical nusinersen studies in the non-ambulant type III SMA population

#	Search string	Hits
1	'spinal muscular atrophy'/exp/mj OR (spinal AND muscular AND atrophy) OR sma OR 'kugelberg welander disease'	73,838
2	(type AND 3 OR 'non-ambulant' OR sma3 OR type) AND iii OR sitt*	216,093
3	nusinersen OR spinraza	874
4	#1 AND #2 AND #3	**100**
5	[2017-2020]/py	6,173,086
6	#4 AND #5	**98**

Study selection

Potentially relevant publications were reviewed and assessed in two steps to collate a final set of studies for clinical data extraction. First, to identify any potentially relevant papers, an initial screening of titles and abstracts against the inclusion/exclusion criteria (Table 42) was undertaken. Then, using the same inclusion/exclusion criteria, a full-text screening of the possibly relevant papers identified in the initial screening was undertaken. Decisions on the selection of studies were made by two researchers who screened the titles and abstracts, and the full papers, independently. For any studies where the researchers had a disagreement that could not be resolved, a third researcher made the final decision based on the inclusion criteria.

Table 42. Inclusion and exclusion criteria used in the clinical literature review

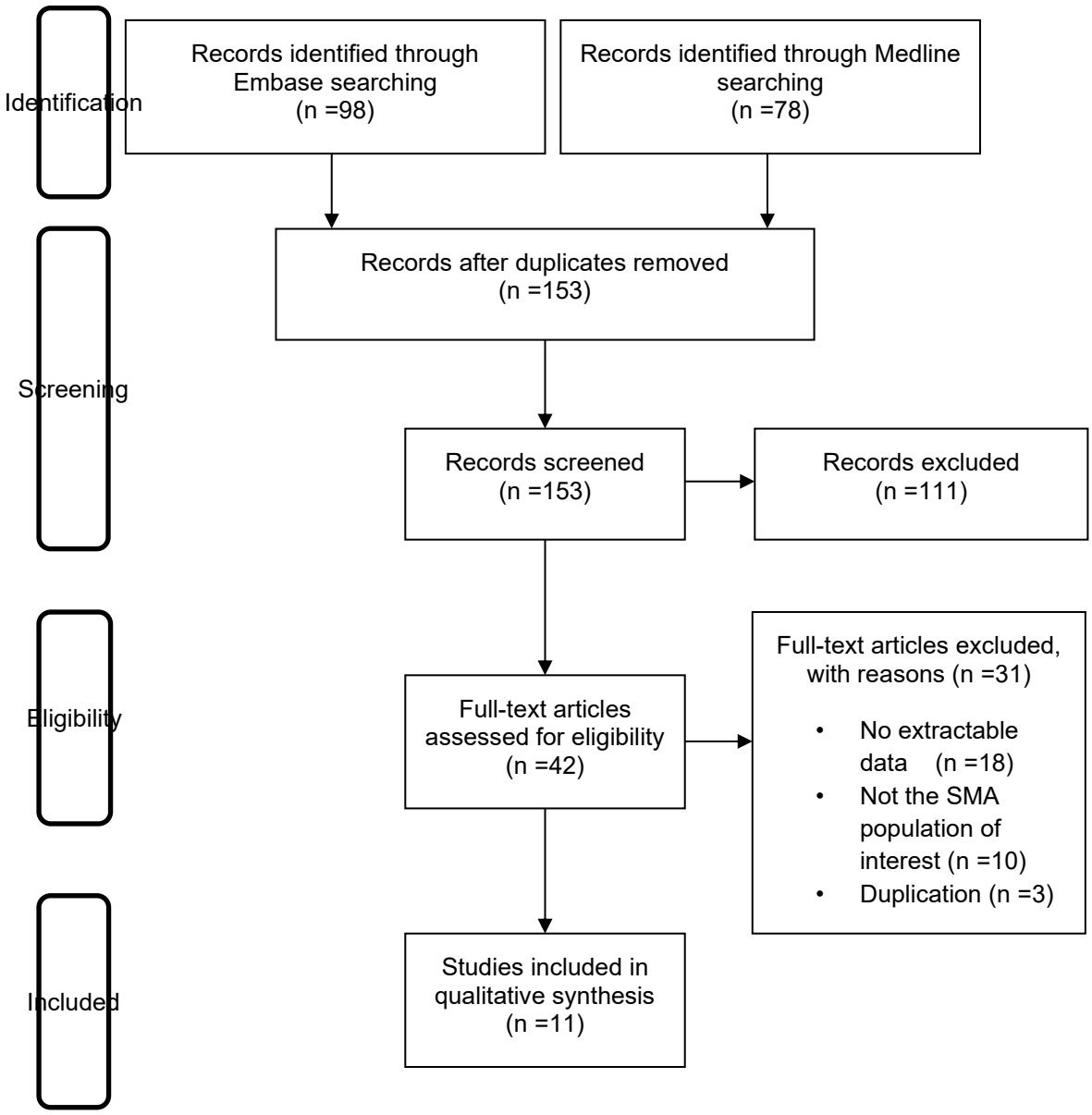
Characteristics	Inclusion criteria	Exclusion criteria
Population	Non-ambulant type III SMA patients (paediatric and adult)[1]	other types of SMA[1]
Interventions	nusinersen	
Comparators	best supportive care	
Outcomes	No limitations on inclusion based on reported clinical outcomes. Specific outcomes of interest include: motor function (e.g. HFMSE and RULM score) Respiratory function Bulbar function Complications of SMA (incl. scoliosis) Stamina and fatigue Mortality Adverse events related to treatment	Economic models Budget impact
Study design	RCTs Non-RCTs Observational studies Registry data	
Language	English	Non-English publications
Publication type and status	Manuscripts Conference proceedings	
Date of publication	October 2017[2]–present	pre–October 2017[2]

Abbreviations: RCT, randomised controlled trial; SMA, spinal muscular atrophy.
Notes: [1] data for the non-ambulant type III population needs to be presented separately, otherwise the study will be excluded. [2] This SLR aims to identify any evidence published since the original submission to NICE in 2018, no clinical SLR was conducted for that submission, however, searches for economic, HRQoL/utility SLRs were conducted in October 2017.

A PRISMA diagram is presented in Figure 9. Searches were conducted on 21 October 2020. A total of 176 potentially relevant papers and abstracts were identified for review. A de-duplication step was performed to remove studies that overlapped across the databases; 23 of the studies were identified as duplicated and excluded. The remaining studies were screened based on the information reported in their titles and abstracts. Of these, 111 were excluded at the primary screening stage as they did not include any information regarding the clinical outcomes of treatment with nusinersen in the non-ambulant type III SMA population.

A total of 42 articles were assessed in full for further evaluation. Of these, 31 were excluded for reasons such as having no extractable data (n=18), not investigating the population of interest (n=10) or duplication (n=3). Therefore, a total of 11 citations were included for this SLR. Of these 11 citations, two of the papers cover the same clinical trial population (CS2/12).

Figure 9. PRIMSA flow for clinical SLR



Complete reference lists for included studies and excluded studies

Table 43. Studies included in clinical SLR

Author	Year	Title	Journal
Barp, A., et al.	2020	Muscle MRI in two SMA patients on nusinersen treatment: A two years follow-up	Journal of the Neurological Sciences, 417.
Cordts, I., et al.	2020	Intrathecal nusinersen administration in adult spinal muscular atrophy patients with complex spinal anatomy.	Ther Adv Neurol Disord, 13, 1756286419887616.
Darras, B. T., et al.	2019	Nusinersen in later-onset spinal muscular atrophy: Long-term results from the phase 1/2 studies	Neuromuscular Disorders, 30, S120.
Deconinck, N., et al.	2019	Nusinersen experience in teenagers and young adults with spinal muscular atrophy (SMA): Results from CS2/CS12 and SHINE	European Journal of Neurology, 26, 143-144.
Kirschner, J., et al.	2018	Nusinersen experience in individuals with spinal muscular atrophy type III: A case series	Journal of Neuromuscular Diseases, 5, S366-S367.
Maggi, L., et al.	2020	Nusinersen safety and effects on motor function in adult spinal muscular atrophy type 2 and 3	Journal of neurology, neurosurgery, and psychiatry.
Muntoni, F., et al.	2020	Longer-term experience with nusinersen in teenagers and young adults with spinal muscular atrophy: Phosphorylated neurofilament heavy chain (pNF-H) and efficacy results from the CS2-12/SHINE studies	European Journal of Neurology, 27, 948-949.
Okamoto, K., et al.	2020	Survey of patients with spinal muscular atrophy on the island of Shikoku, Japan	Brain Dev, 42, 594-602.
Shah, J. S., et al.	2020	Two Years of Improved Neurological Function With Nusinersen in a 48-Year-Old Patient With Spinal Muscular Atrophy Type 3	Neurologist, 25, 141-143.
Walter, M. C., et al.	2019	Safety and treatment effects of nusinersen in longstanding adult 5q-SMA type 3 – A prospective observational study	Journal of Neuromuscular Diseases, 6, 453-465.
Yeo, C. J. J., et al.	2020	Prospective Cohort Study of Nusinersen Treatment in Adults with Spinal Muscular Atrophy	J Neuromuscul Dis, 7, 257-268.

Table 44. Studies excluded in clinical full-text screening and reasons for exclusion

Author	Year	Title	Journal
No extractable data			
Ayaki, T., et al.	2019	Clinical outcomes in adult spinal muscular atrophy treated with nusinersen	Clinical Neurology, 59, S258.

Belter, L., et al.	2018	An overview of the Cure SMA membership database: Highlights of key demographic and clinical characteristics of SMA members	Journal of Neuromuscular Diseases, 5, 167-176.
Brener, A., et al.	2020	The endocrine manifestations of spinal muscular atrophy, a real-life observational study	Neuromuscul Disord, 30, 270-276.
Caumo, L., et al.	2019	Longitudinal functional changes in a cohort of adult nusinersen-treated spinal muscular atrophy patients at the Padova Neuromuscular Center	Acta Myologica, 38, 128.
Darras, B. T., et al.	2019	An Integrated Safety Analysis of Infants and Children with Symptomatic Spinal Muscular Atrophy (SMA) Treated with Nusinersen in Seven Clinical Trials	CNS Drugs, 33, 919-932.
Faravelli, I., et al.	2020	Nusinersen treatment and cerebrospinal fluid neurofilaments: An explorative study on Spinal Muscular Atrophy type 3 patients	J Cell Mol Med, 24, 3034-3039.
Hodgkinson-Brechenmacher, V., et al.	2020	SMA: registries, biomarkers & outcome measures: p.174 The Canadian neuromuscular disease registry: A national spinal muscular atrophy (SMA) registry for real world evidence	Neuromuscular Disorders, 30, S97-S98.
Langton, E. L., et al.	2019	Safety and efficacy of nusinersen in adult and adolescent patients with spinal muscular atrophy: A retrospective case series	Annals of Neurology, 86, S107.
Lilien, C., et al.	2020	SMA: registries, biomarkers & outcome measures: p.182 ActiMyo®: Upper limb activity in non-ambulant patients with spinal muscular atrophy treated with Spinraza	Neuromuscular Disorders, 30, S100.
Mendonça, R. H., et al.	2020	Real-World Data from Nusinersen Treatment for Patients with Later-Onset Spinal Muscular Atrophy: A Single Center Experience	J Neuromuscul Dis
Moshe-Lilie, O., et al.	2020	Nusinersen in adult patients with spinal muscular atrophy: Observations from a single center	Neurology, 95, e413-e416.
Özütemiz, C., et al.	2020	Nusinersen injections in adults and children with spinal muscular atrophy: a single-center experience	Diagn Interv Radiol
Sheikh, G., et al.	2019	Treatment of spinal muscular atrophy with nusinersen produces improvement in pulmonary function in children with SMA II and SMA III	Journal of Respiratory and Critical Care Medicine, 199.
Stolte, B., et al.	2018	Feasibility and safety of intrathecal treatment with nusinersen in adult patients with spinal muscular atrophy	Ther Adv Neurol Disord, 11, 1756286418803246.
Szabó, L., et al.	2020	Efficacy of nusinersen in type 1, 2 and 3 spinal muscular atrophy: Real world data from Hungarian patients	Eur J Paediatr Neurol, 27, 37-42.

Veerapandiyan, A., et al.	2019	Intrathecal nusinersen in older children and adults with spinal muscular atrophy	Annals of Neurology, 86, S130.
Wurster, C. D., et al.	2019	Intrathecal administration of nusinersen in adolescent and adult SMA type 2 and 3 patients	J Neurol, 266, 183-194.
Young, S. D., et al.	2020	SMA - CLINICAL: P.79 Analysis of Cobb angle and clinical characteristics in children with spinal muscular atrophy who enrolled in CHERISH and SHINE	Neuromuscular Disorders, 30, S70.
Not investigating the population of interest			
Bertini, E.	2019	The importance of early treatment: New NURTURE data	Acta Myologica, 38, 90.
Castro, D., et al.	2020	Nusinersen in infantile-onset spinal muscular atrophy: Results from longer-term treatment from the open-label shine extension study	Neurology, 94.
Chacko, A., et al.	2020	Polysomnography findings in pediatric spinal muscular atrophy types 1-3	Sleep Med, 68, 124-130.
Chiriboga, C. A., et al.	2020	Longer-term treatment with nusinersen: Results in later-onset spinal muscular atrophy from the shine study	Neurology, 94.
Chiriboga, C., et al.	2019	Interim report on the safety and efficacy of longerterm treatment with nusinersen in later-onset spinal muscular atrophy (SMA): Results from the shine study	Annals of Neurology, 86, S117-S118.
Comi, G. P.	2018	Nusinersen in SMA adult patients: First experiences	Acta Myologica, 37, 36.
Darras, B. T., et al.	2019	Interim report on the safety and efficacy of longer-term treatment with nusinersen in later-onset spinal muscular atrophy (SMA): Results from the SHINE study	Neurology, 92.
Kirschner, J., et al.	2019	Interim report on the safety and efficacy of longer-term treatment with nusinersen in later-onset spinal muscular atrophy (SMA): Results from the shine study	Journal of the Neurological Sciences, 405, 248-249.
Kirschner, J., et al.	2019	Interim report on the safety and efficacy of longer-term treatment with nusinersen in later-onset spinal muscular atrophy (SMA): results from the SHINE study	Journal of the Neurological Sciences, 405, 248-249.
Sansone, V. A., et al.	2020	Sometimes they come back: new and old SMA adults in the era of nusinersen	European journal of neurology
Duplication			
Chiriboga, C., et al.	2018	Nusinersen experience in individuals with spinal muscular atrophy (SMA) type III: A case series	Annals of Neurology, 84, S351.
Darras, B., et al.	2020	SMA – THERAPY: P.254 Nusinersen in adolescents and young adults with SMA: Longitudinal experience from an expanded cohort of CS2/CS12 and SHINE participants	*Neuromuscular Disorders,* 30**,** S120.
Day, J. W., et al.	2020	Longer-term experience with nusinersen in teenagers and young adults with	Neurology, 94.

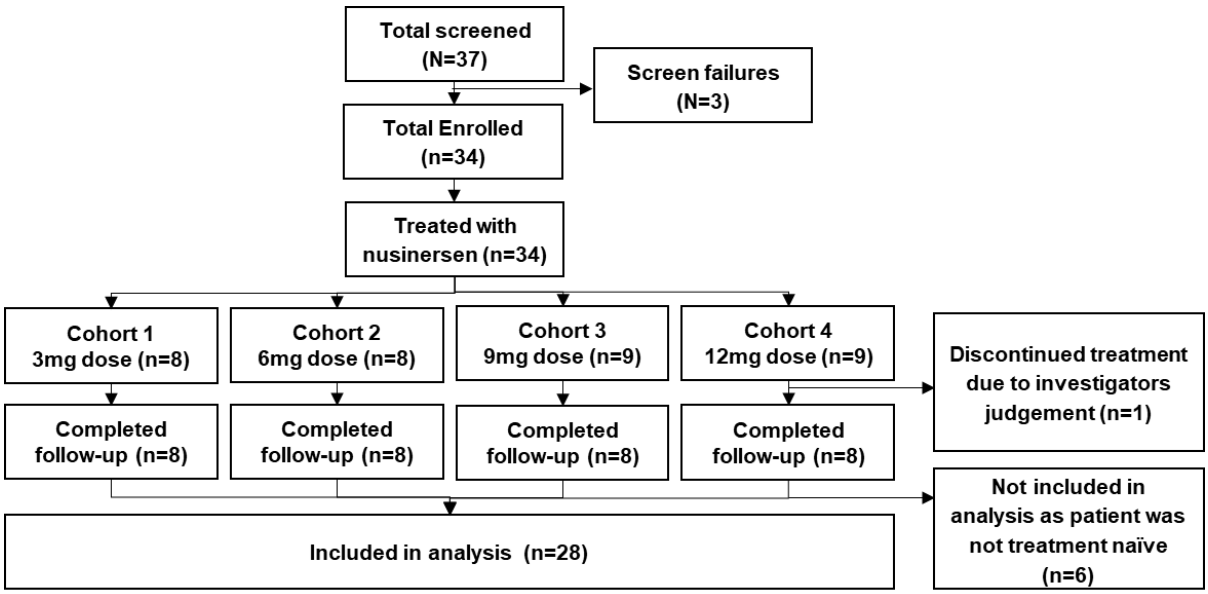
		spinal muscular atrophy: Results from the CS2/CS12 and shine studies	

A.6.2. B1.2 Participant flow in the relevant randomised control trials

CS2: Disposition of patients

A total of 37 patients were screened, a total of three patients failed the screen resulting in a total of 34 patients being enrolled. Of this 34, eight subjects were enrolled in each of the 3- and 6-mg dose cohorts, and nine subjects were enrolled in each of the 9-and 12-mg dose cohorts. One subject in the 12-mg dose cohort discontinued treatment early due to Investigator's judgment. Specifically, the Investigator concluded that the subject and the parents could not tolerate the study procedures associated with dosing and pharmacokinetic draws, and thus the subject was withdrawn.

Figure 10. CS2 patient disposition – flow diagram

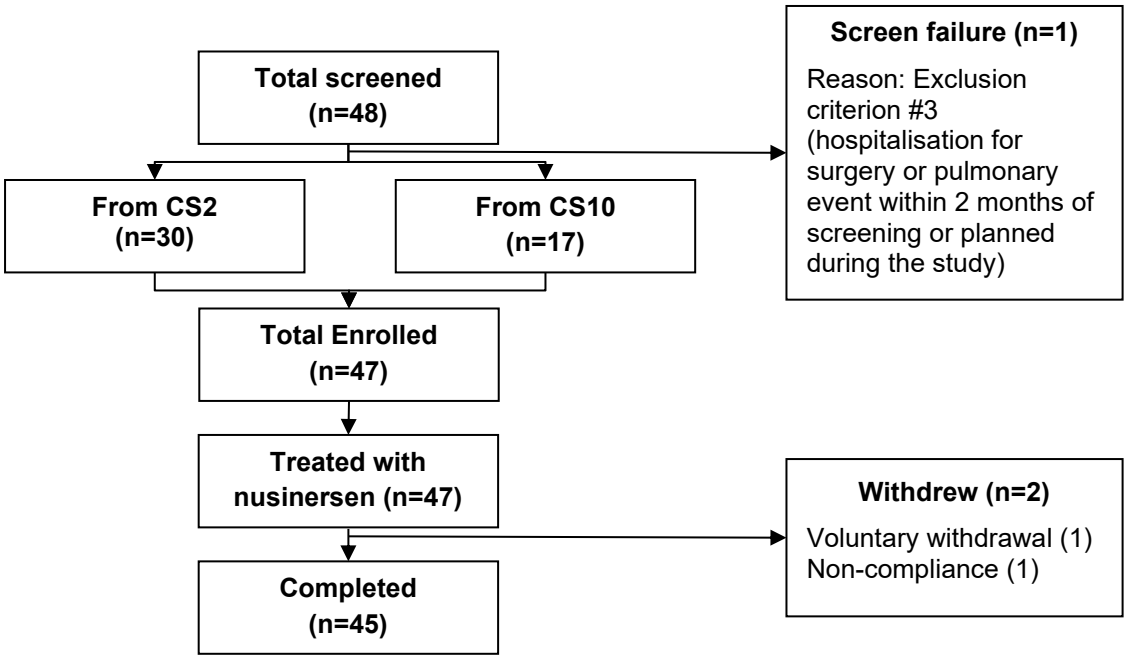


CS12: Disposition of patients

A total of 48 patients were screened, of whom 47 were enrolled and treated at 4 centres in the US. Thirty subjects had previously participated in Study CS2, and 12 subjects had participated in Study CS10. Of the 47 subjects who received treatment, 45 (95.7%) completed study treatment and post-treatment follow-up. Two subjects

(4.3%) discontinued treatment and withdrew from the study: one subject withdrew from the study voluntarily, and one other subject was withdrawn from the study due to noncompliance with the protocol.

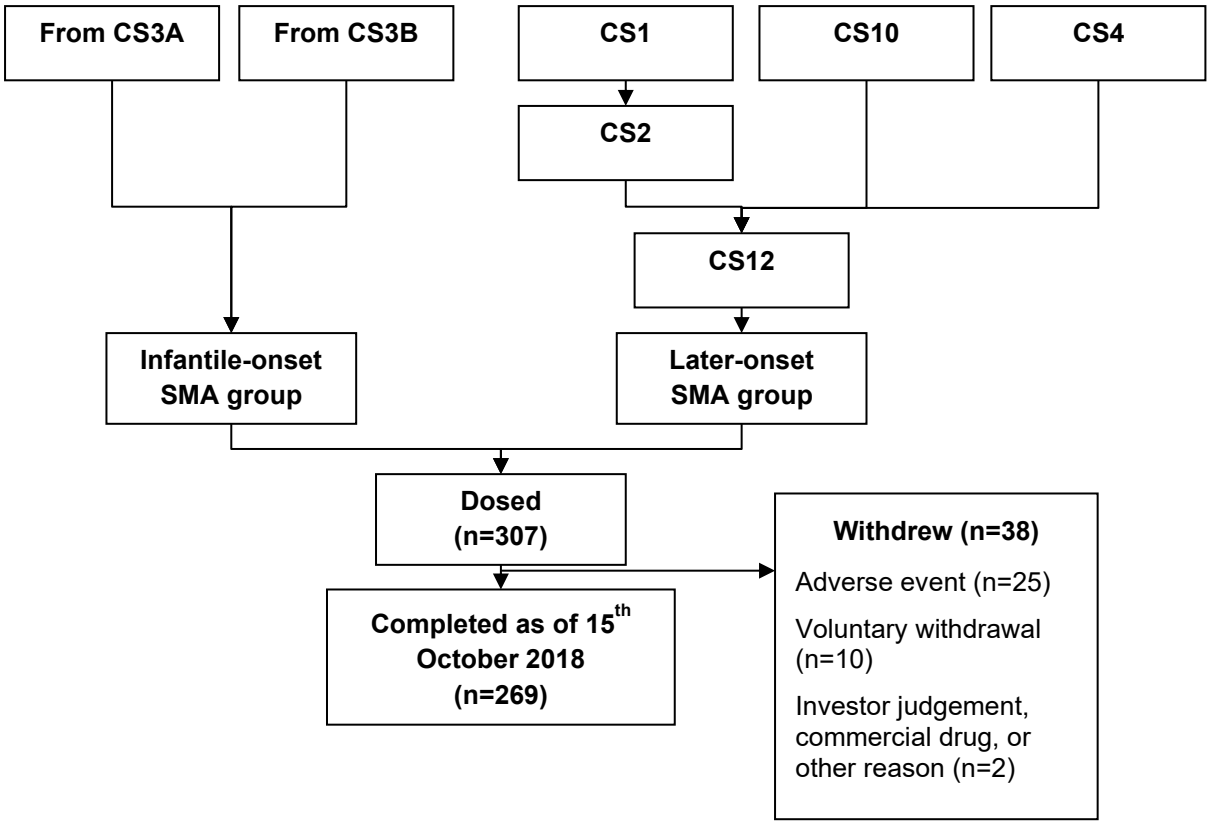
Figure 11. CS12: Disposition of patients – flow diagram



CS11 – Interim data from 15 October 2018: Disposition of patients

In total, 307 subjects were dosed, 182 subjects as part of the later-onset SMA group and 125 subjects as part of the infantile-onset SMA group. A total of 38 subjects (12%) withdrew from the study: 25 subjects (8%) due to an adverse event, 10 participants (3%) due to voluntary withdrawal, and one participant (<1%) due to Investigator Judgement, commercial drug, or other reasons.

Figure 12. CS11: Disposition of patients – flow diagram



Registry data: Disposition of patients

In total 375 patients with type III SMA from three different registries (Italian, German and Spanish) make up the overall registry study population.

Within the Italian registry [redacted] patients were enrolled, of whom [redacted] were eligible and [redacted] were excluded. Of these [redacted] patients, [redacted] patients had type III SMA. Within this subgroup, [redacted] were treated with nusinersen and [redacted] were left untreated. Thirty-six of the untreated group were excluded due to scoliosis, leaving [redacted] patients. Of these [redacted] patients, [redacted] were treated and [redacted] were untreated with a further [redacted] being excluded due to being followed-up less than six months from starting treatment. This allowed 104 treated patients to be used for the overall study population.

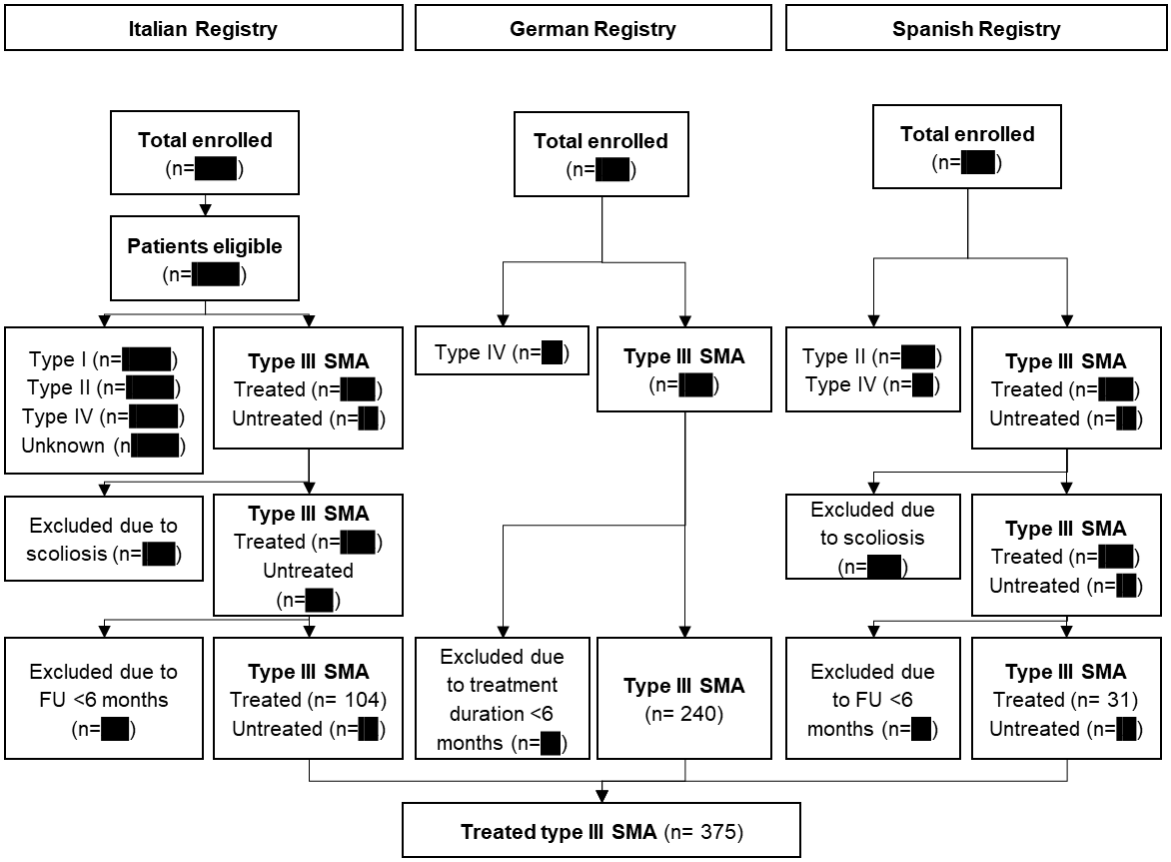
Patients with conditions that may preclude intrathecal treatment with nusinersen were excluded from the analysis of the group of untreated patients as their natural history of functional assessments is not directly comparable. It is expected that these patients

are not treated due to preconditions such as scoliosis or scoliosis surgeries (spinal instrumentation, spinal fusion), which make treatments not or no longer feasible.

Within the German registry, [redacted] patients were enrolled, of whom [redacted] had type IV SMA and [redacted] had type III SMA. Of these [redacted] patients, [redacted] were excluded due to their treatment duration being less than six months. This allowed 240 patients to be used for the overall study population.

Within the Spanish registry, [redacted] patients were enrolled, of whom [redacted] had type II SMA, [redacted] had type IV SMA and [redacted] had type III SMA. Of these [redacted] patients, [redacted] were treated with nusinersen and [redacted] were untreated. [redacted] of the untreated patients were excluded due to having scoliosis, leaving [redacted] untreated patients. Out of the remaining [redacted] patients, [redacted] patient was excluded due to being followed-up less than six months from starting treatment, leaving [redacted] untreated patients and 31 treated patients. This allowed the 31 treated patients to be used for the overall study population.

Figure 13. Registry data: Disposition of patients – flow diagram



A.6.3. B1.3 Quality assessment for each trial

Table 45. Quality assessment for clinical case series studies

	Barp et al, 2020			**Shah et al, 2020**			**Okamoto et al, 2020**			**Cordts et al, 2020**			**Deconinck et al. 2019**			**Muntoni et al. 2019**			**Kirschner et al, 2018**		
Criteria	Yes	No	Other (CD, NR, NA)*	Yes	No	Other (CD, NR, NA)*	Yes	No	Other (CD, NR, NA)*	Yes	No	Other (CD, NR, NA)*	Yes	No	Other (CD, NR, NA)*	Yes	No	Other (CD, NR, NA)*	Yes	No	Other (CD, NR, NA)*
1. Was the study question or objective clearly stated?	×			×			×			×			×				×		×		
2. Was the study population clearly and fully described, including a case definition?	×			×			×			×			×			×			×		
3. Were the cases consecutive?	×					NA	×			×			×			×			×		
4. Were the subjects comparable?	×					NA	×			×			×			×			×		
5. Was the intervention clearly described?	×			×			×			×				×			×		×		

6. Were the outcome measures clearly defined, valid, reliable, and implemented consistently across all study participants?	×					NA	×			×				×	Mainly NR		×	Mainly NR		×	Mainly NR
7. Was the length of follow-up adequate?	×			×					NA	×			×			×			×		
8. Were the statistical methods well-described?			NR			NR	×			×				×			×			×	
9. Were the results well-described?	×			×			×			×			×			×			×		
Quality Rating (Good, Fair, or Poor)	Good			Good			Good			Good			Poor			Poor			Poor		
Rater #1 initials:	KM			KM			KM			KM			KM			KM			KM		
Rater #2 initials:	EW			EW			EW			EW			EW			EW			EW		
Additional Comments (If POOR,													Limited information			Limited information			Limited information		

please state why):					available due to being an abstract	available due to being an abstract	available due to being an abstract
*CD, cannot determine; NA, not applicable; NR, not reported							

Table 46. Quality assessment for observational cohort and cross-sectional studies

	Maggi et al, 2020			Walter et al, 2019			Yeo et al, 2020			Darras et al, 2019		
Criteria	Yes	No	Other (CD, NR, NA)*	Yes	No	Other (CD, NR, NA)*	Yes	No	Other (CD, NR, NA)*	Yes	No	Other (CD, NR, NA)*
1. Was the research question or objective in this paper clearly stated?	×			×			×			×		
2. Was the study population clearly specified and defined?	×			×			×			×		
3. Was the participation rate of eligible persons at least 50%?	×			×			×			×		
4. Were all the subjects selected or recruited from the same or similar populations (including the same time period)? Were inclusion and exclusion criteria for being in the study prespecified and applied uniformly to all participants?	×			×			×			×		
5. Was a sample size justification, power description, or variance and effect estimates provided?	×		Mean and Median	×		Mean and SD	×			×		Mean and SD

6. For the analyses in this paper, were the exposure(s) of interest measured prior to the outcome(s) being measured?	×			×			×			×		
7. Was the timeframe sufficient so that one could reasonably expect to see an association between exposure and outcome if it existed?	×			×			×			×		
8. For exposures that can vary in amount or level, did the study examine different levels of the exposure as related to the outcome (e.g., categories of exposure, or exposure measured as continuous variable)?			NA - all patients received at least 4 of 12 mg nusinersen			NA			NA			NA - all patients received 4 of 12 mg nusinersen
9. Were the exposure measures (independent variables) clearly defined, valid, reliable, and implemented consistently across all study participants?			NA - the only exposure measure was receipt of nusinersen			NA - the only exposure measure was receipt of nusinersen			NA - the only exposure measure was receipt of nusinersen			NA - the only exposure measure was receipt of nusinersen
10. Was the exposure(s) assessed more than once over time?	×			×			×				×	
11. Were the outcome measures (dependent variables) clearly	×			×			×			×		

defined, valid, reliable, and implemented consistently across all study participants?												
12. Were the outcome assessors blinded to the exposure status of participants?			NA - all participants received nusinersen			NA - all participants received nusinersen			NA - all participants received nusinersen			NA - all participants received nusinersen
13. Was loss to follow-up after baseline 20% or less?		×		×			×			×		
14. Were key potential confounding variables measured and adjusted statistically for their impact on the relationship between exposure(s) and outcome(s)?		×			×			×			×	
Quality Rating (Good, Fair, or Poor)	Good			Good			Good			Good		
Rater #1 initials:	KM			KM			KM			KM		
Rater #2 initials:	EW			EW			EW			CP		
Additional Comments (If POOR, please state why):												
*CD, cannot determine; NA, not applicable; NR, not reported												

A.7. Appendix C: Subgroup analysis

A.7.1. Statistics

A mixed-effects model was used to compare nusinersen-treated patients with untreated patients (BSC only). A piece-wise linear mixed model was used to determine the slopes in Hammersmith Functional Motor Scale Expanded (HFMSE) and Revised Upper Limb Module (RULM) scores, for further details see Section A.2.4 of the main submission document.

A.7.2. Baseline characteristics

The comparison of nusinersen-treated patients vs untreated patients (BSC only) was conducted on the full non-ambulant population (n=168); [redacted] vs [redacted] adults and [redacted] vs. [redacted] paediatrics, respectively.

The baseline characteristics for the paediatric and adult subgroups from the European registry data are presented in Table 47.

Table 47. Baseline characteristics, European registries – paediatric and adult subgroups

Baseline Characteristics	**All (n=[redacted])**	**Paediatric (n=[redacted])**	**Adult (n=[redacted])**
Gender, M/F n (%)	[redacted]	[redacted]	[redacted]
Registry, n (%)			
German	[redacted]	[redacted]	[redacted]
Italian	[redacted]	[redacted]	[redacted]
Spain	[redacted]	[redacted]	[redacted]
***SMN2* copies, n (%)**			
1	[redacted]	[redacted]	[redacted]
2	[redacted]	[redacted]	[redacted]
3	[redacted]	[redacted]	[redacted]
4	[redacted]	[redacted]	[redacted]
> 4	[redacted]	[redacted]	[redacted]
Unknown	[redacted]	[redacted]	[redacted]
Age at symptom onset, n (%)	[redacted]		[redacted]
< 3 years	[redacted]	[redacted]	[redacted]
≥ 3 years	[redacted]	[redacted]	[redacted]
Disease duration, years, mean ± SD; median (min–max)	[redacted]	[redacted]	[redacted]

Age at first dose of treatment, years, mean ± SD; median (min–max)	[redacted]	[redacted]	[redacted]
Age at last dose of treatment, years, mean ± SD; median (min–max)	[redacted]	[redacted]	[redacted]
Age at last follow-up, years, mean ± SD; median (min–max)	[redacted]	[redacted]	[redacted]
Number of doses, mean ± SD; Median (min–max)	[redacted]	[redacted]	[redacted]
Feeding			
Unsupported	[redacted]	[redacted]	[redacted]
Oral, no supplements needed	[redacted]	[redacted]	[redacted]
Oral intake solids	[redacted]	[redacted]	[redacted]
No feeding tube	[redacted]	[redacted]	[redacted]
Motor function			
HFMSE score, mean ± SD; Median (min–max)	[redacted]	[redacted]	[redacted]
RULM score mean ± SD; Median (min–max)	[redacted]	[redacted]	[redacted]
Number of subjects who use a wheelchair	[redacted]		[redacted]
Yes (full-time/part-time), n(%)	[redacted]	[redacted]	[redacted]
No	[redacted]	[redacted]	[redacted]
Non-invasive ventilation	[redacted]	[redacted]	[redacted]
Ventilator support	[redacted]	[redacted]	[redacted]
Daily/weekly	[redacted]	[redacted]	[redacted]
Night	[redacted]	[redacted]	
Yes (8h)	[redacted]	[redacted]	
Other	[redacted]		[redacted]
Scoliosis			
Yes	[redacted]	[redacted]	[redacted]
No	[redacted]	[redacted]	[redacted]
Serious respiratory events[1]	[redacted]	[redacted]	[redacted]
n (%)	[redacted]	[redacted]	[redacted]
Events	[redacted]	[redacted]	[redacted]
Total subject months (in registry)	[redacted]	[redacted]	[redacted]

Abbreviations: HFMSE, Hammersmith Functional Motor Scale Expanded; Max, maximum; Min, minimum; SD, standard deviation; SMA, spinal muscular atrophy; SMN, spinal motor neuron; RULM, Revised Upper Limb Module; V0, start treatment.

Notes: [1] in the 12 months before baseline (V0) based on medical records

A.7.3. Results

In the analysis (data cut-off: August 2020) HFMSE and RULM scores were assessed using a standard mixed model, results were expressed as estimates changes in pts/week (95% CI). In both HFMSE and RULM scores the nusinersen-treated patients showed a positive difference in slope compared to the untreated patients – indicating disease stabilisation after treatment with nusinersen. This positive difference was also observed in both HFMSE and RULM scores in both the adult and paediatric subpopulations (Table 48).

Table 48. Motor function (HFMSE and RULM scores) in nusinersen-treated vs untreated (BSC only) patients

	HFMSE estimates changes in pts/week (95% CI)			**RULM** estimates changes in pts/week (95% CI)		
	All	**Paediatrics[1]**	**Adults[2]**	**All**	**Paediatrics[1]**	**Adults[2]**
nusinersen-treated	0.015 (0.003–0.027)	0.013 (−0.015–0.041)	0.015 (0.003–0.028)	0.018 (0.007–0.028)	0.023 (0.006–0.040)	0.014 (0.001–0.027)
untreated	−0.109 (−0.144 to −0.074)	−0.109 (−0.156 to −0.061)	0.012 (−0.051–0.075)	−0.009 (−0.039–0.021)	−0.009 (−0.037–0.019)	−0.013 (−0.077–0.050)
Notes: [1] treated vs untreated; n=[redacted] vs n=[redacted]. [2] treated vs untreated; n=[redacted] vs n=[redacted].						

Sub-cohort analyses (adult and paediatric subgroups)

The HFMSE and RULM score slopes are presented in **Error! Not a valid bookmark self-reference.** and Table 50, respectively, for pre- and post-nusinersen initiation in the paediatric and adult subgroups from the European Registries data. HFMSE and RULM scores in both subpopulations were aligned with the outcome (disease stabilisation post-nusinersen treatment) observed in the overall population (presented in Section A.2.6 of the main submission document). The changes in slopes between pre- and post-treatment initiation for HFSME scores and RULM scores were statistically significant (HFMSE: p=0.008; RULM: p=0.009) in the paediatric subgroup.

Table 49. European Registries' sub-cohort (n=[redacted]) HFMSE score slopes – pre- and post-nusinersen initiation in the adult and paediatric subgroups

	All	Adult (n=[redacted])	Paediatric (n=[redacted])
Slope before initiation of nusinersen			
Estimate ± SE	−0.056 ± 0.004	0.017 ± 0.008	−0.099 ± 0.008
(95% CI)	(−0.064 to −0.048)	(0.001 to 0.032)	(−0.114 to 0.84)
P-value	<0.0001	0.03	<0.0001
Slope after initiation of nusinersen			
Estimate ± SE	−0.010 ± 0.013	0.007 ± 0.01	−0.031 ± 0.021
(95% CI)	(−0.035 to 0.014)	(−0.013 to 0.027)	(−0.073 to 0.010)
P-value	n.s	n.s	n.s
Difference pre- and post-initiation nusinersen	0.002	n.s.	0.009
Abbreviations: CI, confidence interval; HFMSE, Hammersmith Functional Motor Scale Expanded; SE, standard error.			

Table 50. European Registries' sub-cohort (n=[redacted]) RULM score slopes – pre- and post-nusinersen initiation in the adult and paediatric subgroups

	All	Adult (n=[redacted])	Paediatric (n=[redacted])
Slope before initiation of nusinersen			
Estimate ± SE	−0.021 ± 0.004	−0.009 ± 0.006	−0.031 ± −0.006
(95% CI)	(−0.029 to −0.013)	(−0.020 to 0.003)	(−0.043 to −0.019)
P-value	<0.0001	n.s.	<0.0001
Slope after initiation of nusinersen			
Estimate ± SE	−0.002 ± 0.005	0.001 ± 0.006	−0.008 ± 0.010
(95% CI)	(−0.013 to 0.008)	(−0.011 to 0.013)	(−0.027 to 0.012)
P-value	n.s	n.s	n.s
Difference pre- and post-initiation nusinersen	p=0.019	n.s.	0.009
Abbreviations: CI, confidence interval; RULM, Revised Upper Limb Module; SE, standard error.			

A.8. Appendix D: Adverse reactions

No additional studies have been identified.

A.9. Appendix E: Health-related quality-of-life studies

A full SLR was undertaken to identify all studies that provide information on health-related quality of life (HRQoL) of patients with type III SMA. This review was conducted in three stages and followed PRISMA recommendations: a comprehensive and systematic search of the published literature to identify all potentially relevant studies; a systematic selection of relevant studies based on explicit inclusion and exclusion criteria; an extraction of relevant data from eligible studies to assess comparative HRQoL evidence.

A.9.1. Search strategy

Medline (Pubmed) and Embase (Elsevier) were used. Both search strategies were built using a variety of 'free text' and MeSH terms (Table 51 and Table 52). These search terms included terms for type III SMA and terms for various health-related quality of life statements. The timeframe for this SLR was 1st October 2017 to 21st October 2020, capturing new data since the 2017 NICE submission for nusinersen.

Table 51. Search strategy Medline- HRQoL studies in the type III SMA population

#	Search string	Hits
1	(((atrophy, spinal muscular[MeSH Terms]) OR (spinal muscular atrophy)) OR (SMA)) OR (Kugelberg-Welander)	29,013
2	((((Type 3) OR ("non-ambulant")) OR (SMA3)) OR (Type III)) OR (sitt*)	984,583
3	((((((((((((((((((((quality of life[MeSH Terms]) OR (QoL)) OR (HRQoL)) OR (quality of life)) OR (health-related)) OR (patient need)) OR (support need)) OR (symptoms)) OR (needs)) OR (physical n1 function*)) OR (patient-reported outcome*)) OR (PROM)) OR (HRQL)) OR (functional status)) OR (function)) OR (health n1 state)) OR (care*)) OR (medical n3 leave)) OR (sick n3 leave)) OR (informal care)) OR (parent*)) OR (sick n3 day)	21,367,262
4	#1 AND #2 AND #3	**2,923**
5	("2017/10/01"[Date - Publication] : "3000"[Date - Publication])	3,979,885
6	#4 AND #5	**639**

Table 52 Search strategy Embase- HRQoL studies in the type III SMA population

#	Search string	Hits
1	'spinal muscular atrophy'/exp/mj OR (spinal AND muscular AND atrophy) OR sma OR 'kugelberg welander disease'	73,838
2	(type AND 3 OR 'non-ambulant' OR sma3 OR type) AND iii OR sitt*	216,093
3	'quality of life'/exp/mj OR ((((qol OR hrqol OR quality) AND of AND life OR 'health related' OR patient) AND need OR support) AND need) OR symptoms OR needs OR 'physical functio*' OR 'patient-reported outcom*' OR prom OR hrql OR 'functional status' OR function OR 'health state' OR care* OR 'medical ajd3 leave' OR 'sick adj3 leave' OR 'informal care' OR paren* OR 'sick ajd3 day'	9,858,750
4	#1 AND #2 AND #3	**1,016**
5	[2017-2020]/py	6,173,086
6	#4 AND #5	**470**

A.9.2. Study selection

Potentially relevant publications were reviewed and assessed in two steps to collate a final set of studies for HRQoL data extraction. First, to identify any potentially relevant papers, an initial screening of titles and abstracts against the inclusion/exclusion criteria (Table 53) was undertaken. Then, using the same inclusion/exclusion criteria, a full-text screening of the possibly relevant papers identified in the initial screening was undertaken. Decisions on the selection of studies were made by two researchers who screened the titles and abstracts, and the full papers, independently. For any studies where the researchers had a disagreement that could not be resolved, a third researcher made the final decision based on the inclusion criteria.

Table 53. Inclusion and exclusion criteria used in the HRQoL SLR

Characteristics	Inclusion criteria	Exclusion criteria
Population	Type III SMA patients (paediatric and adult)	other types of SMA
Interventions	N/A	
Comparators	N/A	
Outcomes	PROs HRQoL Utilities	Clinical outcomes Economic outcomes
Study design	RCTs Non-RCTs Observational studies Registry data	
Language	English	Non-English publications
Publication type and status	Manuscripts Conference proceedings	
Date of publication	October 2017[1]–present	pre–October 2017[1]

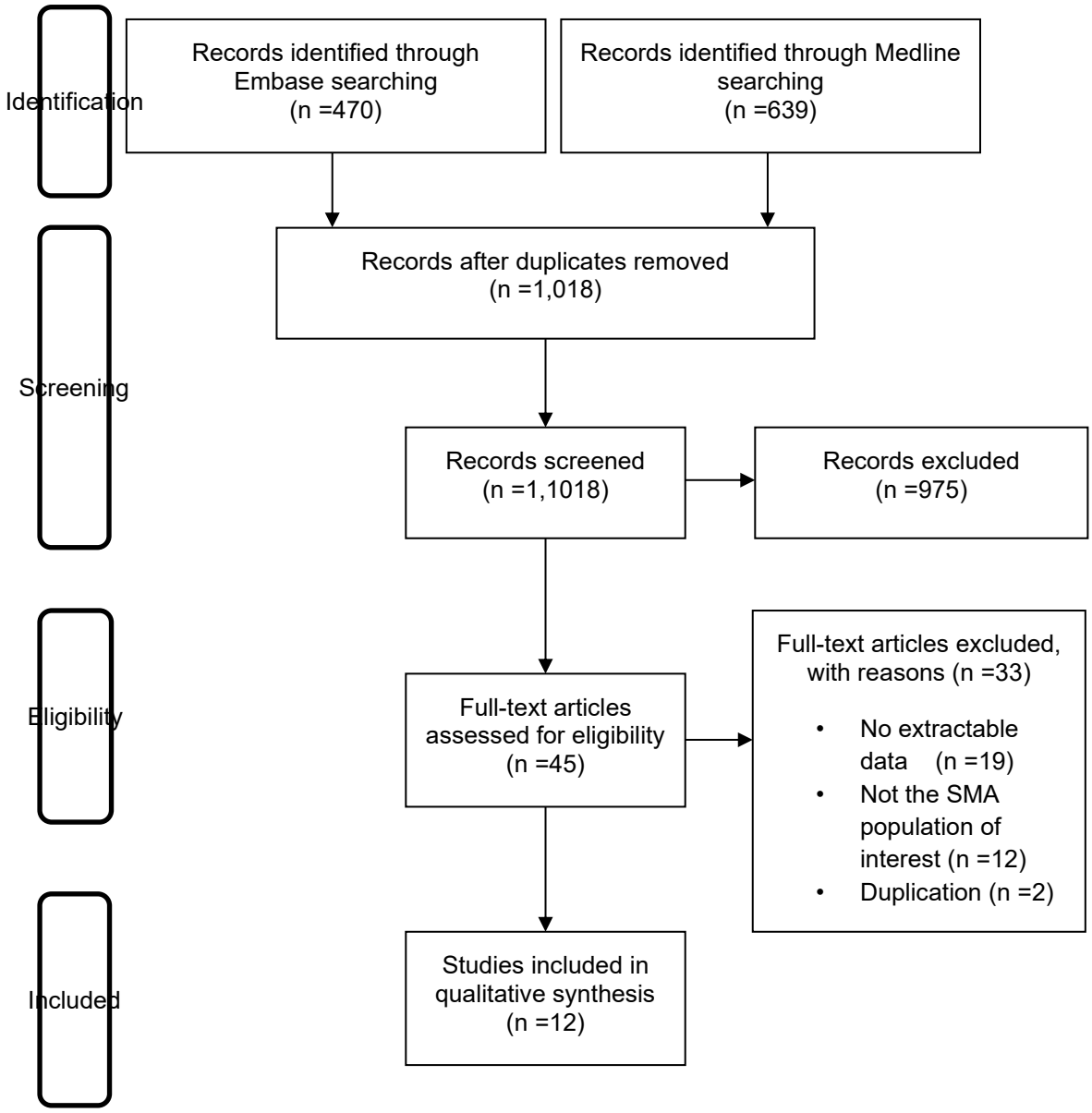
Abbreviations: HRQoL, health-related quality of life; PRO, patient reported outcomes; RCT, randomised controlled trial; SMA, spinal muscular atrophy.

Notes: [1] This SLR aims to identify any evidence published since the original submission to NICE in 2018. The searches for the economic and HRQoL/utility SLR were conducted in October 2017.

A PRISMA diagram is presented in Figure 14. Database searches were conducted on 21 October 2020. A total of 1,109 potentially relevant papers and abstracts were identified for review. A de-duplication step was performed to remove studies that overlapped across the databases; 91 of the studies were identified as duplicated and excluded. The remaining studies were screened based in the information reported in their titles and abstracts. Of these, 975 were excluded at the primary screening stage as they were not relevant to the HRQoL of patients with type III SMA.

A total of 43 articles were assessed in full for further evaluation. Of these, 33 were excluded for reasons such as having no extractable data (n=19), not investigating the population of interest (n=12) or data duplication (n=2). Therefore, a total of 12 citations were included for this SLR.

Figure 14. PRISMA diagram for HRQoL SLR



Included studies

Table 54. HRQoL studies including patients with type III SMA treated with nusinersen

Study	Kirschner, J., et al.	Montes, J., et al.	Weaver, M. S., et al.	Yeo, C. J. J., et al.
Study type	Case series	Post hoc analysis	Prospective crossover survey study	Single centre prospective cohort study
Location	USA	USA	USA	Massachusetts, USA
Population	Patients with type III SMA	Children and adolescents with type II and III SMA	Patients with SMA and their caregivers	Adults with type III SMA
Recruitment information	Patients from the CS2 and CS12 clinical trials	Patients from the CS2 and CS12 clinical trials	Patients receiving neuromuscular consultation care at the American Family Children's Hospital Specialty Clinics	SMA patients at Massachusetts General Hospital
Total sample size	11	14	28-47 dependent on the survey	6
SMA type III sample size	11	13	6-9 dependent on the survey	6
Response rate	N/A	N/A	First survey = 84% Second survey = 57%	N/A
HRQoL measurement Category	Changes in QoL	Fatigue	QoL	QoL
HRQoL related measurement	• PedsQL • Neuromuscular modules	• Using the 6MWT	• PedsQL 3.0 Neuromuscualr module • PedsQL Family impact module • Proxy-Peds QL NM module • CPCHILD questionnaire	• Peds QL multidimensional Fatigue Scale

Abbreviations: CPCCHILD, Caregiver Priorities and Child Health Index of Life with Disabilities; HRQoL, health-related quality of life; PedsQL, Paediatric Quality of Life Inventory; QoL, quality of life; SMA, spinal muscular atrophy; 6MWT, six-minute walk test

Table 55. HRQoL studies including patients with type III SMA

Study	Belter, L., et al.	Darbà, J.	Dunaway Young, S., et al.	Günther, R., et al.	Love, D., et al.	Stam, M., et al.	van der Heul, A. M. B., et al.
Study type	Survey	Registry	Pilot study	Multicentre cross-sectional study	Registry	Case-control	Survey
Location	International	Catalonia, Spain	USA	Germany	Canada	Netherlands	Netherlands
Population	Patients with SMA and/or caregivers	Patients with SMA	Patients with SMA	Patients with type II and III SMA	Children with SMA and caregivers	Patients with type II-IV SMA	Patients with SMA
Recruitment information	Cure SMA	Via PADRIS database	Through participation in a natural history study from the SMA CRC at Columbia University Medical Centre	Across five different centres in Germany	Identified by The Canadian Neuromuscular Disease Registry	Dutch SMA register	Dutch SMA register
Total sample size	478	524	32	70	60	98	118
SMA type III sample size	132	15	25	43	9	27	52
Control sample size	N/A	N/A	N/A	59	N/A	46	N/A
Response rate	12%	N/A	N/A	N/A	N/A	N/A	64%
HRQoL measurement category	• HRQoL • Work productivity • Activity impairment	• Mortality • No. and reason for admissions	• Perceived fatigue • QoL	• Non-motor symptom burden	• QoL	• Fatigue	• Feeding problems • Swallowing problems

HRQoL related measurement	• HUI3 system • WPAI for productivity • PROMIS Fatigue SF parent proxy survey instrument	• Age of mortality • No. of patients admitted for anxiety	• PedsQL Multidimensional Fatigue Scale • FSS • PedsQL Neuromuscular Module • Short-form 36	• NMS questionnaire	• HRQoL HUI2 • HRQoL HUI3	• r9HPT	• DDD(p)NMD questionnaire
Abbreviations: CRC, Clinical Research Centre; DDD(p)NMD, Diagnostic List of Dysphagia and Dysarthria in (paediatric) patients with Neuromuscular Diseases; HRQoL, health-related quality of life; HUI3, Health Utilities Index Mark 3; PADRIS, programme of data analysis for research and innovation in health, PedsQL, Paediatric Quality of Life Inventory; PROMIS, Patient Reported Outcomes Measurement Information System; QoL, quality of life; r9HPT, repeated nine-hole peg test; SMA, spinal muscular atrophy; WPAI, Work Productivity and Activity Impairment Questionnaire; 6MWT, six-minute walk test						

Complete reference lists for included studies and excluded studies

Table 56. Studies included in HRQoL SLR

Author	Year	Title	Journal
Belter, L., et al.	2020	Quality of life data for individuals affected by spinal muscular atrophy: A baseline dataset from the Cure SMA Community Update Survey	Orphanet Journal of Rare Diseases, 15
Chacko, A., et al.	2020	Polysomnography findings in pediatric spinal muscular atrophy types 1-3	Sleep Med, 68, 124-130.
Darbà, J.	2020	Management and current status of spinal muscular atrophy: a retrospective multicentre claims database analysis	Orphanet J Rare Dis, 15, 8.
Dunaway Young, S., et al.	2019	Perceived Fatigue in Spinal Muscular Atrophy: A Pilot Study	J Neuromuscul Dis, 6, 109-117.
Günther, R., et al.	2019	Patient-Reported Prevalence of Non-motor Symptoms Is Low in Adult Patients Suffering From 5q Spinal Muscular Atrophy	Frontiers in Neurology, 10.
Kirschner, J., et al.	2018	Nusinersen experience in individuals with spinal muscular atrophy type III: A case series	Journal of Neuromuscular Diseases, 5, S366-S367.
Love, D., et al.	2019	Utility based health related quality of life in children and adolescents with spinal muscular atrophy	Neuromuscular Disorders, 29, S130.
Montes, J., et al.	2019	Nusinersen improves walking distance and reduces fatigue in later-onset spinal muscular atrophy	Muscle and Nerve, 60, 409-414.
Stam, M., et al.	2018	A continuous repetitive task to detect fatigability in spinal muscular atrophy	Orphanet J Rare Dis, 13, 160.
van der Heul, A. M. B., et al.	2019	Bulbar Problems Self-Reported by Children and Adults with Spinal Muscular Atrophy	J Neuromuscul Dis, 6, 361-368.
Weaver, M. S., et al.	2020	A Prospective, Crossover Survey Study of Child- and Proxy-Reported Quality of Life According to Spinal Muscular Atrophy Type and Medical Interventions	Journal of Child Neurology, 35, 322-330.
Yeo, C. J. J., et al.	2020	Prospective Cohort Study of Nusinersen Treatment in Adults with Spinal Muscular Atrophy	*J Neuromuscul Dis,* 7**,** 257-268.

Table 57. Studies excluded in HRQoL full-text screening and reasons for exclusion

Author	Year	Title	Journal
No extractable data			
Alfano, L., et al.	2019	Utility of functional outcomes in adults with spinal muscular atrophy	Neuromuscular Disorders, 29, S129.
Belter, L., et al.	2019	Work productivity activity impairment results from the cure SMA 2018 community update survey	Neurology, 92

Bienias, K., et al.	2018	Evaluation of activities of daily living in patients with slowly progressive neuromuscular diseases	Neurologia i Neurochirurgia Polska, 52, 222-227.
Bose, M., et al.	2019	Exploring spinal muscular atrophy and its impact on functional status: Indian scenario	Indian journal of public health, 63, 254-257.
Brown, L., et al.	2020	Use of the assessment of caregiver experience with neuromuscular disease (ACEND with SMA) - a caregiver experience from a single center	Neuromuscular Disorders, 30, S145-S146.
Burbridge, C., et al.	2019	Mapping a qualitative exploration of meaningful change in later-onset (type ii or iii) spinal muscular atrophy to the hammersmith functional motor scale expanded (HFMSE)	Value in Health, 22, S284.
Caumo, L., et al.	2019	Longitudinal functional changes in a cohort of adult nusinersen-treated spinal muscular atrophy patients at the Padova Neuromuscular Center	Acta Myologica, 38, 128.
Comi, G. P.	2018	Nusinersen in SMA adult patients: First experiences	Acta Myologica, 37, 36.
Darras, B., et al.	2020	Nusinersen in adolescents and young adults with SMA: Longitudinal experience from an expanded cohort of CS2/CS12 and SHINE participants	Neuromuscular Disorders, 30, S120.
Day, J. W., et al.	2020	Longer-term experience with nusinersen in teenagers and young adults with spinal muscular atrophy: Results from the CS2/CS12 and shine studies	Neurology, 94.
Deconinck, N., et al.	2019	Nusinersen experience in teenagers and young adults with spinal muscular atrophy (SMA): Results from CS2/CS12 and SHINE	European Journal of Neurology, 26, 143-144.
Hodgkinson, V., et al.	2017	Spinal muscular atrophy in Canada: Findings from the Canadian neuromuscular disease registry	Pharmacoepidemiology and Drug Safety, 26, 284-285.
Johnson, N. B., et al.	2020	Evaluation of nusinersen on impact of caregiver experience and hrqol in later-onset spinal muscular atrophy (SMA): Results from the phase 3 cherish trial	Neurology, 94.
Johnson, N. B., et al.	2019	Impact of caregiver experience and HRQoL in later-onset spinal muscular atrophy (SMA): Results from the phase 3 CHERISH trial	Value in Health Regional Issues, 19, S76.
Matsumoto, H., et al.	2020	Improvement of Pulmonary Function Measured by Patient-reported Outcomes in Patients With Spinal Muscular Atrophy After Growth-friendly Instrumentation	Journal of pediatric orthopedics.
Pacione, M., et al.	2019	Perspectives on spinraza (Nusinersen) treatment study: Views of individuals and parents of children diagnosed with spinal muscular atrophy	Journal of Neuromuscular Diseases, 6, 119-131.

Peña-Longobardo, L. M., et al.	2020	The economic impact and health-related quality of life of spinal muscular atrophy. An analysis across europe	International Journal of Environmental Research and Public Health, 17, 1-12.
Zuluaga Sanchez, S., et al.	2019	Improved quality of life for patients and caregivers among patients with later-onset SMA following treatment with nusinersen	Value in Health, 22, S337.
Zuluaga Sanchez, S., et al.	2019	Improved quality of life and life-years in patients with infantile-onset SMA following treatment with nusinersen	Value in Health, 22, S338.
Not investigating the population of interest			
Alfano, L., et al.	2019	The neuromuscular gross motor outcome as an outcome measure in spinal muscular atrophy	Neuromuscular Disorders, 29, S129.
Bent, M., et al.	2018	Incidence and risk factors associated with hip pain in children with SMA and spinal instrumentation	Pediatrics, 142.
Brusa, C., et al.	2019	Secondary outcomes of spinal surgery in patients with spinal muscular atrophy (SMA): A retrospective analysis and a family-centred survey	Archives of Disease in Childhood, 104, A37.
Brusa, C., et al.	2019	P.227 Secondary clinical outcomes of spinal surgery and satisfaction in patients with spinal muscular atrophy (SMA) II and non-ambulant III	Neuromuscular Disorders, 29, S133.
Cruz, R., et al.	2019	Evaluating Benefit-risk Decision-making in Spinal Muscular Atrophy: A First-ever Study to Assess Risk Tolerance in the SMA Patient Community	Clinic Clinical Therapeutics, 41, 943-960.e4.
Lopez Bastida, J., et al.	2019	The economic impact and health-related quality of life of spinal muscular atrophy (SMA). an analysis across three European countries	Value in Health, 22, S848-S849.
McMillan, H., et al.	2020	Disease and treatment burden of spinal muscular atrophy (SMA) on patients and caregivers in Canada	Neuromuscular Disorders, 30, S100-S101.
Montes, J., et al.	2020	Impact of Continued Nusinersin treatment on Caregiver Experience and Health-Related Quality of Life in Later-onset SMA: Results From the SHINE Study	Neuromuscular Disorders, 30, S125.
Rouault, F., et al.	2017	Disease impact on general well-being and therapeutic expectations of European Type II and Type III spinal muscular atrophy patients	Neuromuscular Disorders, 27, 428-438.
Tan, H., et al.	2019	Healthcare Utilization, Costs of Care, and Mortality Among Psatients With Spinal Muscular Atrophy	J Health Econ Outcomes Res, 6, 185-195.
Thokala, P., et al.	2020	Cost effectiveness of nusinersen for patients with infantile-onset spinal muscular atrophy in US	Cost Effectiveness and Resource Allocation, 18.

Vega, P., et al.	2020	Quality of life in children and adolescents with spinal muscular atrophy	Revista Chilena de Pediatria, 91, 512-520.
Duplication of data			
Belter, L., et al.	2019	Ambulation status, role participation and caregiver assistance among individuals with spinal muscular atrophy type III: results from the 2018 cure SMA membership survey	Neuromuscular Disorders, 29, S128-S129.
Belter, L., et al.	2019	Ambulation status, role participation and caregiver assistance among individuals with spinal muscular atrophy type III: Results from the 2018 cure SMA membership survey	Neurology, 92.

Quality assessment for each HRQoL study

Table 58. Observational cohort and cross-sectional studies

	Günter et al., 2019			Belter et al., 2020			Van der Heul et al., 2019			Dunway et al., 2019			Darbà et al., 2020			Love et al., 2019			Weaver et al., 2020		
Criteria	**Yes**	**No**	**Other (CD, NR, NA)***	**Yes**	**No**	**Other (CD, NR, NA)***	**Yes**	**No**	**Other (CD, NR, NA)***	**Yes**	**No**	**Other (CD, NR, NA)***	**Yes**	**No**	**Other (CD, NR, NA)***	**Yes**	**No**	**Other (CD, NR, NA)***	**Yes**	**No**	**Other (CD, NR, NA)***
1. Was the research question or objective in this paper clearly stated?	x			x			x			x			x				x		x		
2. Was the study population clearly specified and defined?	x			x			x			x			x			x			x		
3. Was the participation rate of eligible persons at least 50%?			NR		x		x			x					NR			NR			NR
4. Were all the subjects selected or recruited from the same or similar populations (including the same time period)? Were inclusion and exclusion criteria for being in the study prespecified and applied uniformly to all participants?	x			x			x			x			x			x			x		
5. Was a sample size justification, power description, or variance and effect estimates provided?	x			x			x			x			x			x			x		

6. For the analyses in this paper, were the exposure(s) of interest measured prior to the outcome(s) being measured?			NA			NA			NA			NA			NA			NA			NA
7. Was the timeframe sufficient so that one could reasonably expect to see an association between exposure and outcome if it existed?			NA			NA			NA			NA			NA			NA			NA
8. For exposures that can vary in amount or level, did the study examine different levels of the exposure as related to the outcome (e.g., categories of exposure, or exposure measured as continuous variable)?			NA			NA			NA			NA			NA			NA			NA
9. Were the exposure measures (independent variables) clearly defined, valid, reliable, and implemented consistently across all study participants?	x			x			x			x			x			x			x		
10. Was the exposure(s) assessed more than once over time?			NA			NA			Na			NA			NA			NA			NA
11. Were the outcome measures (dependent variables) clearly defined, valid, reliable, and implemented consistently	x			x			x			x			x			x			x		

across all study participants?																					
12. Were the outcome assessors blinded to the exposure status of participants?			NA			NA			NA			NA			NA			NA			NA
13. Was loss to follow-up after baseline 20% or less?			NA			NA			NA			NA			NA			NA			NA
14. Were key potential confounding variables measured and adjusted statistically for their impact on the relationship between exposure(s) and outcome(s)?			NR			NR			NR			NR	x					NR			NR
Quality Rating (Good, Fair, or Poor)	Good			Fair			Good			Good			Good			Poor			Good		
Rater #1 initials:	EW			EW			EW			EW			EW			EW			EW		
Rater #2 initials:	KM			KM			KM			KM			KM			KM			KM		
Additional Comments (If POOR, please state why):																Love et al, provides limited information. This is because the publication is an abstract.					
*CD, cannot determine; NA, not applicable; NR, not reported																					

Table 59. Quality assessment for HRQoL case control study

	Stam et al, 2018		
Criteria	**Yes**	**No**	**Other (CD, NR, NA)***

1. Was the research question or objective in this paper clearly stated and appropriate?	x		
2. Was the study population clearly specified and defined?	x		
3. Did the authors include a sample size justification?			NR The sample size was not calculated prospectively because of the exploratory nature of this study and unpredictable effect size. Sample size was determined by the number of eligible patients willing to participate.
4. Were controls selected or recruited from the same or similar population that gave rise to the cases (including the same timeframe)?	x		
5. Were the definitions, inclusion and exclusion criteria, algorithms or processes used to identify or select cases and controls valid, reliable, and implemented consistently across all study participants?	x		
6. Were the cases clearly defined and differentiated from controls?	x		
7. If less than 100 percent of eligible cases and/or controls were selected for the study, were the cases and/or controls randomly selected from those eligible?			NR
8. Was there use of concurrent controls?			NR
9. Were the investigators able to confirm that the exposure/risk occurred prior to the development of the condition or event that defined a participant as a case?			NA
10. Were the measures of exposure/risk clearly defined, valid, reliable, and implemented consistently (including the same time period) across all study participants?			NA

11. Were the assessors of exposure/risk blinded to the case or control status of participants?			NR
12. Were key potential confounding variables measured and adjusted statistically in the analyses? If matching was used, did the investigators account for matching during study analysis?	x If the round time in which the incident occurred (dropping pen) was (equal to) the slowest test measurement, the value was removed and treated as missing		
Quality Rating (Good, Fair, or Poor)	Good		
Rater #1 initials:	EW		
Rater #2 initials:	KM		
Additional Comments			
*CD, cannot determine; NA, not applicable; NR, not reported			

Table 60. Quality assessment for HRQoL case series study

	Montes et al., 2019		
Criteria	**Yes**	**No**	**Other (CD, NR, NA)***
1. Was the study question or objective clearly stated?	x		
2. Was the study population clearly and fully described, including a case definition?	x		
3. Were the cases consecutive?	x		
4. Were the subjects comparable?	x		
5. Was the intervention clearly described?	x		
6. Were the outcome measures clearly defined, valid, reliable, and implemented consistently across all study participants?	x		

7. Was the length of follow-up adequate?	x		
8. Was the statistical methods well-described?	x		
9. Were the results well-described?	x		
Quality Rating (Good, Fair, or Poor)	Good		
Rater #1 initials:	EW		
Rater #2 initials:	KM		
Additional Comments (If POOR, please state why):			
*CD, cannot determine; NA, not applicable; NR, not reported			

European Registries

Table 61. Quality assessment – NIH tool

	SMArtCARE			ISMAR			CuidAME		
Criteria	**Yes**	**No**	**Other (CD, NR, NA)***	**Yes**	**No**	**Other (CD, NR, NA)***	**Yes**	**No**	**Other (CD, NR, NA)***
1. Was the research question or objective in this paper clearly stated?	×			×			×		
2. Was the study population clearly specified and defined?	×			×			×		
3. Was the participation rate of eligible persons at least 50%?			NA			NA			NA
4. Were all the subjects selected or recruited from the same or similar populations (including the same time period)? Were inclusion and exclusion criteria for being in the study prespecified and applied uniformly to all participants?	×			×			×		
5. Was a sample size justification, power description, or variance and effect estimates provided?	×		Mean, median, SD	×		Mean, median, SD	×		Mean, median, SD
6. For the analyses in this paper, were the exposure(s) of interest measured prior to the outcome(s) being measured?	×			×			×		
7. Was the timeframe sufficient so that one could reasonably expect to see an association between exposure and outcome if it existed?	×			×			×		
8. For exposures that can vary in amount or level, did the study examine different levels of the exposure as related to the outcome (e.g., categories of			NR			NR			NR

exposure, or exposure measured as continuous variable)?									
9. Were the exposure measures (independent variables) clearly defined, valid, reliable, and implemented consistently across all study participants?			NR			NR			NR
10. Was the exposure(s) assessed more than once over time?			NR			NR			NR
11. Were the outcome measures (dependent variables) clearly defined, valid, reliable, and implemented consistently across all study participants?	×			×			×		
12. Were the outcome assessors blinded to the exposure status of participants?		×			×			×	
13. Was loss to follow-up after baseline 20% or less?			NA			NA			NA
14. Were key potential confounding variables measured and adjusted statistically for their impact on the relationship between exposure(s) and outcome(s)?	x			x			x		
Quality Rating (Good, Fair, or Poor)	Fair			Fair			Fair		
Rater #1 initials:	KM			KM			KM		
Rater #2 initials:									
Additional Comments (If POOR, please state why):	In analysis presented in the main submission document confounding variables were taking into consideration								
*CD, cannot determine; NA, not applicable; NR, not reported									

Item	Characteristic	SMArtCARE	ISMAR	CuidAME
2	Rationale	Longitudinal Data Collection from Patients with SMA: The SMArtCARE Database Establishment of a prospective registry (SMArtCARE) to collect routine clinical data in order to examine the natural course of the disease in patients with SMA and to systematically present treatment effects	ISMAR prospectively collects harmonized data from patients with genetically confirmed 5q-SMA. The main purpose is to learn more about the disease and response to treatments.	Longitudinal data collection from patients with spinal muscular atrophy in a national registry in Spain
3	Objective	The main goal of the independent SMArtCARE registry is to evaluate all 5q-SMA patients, regardless of their current treatment, as well as to plan and monitor therapeutic interventions. The register is not based on any specific hypotheses.	This large collaborative registry creates a structured but flexible system for collecting prospective data that maps all patients with SMA and monitors them over the course of several years.	Establishment of a registry (CuidAME) to record routine clinical data in order to examine the natural course of the disease in patients with SMA and to systematically present treatment effects.
4	Design	SMArtCARE is a prospective, multicentre, non-randomised registry in German-speaking countries. The data for the registry is collected during each routine clinical visit to the SMA patient. Data obtained during regular patient visits prior to inclusion in the registry were documented retrospectively.	ISMAR is a prospective, multicenter, non-randomised registry in Italy, the UK and the USA	CuidAME is a retrospective and prospective, multicenter, non-randomized registry in Spain
5	Setting and location of the study; Relevant timing information, including periods of recruitment, exposure,	The data collection is based on an international consensus for SMA registries (TREAT-NMD, iSMAC). Data for the registry is collected as part of regular, clinically recommended, routine visits to patients depending on their current treatment regimen. The timing and frequency of follow-up examinations depend on the current treatment regimen.	Data is collected from 16 locations in Italy, the UK and the USA. The first patient was included in 2017. The registry collects data on all patients diagnosed with 5q-associated SMA. The ISMAC registry is a web software system that hosts the ISMAC Case Report Form (CRF) and is referred to as the Registro ISMAC-NMD registration portal and is based on copyrighted	Data are collected from six centers in Spain. The first patient was included in the registry in February 2019. The first annual report was published in December 2019. The legality of data collection and use is based on a declaration of consent signed by each patient. The data are pseudo-anonymized: each patient is identified in

	follow-up and data collection	Electronic data are used for data capture with the aid of an electronic data capture (EDC) system. This system is a web-based data entry system administered by the Freiburg University Medical Center. Data is collected from 50 centers in Germany, Austria and Switzerland. The first patients were added to the registry in the first quarter of 2018. The follow-up phase should last as long as possible. The registry collects data on all patients with 5q-associated SMA. The patients are divided into defined cohorts according to their disease characteristics.	software developed by Astir. In Italy, all registry staff fill and review CRFs using the ISMAC registry. Due to the nature of the data collection, the observation periods differ between patients. Corresponding statistical models have taken this into account [37].	the register by a unique patient identification code (patient number).
6	Participants	Inclusion criteria: • Genetically confirmed diagnosis of 5q-associated SMA • Written consent from the patient or legal guardian Exclusion criteria: • Other SMA types (not 5q-associated SMA) • Patients with no legal capacity who are unable to understand the nature, scope and potential consequences of participating in the registry	Inclusion criteria: • Genetically confirmed diagnosis of 5q-associated SMA • Written consent from the patient or legal guardian Exclusion criteria: • Other SMA types (not 5q-associated SMA) • Patients with no legal capacity who are unable to understand the nature, scope and possible consequences of the registration	Inclusion criteria: • Genetically confirmed diagnosis of 5q-associated SMA • Written consent from the patient or legal guardian Exclusion criteria: • Other SMA types (not 5q-associated SMA) • Patients with no legal capacity who are unable to understand the nature, scope and possible consequences of the registration
7	Variables	All data available in the registry are extracted for all 5q-SMA patients.	Data for 5q-SMA	Data for 5q-SMA
7a	List of the codes and algorithms used to classify	Patient identification: The department for clinical studies in Freiburg is informed about newly admitted patients with a registration form. Each patient is identified in the	N/A	The data are pseudo-anonymized. A unique patient identification code (patient number) is assigned to each patient. A system to prevent duplicate patient entries is implemented. Data

	exposures, outcomes, confounders and effect modifiers	register by a unique patient identifier (patient number). A system to avoid duplicate patient entries is implemented. Each center keeps a patient identification record with the names of all patients in the registry and the corresponding identification codes. Co-medication: The co-medication is encoded using the Anatomical Therapeutic Chemical (ATC) code in its latest version. The coding is based on the given active ingredient or trade name.		security is guaranteed in accordance with national and European law (General Data Protection Regulation (EU) 2016/679 ("GDPR")).
8	Data sources	Basic patient information (annually): • Medical history and basic information Results of genetic tests (type of SMN1 mutation (e.g. deletion / point mutation), SMN2 copy number, mutations in other known genetic modifiers, if applicable) • Age at onset of symptoms • Age at diagnosis • Need for mechanical ventilation or nutritional support • Medication • Concomitant medication • Complementary therapies (e.g. physiotherapy) • Medical history (including operations) • Family history Follow-up information for routine patient visits: Current medical history • Lung symptoms and function (use of mechanical ventilation (hours per day),	• The following questions are asked in the form of interviews: o medical history o History of operations o Use of medication o Demographic information (date of birth, gender, place of residence) o Genetic information (information on SMA, result of the genetic tests 5q-associated SMA) o Therapies received o Medication taken o Ingestion of Nusinersen (Spinraza®) and occurrence of side effects on the spine or which can be attributed to the drug itself • Physical examination: o weight o size o blood pressure o Heart rate and breathing rate o general physical examination	The following is recorded within the register: • Ventilation status • Nutritional status • Orthopaedic symptoms (including pain, fatigue, and adverse events) • Clinical examination (including motor milestones and growth parameters in paediatric patients) • CHOP INTEND • HFMSE • RULM • 6MWT

		tracheotomy, peak cough flow, vital capacity, use of cough aids)nutrition • Using a feeding tube • Percentage of oral food intake Orthopaedic symptoms • pain (with localization) • Scoliosis: Cobb angle, surgery Fatigue Adverse Events of Special Interest • death (cause of death) • Hospitalization (reason, duration and need for mechanical ventilation) • Life threatening • Correlation with drug treatment Changes to concomitant drugs and therapies History of motor milestones according to WHO Self-assessment by patients or their parents regarding the course of the disease Patient-reported endpoints (patient reported outcomes, PROs, quality of life / burden on caregivers) Clinical examinations growth • First patient visit: body weight and height • Tracking of body weight with each visit • For pediatric patients, keep track of height and head circumference at each visit until they are fully grown Vital signs • Oxygen saturation	o detailed neurological examinations o Standard motor examination (movement assessment by physiotherapists) o Motor skills questionnaires • Physiotherapy tests: o Assessment of strength o Evaluation of joint flexibility o Assessment of muscle function o SMA-specific motor function scales (e.g. HFMSE)	

		• heart rate • blood pressure Physical examination • Skin • throat, nose and ears • lungs • Heart • Belly • genitals • Neurology Assessment of motor skills WHO engine milestones and / or HINE subscale 2 • Head posture • Sit • crawling • Stand • Go Physiotherapeutic reviews: • SMA type 1: CHOP INTEND • HFSME (if CHOP INTEND> 50 points) • SMA type 2-4: HFSME, RULM, 6 MWT (for ambulatory patients) • Optional for adult patients: ALS functional rating scale Drug treatment (if applicable) • Performing a lumbar puncture • Need for additional sedation or general anaesthesia • Vital functions after lumbar puncture • Adverse events resulting from the procedure • Information on post-puncture headache Adverse events / drug side effects		

		Adverse events of particular interest are collected during each visit and documented in the CRF in a specific UE section. In patients with regular follow-up care, adverse events of particular concern include all serious adverse events that resulted in death, life threatening, or hospitalization. For patients receiving treatment, adverse events of particular concern additionally include possible treatment-related medical events.		
9	Bias	A selection bias appears unlikely, since all patients for whom data were available in the registry centres up to the data cut-off were included in the analysis. In order to avoid a selection bias, the doctors were asked to consistently include the patients according to inclusion and exclusion criteria. The department for clinical studies in Freiburg is informed about newly admitted patients with a registration form. Each patient is identified in the register by a unique patient identifier (patient number). A system to avoid duplicate patient entries was implemented. Each centre keeps a patient identification record with the names of all patients in the registry and the corresponding identification codes. Conservative methods such as multiple imputation or Markov Chain Monte Carlo were used to imputate missing values. Due to the register design, the results are potentially biased. They represent the best currently available evidence with longitudinal data on the course of	A selection bias appears unlikely, since all patients for whom data were available in the registry centres up to the data cut-off were included in the analysis. Due to the design of the registry, the results are potentially skewed. They represent the best currently available evidence with longitudinal data on the course of the disease and treatment influence of Nusinersen in type 3, adult type 3 and type 4 patients. The instruments used to measure disease progression have been validated.	A selection bias appears unlikely, since all patients for whom data were available in the registry centres up to the data cut-off were included in the analysis.

		the disease and treatment influence of Nusinersen in type 3, adult type 3 and type 4 patients. The instruments used to measure disease progression have been validated.		
10	Study size	The study size is determined by the number of patients available in the centres, taking into account the rarity of the disease. There is therefore no sample size estimation. The aim of the registry is to record the data on SMA patients as completely as possible by including all SMA patients in German-speaking countries. It is expected that a total of around 1000 patients will be enrolled in the registry.	No sample size calculation is performed as this registry aims to capture the data of SMA patients as completely as possible by including all SMA patients from the Italian registry. it is expected that a total of approximately 800 patients will be enrolled in the registry.	The study size is determined by the number of patients available in the centres, taking into account the rarity of the disease. There is therefore no sample size estimation. Approximately 450 patients will be included in the registry, regardless of age or gender.
11	Quantitative variables	Investigations growth • First patient visit: body weight and height • Tracking of body weight with each visit • For paediatric patients: Track height and head circumference at each visit until they are fully grown Physiotherapeutic reviews: • SMA type 1: CHOP INTEND • HFSME (if CHOP INTEND> 50 points) • SMA type 2-4: HFSME, RULM, 6MWT (for ambulatory patients) • Optional for adult patients: ALS functional rating scale An increase in the respective instruments indicates a better condition.	The main objective of this registry is to document all patients diagnosed with 5q-SMA. The statistical analysis will be mainly descriptive.	• Clinical examination (including motor milestones and growth parameters in paediatric patients) • CHOP INTEND • HFMSE • RULM • 6MWT
12	Statistics	The main objective of this registry is to document all patients diagnosed with 5q-	Quality control in Italy is carried out by a clinical research assistant and a data manager. Physiotherapists are trained	The statistical analysis will be mainly descriptive. First, the data quality is assessed based on the number of

		SMA. The statistical analysis will be mainly descriptive. a) Continuous variables are calculated according to the arithmetic mean, standard deviation, minimum, 25% quantile, median, 75% quantile, maximum and the number of complete and missing observations Variables can also be represented in categories. Relative frequencies are indicated by the total number in%. Medical data documented at different times, e.g. Laboratory data are summarized. Univariate and multivariate regression analyses are performed to assess the effect of age at the start of treatment, SMN2 copy number, and motor function, which are either CHOP INTEND, RULM, HFMSE score, 6MWT, WHO motor milestones or ALS- FRS-R are defined. Multivariate regression analysis with backward selection of the variables (p = 0.1) was performed. A Spearman correlation analysis is used for correlation analysis. b) Patients are divided into cohorts according to disease characteristics, and analyses are performed in these subgroups if> 10 patients are observed in a cohort. c) Unless otherwise specified in individual cases, missing values are not replaced and only observed cases are analysed. Partially missing data is handled as follows: If the day of a date variable is unknown, the value "15" is inserted as the day and a footnote is displayed in the listings that the day was	once a year and monthly conference calls are held with physiotherapists from the three networks (UK, USA and Italy). Interoperator variability tests take place annually.	recruits and the completeness of the data (percentage of missing values). The time to the event is estimated using the Kaplan-Meier method. Continuous data are grouped according to the arithmetic mean, standard deviation, minimum, 25% quartile, maximum, and the number of complete and missing observations. If necessary, continuous variables can also be represented in categories. Categorical data are grouped according to the total number of patients in each category and the number of missing values. Relative frequencies are shown as a percentage. Analyses on specific research questions can be carried out on request and are described in a specific statistical analysis plan.

		unknown. If the day and month of a date variable are unknown, July 1 is inserted as the day and month, and a footnote appears in the listings indicating that the day and month were unknown. If a date is completely missing, it will not be inserted.		
12a	Data access and cleaning methods	The lead investigator and the CTU are responsible for implementing and maintaining quality assurance and quality control systems with written SOPs. An independent Data Monitoring Committee (DMC) and a steering committee have been established. The role of the DMC / steering body is to monitor the progress of the register. In addition, the DMC / steering committee decides on specific analyses within the register. If necessary, the DMC / steering committee gives the coordinating investigator a recommendation to change or update the registry. The underlying principles for the DMC are ethical and scientific aspects for research within the SMA indication. For this purpose, the DMC must be informed about compliance with the protocol and the corresponding documentation, as well as about patient recruitment. The DMC receives the regular analysis report at the planned analysis times.	Nusinersen treatment Total type 3 and type 4 population in the registry: [redacted] (type 4 only 1) Type 3 population with complete data: [redacted] Adult population with complete data: 38 DMT untreated Total type 3 and type 4 population in the registry: [redacted] Left untreated due to scoliosis Total population: [redacted]	A system will be implemented to prevent duplicate patient entries. Each centre keeps a patient identification protocol with the names of all patients in the registry, with each patient being assigned the appropriate identification code. Data security is guaranteed in accordance with national and European law.
12b	Connection	N/A		Is possible
13	Participants (including flow	Nusinersen treatment	Biogen provides funding to the registry and works with the registry but has no	Nusinersen treatment

	chart for illustration after the table)	Total type 3 and type 4 population in the registry: [redacted] (type 4 only 6) Type 3 population with complete data: Jan. Adult population with complete data: [redacted] DMT untreated Total type 3 and type 4 population in the registry: [redacted] Left untreated due to scoliosis Total population: [redacted]	intellectual property on the data or controls decisions about publication.	Total type 3 and type 4 population in the registry: [redacted] (no type 4) Type 3 population with complete data: [redacted] Adult population with complete data: [redacted] DMT untreated Total type 3 and type 4 population in the registry: [redacted] Left untreated due to scoliosis Total population: [redacted]
22	Financials	Biogen provides financial support for the SMArtCARE registry. This source of funding did not play a role in the design of this register and will not play a role during the implementation, analysis, interpretation of the data or the decision to submit the results. Additional funding from other sources could be possible in the future to ensure the long-term sustainability of the registry.		Biogen provides financial support for the CuidAME registry. This source of funding did not play a role in the design of this register and will not play a role during the implementation, analysis, interpretation of the data or the decision to submit the results. Additional funding from other sources could be possible in the future to ensure the long-term sustainability of the registry.

A.10. Appendix F: Checklist of confidential information

For the overview of the confidential information, and dates until when AiC needs to remain confidential (estimated dates may be provided) please see separate folder as part of the submission files.

A.11. Appendix G: SMA UK – case series and survey

Please find the relevant files in a separate folder as part of the submission files.

A.12. Appendix H: Clinicians' case studies

Please find the relevant files in a separate folder as part of the submission files.

