NICE National Institute for Health and Care Excellence

NICE guidance

Nusinersen and risdiplam for treating spinal muscular atrophy

Technology appraisal guidance
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Your responsibility

The recommendations in this guidance represent the view of NICE, arrived at after careful consideration of the evidence available. When exercising their judgement, health professionals are expected to take this guidance fully into account, alongside the individual needs, preferences and values of their patients. The application of the recommendations in this guidance is at the discretion of health professionals and their individual patients and do not override the responsibility of healthcare professionals to make decisions appropriate to the circumstances of the individual patient, in consultation with the patient and/or their carer or guardian.

All problems (adverse events) related to a medicine or medical device used for treatment or in a procedure should be reported to the Medicines and Healthcare products Regulatory Agency using the Yellow Card Scheme.

Commissioners and/or providers have a responsibility to provide the funding required to enable the guidance to be applied when individual health professionals and their patients wish to use it, in accordance with the NHS Constitution. They should do so in light of their duties to have due regard to the need to eliminate unlawful discrimination, to advance equality of opportunity and to reduce health inequalities.

Commissioners and providers have a responsibility to promote an environmentally sustainable health and care system and should assess and reduce the environmental impact of implementing NICE recommendations wherever possible.

Contents

This guidance replaces TA588 and TA755.

1 Recommendations

Nusinersen

1.1 Nusinersen can be used as an option to treat 5q spinal muscular atrophy (SMA), only if:

- it has not been successfully treated with onasemnogene abeparvovec (see section 3.10)
- nusinersen is not used with risdiplam, and
- the company provides nusinersen according to the commercial arrangement.

1.2 Stop nusinersen if there is sustained deterioration across a range of clinical measures and the treatment is not providing benefit. Assess whether the person is benefitting from treatment based on clinical judgement of their individual needs.

Risdiplam

1.3 Risdiplam can be used as an option to treat 5q SMA type 1, 2 or 3 or with 1 to 4 SMN2 copies, only if:

- it has not been successfully treated with onasemnogene abeparvovec (see section 3.10)
- risdiplam is not used:
  - with nusinersen
  - for presymptomatic SMA when onasemnogene abeparvovec is suitable, and
- the company provides risdiplam according to the commercial arrangement.

1.4 Stop risdiplam if there is sustained deterioration across a range of clinical measures and the treatment is not providing benefit. Assess whether the person is benefitting from treatment based on clinical judgement of their individual needs.

1.5 This recommendation is not intended to prevent risdiplam being used as a bridging therapy until treatment with onasemnogene abeparvovec is possible.

What this means in practice

Nusinersen and risdiplam must be funded in the NHS in England for the condition and population in the recommendations, if it is considered the most suitable treatment option. NHS England has agreed to provide funding from routine commissioning budgets so nusinersen and risdiplam will be funded from 14 May 2026.

There is enough evidence to show that nusinersen and risdiplam provide benefits and value for money, so they can be used routinely across the NHS in this population.

NICE has produced tools and resources to support the implementation of this guidance.

Why the committee made these recommendations

This evaluation reviews the evidence for nusinersen and risdiplam for SMA (NICE technology appraisal guidance TA588 and TA755). It also reviews new evidence collected during the managed access period, which includes evidence from clinical trials and from people having treatment in the NHS in England.

Usual treatment for presymptomatic or type 1 SMA is onasemnogene abeparvovec. When this is not suitable, and for other types of SMA, usual treatment is best supportive care. The managed access agreements specified that people could not have nusinersen or risdiplam if they had already had successful treatment with onasemnogene abeparvovec.

Clinical trial evidence shows that, compared with best supportive care, nusinersen and risdiplam improve motor function and increase how long people live. They have not been

directly compared with onasemnogene abeparvovec in a clinical trial. The results of indirect comparisons are highly uncertain. But they suggest that nusinersen and risdiplam have similar benefits to onasemnogene abeparvovec.

This evaluation considered the condition's severity and its effect on quality and length of life.

For presymptomatic SMA, the most likely cost-effectiveness estimate for risdiplam is only within what NICE considers an acceptable use of NHS resources when onasemnogene abeparvovec is not suitable.

For all other SMA types, the most likely cost-effectiveness estimates are within the range that NICE considers an acceptable use of NHS resources. So, nusinersen and risdiplam can be used.

2 Information about nusinersen and risdiplam

Marketing authorisation indications

2.1 Nusinersen (Spinraza, Biogen) is indicated for 'the treatment of 5q Spinal Muscular Atrophy'.

2.2 Risdiplam (Evrysdi, Roche) is indicated for 'the treatment of 5q spinal muscular atrophy (SMA) in patients with a clinical diagnosis of SMA Type 1, Type 2 or Type 3 or with one to 4 SMN2 copies'.

Dosage in the marketing authorisation

2.3 The dosage schedules for nusinersen are available in the summary of product characteristics for nusinersen 12 mg, nusinersen 28 mg and nusinersen 50 mg.

2.4 The dosage schedule for risdiplam is available in the summary of product characteristics for risdiplam oral solution and risdiplam tablets.

Price

2.5 The list price of nusinersen is £75,000 for 1 vial of 12 mg/5 ml solution for injection, £78,000 for 1 vial of 28 mg/5 ml solution, and £139,286 for 1 vial of 50 mg/5 ml of solution (excluding VAT; company submission). The company has a commercial arrangement. This makes nusinersen available to the NHS with a discount. The size of the discount is commercial in confidence.

2.6 The list price of risdiplam is £7,900 per 60 mg/80 ml oral solution (excluding VAT; BNF online accessed May 2026) and £18,433.00 for a pack of 5 mg tablets (28 tablets per pack; excluding VAT; company submission). The company has a

commercial arrangement. This makes risdiplam available to the NHS with a discount. The size of the discount is commercial in confidence.

Sustainability

2.7 For information, Biogen's Carbon Reduction Plan for UK carbon emissions is published on Biogen's webpage on responsibility.

2.8 For information, Roche's Carbon Reduction Plan for UK carbon emissions is published on Roche's webpage on sustainability.

3 Committee discussion

The evaluation committee considered evidence submitted by Biogen and Roche, an assessment report by the external assessment group (EAG), and responses from stakeholders. The committee held 2 committee meetings. It did not release draft guidance after the first meeting, concluding that further analysis was required from the companies and EAG before it could make a decision. This additional analysis was considered at the second committee meeting. The evidence for nusinersen discussed in this evaluation relates to the 12 mg dosage, unless otherwise stated. A high-dose regimen of nusinersen was considered by the committee after the second committee meeting (see section 3.40). See the committee papers for full details of the evidence.

The condition

Spinal muscular atrophy

3.1 Spinal muscular atrophy (SMA) is a rare, genetic neuromuscular disorder characterised by muscle weakness and progressive loss of movement. People also have difficulty with breathing and swallowing. It is linked to survival motor neuron (SMN) 1 and 2 genes, with the most common cause a defect in the SMN1 gene located on chromosome 5. Most people with SMA have a related gene called SMN2 and the number of SMN2 gene copies a person has can influence the severity of the condition. SMA has historically been categorised into types 0 to 4 with symptom severity and life expectancy varying between types. The number of SMN2 copies increases from 1 copy with type 0, to 4 or more with SMA type 4. SMA type 0 presents before birth with reduced or absent fetal movement. It causes profound muscle weakness, respiratory failure, and often congenital heart defects at birth. Life expectancy is up to 6 months. Type 1 SMA presents at birth or soon after with babies typically being unable to sit and having difficulties breathing and swallowing. Life expectancy without treatment is up to 2 years. Type 2 SMA usually presents at age 6 to 18 months with developmental delays in motor movements. Children will typically be able to sit, but unable to walk as expected. Life expectancy without treatment is between 30 and 50 years. Type 3 SMA normally presents in children over 18 months with variable degrees of weakness, joint contractures and scoliosis. Type 4 SMA typically

presents in adults with milder but variable symptoms. People with type 3 or 4 SMA will usually be able to walk independently, and life expectancy is not expected to be reduced. The committee concluded that SMA ranges in severity and its most severe forms cause profound, wide-ranging disabilities and reduced life expectancy.

SMA types

3.2 The SMA types do not have clear cut offs, so symptoms and life expectancy can vary within each type. Also, the introduction of disease-modifying treatments has significantly improved the prognosis for people with SMA. For example, people with type 1 can reach milestones that were previously unexpected, such as being able to sit or stand. So, the types classification system has become increasingly outdated. The SMA community is increasingly considering SMN2 copy numbers or functional status rather than SMA types alone. The committee concluded that the SMA type classification system has limitations, but it has been used in the marketing authorisation and clinical evidence. So, it is still relevant for this evaluation.

Impact on patients and carers

3.3 The patient experts and patient organisations explained the impact of SMA on patients and carers. The committee also considered a qualitative analysis done by the EAG. This was based on submissions from professional and patient organisations and experts, case studies and free-text registry data. The committee understood that SMA profoundly impacts both patients and their families, creating physical, emotional, and social challenges. For patients, the condition is marked by progressive loss of strength and mobility. This can lead to severe respiratory complications and significant functional limitations. Even small changes in motor function, such as losing movement in a finger, can drastically affect independence, employment and quality of life. Speech difficulties further restrict educational and professional opportunities, and the inability to perform basic tasks often results in social isolation. Mental health is significantly affected by the uncertainty of SMA progression, and continuous grief and anxiety. Delays in diagnosis and inequities in care across the UK exacerbate these burdens. Many

people have to self-fund essential equipment and physiotherapy to maintain independence. The impact extends to carers and families because SMA causes considerable physical and emotional demands. Caring for someone with SMA is a full-time responsibility involving complex tasks such as feeding, bathing and helping with mobility. This often leads to stress, anxiety, back pain and other health issues for carers, who may also experience guilt when prioritising one person's needs over another. Financial strain is common because of the cost of additional support and equipment, compounded by reduced earning capacity because carers frequently give up work. These challenges create a cycle of emotional distress and practical hardship for the entire family. The committee concluded that SMA has a profound impact on people with the condition, and their family and carers.

Clinical management

Diagnosis of SMA

3.4 There is no universal newborn screening programme for SMA in the NHS, so most people are diagnosed after symptoms appear. A small number of babies are diagnosed when presymptomatic, typically when a sibling has already been diagnosed with SMA. The clinical experts advised that the UK National Screening Committee is evaluating the feasibility of newborn screening for SMA. If this is introduced, the number of presymptomatic cases would rise considerably. The committee concluded that most people in the NHS are diagnosed once symptomatic, but in the future most people may be diagnosed presymptomatically.

Treatment options

3.5 There are 3 disease-modifying treatments licensed for use in the UK. These are nusinersen, risdiplam and onasemnogene abeparvovec (OA). NICE's highly specialised technology guidance on onasemnogene abeparvovec for treating presymptomatic spinal muscular atrophy (from here, HST24) recommends OA for treating presymptomatic SMA in babies aged 12 months and under, with up to 3

copies of the SMN2 gene. NICE's highly specialised technology guidance on onasemnogene abeparvovec for treating spinal muscular atrophy recommends OA for treating type 1 SMA in babies if they are 6 months or younger, or they are aged 7 to 12 months and the treatment is agreed by the national multidisciplinary team. NICE's technology appraisal guidance 588 (from here, TA588) recommends nusinersen in managed access for treating presymptomatic SMA, or SMA types 1, 2 and 3. NICE's technology appraisal guidance 755 (from here, TA755) recommends risdiplam in managed access for treating SMA types 1, 2 and 3 or presymptomatic SMA with 1 to 4 SMN2 copies. So, OA is the only treatment routinely available in the NHS, and it is only recommended for babies with presymptomatic or SMA type 1. The 3 treatments have different administration methods and different side-effect profiles. Nusinersen is administered by intrathecal injection every 4 months, risdiplam by daily oral syringe or tablet, and OA by a one-off intravenous infusion. The clinical experts emphasised that there is no single preferred treatment, and all treatment options would be considered. This is because treatment suitability varies between individuals. Also, it is sometimes necessary to switch between treatments to minimise irreversible loss of function, either because of poor response or intolerance. The patient and clinical experts explained that treatment is complemented with multidisciplinary supportive care. This includes respiratory support, physiotherapy, assistive technologies, occupational therapy and social care. The committee noted that decisions about which option to use are made jointly by the healthcare professional, the patient, and their carers or family. These decisions are based on eligibility, clinical suitability and personal preferences. The committee concluded that all 3 disease-modifying treatments are valued by the SMA community.

Treatment availability during managed access

3.6 Nusinersen and risdiplam have been available through managed access since the publication of TA755 and TA588. As part of the managed access agreements, data was collected on a range of outcomes to assess how well the treatments worked in the real world (see section 3.16). The clinical and patient experts reported that having access to treatment during this time had transformed the clinical and lived experience of the condition, delivering substantial improvements in survival, physical health and psychosocial wellbeing. They emphasised that maintaining access to both therapies is critical to keep these survival and health

gains, especially for people who are not eligible for OA or have missed the opportunity to have it. And given the differences between the treatments, access to both nusinersen and risdiplam is needed to account for contraindications, adverse events or poor response. The committee concluded that the SMA community valued having access to nusinersen and risdiplam during managed access. It also understood the profound impact that withdrawing access would have for patients and their carers.

Starting and stopping rules

3.7 The managed access agreements specified that people could not start treatment with nusinersen and risdiplam if they had already had successful treatment with OA or if they were permanently ventilated. And they could not take both nusinersen and risdiplam at the same time. They had to stop treatment if they were diagnosed with an additional life-limiting condition or if they were not receiving benefit from treatment. Loss of treatment benefit was defined as a total worsening in disease score across 2 measurement scales or having permanent ventilation. The committee noted that the marketing authorisations for nusinersen and risdiplam do not include starting or stopping rules for treatment. The committee considered whether the starting and stopping rules used in managed access were also appropriate for routine commissioning.

Permanent ventilation

3.8 The patient experts emphasised that current starting and stopping rules exclude people from treatment who could benefit. The managed access agreements defined permanent ventilation as 16 or more hours per day for 21 consecutive days in the absence of acute reversible infection or tracheostomy at baseline. One patient expert explained that their child had nusinersen through a compassionate use program when permanently ventilated. The treatment resulted in significant improvements including stabilisation of the condition and drastically reduced hospitalisations for infections and respiratory exacerbations. The clinical experts advised that some people had been able to reduce how many hours a day they have ventilation for. They explained that stabilisation meant people were able to retain the ability to use devices such as a mobile phone or

tablet computer, which help them maintain a degree of independence. They also explained that ventilation devices have become more portable, allowing trips outside of the home. The clinical experts also advised that the cohort of people on permanent ventilation should reduce considerably over time as disease-modifying treatments are started earlier in a person's life. The committee concluded that some people had benefited considerably from treatment while having permanent ventilation. It concluded that this alone should not determine whether treatment should start or stop.

Stopping treatment

3.9 The patient experts had concerns about the motor milestone assessments used to monitor clinical benefit, which are used to decide whether treatment can continue. They explained that the scores do not reflect the benefits they see at home and consider valuable, such as being able to lift a cup to drink independently. They also explained the assessments are often done after long journeys to the hospital, or during cold weather. So, people are not assessed at times when they are feeling their best. The assessments also take up valuable clinic time that could be spent on other things, such as agreeing physiotherapy requirements. The clinical experts noted there were only a handful of cases when the criteria for stopping treatment because of deterioration were potentially reached during the managed access period. And even in those cases, the national clinical panel agreed that treatment should continue. The clinical experts advised that there should be more flexibility for clinical judgement in the starting and stopping rules, given that SMA is a very heterogenous condition. They agreed that no clinician would want someone to continue treatment when there was no clear benefit. They explained that for a progressive disease like SMA, stabilisation or slowed progression would represent benefit. The committee concluded that treatment should stop if the person shows sustained deterioration across a range of clinical measures and a clinician considers the person is not benefitting from treatment. But the assessment of benefit should incorporate clinical judgement and allow some flexibility based on individual need.

Combination treatment and successful treatment after OA

3.10 The clinical experts acknowledged that people should not take nusinersen and risdiplam together, or after successful treatment with OA. But they noted that evidence may become available on these treatment approaches in the future. Unsuccessful treatment with OA is defined as either or both:

- a reduction in motor ability, defined as total worsening in scale score corroborated by 2 consecutive measurements from any 2 of the following 3 scales:
  - more than 2 points on the horizontal kick scale or 1 point on other Hammersmith Infant Neurological Examination (HINE) scores excluding voluntary grasp
  - more than 4 points on the Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders (CHOP-INTEND) scale
  - more than 3 points on the Revised Hammersmith scale
- a deterioration in respiratory function defined as:
  - an increasing requirement for respiratory support overnight, and
  - an uncharacteristic increase in respiratory infections requiring hospital treatment that cannot be accounted for by aspiration or intrinsic lung disease.

  The committee understood that during the managed access period it was very rare for anyone to have started nusinersen or risdiplam after treatment with OA. This is because most people had benefited from treatment with OA. The committee concluded that nusinersen and risdiplam should not be used together, or after previous successful treatment with OA as defined in the managed access agreement.

Comparators

3.11 The decision problem for this appraisal included 4 comparators: best supportive care, OA, nusinersen and risdiplam. Given its NICE recommendation, OA is

relevant as a comparator only for presymptomatic and type 1 SMA (see section 3.5). Best supportive care includes multidisciplinary care such as physiotherapy and respiratory support. Because best supportive care should be offered universally to all patients, the evaluation should consider the costs and benefits of active treatment added to best supportive care. Biogen only included comparisons of nusinersen with best supportive care in its original submissions (not risdiplam or OA). Roche included comparisons of risdiplam to nusinersen, best supportive care and OA (when eligible). Roche explained that expert opinion and market research showed that less than 5% of people have best supportive care in the NHS, so it questioned whether it was an appropriate comparator for decision making. Biogen acknowledged that best supportive care does not entirely reflect current clinical practice. But because of limitations in the available comparative data, this comparison was deemed the only feasible approach. The EAG explored risdiplam compared with nusinersen in scenario analyses. But it did not consider this in its base case, because of differences in population characteristics and trial designs. For example, it was concerned that the placebo arm used in the risdiplam trials was not comparable to the sham arm used in the nusinersen trials. It also had concerns that the effective sample sizes were low once matching had been done, because of heterogeneity in the trial populations. It explained its approach of not comparing risdiplam and nusinersen in its base case was necessary to avoid any bias arising out of these differences (see section 3.22). The clinical experts agreed that a meaningful comparison between nusinersen and risdiplam is not possible given the available data. The committee noted that the Institute for Clinical and Economic Review and the Scottish Medicines Consortium (SMC) both concluded there was insufficient data to compare the net health benefits of risdiplam and nusinersen (see the SMC's detailed advice on nusinersen and the Institute for Clinical and Economic Review's evidence report on therapies for SMA). It also noted that there is a distinction between comparators that are appropriate based on current practice, and those that are feasible, given the data limitations. The committee considered that OA is the only active treatment that is routinely commissioned in the NHS. It concluded that nusinersen and risdiplam should not be compared directly and its preferred decision-making comparators were:

- for presymptomatic SMA and type 1 SMA: OA, and best supportive care for people unable to have OA, and for the cohort of people with type 1 SMA who missed the opportunity to have OA and are now not eligible because of age or weight

- for type 2 and 3 SMA: best supportive care.

Clinical effectiveness

Additional evidence

3.12 Since the original technology appraisals were published for nusinersen and risdiplam, additional follow-up data has been collected from the companies' clinical trials.

Presymptomatic SMA

3.13 The committee reviewed the additional efficacy data from presymptomatic SMA trials for nusinersen (NURTURE) and risdiplam (RAINBOWFISH). In NURTURE, which enrolled babies up to 6 weeks of age with 2 or 3 SMN2 copies (most likely to develop type 1 or 2 SMA), outcomes at about 5 years of treatment showed that 100% of children were alive and without permanent ventilation, although 16% needed some respiratory intervention. All children were able to sit without support, 92% were able to walk alone, and 88% reached the maximum CHOP-INTEND score. No motor skills were lost during the observation period, suggesting sustained benefit. At 8-year exploratory follow up, all children were alive and without permanent ventilation, and all children with 3 SMN2 copies reached all 6 WHO motor milestones. For children with 2 SMN2 copies, 87% were able to walk alone. In RAINBOWFISH, which included babies up to 6 weeks of age with 2 or more SMN2 copies (all SMA types), after 1 year of treatment all children were alive and without permanent ventilation. 96% could sit without support, 52% could stand unaided, 32% could stand aided, and 48% could walk independently. At 2-year exploratory analysis, all children were able to sit without support and 87% could walk independently. The committee noted the differences between the companies' trials, such as the different inclusion criteria and follow-up durations. It concluded that presymptomatic treatment with nusinersen or risdiplam improves motor skills and survival. This enables children with SMA to reach major motor milestones such as sitting, standing and walking, at rates approaching normal developmental trajectories.

Type 1 SMA

3.14 The committee reviewed efficacy results from type 1 SMA trials for nusinersen (ENDEAR) and risdiplam (FIREFISH). The ENDEAR results showed that, after 13 months of nusinersen, 51% of children were 'motor milestone responders' compared with 0% in the control group. Nusinersen reduced the risk of mortality or permanent ventilation by 47% (hazard ratio 0.53, p=0.0041) and reduced the risk of permanent ventilation alone by 34% compared with the control group (HR 0.66, p=0.1329). The ENDEAR-SHINE extension study results are confidential and cannot be reported here. The FIREFISH results showed that after 1 year of risdiplam (part 2 of the study), 85% of children were alive and without permanent ventilation, and 78% were 'motor milestone responders' compared with 12% expected from natural history. After 2 years, 44% of children could sit without support for 30 seconds and 90% had an increase in the CHOP-INTEND score of at least 4 points. After 5 years, 81% were alive and without permanent ventilation. The clinical experts advised that without treatment, people would never sit without support and only 25% would survive beyond 14 months. The committee noted the differences between the nusinersen and risdiplam trial designs and duration of follow up. It concluded that treatment with nusinersen or risdiplam enabled people with type 1 SMA to survive and reach milestones that would not be possible without treatment.

Type 2 and 3 SMA

3.15 The committee considered efficacy results from type 2 and 3 SMA trials for nusinersen (CHERISH) and risdiplam (SUNFISH). In CHERISH, at 15-month follow up, the mean change in Hammersmith Functional Motor Scale for SMA (HFMSE) score was +3.9 for nusinersen compared with -1.0 for control, and 19.7% of children reached new motor milestones compared with 5.9% in the control group. A motor milestone response (3 or more points increase in HFMSE) was observed in 56.8% of children having nusinersen compared with 26.3% in the control group. Upper limb function also improved, with a mean Revised Upper Limb Module (RULM) change of +4.2 points for nusinersen compared with +0.5 for control. In the SUNFISH study of risdiplam, after 1 year the mean motor function change was +1.36 points in the 32-item motor function measure (MFM-32) compared with -0.19 for placebo, and upper limb function improved by +1.61 points

compared with +0.02 for placebo. Longer follow-up data from extension studies was also considered by committee for both trials. The committee concluded that treatment with nusinersen or risdiplam resulted in stabilisation or slight improvement for people with type 2 or 3 SMA, in contrast to an expected gradual decline without treatment.

Registry data collected during managed access

3.16 The committee considered evidence gathered in SMA REACH UK and Adult SMA REACH registries as part of the managed access agreements for nusinersen and risdiplam. Data was collected from about 400 children and 400 adults with SMA from 17 centres across England. For children, nusinersen had a longer follow-up period for motor outcomes than risdiplam (about 4 years compared with 3 years). For adults, follow up was about 4 years for both treatments. But the managed access period started for nusinersen before risdiplam, so there is more data available for nusinersen at later time points. Outcome data was collected for motor milestones and functional scores, survival, permanent ventilation and treatment discontinuation. The results suggested maintenance or improvement in motor milestones across all SMA types assessed for both treatments, with most gains observed for motor outcomes. Patient-reported outcome measures (PROMs), such as quality of life and independence, were also collected. Quantitative PROMs data was limited for both treatments and showed mixed results. The exact results are confidential and cannot be reported here. Biogen, Roche and clinical experts noted differences between the registry and real-world incident populations. Registry patients (prevalent population) had longer SMA duration, higher symptom burden and higher baseline severity than expected in future real-world incident populations. The committee acknowledged the significant efforts the SMA community has put into data collection during the managed access period. It concluded that the registry data provides important, supportive evidence that nusinersen and risdiplam can maintain or improve motor function in the longer term. But it noted that uncertainty remains about the generalisability of the results to the incident population.

Sensitivity and relevance of assessment tools

3.17 Several scales are used to assess the severity of SMA. Previous appraisals for nusinersen and risdiplam raised concerns that the assessment tools are not sensitive enough to fully capture small changes in the condition. And although the tools focus on motor function, other aspects such as respiratory function, bulbar function, pain and physical impairment also affect health-related quality of life (HRQoL). The patient and clinical experts confirmed that small gains in upper limb and hand function can profoundly impact quality of life. For example, the ability to operate an electric wheelchair or computer mouse enables people to maintain their independence, but this is not captured by SMA assessment tools. A clinical expert from the registry noted difficulties in consistently capturing treatment benefits, especially for stamina and fatigue. To address these issues, during managed access Roche collected additional HRQoL data from people with SMA and their carers, including a utility study. But the data was limited by small sample sizes, which restricted its use in Roche's base case. Biogen considered including interim milestones for more granular outcomes but noted this would create substantial data gaps. The EAG agreed that motor function tools lack granularity and focus mainly on gross motor skills (such as crawling and sitting), but do not capture fine motor skills (such as wheelchair control) despite these being crucial for patients and carers. Roche also emphasised that the SMA community considers condition-related complications such as scoliosis, respiratory complications and bulbar function critical to quality of life. These are often not captured in standard SMA assessment tools. The committee concluded that the scales used to assess severity of SMA focus predominantly on overall motor skills and do not reflect the full impact of the condition. They also lack the sensitivity to capture small changes that can have a large impact on a person's quality of life and independence.

SMA UK survey after the first committee meeting

3.18 At the first committee meeting in November 2025, the committee identified several uncertainties and gaps in the available data. To help address these uncertainties, SMA UK did a survey of 113 people in the UK having nusinersen or risdiplam between December 2025 and January 2026. In the sample, 15% of people had type 1 SMA, 58% had type 2 and 27% had type 3. In the group, 29% of

people were having nusinersen and 71% were having risdiplam. The survey found that the number of carers a person with SMA had ranged from 0 to 10 carers. But most people had between 2 and 4 carers with an average of 3.67, which included paid and unpaid carers. After treatment with nusinersen or risdiplam, average unpaid care support dropped from 12.6 to 9.7 hours (23% reduction). The number of people being 'fully reliant' on unpaid care dropped from 67 to 49 (27% reduction). Hours of paid care increased over time because of a person's growth and development and a shift from family to professional care. Survey respondents reported that nusinersen and risdiplam improved mental health, sleep, physical health and economic participation of carers. No survey respondents reported that nusinersen or risdiplam worsened their condition, and 74% and 63% reported their motor function and respiratory function improved respectively. People also reported significant reductions in emergency care, GP visits and reliance on specialist medical equipment after treatment. Improvements in school and work attendance, socialising, confidence and mental wellbeing were also reported after treatment. The committee acknowledged the considerable efforts of SMA UK and the SMA community to provide data to support its decision making. It noted that the survey had not been reviewed by the EAG. So, the methodology, design and potential biases in the study had not been scrutinised. But the committee concluded that the survey results provided valuable supportive evidence to help address the key uncertainties it had identified.

Treatment efficacy compared with best supportive care

Biogen's approach for nusinersen

3.19 For presymptomatic SMA, Biogen used the NURTURE trial to inform the effectiveness of nusinersen. NURTURE was a single-arm study, so the efficacy of best supportive care was estimated using data from ENDEAR or CHERISH, depending on the number of SMN2 copies. For type 1 SMA, Biogen used ENDEAR and SHINE to inform the nusinersen treatment effect. The efficacy of best supportive care was based on the comparator arm of ENDEAR. For type 2 or 3 SMA, Biogen used CHERISH and SHINE data to inform the nusinersen treatment effect. It used the comparator arm from CHERISH for best supportive care. The

EAG's base case for nusinersen used the same treatment-effect data as Biogen for all SMA types. The committee concluded that the approach taken by Biogen and the EAG to compare the effectiveness of nusinersen with best supportive care was appropriate.

Roche's approach for risdiplam

3.20 For presymptomatic SMA, Roche used data from the RAINBOWFISH trial to inform the effectiveness of risdiplam. RAINBOWFISH was a single-arm study, so it could not be used to estimate the efficacy of best supportive care. Roche explored a matching-adjusted indirect comparison (MAIC) or simulated treatment comparison (STC) but concluded they were unsuitable. This was because of very small sample sizes, baseline differences, inconsistent assessment schedules and differences in reporting motor milestones. So, Roche modelled the effectiveness of best supportive care using internal natural history data. The EAG's base case for risdiplam used the same approach. For type 1 SMA, Roche used FIREFISH data to inform the risdiplam treatment effect. For best supportive care, it used the placebo arm of ENDEAR (as in TA755). The EAG's base case used an unanchored MAIC of FIREFISH and ENDEAR data from Ribero et al. For type 2 or 3 SMA, the treatment effects of risdiplam and best supportive care were taken from SUNFISH data. The committee concluded that the approach taken by the EAG to compare the effectiveness of risdiplam with best supportive care was appropriate.

Treatment efficacy compared with OA

3.21 Because of the lack of comparative data between nusinersen and risdiplam compared with OA, the companies did indirect treatment comparisons (ITCs) for presymptomatic and type 1 SMA. This included unanchored MAICs and STCs. Biogen said that using the MAICs created implausible results for the presymptomatic and type 1 population, with some outcomes better than the general population. So, it assumed equal efficacy for nusinersen and OA for the first 18 months. Then the MAIC risk differences were applied from months 18 to 60. After this, people could only maintain or lose motor milestones. Roche reported that MAICs and STCs were not feasible for presymptomatic SMA. So, it

assumed equal efficacy of risdiplam compared with OA. For type 1 SMA, it did an unanchored MAIC on the Bayley Scales of Infant Development (BSID)-III endpoint.

Both companies acknowledged that the ITC results had considerable uncertainty and that it was not possible to draw robust conclusions from them. Biogen said the results were not suitable for decision making because of significant differences in baseline characteristics across trials, inconsistent assessment schedules, use of different motor milestone scoring systems and very small effective sample sizes because of poor covariate overlap. The EAG said both companies made clear attempts to produce plausible analyses but agreed that the ITCs had significant limitations. For presymptomatic SMA, the EAG aligned with Roche, assuming equal efficacy of nusinersen compared with OA and risdiplam compared with OA. For type 1 SMA, it maintained the preferences of the respective company's base cases. The committee noted the concerns about the results of the OA ITCs. But it decided the ITCs were the most appropriate sources of comparative evidence available, despite the uncertainties. So, the committee concluded that the EAG's approach to estimating comparative efficacy compared with OA was suitable for decision making.

Economic models

Company and EAG's modelling approaches

3.22 Biogen and Roche each submitted 3 Markov models with separate models for presymptomatic SMA type 1, and types 2 and 3. No cost-effectiveness evidence was submitted for types 0 or 4. The models used similar structures in which people move between different health states defined by motor milestone (such as 'not sitting' and 'sitting without support'). Presymptomatic and type 1 SMA models also included a 'permanent ventilation' health state. The health states were not equivalent between the Biogen and Roche models because different motor scales were used to define the states. For example, Biogen includes 'standing with support' and 'walking independently', whereas Roche has 'standing' and 'walking'. Biogen mostly used WHO motor milestones, whereas Roche used HINE-2 for presymptomatic and SMA type 1, and MFM-32 and HFMSE for SMA types 2 and 3. Additional differences in approach between the

company models included time horizon, treatment-effect duration, survival modelling, treatment discontinuation, utility values, adverse events and health-state costs. The EAG did not create a combined model for both treatments because of differences in population characteristics and outcome measures used in the clinical trials. It explained the approach was necessary to avoid any bias arising out of the differences. Instead, it made adjustments to align the models when possible. The committee concluded that it would have been preferable to consider nusinersen and risdiplam together in a single model for each SMA type. But it accepted that the models and data that underpin them were too different to combine in a robust way.

Treatment discontinuation

3.23 Both companies' models assumed that people who stop treatment switch to best supportive care. Biogen used data collected during the managed access period to inform treatment discontinuation rates. In Roche's original submission, it assumed that people only stopped treatment when they were permanently ventilated or when treatment effect was lost (as determined by health state). After the first committee meeting, Roche shared alternative approaches which removed the permanent ventilation stopping rule. It added a constant treatment discontinuation rate across all health states. Roche provided scenarios using data from the managed access period and data from its clinical trials. Roche explained that discontinuation rates from the managed access period would not reflect long-term clinical practice. It said that treatment discontinuation was typically temporary and the managed access data does not reflect re-initiation of treatment. It reiterated its preference for modelled stopping rules that reflect a loss of treatment benefit. Biogen said it is appropriate to include treatment discontinuation for the comparison of nusinersen with best supportive care, but argued that treatment discontinuation should be removed for comparisons with OA. This is because OA is a one-off disease-modifying treatment with no discontinuation, and the on-treatment utility benefit will be maintained until death. But most people in the model stop nusinersen in the long term. So, this approach is highly likely to overestimate the effectiveness of OA compared with nusinersen. This will also overestimate the quality-adjusted life year (QALY) gains. The EAG included treatment discontinuation from the managed access registry data (April 2025 data cut) in its base case. But it acknowledged that the managed

access data likely overestimates treatment discontinuation because it is based on short-term data. The EAG also questioned whether all people who stop treatment would then have best supportive care, instead of other disease-modifying treatments. The clinical experts said that most treatment discontinuation is because of switching treatment (including ending bridging therapy), and that very few people stop treatment altogether. They said less than 5% of the paediatric population are not receiving treatment. The committee concluded that treatment discontinuation should be included in the modelling. And this should use data from the latest registry data cut as in the EAG's base case. It considered the concerns about overestimating treatment discontinuation, especially compared with OA. It agreed that including treatment discontinuation likely overestimated the QALY gains associated with OA, because of the on-treatment utility benefits that are modelled for OA until the end of the model time horizon (see section 3.27). So, the committee concluded that treatment discontinuation should be excluded in the comparisons of nusinersen and risdiplam compared with OA.

Modelling treatment when on permanent ventilation

3.24 The committee recalled its earlier conclusion that being permanently ventilated alone should not determine whether treatment should start or stop (see section 3.8). It considered how this would impact treatment discontinuation in the modelling. The original company submissions did not include treatment when permanently ventilated. Biogen explained that when it included treatment when permanently ventilated in the modelling, the results were not clinically plausible. This is because some people survived a very long time in the model. It also noted that the data was very uncertain because it was based on only 5 or 6 people who are permanently ventilated and having nusinersen. So, Biogen stated that permanent ventilation should not stop treatment in clinical practice. But the model should not include treatment when permanently ventilated because of the uncertainty. Roche agreed that permanent ventilation should not stop treatment in clinical practice. The EAG provided scenarios that included and excluded treatment when permanently ventilated. The committee recalled its decision that starting treatment with nusinersen and risdiplam should not be precluded, or stopped, in clinical practice because of a requirement for permanent ventilation alone (see section 3.8). But it also acknowledged that the modelling becomes

significantly more uncertain when accounting for treatment in permanently ventilated states. So, the committee concluded that treatment when permanently ventilated should not be included in the modelling for either nusinersen or risdiplam.

Utility values

Patient utility values

3.25 The EAG explained that there is considerable variation in the utility values used for severe health states across previous SMA appraisals and the company base cases. This introduces significant uncertainty into the cost-effectiveness results. The size of the modelled benefit is highly sensitive to the utility values used. The EAG noted that some values applied by the companies were close to, or even lower than, the utility of being in the 'dead' state. The patient experts said this underestimated quality of life for people with SMA. The EAG advised that negative utility values are implausible and unlikely to reflect people's preferences. Biogen's base case applied values from HST24 for all SMA types. Roche used different sets of values for presymptomatic or type 1 SMA and SMA types 2 or 3, including negative utilities for the permanent ventilation state (-0.02 for type 1 SMA) and the 'not sitting' state (-0.17 for SMA type 2 or 3). The EAG applied the same values across all SMA types. The committee noted that it did not expect any health states to have negative utility. Also, there was no clear justification for utility values to vary by SMA type as well as by health state. So, the committee concluded that the utility values used by Biogen and the EAG from HST24 should be used for decision making.

Carer utility values

3.26 Qualitative evidence consistently shows SMA has profound physical, emotional and financial impacts on carers (see section 3.3). Previous appraisals for nusinersen and risdiplam considered how carer HRQoL could be accounted for in modelling. In TA588, the committee concluded that carer utility should be considered but quantifying it was extremely difficult. In TA755, the company

applied an additive absolute utilities approach. This assumed carer utility was zero after a person died, which the EAG criticised as unrealistic. The EAG adopted a disutility approach but the committee decided this was uncertain because of the 'carer QALY trap' for type 1 SMA. This is when increased survival leads to reduced cost effectiveness because the carer disutility is maintained for longer. For this appraisal, Biogen's base case adopted an increment approach. This applied a utility gain for carers for each patient health state relative to the worst state. This approach assumes 1 carer per patient and zero utility increment for the worst health states and death. It uses the same increments across all SMA types. This was based on the assumption that the health state, not the SMA type, determines carer impact. This method rewards survival gains and provides a clear link between health state improvements and carer benefits, avoiding the carer QALY trap. Biogen argued that this approach aligns with the purpose of cost-effectiveness analysis, which is to capture the impact of interventions on both patients and carers. In its original submission, Roche used a decrement approach, applying a utility loss for carers relative to the best health state. This approach assumed 2.2 carers per patient based on a Roche Burden of Illness study. It stopped disutility after death, with no adjustment for bereavement effects or for the carer QALY trap. Roche explained that the carer QALY trap could be accounted for by adding bereavement disutilities or limiting carer disutility to the life expectancy of best supportive care. Roche applied different carer utility values for type 2 or 3 SMA. Roche noted that its approach penalises occupancy of worse health states through decrements, but Biogen's approach rewards occupancy of better health states through incremental gains. For the second committee meeting, Roche adopted Biogen's approach to carer utility to support consistency between the modelling of nusinersen and risdiplam. The EAG did not include carer utility in its original base case because of concerns about robustness and lack of standardised data and methodology. It also noted uncertainty about whether carer utility varies by SMA type, health state, age or duration of care. The patient and professional organisations emphasised that excluding carers' quality of life undervalues the impact on families and risks underestimating treatment benefits. SMA UK also referred to its recent survey (see section 3.18). It explained that the average of 3.67 carers included paid and unpaid carers. The average number of unpaid carers was 2.14. The committee noted that the incremental cost-effectiveness ratios (ICERs) are highly sensitive to including carer quality of life. It acknowledged that SMA has a substantial physical, emotional and financial impact on carers, and excluding carer quality of

life risks undervaluing treatment benefits. The committee concluded that an increment approach to including carer quality of life with an average of 2.2 carers per person should be used.

Capturing treatment benefit in utility values

3.27 Previous appraisals for nusinersen and risdiplam raised concerns that the utility values may not fully capture SMA-related changes that are meaningful to patients. This is in part because the health states are very broadly defined, such as sitting unaided. So, using 1 utility value for this health state may not capture the differences in functional abilities of someone having treatment compared with someone off treatment in the same health state. Biogen's original base case for this evaluation included an on-treatment utility increment of 0.1 for nusinersen, based on clinical expert opinion. This was to account for improvements such as upper limb function that are not captured in health-state utilities. Roche's base case included disutility for bulbar function. It also included other complications such as scoliosis and respiratory support in scenario analyses. The EAG applied a 10% utility uplift in its original base case to account for unmeasured improvements, but did not add separate disutilities for SMA complications to avoid double counting. It explored complications in scenarios by including bulbar function disutility and associated healthcare costs for type 2 and 3 SMA. But the analysis was limited by data availability and limiting assumptions. The EAG was unable to add a bulbar function scenario for presymptomatic and type 1 SMA because relevant data was lacking. Also, usable data was not identified for stamina and fatigue, which were identified as important by patients. The patient organisations cited caregiver survey data (n=58) showing a mean EQ-5D-Y gain of 0.15 (95% confidence interval 0.12 to 0.18) when a child moves from total feeding dependence to independent self-feeding. At the first meeting, the committee acknowledged that utility values may underestimate the full benefits of treatment because they do not capture all functional gains or SMA-related complications. It concluded that a 10% utility increment is inappropriate because it gives greater benefit to the less severe health states than to the more severe health states. So, it preferred to use an absolute utility increment. At the second committee meeting, Roche used an absolute utility increment of 0.16. This was informed by a reported decrement for preserved upper limb function compared with mildly impaired upper limb or moderately impaired upper limb function in

Duchenne muscular dystrophy from Audhya et al. (2023). Biogen used the 0.15 values from the SMA UK survey, citing the committee conclusion that the full benefits of treatment were not captured with a 0.1 increment. Roche also stated that an increment of 0.16 was still underestimating treatment benefits. It cited the results from the SMA UK survey that showed significant improvements in respiratory function as well as motor function. It also noted that respiratory function improvements are not captured in the current modelling because it is difficult to collect robust data. The committee concluded that a 0.16 utility increment for people having disease-modifying treatments was appropriate. It acknowledged that treatment benefits may still be underestimated, but that no alternative data was available. So, 0.16 was a conservative assumption. The committee also concluded that a disutility for disease-related complications (such as bulbar function) should not be included in the modelling because of a lack of robust data across all SMA types and the potential for double counting.

Costs

Health-state costs

3.28 At the first committee meeting, Biogen and Roche used different annual health-state costs in their base cases. Biogen used health-state costs that were proposed by the EAG in HST24. Roche did a modified Delphi panel to gather expert consensus because a feasibility study showed real-world hospital data could not be linked to SMA health states. The patient and clinical experts outlined that health-state costs would likely be lower when taking disease-modifying treatments. This is because of significantly reduced hospitalisations for respiratory conditions. The committee asked to see a breakdown of the component costs used in the company base cases. And it would like to see health-state costs split for people on and off disease-modifying treatments. At the second committee meeting, Biogen provided a component breakdown of the costs used in HST24. This included the costs of medicines, tests, medical visits, emergency hospital visits, other materials, social services and hospitalisations. It inflated the costs to the most recent inflation year to estimate off-treatment health-state costs. Biogen created on-treatment costs by reducing off-treatment hospitalisation costs by the reduction in hospitalisations for serious respiratory

events with nusinersen seen in SHINE. The exact figure is confidential. Roche followed a similar approach, using HST24 costs to define off-treatment costs, but it did not inflate these costs from HST24. It used data from Zhu et al. 2024 to reduce off-treatment costs seen with disease-modifying treatments to estimate on-treatment health-state costs. This included reducing hospitalisations by 47% and emergency visits by 8%. Biogen explained that Zhu et al. required 12 months of follow-up data before and after the study and so excludes patients with very severe SMA. So, it stated that the data underestimated hospitalisations. It noted that the SHINE data covered 7 to 8 years. The EAG advised that Biogen's approach might overestimate the reduction in hospitalisations because it used a specific respiratory measure as a general measure of hospitalisations. Also, Biogen's approach may include double counting because reduced permanently ventilated costs were already modelled. The EAG advised that Zhu et al. used by Roche was more appropriate. Although it used US data, Roche's approach was based on routine healthcare use rather than a trial setting. So, the EAG's base case used the inflated HST24 costs (as in Biogen's approach) but reduced these costs by the resource use reductions for hospitalisations and emergency visits from Zhu et al. (as used by Roche). One of the patient experts explained that before treatment, their child would be hospitalised with respiratory infections 3 to 4 times a year. While having treatment, their hospitalisations dropped to 0 over the last 7 years. The patient experts also noted that hospitalisations are shorter and require less intensive treatment. They noted there was a crucial difference in hospitalisations because of SMA alone (which rarely happened) and because of respiratory infections (which happened a lot before treatment). The clinical experts added that previously each respiratory event would cause a reduction in baseline respiratory function, but many people now recover back to baseline in a week. The committee concluded that Biogen and Roche had made efforts to estimate health-state costs on and off disease-modifying treatments. But it decided the estimates were uncertain. It also recalled its earlier conclusion that treatment benefits were underestimated. So, it concluded that Biogen's approach was suitable for decision making because it used inflated HST24 costs and used a higher reduction in hospitalisation costs. It also decided that the Biogen approach was more aligned with the patient and clinical experts' statements about reduced hospitalisations. But the committee acknowledged that health-state costs for disease-modifying treatments may still be overestimated because only hospitalisation costs had been adjusted.

High background care costs

3.29 Because of the severity of SMA, the costs of caring for people with the condition can be very high. The committee understood that most of these costs are attributable to hospitalisations (because of respiratory infections, for example) and social services. So, the committee considered section 4.4.16 of NICE's technology appraisal and highly specialised technologies guidance manual. This states that in cases where a technology increases survival in people for whom the NHS is currently providing care that is expensive or would not be considered cost effective at NICE's normal levels, the committee may consider alongside the reference-case analysis a non-reference-case analysis with the background care costs removed. The committee considered that high background care included in the severe health-state costs may penalise treatments that extend survival (making it difficult for technologies that extend life to be considered cost effective). It consulted the NICE Decision Support Unit's report on assessing technologies that are not cost effective at £0. The committee asked the EAG to produce scenarios with health-state costs removed for the period of additional survival for the treatment over best supportive care. This meant removing health-state costs for the period of time when modelled life years for nusinersen or risdiplam exceeded mean life years for best supportive care. The cost-effectiveness results were significantly improved, but the exact ICERs cannot be reported here as they are confidential. The committee noted that its preferred approach to modelling health-state costs greatly reduced hospitalisation costs with disease-modifying treatments (see section 3.28). It also recalled that hospitalisations are the largest cost component, accounting for over 60% of health-state costs. It decided that removing background care costs in addition to reducing health-state costs may result in double counting. So, the committee concluded that background care costs should not be removed in the cost-effectiveness modelling.

Background social care costs

3.30 Having concluded that its preferred health-state costs for disease-modifying treatments may still be overestimated, and background care costs should not be removed, the committee considered whether social care costs should be removed in the modelling. Biogen raised concerns about including social care

costs because of concerns raised in HST24 that social care costs were uncertain. This is because the costs used by the company could not be validated by the EAG. So, Biogen excluded social care costs in scenario analyses of its base-case models. The committee concluded that removing social care costs entirely was not appropriate. But it considered scenario analyses with social care costs removed for the period of extended survival for nusinersen and risdiplam compared with best supportive care. This resulted in significant improvements in the cost-effectiveness results. The committee concluded that the partial removal of social care costs should not be included in its preferred modelling because it had not been presented with robust, evidence-based estimates for the reduction in social care costs. But it decided the analysis was informative for its decision making, especially when taken together with its conclusion that its preferred health-state costs for disease-modifying treatments may be overestimated. The committee considered this further when determining the most plausible cost-effectiveness estimates (see section 3.36).

Severity

3.31 The committee may apply a greater weight to QALYs (a severity modifier) for technologies that treat conditions with a high degree of severity. This is assessed by considering the future health lost by people living with the condition and having standard care in the NHS (the QALY shortfall). At the first committee meeting, Biogen, Roche and the EAG provided absolute and proportional QALY shortfall estimates in line with NICE's health technology evaluations manual. The committee concluded that the same severity weights should be used for the same SMA populations. So, based on the highest severity weights estimated by the EAG's base cases, the committee concluded that, for comparisons with best supportive care, a severity weight of 1.7 should be applied for presymptomatic and type 1 SMA, and that a severity weight of 1.2 should be applied for type 2 or 3 SMA. At the second committee meeting, the companies had made changes to their base cases and provided updated severity weight calculations. Biogen estimated severity weights of 1.7 for presymptomatic and type 1 SMA, and 1.2 for type 2 or 3 SMA. Roche estimated severity weights of 1.7 for all SMA types. The EAG agreed that the companies had accurately estimated the severity weights for their base cases. But the EAG maintained the committee preference from the first committee meeting in its base case. Roche said that the modelling does not

capture the full impact of SMA on HRQoL for people on best supportive care. So, the severity of the condition may be underestimated in the modelling. It also noted that its models included disutilities for bulbar function, which the Biogen model did not (see section 3.27). Taking these things into account, it felt the most appropriate modifier to reflect the totality of the condition would be 1.7x across all types for both treatments. The committee recalled its earlier conclusion that the scales used to assess severity of SMA focus predominantly on overall motor skills and do not reflect the full impact of the condition (see section 3.17), and that the same severity weights should be used for the same SMA populations. It also noted that the 1.7 severity weight was met in the Roche base case for all SMA types. So, the committee concluded that a severity weight of 1.7 applied to the QALYs for all SMA types for both nusinersen and risdiplam models was appropriate for comparisons with best supportive care.

Cost-effectiveness estimates

Committee's preferred assumptions

3.32 The committee's preferred assumptions are:

- 2.2 carers for all SMA types and health states
- 0.16 on-treatment utility for disease-modifying treatments
- exclude disutility for disease-related complications (such as bulbar function)
- HST24 health-state costs inflated to recent year with hospitalisation costs reduced based on confidential data from SHINE
- include treatment discontinuation using latest registry data, except for comparison with OA
- exclude treatment costs and efficacy when permanently ventilated
- 1.7 severity modifier for all SMA types for both nusinersen and risdiplam for comparisons with best supportive care.

The exact cost-effectiveness results cannot be reported here because they

include confidential discounts for nusinersen, risdiplam and the comparator treatments.

Presymptomatic SMA

3.33 For presymptomatic SMA, the base-case ICERs showed nusinersen dominated best supportive care and risdiplam was below the range normally considered to be cost effective. The corresponding ICERs compared with OA showed that it dominated risdiplam. This is because equal efficacy was assumed (see section 3.21) but the costs of OA were lower than the costs of risdiplam. When comparing nusinersen with OA, the treatments had similar efficacy and similar costs.

Type 1 SMA

3.34 For type 1 SMA, the base-case ICER for nusinersen compared with best supportive care was within the range normally considered to be cost effective. The base-case ICER for risdiplam compared with best supportive care was above the range normally considered to be cost effective. The corresponding ICER for nusinersen compared with OA was in the south-west quadrant of the cost-effectiveness plane (that is, less costly but less effective than OA). So, the committee considered net monetary benefit, which was positive for nusinersen. The ICER for risdiplam compared with OA showed risdiplam dominated OA.

Type 2 or 3 SMA

3.35 For type 2 or 3 SMA, the base-case ICER for nusinersen compared with best supportive care was within the range normally considered to be cost effective. The corresponding ICER for risdiplam compared with best supportive care was below the range normally considered to be cost effective.

Scenario partially removing social care costs

3.36 The committee recalled its conclusion that the health-state costs for disease-modifying treatments may be overestimated. So, it considered the scenario analysis that removed social care costs for the period of extended survival for nusinersen and risdiplam over best supportive care. This scenario substantially improved the cost-effectiveness estimates for nusinersen and risdiplam compared with best supportive care. It did not materially improve the cost-effectiveness results compared with OA. The committee concluded that it did not want to include this scenario in its base case because it had not been presented with robust evidence-based estimates for the reduction in social care costs. But it decided that any realistic reductions in social care costs would reduce all the ICERs for nusinersen and risdiplam compared with best supportive care to below or within the range normally considered to be cost effective. This included the ICER for risdiplam compared with best supportive care in type 1 SMA.

Acceptable ICER

3.37 NICE's technology appraisal and highly specialised technologies guidance manual notes that, above a most plausible ICER of £25,000 per QALY gained, judgements about the acceptability of a technology as an effective use of NHS resources will take into account the degree of certainty around the ICER. The committee will be more cautious about recommending a technology if it is less certain about the ICERs presented. But it will also take into account other aspects including uncaptured health benefits. The committee noted the high level of uncertainty, specifically that:

- SMA assessment tools lack sensitivity and relevance
- comparative treatment efficacy for nusinersen and risdiplam compared with best supportive care and OA is highly uncertain
- modelling treatment discontinuation is highly uncertain, especially compared with OA
- treatment when permanently ventilated is not included in the modelling because of high uncertainty

- health-state costs for disease-modifying treatments are highly uncertain
- estimates for severity weighting are impacted by different company approaches to modelling treatment benefit.

The committee considered the adjustments it had made to its decision-making preferences to account for uncaptured benefits, specifically:

- accepting a 0.16 utility increment for disease-modifying treatments to capture improvements in motor function
- excluding treatment discontinuation in the comparisons of nusinersen and risdiplam compared with OA
- accepting a higher reduction in health-state costs for disease-modifying treatments
- considering scenario analyses with social care costs partially removed
- accepting a 1.7 severity modifier for all SMA types.

The committee concluded that it had made considerable efforts to account for additional benefits of nusinersen and risdiplam in the cost-effectiveness modelling. It recognised that nusinersen and risdiplam are innovative treatments and there would be significant unmet need if these treatments were not available, particularly for people with SMA types 1, 2 and 3. But it balanced this against the high level of uncertainty in many of the parameters and comparisons. So, it concluded that an acceptable ICER would be around the middle of the range NICE considers a cost-effective use of NHS resources (£25,000 to £35,000 per QALY gained).

Other factors

Lack of data for type 0 and type 4 SMA

3.38 Neither company submitted cost-effectiveness evidence for people with type 0 or type 4 SMA. Biogen said the data available for these subgroups was insufficient for health technology assessment. Roche noted that the marketing

authorisation for risdiplam is for SMA type 1, type 2 or type 3, or with 1 to 4 SMN2 copies. So, it may not include all people with type 0 or type 4 SMA. SMA REACH noted there were also significant data limitations for SMA type 0, with only a few international case reports available. The patient and professional organisations raised concerns about equity of treatment access for these subgroups. The Association of British Neurologists said that adults with SMA type 4 have the same biological plausibility of treatment benefit as other SMA types. Adult SMA REACH emphasised the unmet need for people with SMA type 4, estimating there are currently 10 to 15 people with SMA type 4 in the UK who cannot access treatment. The EAG confirmed that there was insufficient clinical data on SMA type 4 and type 0 for cost-effectiveness modelling. The committee considered the equality implications of excluding people with SMA type 0 and type 4 from treatment. It also considered if that would widen health inequalities. The committee noted that it had not seen clinical and cost-effectiveness evidence related to type 0 and type 4 SMA. But it concluded that the SMA 'type' classification system for SMA is somewhat arbitrary and is becoming outdated. And it heard from clinical experts that people with type 4 SMA may benefit from treatment. So, it decided not to exclude people with type 4 or type 0 SMA from its recommendation and concluded that decisions about potential to benefit from treatment should be made by clinical teams.

Additional equality considerations

3.39 The committee considered potential equalities issues including those related to age and disability, which are protected characteristics under the Equality Act 2010. The clinical experts advised that excluding people who need long-term ventilation could raise equality concerns because they can be considered disabled. Also, NHS England noted challenges in assessing benefit for severely disabled people because fine motor skills are not well captured by current tools. The committee also considered treatment access affected by age. The clinical experts explained that if nusinersen was recommended and risdiplam was not recommended, people who have had spinal fusion surgery would lose treatment options. This is because spinal access is needed for nusinersen but not risdiplam. This would disproportionately affect people aged about 25 years and over because their historic spinal fusion surgeries did not preserve the intrathecal access route for nusinersen (because it was not yet available as a treatment

option). NHS England also noted challenges in assessing benefit in children and young people because it is difficult to separate motor milestone gains from a person growing normally and the direct impact of treatment. The patient and clinical experts also advised that geographic inequality is a concern. This is because access to routine treatments and best supportive care varies significantly across the country. So, some people have to travel long distances to access treatment. Treatments also have different contraindications, making it crucial that all 3 options remain available. The committee concluded that its recommendations do not restrict access to treatment for some groups of people over others, so these were not potential equalities issues. It also recalled its conclusion about treatment access for SMA types 0 and 4 (see section 3.38).

High-dose nusinersen

3.40 Following the second committee meeting, a new high-dose regimen of nusinersen was granted marketing authorisation in the UK. This regimen consists of two 50 mg loading doses administered 14 days apart, followed by one 28 mg maintenance dose injection administered every 4 months. People transitioning from the original 12 mg regimen have one 50 mg dose in place of their next 12 mg dose, and then have maintenance doses. The committee considered whether its recommendations for the 12 mg dose could also apply to the high-dose regimen. The company provided data from the DEVOTE trial and updated its cost-effectiveness modelling using the committee's preferred assumptions from the second committee meeting. DEVOTE was a phase 2 and 3 trial comprising 3 parts. Part A assessed the safety and tolerability of 28 mg dosing. Part B was a double blind, randomised controlled trial for 50 mg loading doses plus 28 mg maintenance doses compared with 12 mg loading and maintenance doses. Part C was open label, assessing the outcomes for people transitioning from 12 mg dosing to the high-dose regimen. The EAG provided a critique of DEVOTE, commenting that results show a similar adverse-event profile and clinical outcomes between the 12 mg regimen and the high-dose regimen for people who have not had previous treatment. For people who have had treatment with 12 mg nusinersen, results suggest moving to the higher doses may improve outcomes. Safety data was not reported for this comparison. The EAG cautioned that all findings are based on small samples with potential risks of bias and high uncertainty. But it commented that the company had implemented the high-dose

regimen into the modelling appropriately. This was done as a cost comparison by assuming the same clinical outcomes regardless of dosing regimen. The committee noted the clinical evidence from DEVOTE is limited. But it understood this was expected given the rarity of the condition and the purpose of comparing dosing regimens. It also noted the Medicines and Healthcare products Regulatory Agency decided the trial evidence sufficiently demonstrated the efficacy and safety of the high-dose regimen. So, the committee concluded that it was appropriate to assume the same clinical outcomes with the high-dose regimen as with the 12 mg regimen, despite the uncertainty. The cost-effectiveness estimates for high-dose nusinersen in people who have and have not had previous treatment with nusinersen were broadly similar, compared with the 12 mg regimen. So, the committee concluded that the high-dose regimen represents a cost-effective use of NHS resources and that its recommendations apply to both the original 12 mg regimen and the high-dose regimen (50 mg and 28 mg) of nusinersen.

Conclusion

Recommendation

3.41 The committee considered the cost-effectiveness estimates resulting from its preferred assumptions. It also recalled its conclusion that any reasonable reductions in social care costs would reduce all the ICERs for nusinersen and risdiplam compared with best supportive care to within the range normally considered to be cost effective. This meant that all ICERs for nusinersen and risdiplam for all SMA types were around or below the acceptable ICER, apart from for risdiplam compared with OA in presymptomatic SMA. So, the committee recommended:

- nusinersen as an option to treat 5q SMA and
- risdiplam as an option to treat 5q SMA types 1, 2 or 3, or with 1 to 4 SMN2 copies, apart from when the condition is presymptomatic and OA is suitable.

  Nusinersen and risdiplam should not be used together, and neither treatment should be used after successful treatment with OA.

4 Implementation

Implementation for nusinersen and risdiplam

4.1 Section 7 of the National Institute for Health and Care Excellence (Constitution and Functions) and the Health and Social Care Information Centre (Functions) Regulations 2013 requires integrated care boards, NHS England and, with respect to their public health functions, local authorities to comply with the recommendations in this evaluation within 90 days of its date of publication. NHS England has agreed to provide funding from routine commissioning budgets so nusinersen and risdiplam will be funded from 14 May 2026.

4.2 The Welsh ministers have issued directions to the NHS in Wales on implementing NICE technology appraisal guidance. When a NICE technology appraisal guidance recommends the use of a drug or treatment, or other technology, the NHS in Wales must usually provide funding and resources for it within 60 days of the first publication of the final draft guidance.

4.3 When NICE recommends a treatment 'as an option', the NHS must make sure it is available within the period set out in the paragraphs above. This means that, if a patient has spinal muscular atrophy and the healthcare professional responsible for their care thinks that nusinersen or risdiplam is the right treatment, it should be available for use, in line with NICE's recommendations.

5 Evaluation committee members and NICE project team

Evaluation committee members

The 4 technology appraisal committees are standing advisory committees of NICE. This topic was considered by committee C.

Committee members are asked to declare any interests in the technologies being evaluated. If it is considered there is a conflict of interest, the member is excluded from participating further in that evaluation.

The minutes of each evaluation committee meeting, which include the names of the members who attended and their declarations of interests, are posted on the NICE website.

Chair

Richard Nicholas
Vice chair, technology appraisal committee C

NICE project team

Each evaluation is assigned to a team consisting of 1 or more health technology analysts (who act as technical leads for the evaluation), a technical adviser, a project manager and an associate director.

Owen Swales
Technical lead

Alexandra Sampson
Technical adviser

Louise Jafferally and Kate Moore

Project managers

Ross Dent
Associate director

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