

Nusinersen for treating spinal muscular atrophy

Technology appraisal guidance

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1 Recommendations

1.1 Nusinersen is recommended as an option for treating 5q spinal muscular atrophy (SMA) only if:

- people have pre-symptomatic SMA, or SMA types 1, 2 or 3 and
- the conditions in the [managed access agreement](#) are followed.

Why the committee made these recommendations

SMA is a rare genetic condition, the most severe types of which affect babies and young children. Currently, there is an unmet need for effective treatments that could slow disease progression.

Clinical trial evidence shows that nusinersen improves a range of outcomes that are important to people with early- (type 1) and later-onset (types 2 and 3) SMA. Also, there is some evidence suggesting that nusinersen is effective for pre-symptomatic SMA. However, there is no long-term evidence, so the long-term benefits are highly uncertain. The committee considered that further data collection would help address these uncertainties.

The cost-effectiveness estimates presented are higher than what NICE usually considers a cost-effective use of NHS resources. However, these estimates are difficult to interpret because of the limited evidence base to substantiate longer-term benefits, the difficulty in clearly distinguishing between the SMA subtypes, and the difference in what can be achieved for these various patients without nusinersen.

The proposed managed access agreement details various risk management strategies, including patient selection, starting and stopping rules, data collection, patient consent, exit strategy and commercial offer. Taking these into account, nusinersen is recommended for people with pre-symptomatic SMA, or SMA types 1, 2 or 3 if the conditions in the managed access agreement are followed, including the collection of more data to address the uncertainties. This recommendation will be reviewed based on data collected in the managed access arrangement. The review of the guidance will be published by the end of the fifth year.

2 Information about nusinersen

Marketing authorisation indication

- 2.1 Nusinersen (Spinraza, Biogen Idec) has a marketing authorisation for 'the treatment of 5q spinal muscular atrophy'.

Dosage in the marketing authorisation

- 2.2 12 mg, by intrathecal infusion, on days 0, 14, 28 and 63, then every 4 months.

Price

- 2.3 The list price is £75,000 per vial (excluding VAT; BNF, accessed June 2018).
- 2.4 At the list price, the total annual treatment cost is £450,000 for the first year and £225,000 for subsequent years. Over 5 years, the treatment costs per person would be £1.35 million.
- 2.5 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. It is the company's responsibility to let relevant NHS organisations know details of the discount.

3 Committee discussion

The [appraisal committee](#) considered evidence submitted by Biogen Idec and a review of this submission by the evidence review group (ERG). See the [committee papers](#) for full details of the evidence.

Clinical need

Spinal muscular atrophy is a neuromuscular disorder; the most severe types affect babies and young children

- 3.1 Spinal muscular atrophy (SMA) is a rare, progressive neuromuscular disease caused by a genetic mutation in the SMN1 gene on chromosome 5q. People with the condition have a range of symptoms, including muscle weakness, and have worsening physical disability, mobility loss and respiratory dysfunction. SMA can be grouped into 5 main types (types 0 to 4), based on the age of onset and the maximum motor function reached. Type 0 SMA, the most severe, affects babies before birth. The babies do not develop any motor skills and often survive for only a few weeks after birth. Babies with SMA type 1 are unable to sit or roll because of severe muscle weakness, which gets worse over time. The muscle weakness also affects swallowing and breathing, and typically results in death within 2 years. In type 2 SMA, the onset of symptoms is between 7 months and 18 months. People with this condition can sit independently at diagnosis. However, progressive loss of motor function means they have a reduced life expectancy compared with the general population. In type 3 SMA, there are varying degrees of muscle weakness, which appear between 18 months and 18 years. People with this condition can have a normal lifespan, and walk or sit unaided at some point, but many lose mobility over time. Type 4 SMA, the least severe, affects adults, who may have only mild motor impairment and live a normal lifespan. The clinical experts suggested that, of all diagnosed cases of SMA, around 60% are type 1 and around 40% are types 2 and 3; types 0 and 4 are rarely diagnosed. The committee acknowledged the extreme challenge that people with SMA experience every day, especially those with type 1. It concluded that the most severe types of SMA affect babies and young children.

The current SMA classification system is the best system available

- 3.2 The patient experts commented that the SMA classification system is useful but does not always reflect the full extent of the disease: boundaries between the different SMA classifications are blurred and can be subjective. The clinical experts accepted these limitations, but nevertheless acknowledged that the current classification system is the most accurate predictor of severity and prognosis available. The committee acknowledged the difficulties with current SMA classification but concluded that it was the best classification system available.

SMA severely affects the quality of life of patients, carers and their families

- 3.3 The clinical and patient experts explained that most people with SMA need constant support. This can include full-time care and attention, needing physical effort (such as lifting and carrying) and causing loss of sleep for patients and carers, stress, and fear at loss of abilities. All these factors have a major effect on family members' health-related quality of life. The committee heard from parents and carers that living with the condition involves daily care, exercises and constant vigilance (especially at night, when people with SMA need assistance in bed). SMA also causes anxiety, emotional distress and disruption to work and family finances, as well as straining relationships. Following consultation, the committee heard from patient experts that SMA often has a major impact on the quality of life of multiple members of an extended family, with grandparents, siblings and family friends often severely affected. The committee concluded that SMA has a substantial effect on the quality of life of patients, carers and their families.

Current treatments

There is an unmet need for an effective treatment

- 3.4 There are no disease-modifying therapies for SMA. Current treatments are based on symptom control and aim to maintain movement and function for as long as possible and to improve quality of life. This involves a multidisciplinary approach including respiratory, gastroenterology and orthopaedic care, as well as nutritional support, physiotherapy, assistive technologies, occupational therapy and social care. However, the clinical and patient experts emphasised that current treatments do not affect disease progression, so people with SMA will ultimately become totally dependent on their families and carers. The committee recognised that treatment options are limited and there is an unmet need for people with SMA.

The technology

Nusinersen has a marketing authorisation for all types of SMA but the company only presented clinical evidence for pre-symptomatic SMA and symptomatic SMA types 1 to 3

- 3.5 Nusinersen has a marketing authorisation for all types of SMA. The clinical experts agreed that it may benefit people with any type of SMA. However, they considered that it may have a relatively greater benefit for those with more severe types of SMA (although using nusinersen in type 0 SMA might be futile because of the degree of established damage at the time treatment could be started). The committee heard that the presence of SMN2 can compensate for the SMN1 deletion to some degree because it is a similar gene, and that the number of SMN2 gene copies is inversely related to the severity of SMA and can be used to predict the course of the disease. However, the clinical experts stated that gene testing may lead to delays in starting treatment. The experts considered that the correlation between copy number and disease severity is much less reliable than the clinical classification system in identifying the likely course of SMA. The committee acknowledged that nusinersen should be

considered within its marketing authorisation (that is, for all types of SMA). However, the company only presented clinical evidence for pre-symptomatic SMA and symptomatic SMA types 1, 2 and 3, so restricted its recommendations to these types of SMA (excluding type 0 and type 4).

Clinical trial evidence

Evidence from the clinical trials, including ENDEAR and CHERISH, is uncertain but relevant for decision making

3.6 The main clinical-effectiveness evidence for nusinersen came from 2 clinical trials:

- ENDEAR, a randomised, double-blind, multicentre (including the UK), phase 3, sham, procedure-controlled trial. The trial recruited 122 children who developed SMA symptoms between 2 weeks and 6 months, which corresponds to type 1 SMA (described by the company as 'early-onset' SMA).
- CHERISH, a randomised, double-blind, multicentre, phase 3, sham, procedure-controlled trial. The trial recruited 126 patients who developed SMA symptoms between 6 months and 12 years and who were able to sit independently but never had the ability to walk independently. This corresponds with type 2 SMA and the more severe presentations of type 3 SMA (described by the company as 'later-onset' SMA).

There are also 3 ongoing studies: NURTURE, a phase 2, single-arm study for pre-symptomatic infants genetically diagnosed with SMA; SHINE, which is a continuation of ENDEAR, CHERISH, CS12 and CS3A; and EMBRACE, for patients with SMA not eligible to participate in the clinical studies ENDEAR and CHERISH. The ERG considered that there were limitations in the clinical evidence. In particular, in ENDEAR, the nusinersen population had a poorer baseline prognosis than the control group and, in CHERISH, the strict entry criteria resulted in a more homogeneous population than would be expected in clinical practice. The ERG also explained that the dose regimen in CHERISH was not consistent with nusinersen's marketing authorisation because the maintenance doses were less frequent. Follow-up periods were relatively

short for both ENDEAR and CHERISH, so the long-term benefits of nusinersen are unknown. The committee concluded that although the evidence had uncertainties, it was suitable for decision making.

Nusinersen improves survival and motor function for people with early-onset SMA

3.7 Results from ENDEAR showed that, compared with sham, nusinersen statistically significantly improved event-free survival, overall survival and motor function in patients with type 1 SMA:

- The hazard ratio for event-free survival (defined as time to death or permanent ventilation) was 0.53 (95% confidence interval [CI] 0.32 to 0.89; $p=0.005$).
- The hazard ratio for overall survival was 0.37 (95% CI 0.18 to 0.77; $p=0.004$).
- In terms of motor function, 51% of patients in the nusinersen group reached motor milestone responses compared with none in the control group (as measured by a modified version of module 2 of the Hammersmith Infant Neurological Examination [HINE-2]).

Based on the strength of the motor benefit shown, ENDEAR was stopped early. The committee agreed that the trial showed a substantial benefit in survival for nusinersen compared with sham. Data from SHINE appeared to show that patients having nusinersen in both ENDEAR and SHINE had improved outcomes in terms of time to death or permanent ventilation compared with patients who started nusinersen in SHINE.

Other health benefits of nusinersen for early-onset SMA are less certain

3.8 ENDEAR measured other important outcomes at 6 months including:

- Overall hospitalisation rate ratio was 0.759 (95% CI 0.55 to 1.05; $p=0.965$).

- Mean treatment difference (measured as least-squares mean) for the proportion of time spent hospitalised for respiratory reasons was –8.638% (95% CI –14.190 to –3.086, $p=0.0026$).
- The odds ratio for infants not needing ventilation started among infants who were not having ventilation support at baseline was 11.6 (95% CI 1.5 to 92.1, $p=0.021$).
- The rate ratio of respiratory events leading to hospitalisation and the mean treatment difference for the number of days needing ventilation support for 16 hours or more per day were not statistically significant.

The committee noted that nusinersen appeared to improve respiratory outcomes as measured by the hospitalisation rate. However, the results were not as substantial as those seen for survival, and some of the other respiratory outcomes were not statistically significant (see [section 3.7](#)). The committee considered it counterintuitive that an observed substantial survival benefit was not associated with a substantial benefit in other outcomes. The company noted at consultation that the trial was not powered to detect differences between the groups in respiratory outcomes, which would need a much larger cohort. The clinical experts noted that it is difficult to measure respiratory function in infants. They also explained that, although nusinersen would likely improve respiratory function, any improvements in motor function may in turn place greater stress on the respiratory system. Patient experts and consultees emphasised that the benefits of nusinersen seen in the trials and in clinical practice (which were not always measured) were valuable to patients and their families. They emphasised the importance of any stabilisation and even small improvement in symptoms, especially any improvement in motor function. The committee recognised that any improvements would be highly valued by people with SMA, and that nusinersen provides important health benefits for people with early-onset SMA. However, it concluded that the size of some of these benefits remained uncertain.

Nusinersen substantially improves motor function for people with later-onset SMA but the effect on survival is unclear

- 3.9 Results from CHERISH showed that, compared with sham, nusinersen statistically significantly improved motor function of children with later-onset SMA. Motor function as measured by Hammersmith Functional Motor Scale-Expanded (HFMSE) had a least-squares mean difference of 4.9 (95% CI 3.1 to 6.7; $p < 0.0000001$). The committee agreed that nusinersen provides important health benefits for people with later-onset SMA, but it was unclear how this affects survival because there were no deaths during the CHERISH trial.

Nusinersen may be more effective if administered early

- 3.10 Subgroup analyses from ENDEAR and CHERISH showed that nusinersen may result in a more prolonged survival and greater motor milestone results in patients with 12 weeks or less disease duration. Also, interim results from the NURTURE trial suggest that nusinersen has a benefit in people with pre-symptomatic SMA. However, the size of the benefit in this patient group has not been established compared with benefits seen in people with symptomatic SMA (that is, in ENDEAR and CHERISH). Also, these results were based on ad-hoc subgroup analyses that may not have been powered sufficiently or on interim study results. The committee also noted that the results on the use of nusinersen in people with pre-symptomatic SMA were not examined in economic analyses. However, it was encouraged by the potential of nusinersen to be used earlier, and suggested that the group of people with pre-symptomatic SMA should be included within the managed access agreement and further data collected.

Long-term benefits with nusinersen are uncertain

- 3.11 The committee noted that both ENDEAR and CHERISH had short follow-up periods: ENDEAR had a follow-up of only 13 months, 16% of people having nusinersen and 39% of those having sham died; CHERISH had a follow-up of only 15 months, and there were no deaths. It heard from the clinical experts that there was considerable uncertainty surrounding the long-term benefits of nusinersen, although consultation comments indicated that there is no biological mechanism

that would suggest that nusinersen would become less effective over time. However, it is possible that some people with SMA may not reach motor function milestones despite having nusinersen, and it is unclear what the relationship is between improvements in motor function and a long-term survival benefit. The ERG considered that this was a source of substantial uncertainty in the clinical evidence base. In addition to the trial evidence, the company submitted interim data from the SHINE extension study for early-onset SMA, which had a follow-up period up to around 2.5 years for a few people. The ERG noted that a few people having nusinersen had a first response at later assessment points, including as late as 2.2 years. This showed that there may be a delayed response to nusinersen for some people. The committee considered that the results from SHINE showed that there are improvements in motor function with nusinersen, which were maintained or improved for up to 2.0 years. It noted that nusinersen is expected to be used for decades for those with later-onset SMA, when life expectancy is likely to be longer than for early-onset SMA, so these results did not show what the long-term survival benefits might be. The committee concluded that, although nusinersen would likely provide long-term benefits, the size and nature of these benefits were uncertain.

All relevant clinical evidence is considered

3.12 Following consultation, the committee heard that there was real-world evidence that would be relevant for the committee's decision making that had not been considered by the company. The company stated that this was because the results were consistent with the clinical data that it had presented and, in comparison, the data were immature, would be from non-UK sources and would only include SMA type 1. The committee stated that it would have liked the company to identify supportive real-world evidence, given the clinical uncertainties identified. However, it considered a wide range of evidence, including:

- that presented during consultation (that is, the testimony of parents, carers and clinical experts)
- interim results from the NURTURE trial in patients who were pre-symptomatic submitted by the company (see [section 3.10](#))

- supplementary evidence on nusinersen use in the UK and Ireland in early-onset SMA as part of the Expanded Access Programme
- newly published data on the use of nusinersen in patients with later-onset SMA (from study CS2 and study CS12)
- newly published data on the use of nusinersen in patients with early-onset (type 1) SMA (from study CS3A).

The committee concluded that it had considered a wide range of clinical evidence and this was taken into consideration within its final decision (see [section 3.29](#) and [section 3.30](#)).

The company's economic model

The company's economic models are overly complex and cannot reflect the proposed stopping rule

- 3.13 The company presented 2 separate models: an early-onset model, for type 1 SMA (with a cohort age of 5.58 months) and a later-onset model, for types 2 and 3 SMA (with a cohort age of 43.71 months). Both models compared nusinersen with standard care, and transitions through health states were based on assessments of motor milestones using HINE-2 for early-onset SMA, and HFMSE and World Health Organization criteria for later-onset SMA. Although the model structure was based solely on motor milestones, the ERG explained that motor function was not the only factor affecting health-related quality of life; factors such as participating in activities, respiratory function, pain and physical impairment were also important. There were several iterations of the economic models and the model structures for all of them were overly complex. This led to difficulties in making any structural changes and, for the ERG, in checking the models and in understanding the underlying logic. The committee acknowledged that the model structure was consistent with the main outcomes of the clinical trials, but would have preferred a simpler model. Furthermore, the final versions of the models were structurally unable to accurately reflect the company's proposed stopping rules within their proposed data collection plans (including 2 consecutive

'worsenings'; see [section 3.22](#)). The committee concluded that the complexity of the model prevented a thorough understanding of its functioning and added to uncertainty in estimates of cost effectiveness.

The use of a plateau is clinically plausible but the incremental cost-effectiveness ratio (ICER) is sensitive to the assumptions related to the plateau

3.14 Previously, the committee had concluded the company had substantially overestimated the proportion of people who would reach the best health states while on nusinersen because the models assumed that those who remained on treatment would continue to improve indefinitely. The company's final iteration of the early-onset model included an option for patients to plateau while remaining on treatment, resulting in a more plausible proportion of patients who could reach the best health states. This occurred at 2 timepoints: 54 months (4.5 years) and 66 months (5.5 years) for the early-onset model and 15 months and 27 months for the later-onset model. This assumption was based on clinical expert opinion that people taking nusinersen who have not reached the ability to stand by 5 years or 6 years or have not reached the ability to walk before their sixth or seventh birthday would be unlikely to have gained these abilities. The ERG's clinical adviser agreed with the company's clinical adviser. However, the ERG noted that the assumptions related to the plateau (time at which the plateau was applied and whether people who plateau subsequently worsen) were key drivers in the model. The committee concluded that the addition of the plateau submodel and the assumptions about when patients plateau were both clinically plausible. However, it noted the uncertainty around cost-effectiveness estimates related to a lack of robust evidence on these parameters.

The company's transition probabilities are generally clinically plausible but highly uncertain

3.15 The company's final version of both models assumed that patients considered 'improvers' can only lose treatment benefit and stop at the 2 timepoints during which patients were in the plateau state of the model (see [section 3.14](#)). The ERG

was concerned with the removal of the ability to model worsening at other timepoints because people in clinical practice may worsen at any time. Additionally, the company's models assumed that improvers could worsen but remain as improvers and on treatment. This was because the company noted that some patients in the trial appeared to improve after an episode of worsening. The ERG noted that this assumption was a key driver in the early-onset model. Additionally, the early-onset model was sensitive to the extent to which people walk unaided. However, the ERG noted that there was evidence showing that, very occasionally, people reach this milestone. The ERG noted that the latest version of the later-onset model included an assumption that some patients in the model would lose the ability to sit without support. While the ERG's clinical adviser considered this to be a reasonable assumption, the ERG noted that this was not based on the available trial evidence and that this was a key driver in the model. Despite the complexity of the model, the ERG noted that the latest iteration of the models was, unlike earlier iterations, based on more clinically plausible assumptions. The committee concluded that the company's approach to applying transition probabilities was generally reasonable and clinically plausible, but that there was a high level of uncertainty given the sparsity of evidence.

The modelled long-term overall survival benefit is highly uncertain

- 3.16 The company presented simpler and more conservative assumptions related to survival for both models than earlier iterations of the models. For both the early- and late-onset models, the company applied a mortality adjustment factor to the nusinersen group. A factor of 0.75, based on clinical opinion, was applied to the best health states so that people in those health states were attributed to 75% of the improved survival probability and 25% of the worst survival probability. However, the ERG noted that the company's clinical advisers had suggested a wide range of adjustment factors (0.5 to 1.0), indicating a high degree of uncertainty. The ERG also noted that the company's approach to estimating the proportion of mortality risk from 2 separate survival functions was unconventional. In the extrapolation period of the early-onset model, the hazard ratio from the trial was tapered for 120 months. The ERG noted that it was not clear why this length of time was chosen, and also noted that the use of a hazard

ratio with tapering was inconsistent with the assumption of proportional hazards. The ERG's clinical adviser felt that the overall mean survival estimates from the model for both groups (8.50 years with nusinersen versus 2.14 years with best supportive care in the early-onset model and 38.50 years with nusinersen versus 36.70 years with best supportive care in the later-onset group) were reasonable and may even have been underestimates. The adviser suggested that there may be an initial higher mortality rate but that it may lower and flatten out. Overall, the ERG considered the company's assumptions were more conservative than previous iterations of the models, but were still associated with substantial uncertainty. They noted that the overall survival gain for the early-onset model was a key driver of the results. The committee recalled the overall survival gain with nusinersen for early-onset SMA seen in clinical trials, and heard that this gain had also been seen in clinical practice. The clinical expert explained that nusinersen may help to preserve respiratory muscle function, so it would be reasonable to predict a longer-term survival benefit. The committee concluded that the long-term benefits of nusinersen were highly uncertain (see [section 3.11](#)).

Utility values in the economic model are highly uncertain and may not have captured all the benefits of using nusinersen

- 3.17 The committee recognised that identifying robust utility values in babies and young children is exceptionally challenging. The most recent version of the models used patient utilities that were mainly generated by the company from their clinical advisers. The ERG considered this the most appropriate approach, given the issues with existing preference-based utility estimates, which have limited face validity. However, the ERG noted that the utility estimates should be considered cautiously because they are not based on formal elicitation methods, may be different if other clinicians valued the health states and may not accurately reflect the view of people with SMA or their carers. Patient and clinical experts noted concerns that the health states appeared to be valued based on motor function, but that this may not have captured other benefits of gaining specific motor skills, such as independence or the ability to self-care. The ERG noted that it was difficult to understand what clinicians were valuing without seeing the questions asked to the company's clinical advisers. Patient and clinical experts also commented that the difference in utilities between some health states were small and may not have captured the added benefit of particular

motor skills such as learning to write or being able to go through the education system. The committee reiterated that identifying robust utility values in babies and young children is exceptionally challenging and considered that none of the available sources of patient utilities were ideal. It concluded that all utility values in the economic model were therefore highly uncertain. The committee agreed that utilities may not have captured the added benefits of gaining particular motor skills.

Including carer-related utilities is important but difficult to quantify

- 3.18 The carer-related utilities used by the company assumed that the best health state was associated with general population utility, and the worst health state was the average carer utility from a literature source, with equal transitions between the 2 points for each health state. In addition, the company's early-onset model assumed 3 carers would be affected, whereas the later-onset model assumed 2 carers would be affected (except for the worst health state, which assumed 3 carers). However, the ERG noted that the estimates of carer burden used in the model should be treated with caution because most were driven by assumptions rather than by evidence. The committee noted that the inclusion of carers increased the ICER substantially in the early-onset model but decreased the ICER in the later-onset model. The ERG noted that this effect in the early-onset model was because of improved survival and removal of the quality-adjusted life year (QALY) gain derived by carers when a patient dies and no longer needs caring for (this is not as much of an issue in the later-onset model because patients are assumed to live longer). Patient experts noted that this seemed perverse because it made a life-extending treatment appear to be less cost effective. The committee recalled that SMA has a substantial impact on carers and families as well as patients, and can affect multiple members of the extended family (see [section 3.3](#)). It therefore considered that including carer disutility in its decision making was appropriate. However, it considered that it was extremely difficult to estimate the size of any disutility. Carer utility was 1 of the key drivers of the results for both models. The committee concluded that it should consider carer utility in its decision making but that quantifying carer-related utility was extremely difficult.

The cost of living with SMA is very uncertain

- 3.19 At consultation, many comments were received stating that the costs of living with SMA were substantially underestimated. In response, the company used a substantially higher estimate from a real-world evidence survey that was cited, but not described, in their original submission. The company estimated the cost of living with SMA from a survey of 9 paediatric neurology centres. Because some centres only deliver outpatient care and the standard of care is evolving rapidly, the company chose to include only 2 of the largest centres to more accurately capture the true costs. Although these costs were substantially higher, they only incorporated costs incurred within a hospital and may still have underestimated total care costs. The committee heard many compelling examples of the financial burden of living with SMA from the patient experts, which would not have been captured by the survey. Many of the costs described by the patient experts would be within the NICE reference case and should have been included. The company's expert advisers considered that the company estimates were still a substantial underestimation of the costs of living with SMA, so the company explored doubling the costs in a scenario analysis. The ERG clinical advisers felt that doubling the costs still substantially underestimated the costs, so it explored this further in scenario analyses with higher costs. The committee noted that healthcare costs were a key driver in the later-onset model. It also acknowledged the difficulty of estimating healthcare costs and concluded that the results were very uncertain.

Results of the cost-effectiveness analysis

The uncertainty in the cost-effectiveness estimates needs to be considered in the decision making

- 3.20 The cost-effectiveness estimates presented for early-onset and later-onset SMA are above the range normally considered cost effective by NICE. The committee struggled to reconcile the difference in the cost-effectiveness estimates across the 2 populations, in particular when considering the associated QALY gains for each population, and that the models suggested it would be more cost effective to treat the later-onset rather than the early-onset population. The committee

agreed it was likely that the existing clinical- and cost-effectiveness evidence may not have fully captured the effects of treatment. The committee could not be certain whether differences in the estimates of cost effectiveness were because of the models or the uncertainties related to the natural history of SMA, or truly represented differences in cost effectiveness between disease subtypes. In addition, the committee heard from the clinical and patient experts that, while the natural history of SMA types 1, 2 and 3 is different, the progression in individual patients cannot be predicted with certainty at diagnosis because the severity and attainment of motor performance in these groups is more on a continuum than distinctly separate in each group. The committee concluded that these uncertainties should be taken into consideration in the decision making.

Many parameters, when changed, reduce the ICER for 1 population but increase it in the other

- 3.21 The committee recalled that several of the parameters, when changed, resulted in an opposite impact on the ICER for the 2 populations (early-onset and late-onset SMA; for 1 example, see [section 3.18](#)). Additionally, the committee noted that using higher resource costs (see [section 3.19](#)) increased the ICER for the early-onset model (because of increased management costs for longer survivors), but it reduced the ICER for the later-onset model (because more patients reached higher milestones that are associated with lower annual management costs). The committee recalled that the resource costs were likely to be underestimated (see [section 3.19](#)), and increasing them further made this inconsistency larger. The committee was concerned about the inconsistent results between models because symptoms and motor attainment or ability are on a continuum and it is difficult to divide individual patients into different SMA types distinctly (see [section 3.2](#)). The committee recalled that SMA type is defined based on the age of onset and this predicted the maximum motor function reached. It also recalled that the boundaries between the different SMA classification levels are blurred and can be subjective. In addition, individuals may have better or worse clinical courses compared with that predicted based on age of onset of muscle weakness. It was more cautious about relying on the outputs of the models as a robust basis for decision making because of the inconsistent effect of modifying parameters between the 2 models.

Other factors

A managed access agreement has been proposed by the company

3.22 The committee noted that the company has engaged with NHS England, stakeholders and NICE to develop a managed access agreement for nusinersen. It was proposed that the agreement should last 5 years with at least 3 years' data collected for analysis, and include defined criteria for starting and stopping nusinersen, and for monitoring and data collection requirements:

- Eligibility criteria:
 - people with early- (type 1) or later-onset (types 2 and 3) SMA, and people with pre-symptomatic SMA with homozygous gene deletion or homozygous mutation or compound heterozygous mutation of the SMN1 gene (chromosome 5) found via pre-symptomatic genetic testing
 - must not have type 4 SMA, that is, must not have symptom onset at or after 19 years of age
 - must not have type 0 SMA
 - intrathecal injection must be technically feasible in the opinion of the treating clinician and not contraindicated
 - no permanent ventilation (16 or more hours per day for 21 consecutive days in the absence of acute reversible infection) or tracheostomy requirement at baseline
 - must not have had spinal fusion surgery after a diagnosis of scoliosis that, in the opinion of the treating clinician, prohibits safe administration of nusinersen
 - must not have severe contractures that, in the opinion of the treating clinician, prohibit measurement of motor milestones
 - if independent ambulation is gained before starting therapy patients must still be independently ambulant, with the exception of paediatric patients who have lost independent ambulation in the previous 12 months.

- Stopping criteria:
 - permanent ventilation (16 or more hours per day for 21 consecutive days in the absence of acute reversible infection) or requirement of insertion of permanent tracheostomy
 - total worsening in motor function scale scores corroborated by 2 consecutive measures (decline of greater than 2 on horizontal kick or 1 on other HINE scores excluding voluntary grasp, decline of greater than 4 points on the Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders scale or decline of greater than 3 points on the Revised Hammersmith Scale)
 - inability to administer nusinersen by intrathecal administration because of spinal fusion surgery
 - inability to regain ambulation within 12 months of nusinersen initiation in paediatric patients who have lost ambulation in the previous 12 months and who have been initiated on nusinersen
 - failure, non-compliance (does not have a maintenance dose without rescheduling) or unforeseen worsening of disease.
- Data collection:
 - clinical data will be collected using the SMA REACH database
 - patient-reported outcome measures of quality-of-life data, activities of daily living, and indirect resource costs for both patients and carers will be collected using a specially developed tool delivered through a bespoke device
 - healthcare costs related to treatment of SMA will be collected through surveys annually or biannually.

All 3 types of data will be matched using pseudoanonymisation to enable analysis.

A managed access agreement has the potential to address

uncertainties

- 3.23 The committee agreed that data from using nusinersen in clinical practice collected through a managed access agreement may be useful to address uncertainties in the evidence. It also acknowledged the need to manage risks associated with the identified uncertainties. It considered the details of the company's proposed eligibility criteria in the managed access agreement and concluded that they were clinically achievable. Patient and clinical experts considered that the eligibility criteria were broadly appropriate. However, they highlighted that advances in scoliosis surgery mean that people who have had the procedure should not be automatically ineligible for nusinersen, provided administration is technically feasible. The committee was aware that patients with later-onset SMA who had gained independent ambulation would still need to be ambulant to have nusinersen. It noted that there was little trial evidence in patients with later-onset disease who had achieved ambulation because the CHERISH trial required that patients never had the ability to walk independently. The clinical benefit in this group of patients was therefore uncertain and estimates of cost effectiveness not calculated. The committee was aware that the managed access agreement starting and stopping criteria included meeting certain motor milestones. The committee considered this could have an adverse impact on people who had, or developed, a disability unrelated to SMA. The committee concluded that if a disability unrelated to SMA disease impacts the measurement of a starting or stopping criterion, the criterion should be ignored. The committee considered that the data collection proposed by the company would be useful, but was aware that collecting data can be burdensome on patients, family, carers and clinicians. The company highlighted that much of these data are already collected by SMA REACH, a wider clinical neuromuscular network that consists of doctors and physiotherapists working in specialist tertiary centres across the UK. The committee was supportive of adapting existing data collection schemes into a managed access agreement to reduce the potential logistical challenges. It considered that the proposed commercial agreement would reduce the risk to the NHS while the data were being collected. The committee recommended that data should be collected for a minimum 3 years, which could then be analysed and form the evidence for a review published in 5 years. The committee stressed the need for high-quality data to address the evidence gaps, and that the resource implications for data collection would be met by the company. It was also aware that data were being collected

in other countries that had provided access to nusinersen, and emphasised that all available data should be provided at the time of a review. In particular, cooperation with other parts of the NHS (Scotland) should be explored to increase the available data.

Nusinersen is the first disease-modifying therapy for SMA

- 3.24 The committee explored whether nusinersen could be considered innovative. The company explained that nusinersen has been recognised in several countries as the first treatment to address the cause and natural history of motor neurone degeneration in SMA. The committee recognised that nusinersen is an innovative treatment and the first disease-modifying therapy for SMA. However, the committee considered that the data presented did not suggest that there were distinct and substantial benefits relating to the innovative nature of nusinersen that had not been captured in the economic analyses.

The nature of the eligible population and the disease was considered in the decision making

- 3.25 The committee noted that the population for which nusinersen is indicated includes children and young people. It considered that the fact that children are affected by the condition is reflected in the clinical evidence and model, and in its understanding of the nature of the condition. The committee was aware of the need to consider whether any adjustments to its normal considerations were needed. It discussed the need to balance the importance of improving the lives of children and their families with fairness to people of all ages. It noted [NICE's social value judgements: principles for the development of NICE guidance](#), which emphasise the importance of considering the distribution of health resources fairly within society as a whole, as well as considering factors other than relative costs and benefits. The committee noted that, because of the burden of administration and ongoing nature of the treatment, not all parents and carers would choose to have treatment. The committee also acknowledged that the population eligible for nusinersen has serious disabilities. It acknowledged and considered the nature of the eligible population as part of its decision making and, in particular, the circumstances in which nusinersen could be recommended

as a cost-effective treatment.

The decision making takes into account the rarity and severity of the disease

- 3.26 Although nusinersen has several features that are commonly seen in [NICE's highly specialised technologies programme](#), it was considered as a single technology appraisal. This was because the population covered by the marketing authorisation is larger than what can be considered in highly specialised technologies evaluations, and because SMA is not commissioned through a highly specialised service. The committee acknowledged the difficulty of appraising drugs for very rare conditions. When developing the social value judgements, the [Citizens Council](#) considered that rarity alone is not a mitigating factor for accepting high ICERs, and that the committee should consider taking into account other factors such as disease severity in its decision making. The committee was aware that SMA is both rare and a very serious condition. It also reflected on the benefits associated with nusinersen, and how they are highly valued by patients and families. The committee was mindful during its decision making of the need to consider whether any adjustments to its normal considerations were needed to take into account the rarity and severity of the disease.

End of life

It is reasonable to accept that nusinersen meets the short life-expectancy criterion for early-onset SMA

- 3.27 The committee considered the advice about life-extending treatments for people with a short life expectancy in [NICE's guide to the methods of technology appraisal](#). The company proposed that nusinersen met NICE's criteria for a life-extending treatment at the end of life in the early-onset SMA population, but did not make a case for meeting the criteria in the later-onset population. The committee accepted that nusinersen did not meet the end-of-life criteria in the later-onset population because, although nusinersen may provide a survival

benefit, life expectancy in children with later-onset SMA, this is likely to be well over 2 years. For early-onset SMA, the company noted that survival depends on the nature and extent of supportive care, which may vary by country, institution and physician, and the preferences of patients and families. The median age of death or permanent respiratory support in published natural history studies was 9 months to 13 months, and the median event-free survival in the control group of ENDEAR was 22.6 weeks. The ERG commented that low survival rates may not reflect current practice; some people with less severe early-onset SMA may survive to school age. The ERG also commented that mean survival for people with early-onset SMA in the model having standard care was 2.14 years. The committee recognised that the life expectancy was uncertain, but considered it reasonable to accept that nusinersen could meet the short life-expectancy criterion for early-onset SMA.

It is likely that nusinersen extends life by more than 3 months

- 3.28 The committee recalled that the long-term survival is very uncertain (see [section 3.16](#)) but concluded it highly likely that nusinersen extends life by more than 3 months.

Conclusion

It is appropriate to be flexible when considering uncertainty

- 3.29 The committee carefully considered the advice about the acceptability of the technology as an effective use of NHS resources and factors influencing cost effectiveness in [NICE's guide to the methods of technology appraisal](#). Specifically, it considered:

- the degree of certainty around the ICER
- whether there are strong reasons indicating that there are substantial benefits not captured by the model, including benefits to families and carers
- the likelihood of decision error and its consequences

- whether the technology meets criteria for special consideration.

The committee recalled the many uncertainties in the clinical trial evidence, particularly concerning long-term benefits (see [section 3.16](#)). The very high cost of nusinersen means that there would be a substantial financial risk to the NHS if the committee was to recommend it for routine use when it may not be cost effective. The committee noted that the risk to the NHS is reduced through the proposed managed access agreement. It recalled that there were uncertain benefits, but it was unclear how this affected the cost effectiveness of nusinersen (see [section 3.17](#)). The committee was prepared to take into account a wide range of factors in its decision making, including the nature of the population (such as that it included children; see [section 3.25](#)), the rarity and severity of the disease (see [section 3.26](#)), and the considerable impact on families and carers. The committee concluded that it was willing to be flexible in its considerations around uncertainty, particularly if access could be managed such that the risk to the NHS was reduced.

Nusinersen is recommended for treating SMA within the managed access agreement

- 3.30 The committee acknowledged that the cost-effectiveness estimates it had been presented with were above the range normally considered cost effective by NICE. However, it was mindful of many other factors it considered important to account for in its decision making. The committee concluded that nusinersen had demonstrated the potential to be cost effective, based on assumptions it considered clinically plausible and acceptable. It also recognised that there is evidence of benefit in early-onset and pre-symptomatic SMA (see [section 3.7](#) and [section 3.10](#)). It also acknowledged the difficulty in distinguishing between SMA types (see [section 3.2](#)). However, the committee acknowledged that all the clinical- and cost-effectiveness evidence presented was subject to uncertainty, reflecting the lack of data. It accepted that more data were needed, and considered that the commercial agreement sufficiently manages the financial risk to the NHS. The committee took into consideration the consultation responses, views of parents, carers and clinical experts, and full consideration of available

evidence. It concluded that nusinersen should be recommended as an option for treating pre-symptomatic and types 1, 2 and 3 SMA, for the duration of and within the conditions set out in the managed access agreement, when the company provides nusinersen with the confidential commercial terms agreed with NHS England. The managed access agreement oversight committee will consider any significant new evidence made available by Biogen in relation to patients with type 3 SMA who are non-ambulant type 3 that may impact the eligibility criteria of the managed access agreement.

4 Implementation

- 4.1 When NICE recommends a treatment as an option for use within a managed access agreement, NHS England will make it available according to the conditions in the managed access agreement. This means that, if a person has pre-symptomatic, or types 1, 2 or 3 spinal muscular atrophy and the doctor responsible for their care thinks that nusinersen is the right treatment, it should be available for use, in line with NICE's recommendations and the criteria in the managed access agreement.
- 4.2 The Welsh ministers have issued directions to the NHS in Wales on implementing NICE technology appraisal guidance when the drug or treatment, or other technology, is approved for use within a managed access agreement. When a NICE technology appraisal recommends the use of a drug or treatment, or other technology, for use within a managed access agreement, the NHS in Wales must usually provide funding and resources for it within 2 months of the first publication of the final appraisal document or agreement of a managed access agreement by the NHS in Wales, whichever is the later.

5 Appraisal committee members and NICE project team

Appraisal 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 technology to be appraised. If it is considered there is a conflict of interest, the member is excluded from participating further in that appraisal.

The [minutes of each appraisal committee meeting](#), which include the names of the members who attended and their declarations of interests, are posted on the NICE website.

NICE project team

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

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