NICE National Institute for Health and Care Excellence

NICE guidance

Onasemnogene abeparvovec for treating spinal muscular atrophy

Highly specialised technologies 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.

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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.

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This guidance is partially replaced by HST24.

1 Recommendations

1.1 Onasemnogene abeparvovec is recommended as an option for treating 5q spinal muscular atrophy (SMA) with a bi-allelic mutation in the SMN1 gene and a clinical diagnosis of type 1 SMA in babies, only if:

- they are 6 months or younger, or
- they are aged 7 to 12 months, and their treatment is agreed by the national multidisciplinary team.

  It is only recommended for these groups if:

- permanent ventilation for more than 16 hours per day or a tracheostomy is not needed
- the company provides it according to the commercial arrangement.

1.2 For babies aged 7 to 12 months, the national multidisciplinary team should develop auditable criteria to enable onasemnogene abeparvovec to be allocated to babies in whom treatment will give them at least a 70% chance of being able to sit independently.

1.3 This recommendation has been updated and replaced by NICE highly specialised technologies guidance on onasemnogene abeparvovec for treating presymptomatic spinal muscular atrophy.

Why the committee made these recommendations

SMA is a rare genetic condition. The most severe types affect babies and young children, and are fatal when treated with best supportive care. Survival is expected to be around 2 years. A few children can be diagnosed with SMA before symptoms appear if a sibling has been diagnosed with SMA. Presymptomatic diagnosis is done through genetic testing. Currently, children with presymptomatic or types 1, 2 or 3 SMA can have treatment with nusinersen within a managed access agreement. If nusinersen is not a treatment option,

then children have best supportive care. Because nusinersen is not routinely commissioned for use in the NHS, it could not be considered as a comparator in this evaluation.

For babies with type 1 SMA who are 6 months or younger at the start of treatment, and who do not need permanent ventilation for more than 16 hours per day or a tracheostomy, evidence from clinical studies suggests that onasemnogene abeparvovec is effective. But the studies are small and do not compare onasemnogene abeparvovec with other treatments, so it is difficult to establish how well it works. Also, there is very limited evidence for babies with type 1 SMA who are older than 6 months at the start of treatment. However, clinical experts advise that some babies aged between 7 and 12 months would be expected to have similar benefit to those 6 months and younger. There is also a lack of long-term evidence, and no evidence in more progressed type 1 SMA.

Because of the uncertainty in the clinical data, the cost-effectiveness estimates for onasemnogene abeparvovec for treating type 1 SMA are uncertain. However, they are likely to be within the range that NICE considers an effective use of NHS resources for highly specialised technologies for:

- babies 6 months and younger
- babies aged 7 to 12 months if it is likely that they will have a similar benefit from treatment with onasemnogene abeparvovec as younger babies.

So, onasemnogene abeparvovec is recommended for use in the NHS for both these groups. Because of the limited trial data for babies aged 7 to 12 months, their treatment should be discussed by a national multidisciplinary team.

There is no evidence available for treatment with onasemnogene abeparvovec in babies with type 2 or 3 SMA with up to 3 copies of the SMN2 gene. Nor is there any evidence for its use in babies with type 1 SMA treated with nusinersen. Also, there are no ongoing clinical trials in these populations. Therefore, no recommendation can be made based on the clinical and cost effectiveness of onasemnogene abeparvovec treatment for these populations.

The evidence in babies with SMA with up to 3 copies of the SMN2 gene who have not yet developed symptoms is uncertain because it comes from a study that is still collecting data. However, some of the uncertainty will be resolved when more data have been

collected. Also, the clinical experts expect the treatment to be effective in babies who do not have symptoms yet. The cost-effectiveness estimates are also uncertain. But onasemnogene abeparvovec could provide value for money within the context of a highly specialised service for this group. Therefore, it is recommended through a managed access agreement while further data are collected.

2 The condition

2.1 Spinal muscular atrophy (SMA) is a rare, progressive neuromuscular condition caused by a genetic mutation in the SMN1 gene on chromosome 5q. This causes a lack of survival motor neuron (SMN) protein, which causes motor neurones to malfunction, deteriorate and eventually die. 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 type 1 SMA generally develop symptoms before they are 6 months old. They 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 6 months and 18 months. People with this condition may be able to sit at diagnosis but are likely to lose this ability over time. 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 10 years. People with this condition can have a normal lifespan, and walk or sit unaided at some point, but many lose mobility over time. Most people with type 2 SMA and a proportion of those with type 3 SMA will develop scoliosis for which surgery will eventually be needed. Type 4 SMA, the least severe, affects adults, who may have only mild motor impairment and a normal lifespan.

2.2 Disease severity is associated with the time of symptom onset, and earlier onset is associated with more severe disease. The SMN2 gene also produces SMN protein, and the presence of SMN2 can compensate for the SMN1 deletion to some degree. 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.

2.3 Babies with type 1 SMA typically have 2 copies of the SMN2 gene (86%) but some will have 3 copies (6%) or 1 copy (7%). Babies with type 2 SMA typically have 3 copies of the SMN2 gene (87%) but some will have 2 copies (13%) and people with type 3 SMA typically have 3 copies (64%) or 4 copies (31%) of the

SMN2 gene, with the rest having 2 copies (less than 1%). It is estimated that about 1 in 10,000 people are born with SMA, suggesting that about 65 people are born with SMA per year in England. About 60% of all new diagnoses of SMA are type 1 SMA.

2.4 SMA can be diagnosed before there are symptoms (that is, presymptomatically), if newborn screening is done. There is currently no newborn screening programme for SMA in England, but genetic testing is offered when a sibling has been diagnosed with SMA. A very small number of people are diagnosed with presymptomatic SMA in England each year.

2.5 Best supportive care for treating SMA consists of a multidisciplinary approach including respiratory, gastroenterology and orthopaedic care, nutritional support, physiotherapy, assistive technologies, occupational therapy and social care. However, the clinical and patient experts emphasised that best supportive care treatments do not affect disease progression, and babies with type 1 SMA have a very short life expectancy. Nusinersen is an active treatment available for treating SMA but not through routine commissioning. It is recommended by NICE through a managed access agreement for presymptomatic SMA and types 1, 2 and 3 SMA.

3 The technology

3.1 Onasemnogene abeparvovec (Zolgensma; Novartis Gene Therapies) is a gene therapy medicinal product that expresses the human survival motor neuron (SMN) protein. It is a non-replicating recombinant viral vector (adeno-associated vector serotype 9; AAV9) modified to contain the cDNA of the human SMN gene. When infused, the vector is expected to carry a functional copy of the SMN1 gene into the motor neurons. This provides an alternative source of SMN protein expression in these cells, which is expected to promote the survival and function of the motor neurons that contain the vector.

3.2 Onasemnogene abeparvovec is administered as a single-dose intravenous infusion and the effects are thought to be lifelong. The dose volume is 1.1×10^{14} vector genome copies per kilogram. Baseline laboratory testing is needed before administering onasemnogene abeparvovec, as detailed in section 4.2 of the summary of product characteristics. It has a conditional marketing authorisation in the UK for treating '5q spinal muscular atrophy (SMA) with a bi-allelic mutation in the SMN1 gene and a clinical diagnosis of SMA Type 1, or 5q SMA with a bi-allelic mutation in the SMN1 gene and up to 3 copies of the SMN2 gene'.

3.3 The adverse reactions listed in the summary of product characteristics for onasemnogene abeparvovec include: thrombocytopenia, vomiting, pyrexia and an increase in transaminases, aspartate aminotransferase, alanine aminotransferase and troponin-I. For full details of adverse reactions and contraindications, see the summary of product characteristics.

3.4 The summary of product characteristics states that: 'there is limited experience in patients 2 years of age and older or with body weight above 13.5 kg. The safety and efficacy of onasemnogene abeparvovec in these patients have not been established.'

3.5 The price for onasemnogene abeparvovec is £1,795,000 (excluding VAT; company submission). The company has a commercial arrangement. This makes onasemnogene abeparvovec 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.

4 Consideration of the evidence

The evaluation committee considered evidence submitted by Novartis Gene Therapies, the views of carers of people with the condition, those who represent them and clinical experts, NHS England and a review by the evidence review group (ERG). See the committee papers for full details of the evidence. In forming the recommendations, the committee took into account the full range of factors that might affect its decision, including in particular the nature of the condition, the clinical effectiveness, value for money and the impact beyond direct health benefits.

Nature of the condition

4.1 Spinal muscular atrophy (SMA) is a serious condition. Disease severity is related to the age at which symptoms first appear, with earlier symptom onset associated with poorer prognosis. Type 1 SMA is a particularly severe form of the condition, with symptoms appearing before 6 months and a life expectancy of 2 years. Babies with type 1 SMA have difficulty breathing because of muscle weakness. The patient experts highlighted that, when type 1 SMA is not treated with a disease-modifying treatment, there is progressive loss of motor functioning, constant hospital appointments and emergency admissions. Swallowing is also difficult and there is a high risk of choking. The committee noted that SMA is a spectrum of disease. It concluded that, as well as type 1 SMA, types 2 and 3 SMA have a considerable effect on the quality of life of those with SMA, and their families and carers.

Impact of the condition on patients and their families

4.2 The patient experts explained that SMA severely affects every aspect of life for the person with SMA and their family. They also said that the wide range of specialties involved in multidisciplinary care can feel overwhelming for parents. They highlighted the need for constant care, which is usually provided by parents and family members. explaining that:

- babies with type 1 SMA need to be repositioned every hour or so to help with

breathing

- babies with type 1 SMA need to have their temperature monitored regularly
- carers need to carefully monitor their babies' diet
- mealtimes take longer because of the risk of choking
- carers need to manage a range of different aspects of care, including invasive treatments and use of medical equipment at home.

The patient experts stated that SMA has a significant financial impact on families. One parent usually has to reduce the number of hours worked or give up their job to provide fulltime care for their child. Caring for someone with SMA is physically and emotionally challenging and is associated with high levels of anxiety. Other siblings may feel that they get less attention and are emotionally affected by the effects of SMA. The committee concluded that SMA is a serious condition that has a substantial effect on family members and carers.

Diagnosis and management

4.3 The classification system used to diagnose people with SMA is based on the age when symptoms appear. The committee was aware that the SMA classification system does not always reflect the full extent of the disease because boundaries between different SMA classifications are blurred and can be subjective. SMA type is a predictor of disease severity and prognosis. The clinical experts explained that newborn screening is not currently available in England. However, when a child in the family has been previously diagnosed with symptomatic SMA, genetic testing to screen for SMA is available for all siblings. NHS England noted that newborn screening may become part of future clinical practice in England. Also, both the NHS England representative and clinical experts highlighted that the availability of new active treatments for SMA is increasing the need for a screening programme. This is so that people who are eligible for treatment are identified and offered treatment as early as possible, and before the onset of symptoms. The patient experts stated that in some cases, SMA diagnosis can be delayed, leading to more anxiety for families.

4.4 NICE has recommended nusinersen within a managed access agreement for treating presymptomatic SMA and types 1, 2 and 3 SMA. The clinical experts highlighted that most people within these groups are having treatment with nusinersen if they meet the eligibility criteria for the managed access agreement. However, because nusinersen is not routinely commissioned for use in the NHS, the committee could not consider it as a comparator in this evaluation. The committee did note though that some people in the long-term follow-up study of onasemnogene abeparvovec (LT-001; see section 4.7) had nusinersen after onasemnogene abeparvovec. It concluded that this added to the uncertainty about the long-term effects of onasemnogene abeparvovec.

4.5 Because no active treatment is routinely commissioned in clinical practice in England for SMA, the committee accepted that best supportive care was the relevant comparator for this evaluation. Best supportive care is based on symptom control. Its aims are 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, nutritional support, physiotherapy, assistive technologies, occupational therapy and social care. However, the clinical and patient experts emphasised that this approach does not affect disease progression. This means that people with SMA not treated with disease-modifying treatments will ultimately become totally dependent on their families and carers and have short life expectancy. The committee recognised that treatment options are limited, and that there is an unmet need for people with SMA.

4.6 The patient experts highlighted that there is an unmet need for new disease-modifying treatments for SMA. They highlighted that onasemnogene abeparvovec has the potential to offer substantial benefits to people with SMA and their carers. They noted that the single-dose administration of onasemnogene abeparvovec is highly valued by patients and carers as it avoids the need for regular travel to have treatment. They stated that the availability of a one-time gene therapy treatment such as onasemnogene abeparvovec could lead to more families with a child who has been diagnosed with SMA choosing to have more children. The committee concluded that patients and their families would welcome onasemnogene abeparvovec as a treatment option for SMA.

Impact of the new technology

Clinical trial evidence

4.7 The main clinical-effectiveness evidence for onasemnogene abeparvovec came from 2 completed open-label single-arm studies (START and STR1VE-US). These studies enrolled babies with type 1 SMA who were, with 1 exception, 6 months or younger when they had onasemnogene abeparvovec and whose disease had not been treated with nusinersen:

- START was a US-based single-centre phase 1/2a study including 15 babies. Twelve babies had the therapeutic dose and 3 had a lower dose. The study had a follow up of 24 months post dosing.
- STR1VE-US was a US-based multicentre phase 3 study including 22 babies, who were followed up until they were 18 months of age.

The company also provided interim evidence from 3 ongoing studies:

- STR1VE-EU is a European-based multicentre open-label single-arm phase 3 study that has enrolled 33 babies with type 1 SMA who were 6 months or younger when they had onasemnogene abeparvovec. Interim data were available from a December 2019 data cut.
- SPR1NT is an open-label single-arm phase 3 study that has enrolled 30 babies with a diagnosis of SMA but who had not yet developed symptoms who were younger than 6 weeks when they had onasemnogene abeparvovec. There are 2 cohorts in the study: cohort 1 consists of babies with 2 SMN2 gene copies and cohort 2 those with 3 copies. Interim data were available from a December 2019 data cut.
- LT-001 is a long-term follow-up study of START and has enrolled 13 babies (including 10 from the START cohort who had the therapeutic dose of onasemnogene abeparvovec). Limited interim data were available from a December 2019 data cut.

There is also a long-term follow up of all onasemnogene abeparvovec studies except for START, called LT-002. There were no data available for the first

committee meeting from this study.

Comparator effectiveness evidence

4.8 Because none of the onasemnogene abeparvovec studies had a control arm, the company identified 4 potential natural history studies to estimate outcomes for best supportive care: NeuroNext, PCNR, ENDEAR and a study by De Sanctis et al. (2016). These studies were all either exclusively or primarily set in the US. The NeuroNext, PCNR and ENDEAR studies all enrolled people with type 1 SMA with 2 copies of the SMN2 gene. The ERG stated that it could not identify whether everyone enrolled in the De Sanctis et al. study had 2 copies of the SMN2 gene. The ERG also explained that all the studies had strengths and weaknesses, but that it preferred NeuroNext because of its relatively mature outcome data and prospective design. The committee considered that the natural history studies all had limitations, including a high proportion of people who have a tracheostomy unlike best supportive care in the NHS. This was because the studies were set in the US where tracheostomy is more commonly used in this population. The committee concluded that NeuroNext was the most appropriate source to estimate outcomes for best supportive care.

Clinical trial outcomes

4.9 In START, safety was a primary objective and survival without permanent ventilation was a primary efficacy measure. Another outcome was changes in motor functioning. In STR1VE-US, the primary outcome measures included the ability to sit unassisted for 30 seconds or more and survival without permanent ventilation. The studies also captured various motor functioning milestones, including:

- rolling from side to side
- holding the head erect unsupported
- sitting with or without assistance (for a range of time thresholds)
- standing with or without assistance

- walking with or without assistance.

The studies also collected data on a range of other outcomes such as change in the fine and gross motor components of Bayley Scales of Infant and Toddler Development (BSID), and change in Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders (CHOP-INTEND) scores. Other outcomes in the studies included the need for nutritional or ventilatory support. The committee concluded that the outcomes reported were appropriate and, in general, corresponded to those listed in the final NICE scope. However, it thought that it should take account of other benefits that are important to patients and their carers when considering clinical effectiveness (see sections 4.10, 4.17 and 4.30).

Clinical trial results

4.10 Most babies in START and STR1VE-US were alive and did not need permanent ventilation at the end of the studies (94.1% overall: 100% in START and 90.9% in STR1VE-US). However, the committee acknowledged, follow up in both studies was short (see section 4.7). The committee was aware that, with best supportive care, survival outcomes are poor in babies with type 1 SMA, with most dying before the age of 2 years. The results from a pooled analysis of START and STR1VE-US showed that, at the end of the studies, 73.5% of babies could sit unassisted for 5 seconds or more, and 67.6% could sit for 30 seconds or more. Also, 8.8% had gained the ability to walk unassisted by the end of the studies. In addition, improvements were seen in the fine and gross motor components of BSID (exact outcomes are academic or commercial in confidence and cannot be reported here), and in the CHOP-INTEND score. The average score increased by 30.7 from baseline to 24 months post dosing in START, and by 14.6 from baseline to 6 months post dosing in STR1VE-US. Further analysis of CHOP-INTEND score thresholds in the pooled analysis showed that 94.1%, 73.5% and 26.5% of babies had CHOP-INTEND scores of equal to or greater than 40, 50 or 60 respectively (the company stated that equal to or greater than 60 is the effective ceiling of this measure). The company highlighted that people with type 1 SMA having best supportive care rarely have and never maintain a CHOP-INTEND score of equal to or greater than 40 and show a rapid decline in CHOP-INTEND scores over time. The committee concluded that, compared with best supportive care, there are

substantial clinical benefits with onasemnogene abeparvovec for people with type 1 SMA. However, it pointed out that, because follow up was short in START and STR1VE-US, the expected long-term outcomes remain uncertain.

4.11 In START, 25% (3 of 12) of people who had the therapeutic dose of onasemnogene abeparvovec had treatment-related adverse events. In STR1VE-US, it was 54.5% (12 of 22). The company stated that all treatment-related adverse events were resolved during the studies. Also, after having onasemnogene abeparvovec, liver function, and platelet and cardiac troponin I levels should be monitored at regular intervals. The summary of product characteristics for onasemnogene abeparvovec also states that, to manage a possible increase in liver transaminases, everyone who has treatment should have oral prednisolone 24 hours beforehand and for 30 days afterwards. The clinical experts explained that people are more vulnerable to infections while taking prednisolone because corticosteroids can cause immunosuppression. In addition, blood tests need to be done regularly to monitor the immune response to the viral vector. The committee concluded that it would consider the adverse events data from the studies, and the comments from the clinical experts, in its decision making.

4.12 The committee agreed that onasemnogene abeparvovec provides important health benefits for babies 6 months and younger with type 1 SMA. However, it thought that the effects on long-term survival were unclear. Because there is limited long-term evidence there is also uncertainty about how long motor milestones that are achieved are maintained (see section 4.14). There is little evidence in babies who have treatment when they are older than 6 months (see section 4.15).

4.13 The clinical experts explained that onasemnogene abeparvovec is likely to result in better outcomes if treatment is given early, particularly before the onset of symptoms. This is because the survival motor neurone (SMN) is expressed early in life. Also, treatment with onasemnogene abeparvovec increases the amount of SMN protein in the cells and, in turn, reduces the loss of motor neurons. The summary of product characteristics states that onasemnogene abeparvovec can rescue viable motor neurons but does not rescue dead motor neurons. The committee was aware that SPR1NT, which includes a presymptomatic population, is ongoing. It noted the expectation that better outcomes would be achieved

when onasemnogene abeparvovec is given before the onset of symptoms but concluded that more clinical trial evidence is needed for decision making.

Long-term effectiveness

4.14 The company provided limited longer-term data from LT-001 (see section 4.7). These data showed that all 10 people from START cohort 2 (therapeutic dose) who had enrolled in LT-001 were still alive at the data cut at December 2019 (median age 4.5 years, range 4.3 to 5.6 years). It also showed that none had lost motor milestones gained during the studies, with some gaining new motor milestones (exact numbers are commercial in confidence and cannot be reported here). The clinical experts explained that it was plausible that more motor milestones could be achieved beyond the follow-up period of START and STR1VE-US. However, they said that the exact number of people who would reach new milestones is difficult to predict. The clinical experts also stated that the ability to maintain motor milestones gained over the long term is clinically plausible. However, they further explained that, because of increase in body size and mass through normal growth, established muscle power may become inadequate to maintain gross motor skills, such as independent walking. This can result in effective loss of skills over a lifetime. The committee concluded that onasemnogene abeparvovec is likely to have long-term health benefits, but the long-term effectiveness data were limited, and the exact amount of benefit was uncertain.

Generalisability of the evidence

4.15 The clinical experts considered that the evidence from START and STR1VE-US was generalisable to NHS clinical practice. They explained that earlier diagnosis of SMA is becoming more common in the NHS because the availability of new treatments has helped raise awareness of the condition. The ERG highlighted that the babies enrolled in STR1VE-US did not need feeding or ventilatory support at baseline, which suggested that they had less severe disease compared with those enrolled in START. The committee was aware that everyone enrolled in START and STR1VE-US had 2 SMN2 gene copies. It understood that some babies with type 1 SMA will have 1 or 3 SMN2 gene copies (see section 2.3). The clinical

experts stated that people with type 1 SMA with 1 SMN2 copy could benefit from the treatment if diagnosis is timely, and that those with 3 copies of SMN2 may be expected to benefit more than those enrolled in the studies. The committee was also aware that the clinical trials excluded babies who were older than 6 months at treatment administration (see section 4.7). The clinical experts explained that, at treatment administration, age alone may not be a good predictor of how effective onasemnogene abeparvovec could be for babies with type 1 SMA. They stated that other factors are likely to affect response such as duration of disease, disease severity, respiratory function, swallowing, nutritional status, weight and CHOP-INTEND score. The committee understood that several factors may affect outcomes and noted that some babies with type 1 SMA are diagnosed late. The clinical experts advised that some babies aged between 7 and 12 months would be expected to have similar benefit to those 6 months and younger. The committee believed that the lack of evidence for babies with type 1 SMA who were older than 6 months at treatment administration meant that the evidence base did not cover the full type 1 SMA population seen in clinical practice. Therefore, the committee considered that the results from the START and STR1VE-US were generalisable to people with type 1 SMA with up to 3 copies of SMN2 gene. However, it recognised that no evidence was presented for babies with type 1 SMA who were older than 6 months at treatment administration and this was a key limitation.

4.16 The marketing authorisation for onasemnogene abeparvovec covers a population with a diagnosis of type 1 SMA and also people diagnosed with SMA with up to 3 copies of the SMN2 gene. The committee noted that the licence wording is therefore broader than the evidence presented by the company and includes a proportion of children diagnosed with types 2 and 3 SMA, because of the overlap between SMA type and SMN2 gene copy number (see section 2.3), or those whose SMA was diagnosed before they developed symptoms. The clinical experts stated that treatment with onasemnogene abeparvovec in the presymptomatic population is expected to produce even better outcomes, and to potentially cure the condition in this population. The ERG noted that presymptomatic results can be expected to be better. However, it explained that babies who have up to 3 SMN2 copies can develop a range of SMA types and that the comparisons with natural history studies including only type 1 SMA is not appropriate (see section 2.3). The committee recalled that the evidence from SPR1NT was limited, but that it was reasonable to assume that outcomes would

be better than those for type 1 SMA. This is because some people in the presymptomatic group would develop type 2 or 3 SMA without treatment with a disease-modifying treatment. The committee noted that those with presymptomatic SMA and up to 3 copies of the SMN2 gene could potentially develop a range of SMA types, and that prognosis differed significantly between SMA types. It concluded that the outcome after treatment with onasemnogene abeparvovec was likely to be better when treating presymptomatic SMA. However, the committee thought that the magnitude of benefit with onasemnogene abeparvovec was unknown because it had not been presented with any comparative data for people with presymptomatic SMA who had not had treatment with onasemnogene abeparvovec.

4.17 The clinical experts stated that they expect that onasemnogene abeparvovec could also provide health benefits for a proportion of children with types 2 and 3 SMA. The patient experts also highlighted that these health gains would be highly valued by those living with types 2 and 3 SMA, and their carers. The committee recalled that SMA is a spectrum of disease and that severity can vary. The summary of product characteristics for onasemnogene abeparvovec gives a dosing schedule for up to 21.0 kilograms, but cautions that there is no evidence to inform safety of the treatment above 13.5 kilograms. The committee was aware that the upper weight of those enrolled in START, STR1VE-US or STR1VE-EU was below 13.5 kilograms (exact upper weight is academic in confidence and cannot be reported here). The clinical experts stated that the efficacy of onasemnogene abeparvovec in general would likely be less than the results seen in the type 1 SMA population. They also noted that they would be cautious about using onasemnogene abeparvovec at higher doses without a treatment plan in place to gather safety data and knowledge. The committee recalled that it had not been presented with any evidence for onasemnogene abeparvovec use in children with types 2 or 3 SMA with up to 3 copies of the SMN2 gene. It concluded that the evidence presented was not generalisable to these SMA types and was unable to make a recommendation about them (see section 1).

4.18 The committee considered the natural history studies that the company identified to estimate outcomes for best supportive care (see section 4.8). The ERG explained that the natural history studies were either exclusively or primarily based in the US, where tracheostomy is more often done when managing type 1

SMA. The ERG's clinical experts highlighted that a tracheostomy has the potential to extend survival significantly, but that palliative care is usually chosen in NHS clinical practice. This is because a tracheostomy does not offer a good quality of life for babies with type 1 SMA. The committee recognised that tracheostomy use in the natural history study affects the generalisability of the evidence to clinical practice in England. However, it agreed that, in the absence of a more suitable data source, it would use NeuroNext in its decision making.

Impact of onasemnogene abeparvovec on patients and their families

4.19 The patient experts highlighted the benefits of onasemnogene abeparvovec for those living with the condition and their carers. They emphasised that the results from the clinical studies showed that onasemnogene abeparvovec significantly improved the quality of life of people with SMA and their carers. They explained that the results showed that people who would otherwise have died had the potential to gain important motor milestones such as independent sitting and walking. Independent sitting and fine motor improvements allows the use of a wheelchair, which greatly improves the quality of life of those with SMA. It also increases the potential for schooling and to participate in society. The patient experts explained that even small gains in motor functioning are important, such as being able to roll from side to side, holding the head erect, fine motor improvements, and lifting the arms. The committee concluded that onasemnogene abeparvovec was associated with substantial benefits for both patients and carers.

Cost to the NHS and value for money

Economic model for type 1 SMA

4.20 The company developed a 6-state Markov model to estimate the cost effectiveness of onasemnogene abeparvovec. The model focused on estimating the cost effectiveness of the treatment for type 1 SMA, reflecting the evidence base. The model health states were based on motor milestone achievement, and

included non-sitting, independent sitting and independent walking (within a broad range of normal development), the need for permanent ventilation and death. The modelling included:

- a short-term model (up to 3 years) based on clinical data from START and STR1VE-US
- a long-term model estimating outcomes beyond 3 years by extrapolating the study data.

The clinical and patient experts highlighted that the structure was based solely on motor milestones. They agreed that the model captured the important motor milestones, but that motor function is not the only factor affecting health-related quality of life. They stated that factors such as reduced fatigue, increased stamina, better respiratory function, ability to swallow and improvements in fine motor movement are also important. The committee concluded that the basic model structure was appropriate. However, it thought that it may not capture all the health benefits associated with onasemnogene abeparvovec for treating type 1 SMA. It did note that additional on-treatment utilities were also included in the analysis to account for additional motor milestones achieved beyond those described in the health states (see section 4.30). Further to this, the committee agreed that the company's model was appropriate for type 1 SMA. However, it was aware that, if there was evidence for onasemnogene abeparvovec for treating types 2 and 3 SMA in the future, it would need to see and consider the appropriate model structure.

4.21 To estimate the cost effectiveness of onasemnogene abeparvovec for treating presymptomatic SMA, the company did not revise its model structure. Instead, it provided 2 exploratory scenario analyses and used the same comparator arm and health states as used in the type 1 SMA analysis (therefore assuming everyone with presymptomatic SMA with up to 3 SMN2 gene copies would develop type 1 SMA). The ERG explained that a sizeable proportion of this population would be expected to develop types 2 and 3 SMA (see section 2.3). The company scenario analyses assumed that either all or most of those with presymptomatic SMA would be walking independently by 3 years. The ERG considered that the scenario analysis presented by the company for the presymptomatic population was not based on observed trial data because the SPR1NT data were immature,

and are therefore uncertain. The committee was aware that the modelling was not robust enough to estimate the potential cost effectiveness of onasemnogene abeparvovec in presymptomatic SMA. It concluded that the modelling of this population was associated with substantial uncertainties.

Clinical evidence in the model

4.22 The company used data pooled from START and STR1VE-US in the economic model. The ERG highlighted that the company made no adjustments to the data when combining the 2 sets of data, but that this was a reasonable approach. This was because adjustments to the data could potentially have reduced the effective sample size without necessarily increasing the precision or accuracy of the results. The company noted that a consideration when combining the data was the difference in length of follow up in the studies (see section 4.7). Follow up in START was 24 months after treatment, which was around age 30 months, whereas in STR1VE-US follow up was limited to age 18 months. The company stated that it was plausible that more motor milestones would have been reached by children enrolled in STR1VE-US when they were aged between 18 and 30 months. In the company's base-case analysis, it assumed that there would be 1 additional child who could sit independently and 1 who could walk independently beyond that seen in the clinical trial data. The ERG's clinical experts stated that it was not unreasonable to assume more motor milestones could be gained during this time period, but that it was difficult to predict this. The ERG, in its base-case analysis, used only the observed data from the studies, and provided a scenario that included the assumption that 1 additional person would gain independent sitting. The clinical experts explained that it was reasonable to assume that people would gain motor milestones. They were more confident in the plausibility of assuming 1 additional sitter than 1 additional walker. The committee concluded that the analysis that includes 1 additional sitter was appropriate for decision making.

4.23 The committee understood another consideration when pooling the data from START and STR1VE-US was the threshold used for independent sitting. In its analysis, the company used a threshold of 5 seconds or more for START data and a threshold of 30 seconds or more for STR1VE-US data. It explained that, if a threshold of 30 seconds was used for START data, 2 people would no longer

contribute to the sitting independently health state in the model. The ERG's clinical experts stated that sitting for 30 seconds was more clinically relevant and that a threshold of 5 seconds or more was too short to be clinically different from the non-sitting health state. The committee concluded that a threshold of sitting independently for 30 seconds or more was appropriate.

Transition through the short-term model

4.24 The transitions between health states in the first 3 years of the model were based on the data from START and STR1VE-US, and a cycle length of 6 months was used. Everyone in the model started in the non-sitting health state, reflecting the type 1 SMA population who have not had treatment with a disease-modifying SMA therapy. People who had treatment with best supportive care could not gain motor milestones or transition to a higher functioning health state in the model. From the non-sitting health state, it was only possible to transition to the permanent ventilation state or death for people on best supportive care. The clinical experts stated that these assumptions were valid because people with type 1 SMA do not gain the ability to sit independently. People who had onasemnogene abeparvovec could transition to permanent ventilation or death health states, but could also transition to the independent sitting and independent walking health states. Transitions in the short-term model were based on the time when they were observed in the clinical study data, offset by 6 months (that is, events were assumed to take place in the next cycle of the model). The ERG stated that the offsetting of events to the next model cycle was appropriate. The committee concluded that transitions through the model in the short-term model (first 3 years) were appropriate.

Long-term effectiveness incorporated in the model

4.25 The outcomes in the model beyond 3 years were based on long-term extrapolations. Overall survival in the non-sitting health state was estimated by fitting standard parametric distributions to NeuroNext, and in the permanent ventilation health state to Gregoretti et al. (2013; a retrospective chart review of people with type 1 SMA). The company assumed that people who were in the independent sitting health state at 3 years have the same life expectancy as

people with type 2 SMA. The overall survival estimates for this group were based on an extrapolation of Kaplan–Meier data from Zerres et al. (1997; a 52-year prospective and retrospective study). The company assumed that people who were able to walk independently by the end of year 3 in the model would have the same life expectancy as people with type 3 SMA (which has been reported not to be statistically significantly different to that of the general population). Therefore, for this group, the company used UK life table data from the office for national statistics. The ERG's clinical experts stated that using type 2 SMA life expectancy as a proxy for people who could sit independently and type 3 SMA life expectancy as a proxy for those who could walk independently after 3 years was reasonable. However, they highlighted that there were no long-term data available. The ERG and committee considered that the company's approach to estimating long-term outcomes was appropriate, but that there was a lack of long-term data to inform these assumptions.

4.26 The company assumed that no motor milestones would be lost, and no further milestones would be gained after the first 3 years in the model. The ERG highlighted that there was no long-term evidence for this beyond the interim data from LT-001 (median age 4.5 years). The clinical experts stated that it was reasonable to expect that motor milestones would not be lost in the long term. However, they noted that there was a lack of available evidence, and that some milestones such as independent walking and sitting may become more difficult in the long term (see section 4.14). The committee concluded that there were limited data to inform long-term outcomes in the model and that this was a key area of uncertainty.

Nusinersen costs in the model

4.27 Nusinersen costs were not included in the company analysis because it is not routinely commissioned in the NHS. However, nusinersen was permitted as a subsequent treatment in LT-001 (the long-term follow up of START). The committee noted that a proportion of people in START cohort 2 who had the therapeutic dose of onasemnogene abeparvovec were having nusinersen treatment at the latest data cut (exact numbers are commercial in confidence and cannot be reported here). The ERG's clinical experts stated that nusinersen was used subsequently in LT-001 because the study was based in the US. This meant

treatment decisions about nusinersen were likely to have been different to those that would be made in the NHS. The clinical experts at the meeting stated that they would not use nusinersen after onasemnogene abeparvovec because of the lack of clinical evidence for this treatment sequence. They also stated that subsequent nusinersen use is not expected to result in significant health benefits beyond those seen with onasemnogene abeparvovec treatment. This is because the 2 treatments have overlapping mechanisms of action (that is, both increase production of SMN). The ERG provided a scenario in which a proportion of people in the analysis had subsequent nusinersen. It included the treatment costs in this analysis because its use in LT-001 may have partially contributed to the company's assumption that no motor milestones are lost in the long term. The committee noted that nusinersen is not considered standard care because it is currently commissioned through a managed access agreement.

Resource use in the model

4.28 The company used various sources and assumptions to calculate the resource use and costs of each health state in the model. It assumed that the resource use associated with the independent sitting health state in the model would be the same as for people with type 2 SMA. In addition, the company also assumed that people who gained the ability to walk unassisted would have the same healthcare resource use as those with type 3 SMA. The ERG's clinical experts stated that, given the lack of information informing healthcare resource use for these health states, using types 2 and 3 SMA as proxies was appropriate.

4.29 The cost of onasemnogene abeparvovec and the associated administration costs were included in the analysis. The onasemnogene abeparvovec arm of the model was assumed to incur the costs of the intervention and health-state costs. The company sourced the model inputs from its own health-state resource use study carried out with UK clinicians who had experience of treating SMA. It used the responses to this study to inform the resource use by each health state in the model. Because no clinician in the company's study had experience of treatment in people who were ventilator dependent, the company sourced these costs from the Noyes et al. (2006) study. The type of ventilatory support and proportion of people in each health state on each type was taken from the company's UK clinical advisory board, and from the Gregoretti et al. (2013) study. The company

also included the costs of scoliosis surgery in each health state, the rate of which was taken from the company's health resource use study. The ERG considered that the company's approach to costing in the model was overly complex. It also highlighted that the model assumed that health-state costs would be the same throughout the lifetime of the model. The ERG's clinical experts stated that it was unlikely that the health-state costs would remain the same in each year of the model. The committee concluded that the company had carried out an extensive costing analysis, but that there was still uncertainty surrounding the health-state cost estimates used in the model. This was because they were based on proxy assumptions and assumed to be constant over time.

Utilities

4.30 No measure was used in the onasemnogene abeparvovec clinical trials to capture changes in health-related quality of life. The company stated that its base-case utility sources were based on the US incremental cost-effectiveness ratio (ICER) report's cost-effectiveness analysis of onasemnogene abeparvovec and on the ERG's preferred sources for utility. A utility value of 0 was chosen for the permanently ventilated state, which was based on the ERG's preference after discussion with its clinical advisers. A utility value of 0.19 was chosen by the company and ERG for the non-sitting health state, based on the Thompson et al. (2017) study (parent-proxy EQ-5D-3L values). For the independent sitting health state, the company and ERG preferred a value of 0.6 used by the US ICER report. This was based on clinical expert opinion that it is not a preference-based utility value. This value was also used during the NICE technology appraisal of nusinersen for SMA. The company assumed that the health-related quality of life for people in the independent walking health state would be equal to that of the general population of the same age and used the Ara and Brazier (2010) study to inform these estimates. This assumption was also based on the US ICER report. The committee noted that assuming a general population utility for this population may be optimistic. The clinical experts stated that although some people could walk independently at the end of the trial period, they may find walking difficult in the long term. They considered it reasonable to assume a general population utility value for this group. The company also provided scenario analyses that used various alternative health-state utility sources including:

- the company's own clinician utility election study
- utilities from Lloyd et al. (2017; clinician proxy vignette study) and Thompson et al. (2017; mapping from the PedsQL to the EQ-5D-Y) studies.

The company stated that other sources of utility values lacked face validity. The ERG agreed with the company's base-case utility choices, and the company's rationale for not using alternative sources for health-state utilities. However, it noted the challenge in estimating utilities in this population. The company also assumed an additional on-treatment utility of 0.1 for the non-sitting and 0.05 for the independent sitting health states to capture interim motor milestones achieved within these health states. This assumption was also based on the published US ICER report and ERG preferences. The committee considered that the additional on-treatment utility was appropriate in the analysis in this situation but only because study outcomes showed benefit beyond that captured in the health states. The clinical experts stated that the utility values in the model appeared reasonable but that the utility value for the independent sitting state may be underestimated. The committee noted that the company did not include any disutility related to adverse events seen in the onasemnogene abeparvovec studies. The company justified this by stating that it is difficult to separate adverse events. This was because of treatment from complications associated with SMA itself, which are accounted for in health-state costs and utilities. The ERG agreed with the company's rationale for not including disutility from adverse events in the modelling. The committee understood that obtaining robust health-utility values was challenging. It considered that there was uncertainty around the health-state utilities used in the model and that they had major effect on estimates of cost effectiveness. However, it concluded that they appeared to be the most appropriate to use in decision making.

4.31 SMA has a significant effect on carers (see section 4.2) but the company did not include caregiver disutility in its base case. The company stated that this was because there was a lack of robust estimates available. When caregiver utilities are included in the analysis, it increases the ICER. This is because caregiver burden is reduced in the short run but longer survival increases the amount of caregiving needed over a lifetime horizon. The ERG ran a scenario analysis that included an estimate of carer disutility and the ICER increased significantly. The

company considered that including caregiver utilities produced counterintuitive results. The company also highlighted that caregiver utility was not included in the US ICER report's base-case cost-effectiveness analysis of onasemnogene abeparvovec for similar reasons. It pointed out that similar issues were reported in the NICE technology appraisal of nusinersen for SMA. The committee understood that onasemnogene abeparvovec is likely to reduce caregiver burden in the short term. However, it acknowledged there were uncertainties around the level of care needed in the long term, with the possibility that it may increase over a lifetime horizon. It also acknowledged the uncertainties on the subsequent effect on carer health-related quality of life. The committee concluded that accounting for carer quality of life was important in appraising treatments for SMA, but that their inclusion in the health economic analysis is complex.

Discounting rate for costs and health benefits

4.32 NICE's guide to the methods of technology appraisal (2013) and its interim process and methods of the highly specialised technologies programme (2017) specify that the discount rate that should be used in the reference case is 3.5% for costs and health effects. However, it also states that a non-reference-case rate of 1.5% for costs and health effects may be used instead when: treatment restores people to full or near-full health when they would otherwise die or have severely impaired lives; if it is highly likely that there will be long-term benefits (normally sustained for at least 30 years); and if the treatment does not commit the NHS to substantial irrecoverable costs. The company used a discount rate of 3.5% for costs and benefits in its base case. The ERG noted that onasemnogene abeparvovec does not restore most of the type 1 SMA population to full or near-full health. This is because most of those enrolled in the completed clinical studies could sit unassisted (but could not walk unassisted) at the study end dates. The ERG's clinical experts stated that this population would still need substantial care. The committee recalled that the patient and clinical experts had explained that, even if independent walking is not achieved, people who can sit independently can have a high quality of life. It highlighted that, if independent sitting is achieved, it enables the use of a wheelchair and provides people with type 1 SMA some independence. In addition, this population would be able to attend school, gain employment and interact with the wider community. These experts also stated that this population would not be cognitively impaired. The

committee also noted that a proportion of people in the completed clinical studies gained the ability to walk independently. This population were assumed to have a health-utility value equal to that of the general population. The committee understood that people with untreated type 1 SMA do not reach motor milestones after symptom onset, with progressive loss of motor functioning and death usually occurring within 2 years. The committee acknowledged that onasemnogene abeparvovec has a high one-off cost, whereas the benefits are accrued over the lifetime of the patient. It considered that it was likely that the alternative 1.5% discounting rate was intended to cover situations similar to this (that is, when costs are incurred upfront, but benefits are accrued over a longer period). The committee acknowledged that the technology was transformative for people who, without treatment, would otherwise die. The committee was uncertain about whether most people who have onasemnogene abeparvovec would be considered to have 'normal or near-normal health' but believed a proportion might. It recalled that the clinical experts said that, biologically, the increase in SMN protein in the motor neurons would be expected to be sustained. However, it also recognised that there were uncertainties in whether the long-term benefits of treatment would be achieved because of the limited evidence. In addition, the committee noted that there may be irrecoverable costs because of the high upfront cost of onasemnogene abeparvovec treatment. However, it considered that there is potential for substantial long-term gains that may enable a high quality of life for people with type 1 SMA and those with presymptomatic SMA with up to 3 copies of the SMN2 gene. It noted that NHS England would put measures in place to make sure the product is directed to the people in whom the greatest clinical benefit is achieved at reasonable cost (see section 4.38). It also noted that using a 1.5% discount rate had the potential to increase the effect of the uncertainties in the cost-effectiveness modelling compared with a 3.5% discount rate (see section 4.35). It acknowledged that there remained considerable uncertainties associated with the long-term benefits of onasemnogene abeparvovec. However, despite these uncertainties, the committee concluded that onasemnogene abeparvovec meets the criteria for using a 1.5% discount rate and this would be used for decision making.

Applying quality-adjusted life year (QALY) weighting

4.33 The interim process and methods of the highly specialised technologies

programme (2017) specifies that a most plausible ICER of below £100,000 per QALY gained for a highly specialised technology is normally considered an effective use of NHS resources. For a most plausible ICER above £100,000 per QALY gained, judgements about the acceptability of the highly specialised technology as an effective use of NHS resources must take account of the magnitude of the incremental therapeutic improvement, as revealed through the number of additional QALYs gained and by applying a 'QALY weight'. The committee noted that the interim process and methods of the highly specialised technologies programme (2017) states that for this weight to be applied, there needs to be compelling evidence that the treatment offers significant QALY gains. It understood that a weight between 1 and 3 can be applied when the QALY gain is between 11 and 29 QALYs. The committee discussed the undiscounted QALY gain associated with onasemnogene abeparvovec and noted it was 18.62 in the scenario considered most plausible (see section 4.35). However, it noted that there was limited long-term effectiveness evidence for onasemnogene abeparvovec and that there were considerable uncertainties in the cost-effectiveness modelling (see section 4.35). To account for these considerable uncertainties, the committee agreed that it would not apply the full QALY weighting of 1.86 but instead would use a lower QALY weighting for its decision making (see section 4.35).

Cost-effectiveness analysis results

4.34 The company and NHS England have agreed a confidential commercial discount. The company considers all ICER results of the economic analysis incorporating this discount commercial in confidence, so ICERs cannot be reported.

4.35 The committee considered the following assumptions to be the most appropriate for decision making:

- using the independent sitting threshold of 30 seconds or more (see section 4.23)
- assuming 1 additional sitter to the observed data from STR1VE-US (see section 4.22)
- applying a 1.5% discount rate for costs and utilities (see section 4.32)

- assuming that motor milestones gained in the first 3 years in the economic model are maintained in the long term (see section 4.26).

  The committee also considered that there was considerable uncertainty associated with the cost-effectiveness analysis of onasemnogene abeparvovec for people with type 1 SMA. It believed that this uncertainty was likely higher than levels typically seen in treatments evaluated through the highly specialised technology programme. The committee recognised that:

- Transitions in the short-term model (first 3 years) are based on small numbers (n=34) from START and STR1VE-US. This meant that differences in baseline characteristics could have a large effect on outcomes. Because of these small numbers, adjustments to the data were not deemed appropriate. There was also uncertainty resulting from the use of natural history studies because these were based in the US, where tracheostomy is more commonly used as part of best supportive care (see section 4.18).

- It had not been presented with sufficient long-term evidence for people with type 1 SMA who have had onasemnogene abeparvovec. So, there was considerable uncertainty about whether motor milestones would be maintained over a lifetime horizon (see section 4.14). Also, some children in LT-001 (long-term follow up of START) had treatment with nusinersen after onasemnogene abeparvovec, and this added to the uncertainty about the long-term outcomes shown in LT-001 (see section 4.4). Also, there were uncertainties surrounding long-term survival because proxy data were used to estimate this in the model (see section 4.26).

- It had not been presented with clinical trial evidence for babies older than 6 months at treatment administration. Also, the clinical experts had explained that, at treatment administration, age alone may not be a good predictor of how effective onasemnogene abeparvovec could be for babies with type 1 SMA, that other factors affect prognosis and that some babies with type 1 SMA are diagnosed late. The lack of evidence for babies with type 1 SMA and older than 6 months at treatment administration meant that the evidence base did not cover the full type 1 SMA population seen in clinical practice (see section 4.15).

- There were outstanding uncertainties around the amount of care that will be

needed in the long term, and further healthcare resource use. In their model, the company assumed that healthcare costs would remain constant over time, but no evidence was presented to support this assumption. Using proxy data to inform health-state costs and resource use was also associated with uncertainty (see sections 4.25 and 4.26).

- There were uncertainties about the health-state utility values used in the modelling, with different sources of data providing markedly different estimates of cost effectiveness. Identifying robust health-utility values for young children was challenging. Key health states in the model were informed by clinical expert opinion and an assumption that people who gained the ability to walk would have the same utility as those in the general population (no decrement in utility assumed). If motor milestones, for example, the ability to walk, are lost in the long term then health utility would likely be reduced (see section 4.30).

- There were complex considerations surrounding the effect on caregiver quality of life. While the company or ERG base case did not include caregiver quality of life, its inclusion in the cost-effectiveness analysis had the potential to substantially increase the ICER estimate (see section 4.31).

- Onasemnogene abeparvovec met the criteria for use of a 1.5% discount rate. Uncertainties about the long-term outcomes and costs associated with the treatment have the potential to increase the ICER. These uncertainties would be expected to have a greater impact on the ICER when using a 1.5% compared with a 3.5% discount rate (see sections 4.25 and 4.32).

- The cost-effectiveness results of the ERG analyses, including the committee-preferred ERG scenario, were deterministic. The ERG could not produce probabilistic ICERs for its analyses because of the model functionality. But the company's base-case probabilistic ICER was higher than the deterministic ICER, suggesting non-linearity in the cost-effectiveness results. Therefore, the deterministic results likely underestimated the ICER.

  To account for these uncertainties, the committee considered that the QALY weighting applied should be reduced from 1.86 (see section 4.33). Although the clinical evidence came from a population who were 6 months or younger at the start of treatment, the committee recalled that some babies aged

between 7 and 12 months would be expected to have similar benefit to those 6 months and younger (see section 4.15). It concluded that the most plausible ICER for onasemnogene abeparvovec in the type 1 SMA population of babies 6 months or younger, or aged 7 to 12 months with a similar level of expected benefit, is likely to be within the range NICE normally considers an effective use of NHS resources for highly specialised technologies when the QALY weighting and the company's confidential discount are applied.

Cost-effectiveness analysis for the presymptomatic SMA population

4.36 The company provided 2 scenario analyses for this population based on assumptions that most people with presymptomatic SMA would gain the ability to walk independently by 3 years if they had onasemnogene abeparvovec. The committee also noted that the interim trial data from the ongoing SPR1NT study were immature. However, it recalled that the clinical experts had stated they expected better outcomes after onasemnogene abeparvovec when used in a presymptomatic population compared with use in type 1 SMA (see section 4.16). The committee noted that the cost-effectiveness model used by the company assumed that everyone diagnosed presymptomatically with up to 3 SMN2 gene copies would develop type 1 SMA (see section 2.3). The ERG highlighted that a proportion of people with 2 SMN2 copies would develop type 2 SMA and that most people with 3 SMN2 copies would develop SMA types other than type 1. Therefore, the model did not represent the appropriate distribution of SMA types likely to develop in the presymptomatic population. The committee concluded that the economic modelling used was not appropriate, and that the company's analysis was based on assumptions rather than trial evidence for the presymptomatic population. Therefore, the cost-effectiveness analyses presented for this population were not robust, highly uncertain, and likely underestimated the ICERs for this population.

Impact of the technology beyond direct health benefits and on the delivery of the specialised service

4.37 The patient experts highlighted that onasemnogene abeparvovec treatment made it possible that children with type 1 SMA could attend school and interact with the wider community. In START, 11 out of 12 babies gained the ability to speak at 2 years after treatment. The company stated that, with best supportive care, people with type 1 SMA rarely gain this ability. The patient experts also stated that a diagnosis of type 1 SMA and treatment with best supportive care often means that carers have to reduce the amount of time they work or stop working. This has a severe financial impact on families. The experts thought that, with onasemnogene abeparvovec treatment, it would be possible to reduce the amount of care needed, which would potentially allow carers to return to work. Also, families experience substantial anxiety if babies with type 1 SMA have treatment with best supportive care because of the poor prognosis. This anxiety could be reduced with the potential outcomes provided by onasemnogene abeparvovec. The committee noted that people with type 1 SMA who have onasemnogene abeparvovec would likely still need care, which may be substantial, from caregivers. Including carer quality of life is complex. It was not included in the ICER estimates (see section 4.31). Therefore, the committee considered this to be an outstanding uncertainty. On balance, the committee agreed that there is the potential for benefits with onasemnogene abeparvovec aside from those gained by the NHS and personal and social services.

Delivery of specialised services

4.38 The committee acknowledged that onasemnogene abeparvovec would only be delivered in a small number of highly specialised centres because there is a need to concentrate expertise. NHS England is currently selecting the centres to provide this service. Families may need to travel significant distances to these centres for treatment. The submissions received from NHS England indicated that it may take time to set up a highly specialised service to provide onasemnogene abeparvovec treatment if it is recommended by NICE. It also stated that additional training and education of staff at the specialist centres would be

needed, but that this would be provided by the company. The committee was aware that a national multidisciplinary team is being established. It suggested that this team should be used to discuss treatment with onasemnogene abeparvovec in babies with type 1 SMA who are aged between 7 and 12 months and expected to have a similar benefit to those 6 months and younger (see section 4.35). The committee understood that, before treatment with onasemnogene abeparvovec, testing for antibodies against the adeno-associated vector serotype 9 virus capsid is needed. The clinical experts stated that this test is currently not routinely available in the NHS. However, they highlighted that it was important this was carried out quickly so that onasemnogene abeparvovec treatment could start as soon as possible. The company has said that it will coordinate and fund this testing. The committee understood that health service arrangements for treating SMA with onasemnogene abeparvovec are still in development but that NHS England would put measures in place to make sure the product is directed to the people in whom the greatest clinical benefit is achieved at reasonable cost. The committee concluded that some changes to staffing and infrastructure will be needed if onasemnogene abeparvovec is made available on the NHS, but that NHS England has commissioning plans in place.

Other factors

4.39 The committee discussed whether any consideration should be made to reflect the fact that the population being considered for this technology are exclusively children. It was aware that type 1 SMA is a devastating condition that begins in infancy, and that all aspects of the lives of people with the condition, and their families and carers, are affected. It considered that the clinical evidence and model reflected the fact that children are affected by the condition, and its understanding of the nature of SMA. The committee concluded that no additional considerations were needed in its decision making.

Innovation

4.40 The company stated that it thought that onasemnogene abeparvovec is a step change in managing SMA because it replaces the faulty SMN1 gene, so directly

addressing the cause of the condition. The committee concluded that onasemnogene abeparvovec is an innovative technology.

Equalities

4.41 The committee enquired about any potential equality issues and asked if race or ethnicity affected SMA diagnosis. The clinical experts stated that the prevalence of SMA is consistent across regions, which suggests that race or ethnicity does not influence the diagnosis of SMA. However, diagnosis may be delayed in some disadvantaged groups. This was 1 of the factors that the committee considered when deciding to recommend treatment with onasemnogene abeparvovec in babies aged 7 to 12 months. The committee concluded that there were no other relevant equality issues related to onasemnogene abeparvovec treatment.

Conclusion

4.42 The committee recalled its earlier decisions and discussed the recommendation it could make for onasemnogene abeparvovec for treating type 1 SMA, taking into account the nature of the condition, the clinical effectiveness, value for money and the impact beyond direct health benefits. It appreciated that SMA is a rare, serious, life-threatening and debilitating condition that has severe effects on the lives of people with the condition, and their families and carers. After considering all the available evidence, and the opinions of the clinical and patient experts, the committee recognised that onasemnogene abeparvovec represents an important development in treating SMA. It also recognised that the results of the trials were uncertain because of low patient numbers and limited long-term evidence. However, it agreed that onasemnogene abeparvovec is a clinically effective treatment that improved survival compared with best supportive care in the trial population. The treatment enables babies with type 1 SMA to gain motor milestones such as independent sitting, independent walking and other motor milestones that are never achieved with best supportive care. The committee recalled that the evidence base for onasemnogene abeparvovec use in babies with type 1 SMA was limited to treatment administration at or younger than 6 months. It also recalled that the clinical experts stated that age alone may not be the best predictor of outcomes and that other factors may determine

prognosis (see section 4.15). However, it agreed that this was a key limitation of the evidence base and noted that some babies with type 1 SMA may have a delayed diagnosis (see section 4.15). It concluded that treatment with onasemnogene abeparvovec in babies with type 1 SMA who are aged between 7 and 12 months should be considered if the national multidisciplinary team were confident that their response would be equal to or better than that seen in babies 6 months or younger (that is, having a 70% chance of being able to sit independently). The committee recalled that it had not been presented with any evidence for using onasemnogene abeparvovec to treat type 1 SMA in babies who had had treatment with nusinersen. Therefore, the committee was unable to make a recommendation based on the clinical and cost effectiveness of onasemnogene abeparvovec treatment for this population. The committee discussed the cost-utility model and the assumptions used. It considered that there were uncertainties associated with parameters used in the model, such as assumptions about no motor milestone loss over time, health utilities and costs used. However, it considered that the model was appropriate for decision making for the type 1 SMA population investigated in the clinical studies. The committee considered that a 1.5% discount rate for costs and benefits was appropriate to use. In addition, it agreed that a lower QALY weight than 1.86 should be considered (see section 4.33). This was based on the incremental QALY gain estimated with onasemnogene abeparvovec, and accounting for the substantial uncertainty in the cost-effectiveness estimates and modelling. The committee considered that onasemnogene abeparvovec is a high-cost technology and uncertainties remained in the clinical evidence. However, it concluded that, using its preferred ERG analysis (see section 4.35) and the 1.5% discount rate, the most plausible ICER was likely to be below the threshold considered to provide value for money in the context of a highly specialised service when the company's confidential discount was applied.

4.43 The committee recalled that the marketing authorisation for onasemnogene abeparvovec includes people with up to 3 copies of the SMN2 gene, irrespective of SMA type. This includes people with presymptomatic SMA. The clinical experts stated that there are likely to be better outcomes when onasemnogene abeparvovec is used in this population, with the potential of it being close to a cure. The committee, however, highlighted that the current company model assumed that everyone with presymptomatic SMA would develop type 1 SMA. The ERG had explained that a significant proportion of this population would be

expected to develop other types of SMA. The committee was also aware that the trial data for this population were immature, but that SPR1NT was due to complete soon. The ICERs produced by the company's model for this population were highly uncertain. However, the committee concluded that they have the potential to show that onasemnogene abeparvovec will provide value for money in the context of a highly specialised service when the company's confidential discount is used. It further concluded that a managed access agreement was appropriate to provide access to onasemnogene abeparvovec to those with presymptomatic SMA who have up to 3 copies of the SMN2 gene while more data are collected in this group to help resolve some of the uncertainties.

4.44 The marketing authorisation allows the use of onasemnogene abeparvovec in people with symptomatic SMA with up to 3 copies of SMN2 gene. This means that onasemnogene abeparvovec could be used in some people with type 2 or 3 SMA. The summary of product characteristics provides dosing information for children weighing up to 21 kilograms. However, it cautions that there is limited experience with onasemnogene abeparvovec in children older than 2 years and children who weigh over 13.5 kilograms. The committee recalled that it was not presented with any clinical trial evidence or cost-effectiveness evidence for people with a diagnosis of type 2 or 3 SMA with up to 3 copies of SMN2 gene. However, the clinical and patient experts highlighted that they expected that onasemnogene abeparvovec could provide health benefits in this population depending on disease severity and the weight of the child at treatment. The committee did not consider that the clinical trial evidence presented was generalisable to types 2 and 3 SMA. It also agreed that the company's economic model was not appropriate to produce cost-effectiveness estimates for this population because it was only relevant to type 1 SMA. The committee also understood that there were no ongoing clinical trials for onasemnogene abeparvovec in type 2 or 3 SMA. So, no safety and clinical-effectiveness evidence is expected to become available and there are no plausible estimates of cost effectiveness. The committee concluded that it was unable to recommend onasemnogene abeparvovec type 2 or 3 SMA in people with up to 3 copies of SMN2 gene.

4.45 The marketing authorisation also allows onasemnogene abeparvovec use for advanced type 1 SMA. This would include people with severe muscle weakness or paralysis, breathing problems or inability to swallow, or who need permanent

ventilation (as described in the summary of product characteristics). The committee pointed out that START and STR1VE-US excluded people who needed invasive ventilation or continuous non-invasive ventilation. The patient experts stated that families would value having the option of onasemnogene abeparvovec treatment in this situation. The clinical experts stated that any decisions about onasemnogene abeparvovec use in this population would need careful discussions with families. The summary of product characteristics states that onasemnogene abeparvovec may not work as well in this group (including in people with type 0 SMA). This is because symptoms such as severe muscle weakness or paralysis, breathing problems and significant malformations such as heart defects imply that there is limited potential for improvement after treatment. The clinical experts stated that very few babies with newly diagnosed type 1 SMA would need permanent ventilation, and that most of the prevalent population would currently be having treatment with nusinersen. The committee concluded that it could not recommend onasemnogene abeparvovec for people who need permanent ventilation (that is, invasive ventilation or non-invasive ventilation for more than 16 hours per day), or for people with type 0 SMA. This was because it could not generalise the clinical evidence beyond the population included in the clinical trials to this group. The committee was uncertain if onasemnogene abeparvovec provided clinical benefits in these groups and how large any benefit might be. It agreed that it had not seen any cost-effectiveness estimates for this group. It concluded that cost-effectiveness estimates would likely be substantially higher than those presented using the current evidence base for people with type 1 SMA.

5 Implementation

5.1 Section 8(6) of the National Institute for Health and Care Excellence (Constitution and Functions) and the Health and Social Care Information Centre (Functions) Regulations 2013 requires clinical commissioning groups, NHS England and, with respect to their public health functions, local authorities to comply with the recommendations in this evaluation within 3 months of its date of publication.

5.2 The Welsh ministers have issued directions to the NHS in Wales on implementing NICE highly specialised technologies guidance. When a NICE highly specialised technologies 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 2 months of the first publication of the final evaluation document.

5.3 When NICE recommends a treatment 'as an option', the NHS must make sure it is available within the period set out in the paragraph above. This means that, if a patient has presymptomatic or type 1 spinal muscular atrophy (SMA) and the doctor responsible for their care thinks that onasemnogene abeparvovec is the right treatment, it should be available for use, in line with NICE's recommendations.

6 Evaluation committee members and NICE project team

Evaluation committee members

The highly specialised technologies evaluation committee is a standing advisory committee of NICE.

Committee members are asked to declare any interests in the technology to be appraised. If it is considered that there is a conflict of interest, the member is excluded from participating further in that appraisal.

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.

NICE project team

Each highly specialised 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.

Alan Moore
Technical lead

Emily Eaton Turner
Technical adviser

Jo Ekeledo
Project manager

Update information

April 2023 Recommendation 1.3 was updated and replaced by NICE highly specialised technologies guidance on onasemnogene abeparvovec for treating presymptomatic spinal muscular atrophy.

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