NICE National Institute for Health and Care Excellence

NICE guidance

Onasemnogene abeparvovec for treating presymptomatic spinal muscular atrophy

Highly specialised technologies guidance
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www.nice.org.uk/guidance/hst24

Your responsibility

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

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

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

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

Contents

This guidance partially replaces HST15.

1 Recommendations

1.1 Onasemnogene abeparvovec is recommended as an option for treating presymptomatic 5q spinal muscular atrophy (SMA) with a biallelic mutation in the SMN1 gene and up to 3 copies of the SMN2 gene in babies aged 12 months and under. It is only recommended if the company provides it according to the commercial arrangement.

Why the committee made this recommendation

This guidance is a partial review of NICE's highly specialised technologies guidance on onasemnogene abeparvovec for treating SMA. It focuses on new clinical trial evidence for onasemnogene abeparvovec for presymptomatic SMA.

SMA is a rare genetic condition. A few children are diagnosed with SMA using genetic testing before symptoms appear if a sibling has been diagnosed with the condition. If untreated, presymptomatic SMA will develop into one of several types of SMA of varying severity and symptoms. There are no routinely commissioned treatments for presymptomatic SMA for use in the NHS. If presymptomatic SMA develops into type 1 SMA, onasemnogene abeparvovec is an available treatment option in certain situations.

Evidence from a clinical trial suggests that onasemnogene abeparvovec is effective for presymptomatic SMA in babies. But it is difficult to estimate how well onasemnogene abeparvovec works, primarily because the trial only included babies aged 6 weeks and under, and treatment before this time point is not always possible in NHS clinical practice. Also, there is a lack of long-term evidence for onasemnogene abeparvovec in presymptomatic SMA.

Despite the high levels of uncertainty, there is evidence that onasemnogene abeparvovec provides substantial health benefits, such as reaching important motor milestones, for babies with presymptomatic SMA. The cost-effectiveness results show a lower overall cost compared with onasemnogene abeparvovec for type 1 SMA and best supportive care for types 2 and 3 SMA for babies aged 6 weeks and under. For babies with presymptomatic SMA aged over 6 weeks to 12 months and under, the cost-effectiveness

estimates are still likely to be within the range that NICE considers an effective use of NHS resources for highly specialised technologies. So, onasemnogene abeparvovec is recommended for use in the NHS for presymptomatic SMA in babies aged 12 months and under, that is, in line with the population in the managed access agreement in NICE's highly specialised technologies guidance on onasemnogene abeparvovec for treating SMA.

2 Information about onasemnogene abeparvovec

Marketing authorisation indication

2.1 Onasemnogene abeparvovec (Zolgensma, Novartis Gene Therapies) is indicated for 'the treatment of patients with 5q spinal muscular atrophy (SMA) with a bi-allelic mutation in the SMN1 gene and a clinical diagnosis of SMA Type 1, or patients with 5q SMA with a bi-allelic mutation in the SMN1 gene and up to 3 copies of the SMN2 gene'.

Dosage in the marketing authorisation

2.2 The dosage schedule is available in the summary of product characteristics for onasemnogene abeparvovec.

Price

2.3 The price for onasemnogene abeparvovec is £1,795,000 for a one-time dose (excluding VAT; company submission).

2.4 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.

3 Committee discussion

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 external assessment group (EAG). See the committee papers for full details of the evidence.

The condition

Presymptomatic spinal muscular atrophy

3.1 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. 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 if untreated. 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. 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. 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 genes 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. SMA can be diagnosed before there are symptoms (that is, presymptomatically), if newborn screening is done. There is currently no routine 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. It is not possible to determine the type of SMA that will develop in a baby with presymptomatic SMA, but age at diagnosis and the number of SMN2 gene copies can influence the severity of SMA that will develop.

Clinical effectiveness

Comparators

3.2 The company considered that best supportive care was the most appropriate comparator. The EAG thought that onasemnogene abeparvovec should also be considered in part of the comparator arm when presymptomatic SMA develops into type 1 SMA. This is because onasemnogene abeparvovec is recommended as an option in NICE's highly specialised technologies guidance on onasemnogene abeparvovec for treating SMA (from now, HST15). The committee was also aware that, although NICE has recommended nusinersen and risdiplam as part of managed access agreements for presymptomatic SMA and other SMA types, they are not routinely available. So, they could not be considered as routine care nor as relevant comparators for this evaluation. The committee concluded that the most relevant comparators were onasemnogene abeparvovec for type 1 SMA and best supportive care for type 2 SMA and type 3 SMA.

Clinical-effectiveness evidence

3.3 The main clinical-effectiveness evidence for onasemnogene abeparvovec for treating presymptomatic SMA came from SPR1NT, an open-label single arm study. This study included babies diagnosed with presymptomatic SMA and consisted of 2 cohorts. Cohort 1 included babies with 2 copies of the SMN2 gene and cohort 2 included babies with 3 copies of the SMN2 gene. All the babies were aged 6 weeks and under at enrolment. There were 14 babies in cohort 1 and follow up was for 18 months. There were 15 babies in cohort 2 and follow up was for 24 months. All the babies in cohort 1 reached the primary outcome of sitting without support for at least 30 seconds. All the babies in cohort 2 reached the primary outcome of standing alone for at least 3 seconds. Interim results from the long-term follow-up study LT-002, which included some babies who had completed SPR1NT, are academic-in-confidence and cannot be reported here. The committee noted that SPR1NT included a small number of babies. It also considered the lack of long-term evidence a key uncertainty (see section 3.7 and section 3.12). Despite this, the committee concluded that the results from SPR1NT suggested that onasemnogene abeparvovec is effective in treating presymptomatic SMA.

Generalisability of SPR1NT to NHS clinical practice

3.4 SPR1NT excluded babies aged over 6 weeks at treatment. The clinical experts stated that, in NHS clinical practice, treatment by 6 weeks may not always be possible. This may be because of a delay in getting the results of a genetic test or contraindications such as elevated levels of AVV9 antibodies (these levels may reduce over time and allow later treatment with onasemnogene abeparvovec). The clinical experts also explained that there is no newborn screening for SMA. So, presymptomatic SMA is only tested for if a sibling has SMA. This can lead to babies who are presymptomatic being identified when they are over 6 weeks. The clinical experts stated that onasemnogene abeparvovec would still be expected to provide important clinical benefits when given for presymptomatic SMA in babies aged over 6 weeks. But, because motor neurone loss increases with age, the delay in starting treatment may affect the effectiveness of onasemnogene abeparvovec. They thought that meeting the 6-week age limit could be difficult in the NHS and that this age restriction should not be introduced in any NICE recommendation. The clinical experts stated that, if there had to be a delay to having onasemnogene abeparvovec in NHS clinical practice, another drug such as nusinersen may be used as a bridging treatment. The committee was aware that there was no clinical trial evidence to estimate the effectiveness of onasemnogene abeparvovec in babies who are presymptomatic and aged over 6 weeks when they have the treatment. It was also aware that the marketing authorisation does not specify an age at which onasemnogene abeparvovec should not be used. The summary of product characteristics for the technology does state that there is limited evidence for its use in people aged 2 years and over and in people who weigh above 13.5 kilograms. SPR1NT also excluded babies with a low compound muscle action potential (CMAP) score. The clinical experts stated that CMAP is not routinely measured in NHS clinical practice, but a lower CMAP score could be associated with a poorer prognosis. The committee considered that the evidence from SPR1NT was not fully generalisable to NHS clinical practice. But it thought that onasemnogene abeparvovec would still be expected to provide clinical benefits to babies aged over 6 weeks, and that treatment may not always be possible by this age in NHS clinical practice. The committee considered the effect of age at treatment in its decision making, taking into account the additional exploratory analyses provided by the company (see section 3.8).

Cost effectiveness

The company's economic model

3.5 The company presented a new Markov model for this evaluation that was broadly based on the model developed for HST15. The model used data from SPR1NT and LT-002 (see section 3.3) to inform transitions in the short term for the onasemnogene abeparvovec arm. The company used natural history studies and data from Wijngaarde et al. (2020) to inform the comparator arm for best supportive care. In the long-term part of the model, the company assumed no motor milestone loss in the onasemnogene abeparvovec arm, and modelled some motor milestone loss in the comparator arm based on data from Wadman et al. (2018). The committee acknowledged that there was limited longer term data for outcomes with onasemnogene abeparvovec treatment. But it noted that this assumption, while uncertain, was accepted for decision making in HST15. The committee considered that the company's economic model was appropriate for decision making.

Adverse events

3.6 The clinical experts explained that risks from onasemnogene abeparvovec treatment increase with age. This may lead to a higher chance of adverse effects such as liver complications, and might need treatment with a longer course of corticosteroids. At the time of the committee meeting, the committee noted that NHS England had made a statement explaining that there have been some serious adverse events related to onasemnogene abeparvovec use in a few children having it in the NHS, particularly older and heavier babies and children. The committee was aware that NHS England has put in place a temporary pause in treatment with onasemnogene abeparvovec for children aged over 12 months, the upper age limit in the recommendations in HST15, because of these reported adverse events. At the time of the committee meeting, the committee was aware that the Medicines and Healthcare products Regulatory Agency was reviewing the data on these adverse events. After the committee meeting, NHS England lifted the temporary pause of treatment with onasemnogene abeparvovec in children aged over 12 months. This followed the conclusion of the Medicines and Healthcare products Regulatory Agency review. The committee noted that treatment adverse events were not explicitly included in the economic model. It understood that it was not within its remit to balance the risks and benefits of treatment with onasemnogene abeparvovec. But it was concerned that possible loss of quality-adjust life years (QALYs) and increased costs of treating adverse events were not included in the model. The committee acknowledged that there had been reported adverse events.

The EAG's scenario analyses

3.7 The EAG's base-case analysis was the same as the company's base-case analysis. But the EAG also provided 2 additional scenario analyses to explore the effect of key assumptions and model inputs. In the first scenario, the EAG assumed the same motor milestone loss in the onasemnogene abeparvovec arm as in the comparator arm. It explained that this was because there was limited long-term evidence on the efficacy of onasemnogene abeparvovec. In the second scenario, the EAG assumed that social care costs were equal to zero. It explained that this was the second largest cost category and noted there was some uncertainty as to how the company had estimated these costs. The committee considered that the EAG's scenario analyses were informative for decision making.

Additional scenario analyses

3.8 NICE requested that the company do additional cost-effectiveness analyses exploring the effect of age at treatment on the cost effectiveness of onasemnogene abeparvovec. NICE asked the company to provide a scenario assuming babies have treatment when aged 12 months. This was in line with the population in the managed access agreement for HST15. NICE also suggested that a scenario assuming an age of 6 months would be informative because this is the time point after which type 1 SMA (the most severe form) would not develop. NICE explained to the company that these analyses should account for the fact that outcomes in the comparator arm would be improved compared with its base-case analysis. This was because of the increasing proportion of people expected to develop type 2 SMA and type 3 SMA at an older age at diagnosis of presymptomatic SMA. The company stated that diagnosis of presymptomatic SMA in babies aged 12 months is unlikely in NHS clinical practice. The company provided 2 analyses in response to NICE's requests. In the first analysis, the company stated that it provided an economic evaluation of onasemnogene abeparvovec in babies who are presymptomatic and aged 6 months and over at treatment (that is, when type 1 SMA is not possible). In this analysis, the company recalculated the probabilities of developing type 2 SMA and type 3 SMA for this population. It based the proportion of SMN2 copy numbers on clinical expert opinion. The company also provided a scenario that assumed an equal probability of developing type 2 SMA and type 3 SMA in the best supportive care arm. The NICE lead team considered this analysis to be the most reflective of a child aged 12 months, and so the most relevant in terms of the request from NICE. A clinical expert at the meeting stated that most people with type 2 SMA would be diagnosed before they are aged 12 months. The company stated that the efficacy of onasemnogene abeparvovec in babies aged 6 months and over could be expected to be the same as that if the treatment is given before 6 weeks (as in SPR1NT). But the company also acknowledged that some irreversible motor neurone damage is possible in a presymptomatic population, which may reduce the potential to benefit from treatment. So, based on clinical expert input, the company also provided scenarios that assumed a reduction in efficacy of 20% for babies with 2 SMN2 gene copies and 10% for babies with 3 SMN2 gene copies in the population assumed to be able to walk. The company's second scenario analysis considered a situation in which diagnosis occurred before 6 weeks, but that there was a short delay in treatment. This delay was associated with an assumed reduction in treatment efficacy, based on clinical expert opinion. The company modelled a treatment delay of 2, 4 and 6 weeks. The committee acknowledged that the company's analyses were highly

Cost-effectiveness results by number of SMN2 gene copies

3.9 The EAG thought that subgroup analysis by number of SMN2 copy number should be considered. This was because higher numbers of SMN2 gene copies can be correlated with less severe disease. SPR1NT also included different primary outcome measures by number of SMN2 gene copies and different lengths of follow up. The type of SMA likely to develop is also influenced by the number of SMN2 gene copy numbers. The clinical experts at the meeting confirmed that the number of SMN2 copy numbers is the most accurate predictive factor available to clinicians in the presymptomatic SMA population. But they said that it was still associated with uncertainty in expected outcomes. The company thought that the analysis should consider the presymptomatic SMA population in general, but provided cost-effectiveness results by SMN2 copy number. The committee agreed that cost-effectiveness results by number of SMN2 gene copies were informative because incremental health benefits and costs are expected to vary for these groups.

Discounting rate for costs and health benefits

3.10 NICE's health technology evaluations manual (2022) specifies that the discount rate that should be used in the reference case is 3.5% for costs and health effects. But 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
- is likely to restore them to full or near-full health
- benefits are likely to be sustained over a very long period.

The company and EAG thought that a 1.5% discount rate should be used in this evaluation. This was because of the results from SPR1NT and the estimated long-term benefits of the treatment. The committee noted that a 1.5% discount rate had been accepted by the committee in HST15. It considered that outcomes for the presymptomatic SMA population were expected to be substantially better compared with the outcomes for the comparator group in HST15, which consisted of babies with symptomatic type 1 SMA. The comparator group in this evaluation may develop a range of SMA types, with varying severity, which added to the uncertainty. The committee was also aware that, following HST15, onasemnogene abeparvovec is now routinely available for most babies who develop type 1 SMA. The committee concluded that, for this evaluation, onasemnogene did not meet the criteria for using a 1.5% discount rate. But it acknowledged the substantial health benefits provided by the technology (see section 3.11). The committee also noted that decision making was not sensitive to the choice of discount rate used (see section 3.12 and section 3.13).

Applying quality-adjusted life year weighting

3.11 NICE's health technology evaluations manual (2022) specifies that a most plausible incremental cost-effectiveness ratio (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 NICE's health technology evaluations manual 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 of between 1 and 3 can be applied when the QALY gain is between 11 and 29 QALYs. The committee noted that the number of undiscounted QALYs gained with onasemnogene abeparvovec was likely to be over 30 in the base-case analysis. It noted that there was uncertainty around this estimated gain because of the small numbers in SPR1NT and the limited long-term evidence. But the committee agreed that onasemnogene abeparvovec would have provided sufficient QALY gain to consider a QALY weighting of 3 to be applied in its decision making. It also took this into consideration when assessing the cost effectiveness of onasemnogene abeparvovec in the population aged 6 weeks and over. The committee noted that none of the cost-effectiveness analyses presented were associated with an ICER estimate above £100,000 per QALY gained (assuming a 3.5% discount rate), so a QALY weighting was not required.

Base-case cost-effectiveness results

3.12 The company and the EAG provided results for onasemnogene abeparvovec for presymptomatic SMA compared with best supportive care and compared with onasemnogene abeparvovec for type 1 SMA, and compared with best supportive care for type 2 SMA and type 3 SMA. The committee considered that the comparisons with onasemnogene abeparvovec for type 1 SMA and with best supportive care for type 2 SMA and type 3 SMA were the most appropriate. This was because onasemnogene abeparvovec has been recommended as an option for type 1 SMA in HST15. The company's and EAG's main analyses included the same key assumptions, such as assuming that motor milestones gained in the clinical trial period were maintained over a lifetime. The committee considered that this assumption was associated with uncertainty because of the limited long-term data to validate it. This was also a key uncertainty in HST15. But the committee agreed that this assumption was reasonable because it was considered in the previous evaluation to be appropriate for decision making and in line with clinical expert opinion. The company's and EAG's base-case analyses suggested that onasemnogene abeparvovec for presymptomatic SMA dominated onasemnogene abeparvovec for type 1 SMA and best supportive care for type 2 SMA and type 3 SMA. This meant that onasemnogene abeparvovec given presymptomatically resulted in more health benefits at a lower overall cost when compared with onasemnogene abeparvovec for type 1 SMA and when compared with best supportive care for type 2 SMA and type 3 SMA. This was also true when considering the EAG's sensitivity analyses. These assumed, for example, some loss of motor function for people treated with onasemnogene abeparvovec and that social care costs, a large component of total costs, equalled zero. These results were also seen in the SMN2 gene copy number subgroup analyses. So, the committee considered that onasemnogene abeparvovec was likely to be cost-effective for treating presymptomatic SMA in babies aged 6 weeks and under (as per the data from SPR1NT).

Additional cost-effectiveness results by age at treatment

3.13 The committee considered the additional cost-effectiveness analyses provided by the company in response to NICE's request to model a scenario based on an older age at treatment (up to age 12 months; see section 3.8). The committee considered that the scenario assuming an equal chance of developing type 2 SMA and type 3 SMA in the comparator arm was most reflective of expected outcomes for babies aged 12 months (see section 3.8). In this scenario, the ICER estimates increased but remained below £100,000 per QALY gained. The committee recalled that a clinical expert at the meeting stated that a baby aged 12 months with presymptomatic SMA would more likely develop type 3 SMA instead of type 2 SMA. But the committee still considered that the ICER would remain below £100,000 for babies aged 12 months. This provided some additional reassurance about making such a decision with a model based largely on expert advice rather than trial evidence. So, the committee considered that onasemnogene abeparvovec was likely to be a cost-effective option for treating presymptomatic SMA for babies aged 12 months and under. This was because it had not been presented with clinical or cost-effectiveness evidence for children aged over 12 months. The committee acknowledged that presymptomatic SMA would usually be diagnosed before 12 months. It understood that earlier treatment in the presymptomatic population would be associated with better health outcomes and this would be the aim within NHS clinical practice. The committee also acknowledged that a recommendation for babies aged 12 months and under was in line with the managed access agreement outlined for HST15.

Other factors

Equality issues

3.14 During the evaluation, some consultees highlighted that, because onasemnogene abeparvovec would be provided at a limited number of highly specialised centres, there was the potential for issues of equity of access based on geographic location. 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. The committee understood that NHS England selected the centres to provide this service and were responsible for implementing this service.

Conclusion

Recommendation

3.15 The committee considered the evidence from SPR1NT and the company's and EAG's cost-effectiveness results. Taking this into account, it concluded that onasemnogene abeparvovec is likely to provide value for money in the context of a highly specialised service if used in babies aged 12 months and under. So, onasemnogene abeparvovec is recommended as an option for presymptomatic SMA in this age group.

4 Implementation

4.1 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 integrated care boards, 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.

4.2 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 draft guidance.

4.3 When NICE recommends a treatment 'as an option', the NHS must make sure it is available within the period set out in the paragraphs above. This means that, if a baby is aged 12 months and under and has presymptomatic 5q SMA with a biallelic mutation in the SMN1 gene and up to 3 copies of the SMN2 gene 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.

5 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 being evaluated. If it is considered there is a conflict of interest, the member is excluded from participating further in that evaluation.

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

Chair

Peter Jackson
Chair, highly specialised technologies evaluation committee

NICE project team

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

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Accreditation

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