

onasemnogene abeparvovec 2×10^{13} vector genomes/mL solution for infusion (Zolgensma[®])

Novartis Gene Therapies

5 February 2021

The Scottish Medicines Consortium (SMC) has completed its assessment of the above product and advises NHS Boards and Area Drug and Therapeutic Committees (ADTCs) on its use in NHSScotland. The advice is summarised as follows:

ADVICE: following a full submission assessed under the orphan medicine process

onasemnogene abeparvovec (Zolgensma[®]) is accepted for restricted use within NHSScotland.

Indication under review: 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.

SMC restriction: for the treatment of

- patients with 5q SMA with a bi-allelic mutation in the SMN1 gene and a clinical diagnosis of SMA type 1, or
- pre-symptomatic patients with 5q SMA with a bi-allelic mutation in the SMN1 gene and up to 3 copies of the SMN2 gene, where patients are expected to develop SMA type 1

In a phase III study of patients with symptomatic SMA type 1 treated with onasemnogene abeparvovec, survival was significantly better than a historical control cohort. In addition, motor milestones achieved generally exceeded the natural history of SMA type 1.

This advice applies only in the context of an approved NHSScotland Patient Access Scheme (PAS) arrangement delivering the cost-effectiveness results upon which the decision was based, or a PAS/ list price that is equivalent or lower.

This advice takes account of the views from a Patient and Clinician Engagement (PACE) meeting.

Indication

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 gene¹

Dosing Information

Patients will receive a dose of nominal 1.1×10^{14} vector genomes (vg)/kg onasemnogene abeparvovec. It should be administered with a syringe pump as a single intravenous infusion with a slow infusion of approximately 60 minutes. The total volume is determined by patient body weight. The summary of product characteristics (SPC) gives the recommended dosing for patients who weigh 2.6kg to 21.0kg.

Treatment should be initiated and administered in clinical centres and supervised by a physician experienced in the management of patients with SMA.

Further details are included in the SPC.¹

Product availability date

15 June 2020

Onasemnogene abeparvovec meets SMC orphan criteria and has conditional marketing authorisation (CMA) from the European Medicines Agency (EMA).

EMA orphan designation (EU/3/15/1509) was granted on 19 June 2015, this was maintained at the time of marketing authorisation.

Summary of evidence on comparative efficacy

Onasemnogene abeparvovec is an advanced therapy medicinal product (ATMP). It is a gene therapy and treatment aims to address the genetic cause of spinal muscular atrophy (SMA) and promote the survival and function of transduced motor neurons. Onasemnogene abeparvovec is a non-replicating recombinant adeno-associated viral (AAV) vector that uses AAV serotype 9 (AAV9) capsid to deliver the survival motor neuron gene 1 (SMN1).^{1,2} Onasemnogene abeparvovec meets SMC orphan criteria.

SMA is a clinical spectrum of disease with disease severity linked to fewer numbers of SMN2 gene copies and a younger age of symptom onset. Five clinical subtypes (type 0, 1, 2, 3, and 4) have been classified according to age of onset and the patient's maximal functional status prior to degeneration. Prognosis worsens the earlier the age of onset of symptoms.²⁻⁴

Patients with SMA type 1 who have onset of symptoms in the first 6 months of life never achieve independent sitting. Without respiratory support and tube-feeding, these patients are unlikely to survive past 2 years of age.²

In patients with pre-symptomatic SMA, it has been estimated that the majority of those with two copies of SMN2 will develop SMA type 1 (approximately 79%).⁵ It is expected that 15% of patients with three copies of SMN2 will develop SMA type 1 and 55% will develop SMA type 2.

The submitting company has requested that SMC considers onasemnogene abeparvovec when positioned for use in 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 pre-symptomatic patients with 5q SMA with a bi-allelic mutation in the SMN1 gene and up to 3 copies of the SMN2 gene, where patients are expected to develop SMA type 1.

Key evidence for the first part of the indication, in patients with a clinical diagnosis (symptomatic) spinal muscular atrophy (SMA) type 1, is from STR1VE-US, a multicentre, open-label, single-arm, phase III study in patients with SMA type 1. STR1VE-US recruited symptomatic patients with bi-allelic SMN1 deletions and two copies of the survival motor neuron gene 2 (SMN2). Patients were <6 months of age when they received study treatment and were required to have a swallowing test prior to administration.^{2, 6} Patients received a single intravenous infusion of onasemnogene abeparvovec 1.1×10^{14} vg/kg. They also received pre-treatment with oral prednisolone 1mg/kg/day 24 hours before onasemnogene abeparvovec infusion. Prednisolone continued for 30 days, after which it was tapered over 4 weeks unless alanine aminotransferase (ALT) and aspartate aminotransferase (AST) values were >2x upper limit of normal.^{2, 6}

Efficacy analyses were performed in the intention-to-treat (ITT) population. The first co-primary outcome, sitting independently for at least 30 seconds at 18 months was achieved by 59% of patients. The second co-primary outcome, survival at 14 months (defined by the avoidance of either death or requiring permanent ventilatory support), was achieved by 91% of patients.

The study included two co-secondary outcomes: the proportion of patients maintaining the ability to thrive (defined as the ability to tolerate thin liquids and to maintain weight [greater than the third percentile for age and gender] without gastrostomy or other mechanical or non-oral nutritional support) at 18 months of age and the proportion of patients who were independent of ventilatory support at 18 months of age.² Exploratory outcomes assessed motor ability and development. Using Bayley Scales of Infant and Toddler Development (Version 3), on average patients displayed gross motor function that was significantly lower than in same age peers, but tracking developmental gains. Fine motor function was largely similar to same-age peers. It is difficult to assess motor ability in patients with SMA as they have limited motor skills. The Children's Hospital of Philadelphia Infant Test for Neuromuscular Disorders (CHOP-INTEND) score is a motor function scale developed and validated for use specifically to monitor motor function status and decline amongst children with SMA type 1. Patients are scored 1 to 4 on 16 items (giving a maximum score of 64) with increasing score indicating improvement.² Results for the key and selected additional outcomes are shown in Tables 1 and 2 below.

Table 1: Co-primary, co-secondary, and selected exploratory outcomes from STR1VE-US.²

Outcome	Proportion of patients who received onasemnogene abeparvovec 1.1 x 10¹⁴ vg/kg achieving outcome
Co-primary outcomes	n=22
Sitting independently for at least 30 seconds at 18 months	59%
Survival* at 14 months	91%
Co-secondary outcomes	n=22
Maintaining the ability to thrive at 18 months	41%
Independent of ventilatory support at 18 months	82%
Exploratory outcome	n=16
Mean CHOP-INTEND scores at 18 months (SD)	51.2 (5.67)
Mean change from baseline in CHOP-INTEND scores (SD)	19.3 (9.13)

* defined by the avoidance of either death or requiring permanent ventilatory support

CHOP-INTEND: Children's Hospital of Philadelphia Infant Test for Neuromuscular Disorders; SD: standard deviation

Table 2: Selected video confirmed developmental milestones achieved in STR1VE-US.²

Milestone	Patients achieving milestone	Median age to the milestone achievement (Months)
Head control	85% (17/20*)	6.8
Rolls from back to sides	59% (13/22)	11.5
Sits without support for 30 seconds (Bayley)	64% (14/22)	12.5
Walking alone	4.5% (1/22)	-

*Two patients had head control reported by clinician assessment at baseline and therefore were not included.

The company also presented information about STR1VE-EU and START (and its long-term extension LT-001) studies which provide supportive data in patients with symptomatic SMA type 1. STR1VE-EU is an on-going multicentre, open-label, single-arm, phase III study of onasemnogene abeparvovec in patients with symptomatic SMA type 1; updated results are awaited.²

START was a single-centre, open-label, phase I study of onasemnogene abeparvovec in patients with symptomatic SMA type 1 (n=15). START included two sequential dosing cohorts: cohort 1 (low dose): 6.7 x 10¹³ vg/kg (three patients) and cohort 2 (therapeutic dose): 2.0 x 10¹⁴ vg/kg (12 patients). The EMA stated that this study could only be considered as supportive because comparability of process A (used to manufacture vectors in START) and process B (used in STR1VE-US, STR1VE-EU, and SPR1NT studies) cannot be concluded. At 24 months of follow-up post-dose, all patients were alive and 93% (14/15) did not require permanent ventilation. In cohort 2, at 24 months of follow-up, 75% (9/12) patients could roll (back to side, both sides), 75% (9/12) could sit without support for ≥30 seconds and 17% (2/12) patients could walk independently.^{2, 7}

LT-001 is the ongoing, long-term extension study of patients who completed the START study. Thirteen patients were enrolled (three from cohort 1 [low dose] and 10 from cohort 2 [therapeutic dose]). As of 31 December 2019, the median follow-up in cohort 2 was 4.4 years. Four patients in cohort 2 (40%) had received ongoing nusinersen. At this date, in cohort 2, all patients were alive without permanent ventilation. There was no loss of milestones. Two patients achieved new video-confirmed motor milestones (stands with assistance) and neither of these patients were reported to have received nusinersen.²

Key evidence for the pre-symptomatic patients with SMA and up to three copies of the SMN2 gene, comes from the SPR1NT study. SPR1NT is an ongoing, multi-centre, open-label, single-arm, single-dose, phase III study of onasemnogene abeparvovec in pre-symptomatic patients expected to develop SMA, with bi-allelic deletion of SMN1 and two or three copies of SMN2. Eligible patients were up to 6 weeks old. Patients receive a single infusion of onasemnogene abeparvovec 1.1×10^{14} vg/kg.^{1, 2} As of the 31 December 2019 data cut-off, 14 patients were enrolled and treated within cohort 1 (two SMN2 copies) and 15 patients were enrolled and treated in cohort 2 (three SMN2 copies). At this data cut-off, the median age of patients at the last visit was 10.5 months in cohort 1 and 9.6 months in cohort 2. All patients in the study were alive and free of permanent ventilation. Selected motor milestone outcomes are shown in Table 3. Patients in both cohorts had motor milestones development largely within the range for normal development. Further updated results are awaited.²

Table 3: Selected motor milestone outcomes from SPR1NT (data cut-off 31 December 2019).²

Motor milestone achieved	Cohort 1, two SMN2 copies (n=14)	Cohort 2, three SMN2 copies (n=15)
Turns from back to both sides	57%	60%
Sits alone without support for at least 30 seconds	57%	67%
Stand without support for at least 3 seconds	Figure cannot be presented due to company requirement for commercial confidentiality	27%
Walks with assistance*	36%	Figure cannot be presented due to company requirement for commercial confidentiality

SMN2: survival motor neuron gene 2

*Bayley Scales definition

A naïve indirect treatment comparison (ITC) using a Bayesian framework and a matching-adjusted indirect comparison (MAIC) with propensity score matching were conducted to compare the efficacy of onasemnogene abeparvovec (data from START and STR1VE-US studies) with nusinersen (data from two published studies) in patients with SMA type 1 with two copies of the SMN2 gene. The ITC and MAIC assessed the following outcomes: event-free survival (EFS) defined as avoidance of either death or permanent ventilation, overall survival and motor milestone achievements (independent sitting and walking). In addition, the ITC also assessed treatment-related adverse events. Results from the MAIC were used to inform the economic base case.

Overall, the results of the MAIC indicated that EFS was better with onasemnogene abeparvovec than nusinersen. For the overall survival outcome and the majority of the timepoints for independent sitting/walking outcomes, credible intervals (CrIs) were wide and spanned 1 indicating that no difference was identified and there was uncertainty in the results. The results of the naïve ITC favour onasemnogene abeparvovec over nusinersen for the EFS and overall survival outcomes and some time-points for independent sitting. For the independent walking outcome all CrIs spanned 1.

[Other data were also assessed but remain confidential.*](#)

Summary of evidence on comparative safety

No comparative safety data are available. Refer to the SPC for details.¹

The EMA concluded that onasemnogene abeparvovec appears to be a relatively safe treatment with a mild and manageable safety profile. Safety data were only available for small patient numbers (98 patients as of 31 December 2019 who received the proposed therapeutic dose via the proposed route of administration) and long-term safety data are not yet available.² The most commonly reported adverse events (AEs) after administration of onasemnogene abeparvovec were transient hepatic transaminase increase (12%) and vomiting (8.2%). Other commonly reported AEs were thrombocytopenia, pyrexia, raised aspartate aminotransferase, raised alanine aminotransferase, and raised troponin-I.¹ The most frequently occurring serious AE across studies was pneumonia. All patients developed an immune response against the AAV9 capsid. No immune response against the transgene protein occurred.² The EMA considered that cardiac toxicity may be a potential AE based on non-clinical studies and the increase in troponin-I and creatine kinase-MB (CK-MB) isoenzymes in clinical studies. However, it is unclear whether the cardiovascular effects are due to the disease or related to onasemnogene abeparvovec.²

In the key study, STR1VE-US, all patients had at least one treatment-emergent AE, 46% were grade 3 or above, 55% were related to study treatment, 46% were serious AEs, and 9.1% resulted in study discontinuation.⁸

Two deaths had occurred in the clinical study programme by 31 December 2019. One patient in STR1VE-US died aged 7.8 months of respiratory arrest not related to onasemnogene abeparvovec.⁶ One patient died in STR1VE-EU aged 6.8 months, and the cause of death was recorded as hypoxic/ischaemic brain damage due to respiratory tract infection due to SMA type 1 (on experimental therapy).²

Summary of clinical effectiveness issues

SMA is an inherited, autosomal recessive, neurodegenerative disorder resulting from deletions or mutation in the gene (SMN1) that codes for the survival of motor neuron (SMN) protein. This reduces levels of the SMN protein leading to a loss of spinal (and lower bulbar) motor neurons and progressive muscle weakness. A second SMN gene (SMN2) produces a shortened and less functional SMN protein.

Treatment options are limited. Nusinersen has been accepted by SMC for restricted use in patients with symptomatic SMA type 1. Administration is by intrathecal injection and treatment is lifelong which may be challenging due to spinal complications that often affect patients with SMA. There are no current treatments for patients with pre-symptomatic SMA.

Supportive management for patients with SMA type 1 involves a multidisciplinary approach including orthopaedic rehabilitation, nutritional and hydration management, swallowing and pulmonary management (airway clearance with chest physiotherapy and oral suctioning, non-invasive ventilation, nebulised bronchodilators, and antibiotics if required), and palliative care.²⁻⁴

There are limited published data for onasemnogene abeparvovec when given to patients >6 months of age and/or in advanced stages of the disease. Since SMA results in non-reversible damage to motor neurons, the benefit of treatment is dependent on disease burden at the time of treatment.

The main clinical studies were not designed to assess the efficacy of onasemnogene abeparvovec in infants previously treated with nusinersen therefore it is unclear whether the results would be generalisable to these patients. Limited real-world data suggest that treatment with onasemnogene abeparvovec may have a beneficial effect in patients previously treated with nusinersen.

Clinical experts consulted by SMC considered that onasemnogene abeparvovec fills an unmet need and is a therapeutic advancement, as it is administered as a one-off intravenous infusion. The extremely high upfront acquisition cost for this single-dose treatment is likely to have significant service implications and is associated with financial risk to the service if the long-term predicted clinical benefits do not materialise.

Key strengths

- Key evidence for patients with clinically diagnosed (symptomatic) SMA type 1 comes from the STR1VE-US study. The first co-primary outcome, sitting independently for at least 30 seconds at 18 months was achieved by 59% of patients. This outcome is favourable compared to the natural history of the disease where patients with SMA type 1 never achieve independent sitting². The second co-primary outcome, survival at 14 months, was achieved by 91% of patients. This outcome was favourable compared with the Paediatric Neuromuscular Clinical Research Database which was used as a natural history cohort and

where survival was 25% at 13.6 months.² The EMA concluded that the co-primary outcomes were outstanding and the survival and motor milestones achieved largely exceed the natural history of SMA type 1.²

- In the long-term follow-up study LT-001, all patients were alive with no loss of motor milestones at the 1 year follow-up visit.²
- Key evidence for patients with pre-symptomatic SMA and up to three copies of the SMN2 gene comes from the on-going SPR1NT study. Preliminary data were considered by the EMA to be supportive of the use of onasemnogene abeparvovec in this patient group.²

Key uncertainties

- The available evidence is from small open-label single-arm studies which are prone to bias. The lack of randomisation in particular weakens the internal validity of the findings. Long-term safety and efficacy data are limited, especially in patients with pre-symptomatic SMA.
- No direct comparative data are available versus nusinersen, the relevant comparator in patients with symptomatic SMA type 1. The submitting company presented indirect treatment comparisons to address this. Key limitations of the ITC and MAIC were: small patient numbers included (reduced further after matching in the MAIC), single-arm, open-label studies, no common comparator arm, differences in baseline characteristics that were not able to be matched in the MAIC and not matched in the naïve ITC, some clinically relevant outcomes were not included, data immaturity, and for the results CrIs were generally wide and spanned 1 for some outcomes. Overall, despite the limitations, the MAIC and ITC results suggest that EFS was better with onasemnogene abeparvovec than nusinersen. Results for other outcomes are uncertain.
- There is heterogeneity in the natural history of pre-symptomatic patients with three copies of SMN2 and it is unclear whether outcomes observed in cohort 2 (three copies) of SPR1NT exceed expected development.

Patient and clinician engagement (PACE)

A patient and clinician engagement (PACE) meeting with patient group representatives and clinical specialists was held to consider the added value of onasemnogene abeparvovec, as an orphan medicine, in the context of treatments currently available in NHSScotland.

The key points expressed by the group were:

- Spinal muscular atrophy (SMA) is a devastating muscle wasting condition associated with multiple major complications requiring complex medical and supportive care. Patients with SMA Type 1 rapidly lose motor and respiratory function leading to death, usually before 2 years of age. Patients are likely to need assisted ventilation and feeding support prior to this. Care is required 24 hours a day which has a huge impact on parents/carers.

- Onasemnogene abeparvovec addresses the genetic abnormality in SMA. It has the potential to make a significant difference to survival rates and promote motor development and acquisition of motor milestones in children with SMA Type 1.
- PACE clinicians noted that the greatest benefit is likely to be seen when it is administered to pre-symptomatic infants. A comprehensive newborn screening programme would be required to identify patients and maximise benefit.
- Onasemnogene abeparvovec is administered as a single intravenous infusion. Nusinersen, the current standard of care for patients with SMA Type 1, involves repeated lumbar punctures for intrathecal administration every 4 months. This can be very stressful for patients and their families, often requires a general anaesthetic, is associated with risks and can become very difficult to administer when patients develop scoliosis.
- Patients who respond could potentially have less disability burden over time, although long-term data are awaited. This would be likely to improve quality of life. A potential reduction in care requirements and removing the need for frequent hospital visits would also have a positive impact on parents and the wider family.

Additional Patient and Carer Involvement

We received a patient group submission from Treat SMA and a joint patient group submission from Spinal Muscular Atrophy UK and Muscular Dystrophy UK. Treat SMA is a charitable incorporated organisation. Spinal Muscular Atrophy UK and Muscular Dystrophy UK are registered charities. Treat SMA has not received any pharmaceutical company funding in the past two years. Spinal Muscular Atrophy UK has received 4.2% pharmaceutical company funding in the past two years, including from the submitting company. Muscular Dystrophy UK has received 1.1% pharmaceutical company funding in the past two years, including from the submitting company. Representatives from all three organisations participated in the PACE meeting. The key points of their submissions have been included in the full PACE statement considered by SMC.

Summary of comparative health economic evidence

The economic evaluation provided a cost-utility analysis of onasemnogene abeparvovec compared with nusinersen for patients with 5q SMA with a bi-allelic mutation in the SMN1 gene and a clinical diagnosis of SMA type 1. An exploratory scenario analysis was also provided comparing onasemnogene abeparvovec with best supportive care for pre-symptomatic patients with 5q SMA with a bi-allelic mutation in the SMN1 gene and up to three copies of the SMN2 gene, as nusinersen has not been accepted for use for this population of interest. This analysis was exploratory owing to the absence of available data sufficiently mature enough to populate the full economic model.

As noted above, the company requested that SMC consider onasemnogene abeparvovec for use in 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 pre-symptomatic patients with 5q SMA with a bi-allelic

mutation in the SMN1 gene and up to 3 copies of the SMN2 gene, where patients are expected to develop SMA type 1.

The perspective for the economic evaluation was health and social care. For patients diagnosed with SMA type 1, a Markov state-transition model was used to estimate costs and utilities over a lifetime time horizon. The model contained six states defined by patient milestones for selected motor development outcomes from birth ranging from within a broad range of normal development (state A), walking unassisted (state B), sitting unassisted (state C), not sitting (state D), permanent assisted ventilation (state E) and death. Model cycle length was six months for the first three years and annually thereafter.

Clinical data in the model base case used the MAIC values from the indirect treatment comparison (the unadjusted naïve comparison was used in scenario analysis). However, base case values had to be adjusted to account for the fact that the states patients transition to relate to meeting motor development milestones and so are based on patient age rather than time since treatment commenced. The clinical data were supplemented by natural history datasets, with the NeuroNext dataset used in the base case but tested in sensitivity analysis. Additional data sources include expert advice from clinicians and proxy use of best supportive care survival outcomes for patients with SMA type 2 and SMA type 3, because even though these groups are not included in the population of interest for the intervention, longer term clinical outcomes for SMA type 1 in the absence of treatment were not available because the prognosis was life limiting. Distributions were applied to states to model longer-term overall survival and event-free survival whereby permanent assisted ventilation was avoided. The choice of distributions used was tested in additional sensitivity analysis provided by the company.

For the analysis versus against best supportive care in pre-symptomatic patients, two exploratory scenarios were conducted that both use pooled indirect treatment comparison (ITC) data. Scenario A assumed age-appropriate milestones are observed for all (100%) pre-symptomatic infants treated with onasemnogene abeparvovec (delayed only by 1 model cycle), whereas in scenario B 100% were assumed to reach the sitting milestone and 82% reach the walking milestone, although for both milestones the scenario assumes achievement is delayed in 50% of patients.

Regression from states (i.e. deterioration) was only possible upon cessation of treatment which itself was only possible for the comparator treatment nusinersen as onasemnogene abeparvovec is administered in a single dose. Remaining on treatment, patients would stay in the state for which they had achieved the highest motor milestone.

Being on treatment conferred a utility increment to account for the health benefits associated with motor (and non-motor) development milestones being met in between those assigned to states in the model. More generally, utility values were sourced from the literature using proxy parental or carer values and/or clinical advice. These utility values were tested in scenario analysis using an alternative source of data for states that were notably optimistic. Caregiver disutility was

included in scenario analysis, although it was estimated using a sample of parents or carers of children with spina bifida owing to the small numbers who will be affected by SMA type 1 and the fact that disutilities experienced by parents or carers of children with SMA type 1 were expected to be similar in severity to the experience of parents or carers of children with spina bifida. Some resource use items suggested that family-based interventions were also included in base case costs.

Resource use was estimated via telephone survey of a number of clinicians in the UK and included the cost of specialist visits, hospitalisations, tests, equipment (e.g. orthotics), medicines and surgical interventions. Annual hospitalisations and social services costs incurred the greatest proportion of costs associated with each state in the model, aside from the costs of the medicines. Routine unit cost sources were applied to estimate costs, and this was tested in scenario analysis using Scottish Health Service Costs where available.

A Patient Access Scheme (PAS) was submitted by the company and assessed by the Patient Access Scheme Assessment Group (PASAG) as acceptable for implementation in NHSScotland. Under the PAS, a confidential discount was offered on the list price. A PAS discount is in place for nusinersen and this was included in the results used for decision-making by using estimates of the comparator PAS price.

Base case results versus nusinersen are provided in Table 4 using list prices for both treatments and show onasemnogene abeparvovec to be dominant (cheaper, more effective than nusinersen). The results presented do not take account of the PAS for nusinersen or the PAS for onasemnogene abeparvovec but these were considered in the results used for decision-making. SMC is unable to present the results provided by the company which used an estimate of the PAS price for nusinersen due to commercial confidentiality and competition law issues.

Exploratory analyses versus best supportive care are presented in Table 5 at the PAS price for onasemnogene abeparvovec.

Table 4: Base case results versus nusinersen for patients with SMA type 1, at list prices

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£) (versus nusinersen)	Incremental LYG (versus nusinersen)	Incremental QALYs (versus nusinersen)	ICER (£/QALY) (versus nusinersen)
Onasemnogene abeparvovec	2,704,737	12.87	7.50	-95,853	4.41	3.72	-25,740
Nusinersen	2,800,590	8.46	3.77	N/A	N/A	N/A	N/A

LYG = life-years gained, QALY = quality-adjusted life-years, ICER = incremental cost-effectiveness ratio

Table 5: Two exploratory scenarios of onasemnogene abeparvovec versus BSC

In patients with pre-symptomatic disease who have 5q SMA with a bi-allelic mutation in the SMN1 gene and up to three copies of the SMN2 gene, at PAS price

Analysis	ICER (£/QALY) (versus BSC)*
Proxy pre-symptomatic scenario A based on POOLED ITC data	58,996
Proxy pre-symptomatic scenario B based on POOLED ITC data	74,000

ICER = incremental cost-effectiveness ratio

* The economic model was built to reflect the treatment pathway of symptomatic SMA type 1 patients which is likely to differ from the treatment pathway of pre-symptomatic SMA infants.

One way sensitivity analysis found the model to be sensitive to the cost of treatments but also to annual discontinuations (until 13 years of age) in the comparator treatment for states with poorer motor milestone development but avoiding (state E) permanent assisted ventilation, ie states C & D, as well as the costs of hospitalisations and social services in state C, and utilities for this state.

Additional key scenario analyses are provided in Table 6, the model was sensitive to the discount rate and assumptions about delays to and numbers of patients reaching the milestones of interest. Of note is that including caregiver disutility did not considerably change the ICER, which related to the ability of patients who receive nusinersen to discontinue treatment, resulting in regression down the states towards death. These states have poorer quality of life for patients and so will confer greater caregiver disutilities, but likely for a shorter time compared with the life expectancy associated with onasemnogene abeparvovec patients given that discontinuation is not possible with this treatment.

Table 6: Key Scenario Analyses (at list price) for patients with SMA type 1 versus nusinersen

		ICER (£/QALY) ON-A vs nusinersen
	Base case results	-25,740
1	Costs at 0%, effects at 6%	-315,992
2	Costs at 6%, effects at 0%	25,577
3	Use of POOLED ITC dataset for onasemnogene abeparvovec's milestones achievement and survival (with no amends to milestones data)	-17,896
4	Use of POOLED ITC dataset for onasemnogene abeparvovec's milestones achievement and survival with one additional sitter and one additional walker in STR1VE-US after 18 months of age. The additional sitter sits and the additional walker walks between 24 and 30 months of age and therefore moves to sitting and walking in cycle ending 36 months, respectively	-16,354
5	Caregiver disutility scores included	-26,212
6	Use of POOLED MAIC dataset for onasemnogene abeparvovec with milestones that are not 'offset' by a model cycle (i.e. not 'offset' by 6 months)	-43,941

For the pre symptomatic cohort, the data informing these values are less robust as they were not sufficiently mature enough to populate the full economic model.

The main weaknesses relate to:

- as noted in the clinical effectiveness section, a range of issues with the clinical data give rise to weaknesses and considerable uncertainty in the economic evaluation, for example, the lack of direct data versus the relevant comparator and the paucity of both longer term data and sufficient sample sizes informing the analysis. The uncertainties are particularly high in the analysis for pre-symptomatic SMA patients given the limits on the available data to inform the economic model.
- the weaknesses with the clinical data create challenges in validating assumptions regarding the choices of extrapolation distributions used, and assumptions surrounding longer term treatment benefit more generally may not reflect what will be seen in clinical practice. This is a particular issue in relation to the possibility that treatment response could wane over time. The model assumed that patients treated with onasemnogene abeparvovec would be maintained in the state in which they achieved their highest motor milestone for the lifetime horizon of the model and this was not tested in any sensitivity analysis. This assumption would be a key driver of cost-effectiveness.
- considerable uncertainty regarding utility values for patients who are infants (a methodological problem more generally), and this is evident here given the base case values ranged from 0.00 in state E to general population norms for states A and B, while sensitivity analysis values ranged from 0.73 in state E to general population norms for state A. On-treatment utilities and the inability to separate treatment-related disutilities from disease related disutilities (i.e. incorporate adverse events) confounds the problem. However it is notable that utility values did not impact considerably on the model conclusions.

The Committee also considered the benefits of onasemnogene abeparvovec in the context of the SMC decision modifiers that can be applied when encountering high cost-effectiveness ratios and agreed that a number of the criteria were satisfied: a substantial improvement in life expectancy in the patient population targeted in the submission; and a substantial improvement in quality of life. In addition, as onasemnogene abeparvovec is an orphan medicine, SMC can accept greater uncertainty in the economic case.

After considering all the available evidence, the output from the PACE process, and after application of the appropriate SMC modifiers, the Committee accepted onasemnogene abeparvovec for restricted use in NHSScotland.

*Other data were also assessed but remain confidential.**

Additional information: guidelines and protocols

In July 2020, a European ad-hoc consensus statement on gene replacement therapy for SMA was published. This consensus statement notes that nusinersen was the first medicine to be approved by the EMA for the treatment of SMA and that onasemnogene abeparvovec has recently been approved. Nusinersen is an antisense-oligonucleotide that increases SMN protein concentration by modifying the splicing of the SMN2 gene. Onasemnogene abeparvovec is an adeno-associated viral vector-based gene therapy designed to deliver a functional copy of the SMN1 gene to the motor neurons. Some key points from the consensus statement are summarised below:

- In symptomatic patients, age at onset, disease duration and motor function status at the start of treatment are the most important factors that predict response to gene therapy treatment. SMA types (type 0, 1, 2, 3, 4) alone are not sufficient.
- In presymptomatic patients, SMN2 copy number is the most important predictor of clinical severity and age of onset.
- If onasemnogene abeparvovec is given after 6 months of age and/or in advanced stages of the disease, parents or patients should clearly be made aware that there are so far no published data on efficacy and safety and the risk/benefit should be carefully considered.
- In patients with symptoms at birth, treated after a long disease duration, or with already severe evolution, parents should be clearly made aware that despite the use of gene therapy there is a high risk of living with a very severe disability. Palliative care should be discussed as an alternative treatment option in these circumstances.
- Patients weighing >13.5kg should only receive treatment in specific circumstances as the risk of gene therapy increases with dose. For these patients, treatment with other disease modifying therapies or future intrathecal administration of nusinersen should be considered as an alternative.
- At the time of publication of the consensus statement there is no published evidence that combination of gene therapy and nusinersen is superior to any single treatment alone.

Early initiation of treatment, preferably in the pre-symptomatic stage of the disease, is associated with notably better outcome than starting treatment later. In newly diagnosed patients treatment delays should be avoided.⁹

In 2007, an International Conference on the Standard of Care for SMA published a consensus statement on SMA standard of care, this was updated in November 2017. All care considerations should start with a focus on a patient's clinical symptoms, signs and risk factors. In type 1 patients (infants unable to sit unsupported) supportive care includes rehabilitation (involving positioning, stretching and mobility), nutritional and hydration management, swallowing (short-term nasogastric or nasojejunal tube then long term gastrostomy tube) and pulmonary management (airway clearance with chest physiotherapy and oral suctioning, non-invasive ventilation, nebulised bronchodilators, and antibiotics if required). The consensus statement notes that nusinersen has received a licence in Europe and USA. This guidance pre-dates the availability of onasemnogene abeparvovec.^{3, 4}

Additional information: comparators

Nusinersen, supportive care.

Additional information: list price of medicine under review

Medicine	Dose Regimen	Cost per course (£)
onasemnogene abeparvovec	Single intravenous infusion of 1.1×10^{14} vg/kg.	1,795,000

Costs from company submission. This is the cost per patient for a single-dose. Costs do not take patient access schemes into consideration.

Additional information: budget impact

The submitting company estimated there would be 3 patients eligible for treatment in year 1 and again each year thereafter resulting in a cumulative total of 13 patients eligible by year 5. Treated patient numbers were estimated at 2 patients in year 1 and a cumulative total of 10 patients by year 5.

SMC is unable to publish the with PAS budget impact due to the company's requirement for commercial confidentiality. A budget impact template is provided in confidence to NHS health boards to enable them to estimate the predicted budget with the PAS. This template does not incorporate any PAS discounts associated with comparator medicines.

*Other data were also assessed but remain confidential.**

References

1. Novartis Gene Therapies. Onasemnogene abeparvovec (Zolgensma) solution for infusion. Summary of Product Characteristics. www.medicines.org.uk Last updated November 2020.
2. European Medicines Agency. Zolgensma: European Public Assessment Report - EPAR. Procedure No. EMEA/H/C/004750/0000. Available at: www.ema.europa.eu 26 March 2020.
3. Finkel RS, Mercuri E, Meyer OH, Simonds AK, Schroth MK, Graham RJ, *et al.* Diagnosis and management of spinal muscular atrophy: Part 2: Pulmonary and acute care; medications, supplements and immunizations; other organ systems; and ethics. *Neuromuscular disorders : NMD.* 2018;28(3):197-207. Epub 2018/01/07.
4. Mercuri E, Finkel RS, Muntoni F, Wirth B, Montes J, Main M, *et al.* Diagnosis and management of spinal muscular atrophy: Part 1: Recommendations for diagnosis, rehabilitation, orthopedic and nutritional care. *Neuromuscular disorders : NMD.* 2018;28(2):103-15. Epub 2018/01/02.
5. Calucho M, Bernal S, Alías L, March F, Venceslá A, Rodríguez-Álvarez FJ, Aller E, Fernández RM, Borrego S, Millán JM, Hernández-Chico C, Cuscó I, Fuentes-Prior P, Tizzano EF. Correlation between SMA type and SMN2 copy number revisited: An analysis of 625 unrelated Spanish patients and a compilation of 2834 reported cases. *Neuromuscul Disord.* 2018 Mar;28(3):208-215. doi: 10.1016/j.nmd.2018.01.003. Epub 2018 Jan 11. PMID: 29433793.
6. Novartis Gene Therapies. Data on file. Clinical Study Report (CSR). STR1VE-US. 2020.
7. Mendell JR, Al-Zaidy S, Shell R, Arnold WD, Rodino-Klapac LR, Prior TW, *et al.* Single-Dose Gene-Replacement Therapy for Spinal Muscular Atrophy. *The New England journal of medicine.* 2017;377(18):1713-22. Epub 2017/11/02.
8. Novartis Gene Therapies. Data on file. Safety Update onasemnogene abeparvovec [data cut 31 December 2019]. 2020.
9. Kirschner J, Butoianu N, Goemans N, Haberlova J, Kostera-Pruszczyk A, Mercuri E, *et al.* European ad-hoc consensus statement on gene replacement therapy for spinal muscular atrophy. *Eur J Paediatr Neurol.* 2020:S1090-3798(20)30142-2.

This assessment is based on data submitted by the applicant company up to and including 14 December 2020.

**Agreement between the Association of the British Pharmaceutical Industry (ABPI) and the SMC on guidelines for the release of company data into the public domain during a health technology appraisal: http://www.scottishmedicines.org.uk/About_SMC/Policy*

Medicine prices are those available at the time the papers were issued to SMC for consideration. SMC is aware that for some hospital-only products national or local contracts may be in place for comparator products that can significantly reduce the acquisition cost to Health Boards. These contract prices are commercial in confidence and cannot be put in the public domain, including via the SMC Detailed Advice Document. Area Drug and Therapeutics Committees and NHS Boards are therefore asked to consider contract pricing when reviewing advice on medicines accepted by SMC.

Patient access schemes: A patient access scheme is a scheme proposed by a pharmaceutical company in order to improve the cost-effectiveness of a medicine and enable patients to receive access to cost-effective innovative medicines. A Patient Access Scheme Assessment Group

(PASAG), established under the auspices of NHS National Services Scotland reviews and advises NHSScotland on the feasibility of proposed schemes for implementation. The PASAG operates separately from SMC in order to maintain the integrity and independence of the assessment process of the SMC. When SMC accepts a medicine for use in NHSScotland on the basis of a patient access scheme that has been considered feasible by PASAG, a set of guidance notes on the operation of the scheme will be circulated to Area Drug and Therapeutics Committees and NHS Boards prior to publication of SMC advice.

Advice context:

No part of this advice may be used without the whole of the advice being quoted in full.

This advice represents the view of the Scottish Medicines Consortium and was arrived at after careful consideration and evaluation of the available evidence. It is provided to inform the considerations of Area Drug & Therapeutics Committees and NHS Boards in Scotland in determining medicines for local use or local formulary inclusion. This advice does not override the individual responsibility of health professionals to make decisions in the exercise of their clinical judgement in the circumstances of the individual patient, in consultation with the patient and/or guardian or carer.