NICE National Institute for Health and Care Excellence

Highly Specialised Technology Evaluation

Onasemnogene abeparvovec for treating spinal muscular atrophy [ID1473]

Evaluation Report

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Highly Specialised Technology Evaluation

Onasemnogene abeparvovec for treating type 1 spinal muscular atrophy [ID1473]

Contents:

Any information supplied to NICE which has been marked as confidential has been redacted. All personal information has also been redacted.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Highly Specialised Technologies Evaluation Programme

INTERIM

ZOLGENSMA® (onasemnogene abeparvovec) for treating spinal muscular atrophy type 1 [ID1473]

Specification for company submission of evidence

19 August 2019

Contents

Instructions for companies

This is the template for submission of evidence to the National Institute for Health and Care Excellence (NICE) as part of the Highly Specialised Technologies Evaluation Programme. It shows companies what information NICE requires and the format in which it should be presented. Use of the submission template is mandatory. Sections that are not considered relevant should be marked 'N/A' and a reason given for this response.

The purpose of the submission is for the company to collate, analyse and present all relevant evidence that supports the case for national commissioning of the technology by NHS England, within the scope defined by NICE. Failure to comply with the submission template and instructions could mean that the NICE cannot issue recommendations on use of the technology.

The submission should be completed after reading the 'Interim Process and Methods of the Highly Specialised Technologies Programme'. After submission to, and acceptance by NICE, the submission will be critically appraised by an independent Evidence Review Group appointed by NICE, before being evaluated by the Highly Specialised Technology Evaluation Committee.

The submission should be concise and informative. The main body of the submission should not exceed 100 pages (excluding the pages covered by the template and appendices). The submission should be sent to NICE electronically in Word or a compatible format, and not as a PDF file.

The submission must be a stand-alone document. Additional appendices may only be used for supplementary explanatory information that exceeds the level of detail requested, but that is considered to be relevant to the Highly Specialised Technology Evaluation Committee's decision-making. Appendices will not normally be presented to the Highly Specialised Technology Evaluation Committee when developing its recommendations. Any additional appendices should be clearly referenced in the body of the submission. Appendices should not be used for core information that has been requested in the specification. For example, it is not acceptable to attach a key study as an appendix and to complete the clinical evidence section with 'see appendix X'. Clinical trial reports and protocols should not form part of the submission, but must be made available on request.

All studies and data included in the submission must be referenced. Studies should be identified by the first author or trial ID, rather than by relying on numerical referencing alone (for example, 'Trial 123/Jones et al.[126], rather than 'one trial[126]').

The sponsor should provide a PDF copy of all studies included in the submission. For unpublished studies for which a manuscript is not available, provide a structured abstract about future journal publication. If a structured abstract is not available, the sponsor must provide a statement from the authors to verify the data provided.

If a submission is based on preliminary regulatory recommendations, the sponsor must advise NICE immediately of any variation between the preliminary and final approval.

Unpublished evidence is accepted under agreement of confidentiality. Such evidence includes 'commercial in confidence' information and data that are awaiting publication

(‘academic in confidence’). When data are ‘commercial in confidence’ or ‘academic in confidence’, it is the sponsor’s responsibility to highlight such data clearly. For further information on disclosure of information, submitting cost models and equality issues, users should see section 18 of this document ‘Related procedures for evidence submission’.

List of tables and figures

Abbreviations

AAN	American Academy of Neurology
AANEM	American Association of Neuromuscular & Electrodiagnostic Medicine
AAV9	Adeno-associated virus subtype 9
ACM3	Appraisal committee meeting
AE	Adverse event
A&E	Accident and emergency department
AIC	Akaike information criterion
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
BIC	Bayesian information criterion
BID	Twice daily
BGH	Bovine growth hormone
BNF	British national formulary
BiPAP	Bi-level positive airway pressure
BSC	Best supportive care
CADTH	Canadian Agency for Drugs and Technologies in Health
CB	CMV enhancer/beta-actin
CHMP	Committee for Medicinal Products for Human Use
CHOP-INTEND	Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders
CI	Confidence interval
CMAP	Compound motor action potential
CMV	Cytomegalovirus
CNS	Central nervous system
CSF	Cerebrospinal fluid
CSR	Clinical study report
ddPCR	Droplet digital polymerase chain reaction
DILI	Drug-induced liver injury
DNA	Deoxyribonucleic acid
DSU	Decision Support Unit
EAP	Early access programme
ECG	Electrocardiogram
EFS	Event-free survival
EMA	European Medicines Agency
ERG	Evidence review group
EQ-5D	EuroQol-Five Dimension
EU	Europe
FAS	Full analysis set
FDA	Food and Drug Administration

GGT	Gamma-glutamyl transferase
GP	General practitioner
HCP	Healthcare practitioner
HCRU	Healthcare resource utilisation
HFMSE	Hammersmith Functional Motor Scale–Expanded
Hgb	Haemoglobin
HINE-2	Hammersmith Infant Neurological Examination-2
HIV	Human immunodeficiency virus
HRQoL	Health-related quality of life
HST	Highly specialised technology
HSUV	Health state utility value
HTA	Health technology assessment
HUI	Health Utility Index
ICER	Incremental cost-effectiveness ratio
ICNMD	International Congress on Neuromuscular Diseases
ID	Identification
IMP	Investigational medicinal product
IPD	Individual-patient data
IT	Intrathecal
ITC	Indirect treatment comparison
ITR	Inverted terminal repeat
ITT	Intention to treat
IV	Intravenous
KM	Kaplan meier
KOL	Key opinion leader
LT-FU	Long-term follow-up
LY	Life-years
LYG	Life-years gained
MAA	Managed access agreement
MAIC	Matching-adjusted indirect comparison
MDT	Multidisciplinary team
MGRS	Multicentre Growth Reference
mITT	Modified intention-to-treat
MUNE	Motor unit number estimation
N/A	Not applicable
NA	Not available
NeuroNext	Network for Excellence in Neuroscience Clinical Trials
NHS	National Health Service
NHSE	National Health Service England
NICE	National Institute for Health and Care Excellence

NINDS	National Institute of Neurological Disorders and Stroke
NIV	Non-invasive ventilation
NR	Not reported
NNH	Number needed to harm
NNT	Number needed to treat
Nus	Nusinersen
OD	Once daily
ON-A	Onasemnogene abeparvovec
ONS	Office for National Statistics
OOP	Out of pocket
OS	Overall survival
PAV	Permanent assisted ventilation
PedsQL	Pediatric quality of life inventory
PICOS	Population, intervention, comparators, outcomes, and study design
PNCR	Pediatric Neuromuscular Clinical Research database
PPPY	Per person per year
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-analyses
PSA	Probabilistic sensitivity analysis
PSS	Personal and social services
Q	Quarter
QALY	Quality-adjusted life-year
QoL	Quality of life
qPCR	Quantitative polymerase chain reaction
RCT	Randomised controlled trial
RNA	Ribonucleic acid
RSV	Respiratory syncytial virus
RWE	RWE
SAE	Serious adverse event
SAS	Safety analysis set
SC	Subcutaneous
SD	Standard deviation
SE	Standard error
SF	Short form
SIGN	Scottish Intercollegiate Guidelines Network
SLR	Systematic literature review
SMA	Spinal muscular atrophy
SMC	Scottish Medicines Consortium
SMN	Survival motor neurone
SmPC	Summary of product characteristics
STA	Single technology appraisal

sv40	Simian virus 40
TEAE	Treatment emergent adverse event
TID	Three times a day
TLV	Swedish Dental and Pharmaceutical Benefits Agency
TP	Transition probability
TTO	Time-trade off
UK	United Kingdom
ULN	Upper limit of normal
US	United States
VPA	Valproic acid
WBC	White blood cell count
WHO	World Health Organization
WTP	Willingness to pay

Executive Summary

The technology (Section 2)

Onasemnogene abeparvovec is a one-time gene replacement therapy that addresses the genetic root cause of spinal muscular atrophy (SMA) by delivering a stable, functional human survival motor neurone (*SMN)* gene that rapidly restores continuous SMN protein expression, thus preventing motor neurone loss in symptomatic infants with SMA type 1 and pre-symptomatic infants genetically predicted to have SMA (1).

Onasemnogene abeparvovec uses a non-replicating, adeno-associated virus subtype 9 (AAV9) derived capsid (carrier shell) as a vector, which is able to cross the blood brain barrier, to deliver a fully functional copy of the human *SMN* gene to a patient's cells (1, 2). Once inside the cell, the vector releases the *SMN* gene into the cell nucleus, where it resides without modifying the existing deoxyribonucleic acid (DNA) of the patient (2, 3). Onasemnogene abeparvovec also includes a promotor, which ensures continuous and sustained production of SMN protein necessary for a durable therapeutic effect. The SMN protein is critical to preventing motor neurone cell death and enabling patients to gain motor function and achieve key developmental and motor milestones (1, 2). It is anticipated that the *SMN* gene will remain indefinitely in non-mitotic (non-dividing) cells, eliminating the need for repeat administration.

Onasemnogene abeparvovec is an Advanced Therapy Medicinal Product (ATMP) and is anticipated to be the first ever gene therapy approved for a neuromuscular condition. It is expected to be indicated for the single treatment of 5q13 SMA type 1 and is administered as a single, peripheral, intravenous (IV) infusion, over 60 minutes, at a dose of $1.1x10^{14}$ vg/kg (1). [redacted]

Nature of the condition (Section 6.1)

SMA type 1 is an ultra-rare genetic disease in which greater than 90% of untreated infants die or require permanent ventilation by the age of two years. SMA type 1 is the most severe form of SMA and is estimated to affect 35 babies in England each year (4-7). Infants with SMA type 1 commonly show onset of symptoms before 6 months of age. Without disease modifying treatment, infants with SMA type 1 suffer rapid muscle atrophy as a result of motor neurone loss, leading to the inability to breathe or swallow, and will never be able to roll over, sit, walk, or achieve any development milestones. Respiratory failure is the usual cause of death (8). As motor neurone loss in SMA type 1 is progressive and irreversible (9, 10), there is a need for early intervention with an effective treatment, that results in rapid restoration of SMN protein in the targeted cells.

SMA type 1 is associated with extremely high infant mortality and disability, representing a significant burden to patients, caregivers, and the healthcare system (7, 11-13). Prior to the availability of effective pharmacotherapy, SMA type 1 was the leading genetic cause of infant death (2). The devastatingly poor overall survival of babies with SMA type 1 is highlighted by

real-world data from a retrospective observational study in England (2007 to 2017) in which 50% of SMA type 1 patients died before 1 year of age (14).

When no routinely-commissioned disease-modifying treatment was available, babies with SMA type 1 in England were managed with best supportive care (BSC), which consists of nutritional, respiratory (temporary non-invasive, permanent non-invasive, or permanent invasive ventilation), and orthopaedic support (15, 16). However, BSC does not halt the underlying disease progression of SMA type 1 and is primarily palliative (15-18). The care of babies with SMA type 1 requires a multidisciplinary team (MDT) of health care practitioners including neurologists, pulmonologists, physiotherapists, nurses, and health visitors (18).

Nusinersen was recently (ID1069, July 2019) recommended as an option for use, in England, in all patients with 5q SMA (pre-symptomatic SMA, or SMA types 1, 2 or 3) via a managed access agreement (MAA) but was not yet considered established standard of care at the time of this submission (19, 20). Nusinersen is an *SMN2*-directed antisense oligonucleotide for the treatment of SMA and has demonstrated an improvement in some clinical outcomes versus BSC, but only temporarily increases SMN protein expression and therefore requires repeated and lifelong intrathecal administration (21, 22). This treatment regimen incurs associated ongoing healthcare costs and represents a burden to patients, caregivers, and payers (21-23).

A significant unmet need still remains to further improve the survival and development of infants with SMA type 1 without the burden of chronic, life-time invasive therapy.

Impact of the new technology (Section 9.6.1)

Onasemnogene abeparvovec halts disease progression and prevents motor neuron loss in symptomatic infants with SMA type 1 and pre-symptomatic infants genetically predicted to have SMA Type 1.

Onasemnogene abeparvovec versus best supportive care

The clinical development programme for onasemnogene abeparvovec delivered by one-time peripheral IV infusion comprises a series of Phase I–III clinical trials in patients with SMA type 1 and pre-symptomatic SMA.

To date, the Phase I/IIa study, START, is complete and three Phase III studies (STR1VE-EU, STR1VE-US, and SPR1NT) are ongoing. Given the poor prognosis of babies with SMA type 1 under BSC, coupled with the unprecedented efficacy and safety profile of onasemnogene abeparvovec observed in START, it was considered unethical to include placebo patients in Phase III onasemnogene abeparvovec trials. All interventional studies in the clinical development programme therefore had an open-label design with all patients receiving a one-time dose of onasemnogene abeparvovec.

START

START was designed as an open-label dose-escalation study in a small SMA type 1 patient population (n=15), to assess the safety of onasemnogene abeparvovec. The study was

conducted at a single US site and included 15 patients who received a one-time IV infusion of onasemnogene abeparvovec (Cohort 1: low dose, n=3; Cohort 2: therapeutic dose, n=12) (2, 24, 25). The primary objective of the study was assessment of the safety of onasemnogene abeparvovec. Secondary and exploratory objectives of START included assessment of event (permanent ventilation) free survival and functional and motor milestone achievement.

Treatment-related adverse events (AEs) (elevated serum aminotransferase levels) occurred in 4 of 15 (27%) patients. All of these events were asymptomatic and resolved with prednisolone.

When treated with onasemnogene abeparvovec, all infants in START experienced unprecedented survival without the need for permanent ventilatory support and broad achievement of developmental and motor milestones over the study period of 24 months:

- All patients (n=15) who received a single IV infusion of onasemnogene abeparvovec were alive at 24 months post-dose and none required permanent ventilation, compared with only 8% in an external natural history control study (2, 12, 24, 25)
- Based on independent video confirmation, motor milestones were achieved and maintained over time in START. In contrast, no patients in natural history cohorts achieved any motor milestones (6, 25). No patients (n=15) in START lost motor milestones during the 24-month study period
- In Cohort 2 in START (n=12, therapeutic dose), at the end of the study (24 months post-dose):
    - 11/12 (91.7%) patients were able to hold their head erect without support for ≥3 seconds
    - 11/12 (91.7%) patients were able to sit with assistance
    - 9/12 (75.0%) patients were able to sit unassisted for ≥30 seconds
    - 2/12 (16.7%) patients were able to walk independently
    - 11/12 (91.7%) patients achieved or retained the ability to feed orally
    - 11/12 (91.7%) patients were able to speak
- The Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders (CHOP-INTEND) scores, a measurement of the motor skills of infants with SMA (38, 39), in Cohort 2 (n=12) improved from baseline to study end (24 months post-dose):
    - 11/12 (91.7%) patients achieved a CHOP-INTEND score ≥50, surpassing a threshold effectively never seen in patients with SMA type 1, beyond 6 months of age, and four patients achieved scores of ≥60 approaching the ceiling of the scale (64 points) (26)

- In contrast, CHOP-INTEND scores in natural history cohorts decreased by 10.7 points between 6 and 12 months of age and scores >40 points were not achieved and maintained (12, 27)

The significant milestone achievements observed in START are in contrast with the complete absence of milestone achievement in natural history cohorts and demonstrate a clear departure from the natural history of SMA type 1 with prolonged survival, achievement of motor milestones and significantly better functional motor performance in babies with a devastating ultra-rare genetic disease.

Long Term Safety Follow-Up of START (LT-001)

Interim data from the 15 year long-term follow-up study LT-001, in which 13/15 patients treated in START are enrolled, are available.

For those patients enrolled in LT-001 who received the therapeutic dose of onasemnogene abeparvovec in START (n=10), at the 31 December 2018 data cut-off (28):

- All patients are alive without the need for permanent ventilation (29); the median age of patients was 4 years; with oldest patient aged 4.6 years old
- The median time since onasemnogene abeparvovec administration was 44.8 months, with longest duration of therapy recorded at 49.7 months since dosing
- There has been no loss of previously attained milestones or worsening of ventilatory or nutritional function compared with the end of START
    - Two patients requiring daily ventilatory support at baseline no longer required support
    - Two additional patients achieved the ability to stand without support

No long-term adverse events have emerged in LT-001.

These results indicate that a one-time, IV administration of onasemnogene abeparvovec at the therapeutic dose (Cohort 2) has continued to provide prolonged and durable efficacy.

Phase III Studies – Interim Results

The rapid and unprecedented overall survival and motor milestone achievements observed in START have been broadly replicated in early interim results from ongoing clinical studies. Based on interim data (8 March 2019 data cut):

- Overall survival remains extremely high; of the 77 patients dosed with onasemnogene abeparvovec via a single IV infusion in the clinical trial programme (START, STR1VE-EU, STR1VE-US, and SPR1NT) and for whom data were reported in the latest data cut (8 March 2019), 75 (97.4%) are alive (Section 9.7.2.3 and 9.7.2.4)
- Interim analyses from all ongoing studies indicate that no patients have lost motor milestones following treatment with onasemnogene abeparvovec

- Attainment and maintenance of motor milestones is substantially improved compared with natural history cohorts:
    - For STR1VE-US, the ongoing trial for which the longest follow-up data are available, 50% (11/22) of patients have achieved the ability to sit alone for ≥30 seconds as of the 8 March 2019 data cut
    - In line with START, at 6 months post-dosing, 90% of patients in STR1VE-US with Month 6 data had achieved a ≥4-point increase from baseline CHOP-INTEND score and 75% of patients had achieved a CHOP-INTEND score of ≥40 points

Onasemnogene abeparvovec versus nusinersen

Nusinersen is not yet established as standard of care in England at the time of this submission but its use, in accordance to the associated MAA (19) agreed with NICE (National Institute of Health and Care Excellence) and the NHS (National Health Service), is expected to increase. As nusinersen is the only disease-modifying therapy licensed for the treatment of SMA type 1 in England, AveXis performed an exploratory assessment of the relative efficacy and safety of onasemnogene abeparvovec versus nusinersen for the treatment of patients with SMA type 1 with 2 copies of *SMN2* gene based on currently available data (30).

In the absence of head-to-head trials of onasemnogene abeparvovec and nusinersen, an exploratory indirect treatment comparison (ITC) of onasemnogene abeparvovec versus nusinersen was conducted (30). Findings from the unanchored ITC suggest that onasemnogene abeparvovec may have a better clinical efficacy profile in term of preventing death and use of permanent ventilation and in improving motor function in SMA type 1 patients relative to nusinersen; the outcomes reported for onasemnogene abeparvovec and nusinersen are presented in Table 1. Despite the small sample sizes in all clinical trials used, the analysis performed was the best feasible with the data available at the time. However, as a naïve comparison does not preserve within-study randomisation or take into account differences in study effects, all results should be interpreted with caution.

Table 1: Outcomes reported in an ITC of onasemnogene abeparvovec and nusinersen in infants with SMA type 1

Outcome (timepoint†)	Timepoint	Onasemnogene abeparvovec	Nusinersen
Overall survival, % (n/N)	24 months	100 (12/12)	54.1 (20/37)
Survival free of permanent ventilation% (n/N)	24 months	100 (12/12)	20.0 (10/50)
CHOP-INTEND response ≥4 point improvement from baseline, % (n/N))	START: 24 months SHINE: last available assessment‡	100 (12/12)	67.9 (55/81)
CHOP-INTEND change from baseline	START: 24 months SHINE: Day 698	30.7	16.9

Outcome (timepoint†)	Timepoint	Onasemnogene abeparvovec	Nusinersen
Achieved head control, % (n/N)	START: last available assessment SHINE: last available assessment‡	91.7 (11/12)	28.4 (23/81)
Sitting unassisted, % (n/N)	START: last available assessment SHINE: last available assessment‡	91.7 (11/12)	14.8 (12/81)
Walking unassisted, % (n/N)	START: last available assessment SHINE: last available assessment‡	16.7 (2/12)	0 (0/81)§

† Time post treatment administration (onasemnogene abeparvovec)/ initiation (nusinersen).
‡ As SHINE is subject to loss to follow up, only 17 out of 81 patients had follow up data at the latest available timepoint (698 days). Therefore, the last available assessment for each patient was used for analysis.
§ No patients had yet achieved standing unaided or walking independently, although patients were gaining HINE sub-milestones in both categories (31).

Value for money (Section 12 and 0)

The cost-effectiveness model is a cohort Markov state-transition model, with five functional health states representing different motor function milestones achieved and ventilation status:

- permanent assisted ventilation (E State)
- not sitting (D state)
- sits unassisted (C state)
- walks unassisted (B state)
- patients that are within a broad range of normal development (A state)

Whilst the health states are broadly defined by the motor function milestone achieved, each health state also captures the likely additional clinical features of SMA. The model framework is broadly aligned to the model structure chosen by the US Institute for Clinical and Economic Review (US ICER) model, who recently published an assessment of SMA therapies (32).

The model consists of two parts: 1) a short-term model concordant with observed clinical trial data, and 2) a long-term extrapolation model. Observed clinical outcomes are captured in the model by moving treated patients into higher functioning health states; higher functioning health states are associated with longer survival, improved quality of life, and lower healthcare resource utilisation (HCRU) costs. Patients can only be in one state at a time (mutually exclusive) and all patients must be captured in a state (mutually exhaustive). At model baseline, all patients are in the D state (not sitting). At the end of each cycle of the

model (every 6 months for the first 3 years, then annually), patients can transition into a new health state, or stay in the same health state or die. In line with the final scope for this highly specialised technology (HST), BSC and nusinersen are used as comparators and cost effectiveness is assessed using incremental cost per quality adjusted life years (QALYs).

In the base case analysis (presented in Section 12.5), the incremental cost effectiveness ratio (ICER) for onasemnogene abeparvovec versus BSC was £177,061, from 10.77 discounted incremental QALYs gained (undiscounted incremental QALYs of 24.25). Thus, under the NICE HST willingness to pay (WTP) threshold, onasemnogene abeparvovec is cost effective versus BSC (after applying undiscounted QALY weighting). After discounting costs at 3.5%, onasemnogene abeparvovec was associated with a lifetime total cost of £2,614,400, compared with £707,836 for BSC. Thus, total incremental lifetime costs for onasemnogene abeparvovec were £1,906,564 versus BSC. These incremental lifetime costs are a result of increased technology costs, but also increased management/care costs due to an increased survival for patients on onasemnogene abeparvovec (18.27 total life years [LYs] gained [discounted]) versus BSC (3.44 total LYs gained [discounted]).

The one-way sensitivity analysis shows that the parameters in the model affecting the ICER for onasemnogene abeparvovec versus BSC (excluding the costs of the technology) are the cost of hospitalisations for E state patients, the cost of hospitalisations for C state patients and the C state patient utility value. The results of the deterministic multi-way scenario analysis demonstrated the cost-effectiveness of onasemnogene abeparvovec, even under pessimistic scenarios. For example, applying the pessimistic value (i.e. upper or lower value causing an increase to the ICER) for the three variables (excluding the cost of the technology) with the largest impact on the ICER, the ICER for onasemnogene abeparvovec versus BSC is £223,058 (borderline cost effective; undiscounted incremental QALYs 21.61). The probabilistic sensitivity analysis (PSA) demonstrated combined parameter uncertainty in the model; the mean probabilistic results were greater than the deterministic analysis but the 95% credibility intervals around the ICERs were broad: mean ICER versus BSC was £196,703 (95% credibility interval: £74,877, £278,448).

The ICER for onasemnogene abeparvovec versus nusinersen was £35,788, from 9.61 discounted incremental QALYs gained (undiscounted incremental QALYs of 22.53). Thus, under the NICE HST WTP threshold, onasemnogene abeparvovec is cost effective versus nusinersen (base case ICER <£100,000). After discounting costs at 3.5%, onasemnogene abeparvovec was associated with a lifetime total cost of £2,614,400, compared with £2,270,315 for nusinersen. Thus, total incremental lifetime costs for onasemnogene abeparvovec versus nusinersen were £344,085. As for the comparison to BSC, these incremental lifetime costs are a result of increased technology costs, but also increased management/care costs due to an increased survival for patients on onasemnogene abeparvovec (18.27 total LYs gained [discounted]) versus nusinersen (6.97 total LYs gained [discounted]).

All results in the one-way sensitivity analysis resulted in ICERs that were below £70,000 per QALY gained for onasemnogene abeparvovec versus nusinersen. Similarly, cost-effectiveness was demonstrated in the results of the deterministic multi-way scenario analysis: for onasemnogene abeparvovec versus nusinersen, applying the pessimistic

value for the three variables with the largest impact on the ICER (excluding the costs of the technologies), the ICER is £76,304 (cost-effective as <£100K threshold). The PSA demonstrated combined parameter uncertainty in the model: The mean ICER versus nusinersen was £63,888 (95% credibility interval: −£95,925, £157,917).

The budget impact of treating an individual patient with onasemnogene abeparvovec versus BSC is £1,689,814 in Year 1 but declines in subsequent years to £15,817 in Year 2, −£16,496 in Year 3, –£2,607 in Year 4, and –£1,170 in Year 5, indicating cost savings versus BSC from Year 3 onwards. The budget impact of treating an individual patient with onasemnogene abeparvovec versus nusinersen is £1,263,698 in Year 1 due to the one-time treatment cost of onasemnogene abeparvovec. However, in all subsequent years, onasemnogene abeparvovec is associated with cost savings versus nusinersen, with budget impacts ranging from –£168,285 in Year 2 to −£96,674 in Year 5. The full drug cost of onasemnogene abeparvovec is incurred at the time of the single-dose treatment whereas the costs of nusinersen are incurred in the long term.

The budget impact analysis shows that, in a scenario in which BSC is the only treatment option (nusinersen not available), the total budget impact over 5 years of introducing onasemnogene abeparvovec is £231,624,876, assuming 35 incident cases of SMA type 1 per year in the UK. In a scenario in which nusinersen is available, the total budget impact over 5 years of introducing onasemnogene abeparvovec is £127,072,377, assuming 35 incident cases of SMA type 1 per year.

Impact of the technology beyond direct health benefits (Section 14)

The transformative clinical outcomes associated with onasemnogene abeparvovec have a profound impact on the lives of infants and their caregivers. As a rapidly progressive and life-limiting condition, there are benefits to the effective treatment of SMA type 1 beyond improvements in patient health. By improving infants' abilities to gain motor (e.g. sitting, standing, walking) and developmental milestones (e.g. speech, swallowing, grasping), babies treated with onasemnogene abeparvovec may have the potential to attend school and become independent, significantly decreasing caregiver and broader family burden. A reduction in caregiver burden may allow family members to return to work, providing financial benefits as well as helping to deliver improvements in the overall wellbeing of infants and their families.

Innovation

SMA type 1 is a devastating, progressive, monogenic, neuromuscular disease that leads to rapid and irreversible loss of motor neurones. Gene replacement therapy is a pioneering approach for monogenic diseases, such as SMA, because it is feasible to deliver a functional gene to address the single-gene deficiency that is the root cause of the disease. The ability of onasemnogene abeparvovec to drive rapid and sustained SMN protein expression is also important for the optimal treatment of this rapidly progressing disease, as the SMN protein is critical to the prevention of irreversible motor neurone cell death.

As the first one-time gene replacement therapy for a neuromuscular disease, onasemnogene abeparvovec represents a major step change in the treatment and

management of SMA type 1 which dramatically changes the course of the disease and may eliminate the need for chronic administration of disease modifying treatments.

Prompt diagnosis of SMA and the possibility of newborn screening in future could result in earlier intervention before symptom onset with the potential for further improvement in patient outcomes.

1 Statement of the decision problem

The decision problem is specified in the final scope issued by NICE. The decision problem states the key parameters that should be addressed by the information in the evidence submission. All statements should be evidence based and directly relevant to the decision problem.

The submission covers the technology's expected full marketing authorisation for this indication. The decision problem is outlined in Table 2.

Table 2: Statement of the decision problem

	Final scope issued by NICE (33)	Variation from scope in the submission	Rationale for variation from scope
Population	Children with SMA type 1	As per draft pre-invite scope, however, onasemnogene abeparvovec is expected to be used in infants who are newly diagnosed with SMA type 1 or with a genotype predictive of SMA type 1 (i.e. the incident population) 	Clinical data suggest there are potential benefits in starting treatment as early as possible, therefore onasemnogene abeparvovec is expected to be used in the newly diagnosed (incident) SMA type 1 population or infants with a genotype predictive of SMA type 1 only
Intervention	Onasemnogene abeparvovec	As per scope, but for clarity the intervention is: onasemnogene abeparvovec delivered via a single IV infusion	N/A
Comparator(s)	• Best supportive care • Nusinersen (subject to ongoing NICE appraisal)	As per scope	N/A
Outcomes	The outcome measures to be considered include: • Motor function (including, where applicable, age-appropriate motor milestones such as sitting, standing, walking) • Frequency and duration of hospitalisation. • Speech and communication • Respiratory function	As per scope, but a composite endpoint of permanent ventilation-free survival – often termed as event-free survival (EFS) in the assessment of SMA type 1 – is also assessed As per scope, but health-related quality of life of caregivers will be explored in modelling scenario analyses only	EFS (defined as survival free from permanent ventilation) is a primary or secondary efficacy endpoint in the onasemnogene abeparvovec clinical trial programme

	Final scope issued by NICE (33)	Variation from scope in the submission	Rationale for variation from scope
	• Complications of SMA (including, for example, scoliosis and muscle contractures) • Need for non-invasive or invasive ventilation • Mortality • Adverse effects of treatment • Health-related quality of life (for patients and carers) Clinical effectiveness • Overall magnitude of health benefits to patients and, when relevant, carers • Robustness of the current evidence and the contribution the guidance might make to strengthen it • Treatment continuation rules (if relevant)		Due to the lack of robust utilities for caregivers of SMA type 1 patients
Subgroups to be considered	Within the proposed label, heterogeneity of health benefits within the population will be explored	As per scope, heterogeneity of health benefits within the population is explored qualitatively but no formal quantitative subgroups are presented	N/A
Nature of the condition	• Disease morbidity and patient clinical disability with current standard of care • Impact of the disease on carer's quality of life • Extent and nature of current treatment options	As per scope	N/A

	Final scope issued by NICE (33)	Variation from scope in the submission	Rationale for variation from scope
Cost to the NHS and PSS, and Value for Money	• Cost effectiveness using incremental cost per quality-adjusted life year • Patient access schemes and other commercial agreements • The nature and extent of the resources needed to enable the new technology to be used	As per scope Potential patient access schemes or other commercial agreements will be explored with NICE and NHS England, during this appraisal process, if required	N/A
Impact of the technology beyond direct health benefits, and on the delivery of the specialised service	• Whether there are significant benefits other than health • Whether a substantial proportion of the costs (savings) or benefits are incurred outside of the NHS and personal and social services • The potential for long-term benefits to the NHS of research and innovation • The impact of the technology on the overall delivery of the specialised service • Staffing and infrastructure requirements, including training and planning for expertise	As per scope, however, the assessment of caregiver productivity loss, caregiver/patient out of pocket costs and patient educational achievement/ workforce participation are explored via modelling scenario analyses only	Limited UK-specific data for the SMA type 1 population in relation to costs incurred outside of the NHS and PSS exists, therefore, impacts of the technology beyond direct health benefits are explored by modelling scenario analyses only in Section 14

	Final scope issued by NICE (33)	Variation from scope in the submission	Rationale for variation from scope
Special considerations, including issues related to equality	• There are no special considerations in equality regarding prescribed characteristics, however, the practicalities of families having to travel for treatment at specialised centres should be considered • Guidance will only be issued in accordance with the marketing authorisation • If evidence allows, and included within the marketing authorisation, consideration may be given to a subgroup of people with presymptomatic disease • Guidance will take into account any Managed Access Arrangements	As per scope	N/A

Abbreviations: EFS, event-free survival; N/A, not applicable; NHS, National Health Service; NICE, National Institute for Health and Care Excellence; PSS, personal and social services; SMA, spinal muscular atrophy; *SMN*, survival motor neurone; TBC, to be confirmed.

2 Description of technology under assessment

2.1 *Give the brand name, approved name and when appropriate, therapeutic class.*

Brand name: ZOLGENSMA® (formerly known as AVXS-101)

UK approved name: Onasemnogene abeparvovec

Therapeutic class: Gene replacement therapy

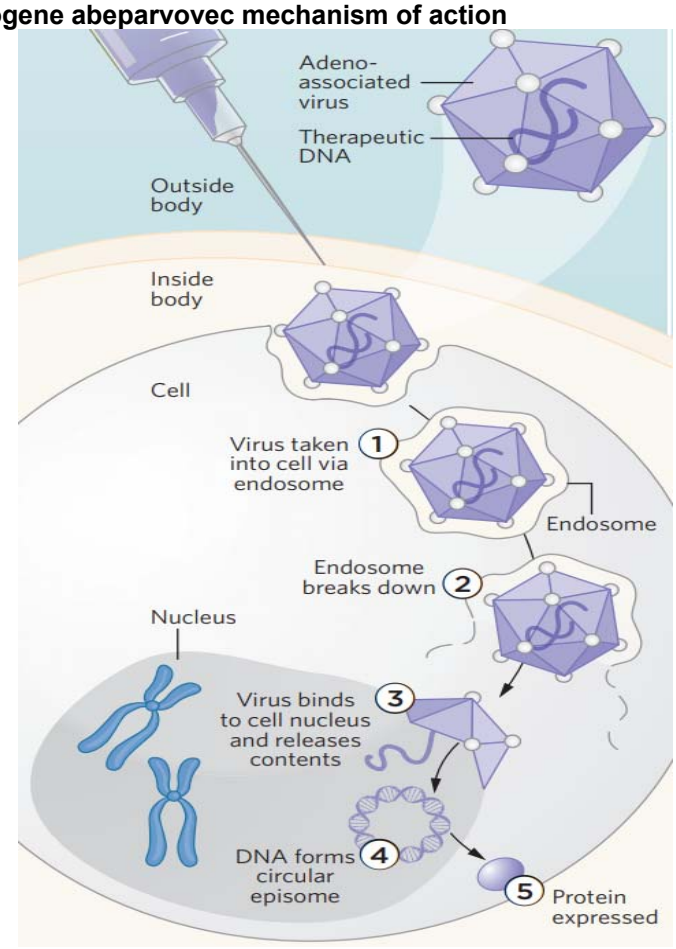
2.2 *What is the principal mechanism of action of the technology?*

Onasemnogene abeparvovec is a one-time, gene replacement therapy, that addresses the genetic root cause of SMA. To aid understanding of the mechanism of action of onasemnogene abeparvovec, a simple description is provided in Box 1.

Onasemnogene abeparvovec uses a non-replicating AAV9-derived capsid vector to deliver a stable, fully functional copy of the human *SMN* gene that rapidly expresses functional SMN protein to patient's cells, replacing the absent or non-functional *SMN1* gene (and salvage *SMN2* gene) as the primary source of SMN protein expression in infants with SMA type 1 (1-3).

Viral vectors such as AAV9 are naturally occurring viruses that have been modified such that the original viral genes have been replaced with a desired transgene; the removal of the viral genes renders the vector unable to replicate or trigger the same immune response as the wild type virus (34). AAVs are non-pathogenic in nature and no association with the development of human disease has been observed. In addition, AAV-derived vectors, in which the transgene exists as an episome (extra-chromosomal genetic material), have a low risk of integrating into the host genome. For this reason, they carry a low risk of insertional mutagenesis and oncogenesis (34, 35). The AAV9-derived vector has high tropism for motor neurones and skeletal cells and crosses the blood-brain barrier, allowing effective dosing of the central nervous system (CNS) with a peripheral IV infusion. The vector is taken into cells via an endosome, which subsequently breaks down to release the *SMN* gene and associated promoter sequence into the cell nucleus (36-39). Once inside the nucleus, the gene sequence is retained within the cell and forms a self-complimentary, transcriptionally-active, DNA molecule (episome), which bypasses the need for rate-limiting cell-mediated DNA synthesis and allows rapid and continued SMN protein expression (Figure 1). The onasemnogene abeparvovec construct also includes a hybrid cytomegalovirus enhanced chicken beta-actin hybrid promoter which activates the gene and enables continuous and sustained SMN protein expression, eliminating the need for repeat administration (Figure 2). Onasemnogene abeparvovec is administered as a one-time peripheral IV infusion (1).

Figure 1: Onasemnogene abeparvovec mechanism of action

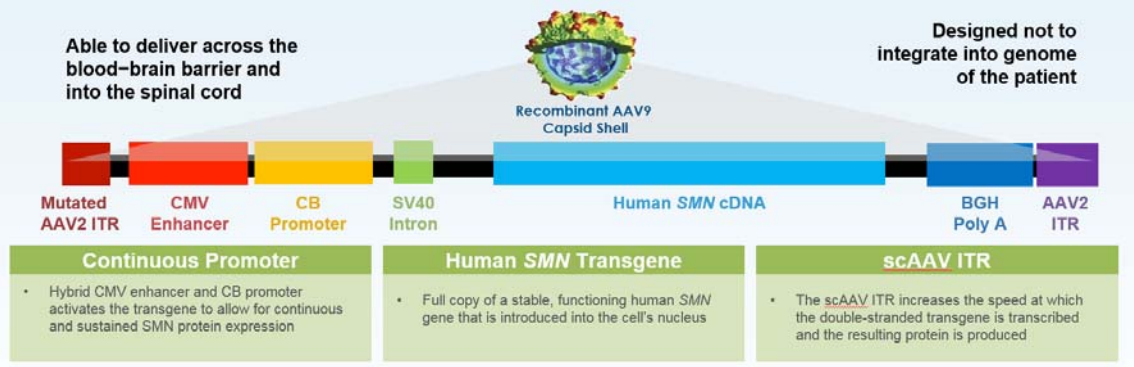


1. Viral capsid is taken into the cell via the endosome; 2. The endosome breaks down; 3. Therapeutic human DNA enters cell nucleus; 4. DNA forms a circular episome (episome folds upon itself to form a self-complimentary double stranded DNA molecule ready for transcription); 5. The resulting transcript leaves the nucleus and travels to the ribosome for translation (protein synthesis).
Source: Adapted from Akst 2012 (40)

Box 1: Mechanism of action of onasemnogene abeparvovec

Onasemnogene abeparvovec replaces the *SMN* gene which is missing (or dysfunctional) in patients with SMA type 1. The *SMN* gene present in onasemnogene abeparvovec is located in a viral vector (AAV9) which acts as a vehicle to carry the gene into patients' cells. As the vector contains no genes from the AAV9 virus, it is incapable of replicating itself. Once inside the cell, the vector releases an *SMN* gene into the cell nucleus. The onasemnogene abeparvovec *SMN* gene is designed not to integrate into the patient chromosome, but rather to reside as a DNA episome – a DNA molecule that exists independently of chromosomal DNA. This means that the AAV9 vector delivers a functional copy of a human *SMN* gene without modifying patients existing chromosomal DNA. The inserted *SMN* gene is in a 'transcription-ready' state (ready to be turned into a genetic messenger [mRNA] telling patients' cells to make SMN protein) as it contains a region of DNA (called a promoter) that initiates transcription of the *SMN* gene. This rapid and sustained production of SMN protein is critical to preventing motor neurone cell death and enabling motor function gains so that patients can achieve key developmental and motor milestones. The introduction of a stable *SMN* gene that remains in non-mitotic (non-dividing) cells indefinitely enables continuous and sustained SMN protein expression, eliminating the need for repeat administration of onasemnogene abeparvovec.

Figure 2: Onasemnogene abeparvovec construct



Abbreviations: AAV, adeno-associated virus; BGH, bovine growth hormone; CB, CMV enhancer/beta-actin; cDNA, complementary deoxyribonucleic acid; CMV, cytomegalovirus; ITR, inverted terminal repeat; sc, self-complementary; SMN, survival motor neurone; sv40, simian virus 40.

2.3 *Please complete the table below.*

Table 3: Dosing Information of technology being evaluated

Pharmaceutical formulation	Clear solution with a nominal concentration of 2.0×10^{13} vg/mL provided in 5.5 mL and 8.3 mL vials
Method of administration	Delivered as a single-dose IV infusion through a venous catheter inserted into a peripheral limb vein. It is delivered as a slow infusion of approximately 60 minutes
Doses	Patients will receive onasemnogene abeparvovec at a dose of 1.1×10^{14} vg/kg
Dosing frequency	Patients will receive a one-time treatment of onasemnogene abeparvovec, via a single IV infusion
Average length of a course of treatment	Onasemnogene abeparvovec will be administered as a one-time treatment over approximately 60 minutes
Anticipated average interval between courses of treatments	N/A
Anticipated number of repeat courses of treatments	N/A
Dose adjustments	Dosing will be adjusted by body weight; patients are to receive 1.1×10^{14} vg/kg

Abbreviations: IV, intravenous; N/A, not applicable.
Source: Onasemnogene abeparvovec draft summary of product characteristics (1).

3 Regulatory information

3.1 *Does the technology have a UK marketing authorisation for the indication detailed in the submission? If so, give the date on which authorisation was received. If not, state the currently regulatory status, with relevant dates (for example, date of application and/or expected approval dates).*

Regulatory approval for onasemnogene abeparvovec is being sought via the European Medicines Agency (EMA) centralised procedure.

The anticipated licensed indication for onasemnogene abeparvovec is for a [redacted] treatment of 5q13 SMA type 1. [redacted]

A positive Committee for Medicinal Products for Human Use (CHMP) opinion is expected ** [redacted], with full marketing authorisation expected in [redacted]

3.2 *If the technology has not been launched, please supply the anticipated date of availability in the UK.*

Onasemnogene abeparvovec is expected to be commercially available in Q1/Q2 2020, in line with the expected publication of NICE HST final guidance and subsequent reimbursement by National Health Service (NHS) England or recommendation in Scotland by the Scottish Medicines Consortium.

3.3 *Does the technology have regulatory approval outside the UK? If so, please provide details.*

Onasemnogene abeparvovec gained regulatory approval by the US Food and Drug Administration (FDA) in May 2019. Regulatory approvals in other jurisdictions (e.g. Switzerland) are ongoing, but are incomplete at this time of this submission.

3.4 *If the technology has been launched in the UK provide information on the use in England.*

Onasemnogene abeparvovec has not yet been launched in the UK. Four patients enrolled in England as part of the ongoing STR1VE-EU study and one patient from England is enrolled in the ongoing SPR1NT study.

4 Ongoing studies

4.1 *Provide details of all completed and ongoing studies on the technology from which additional evidence relevant to the decision problem is likely to be available in the next 12 months.*

One clinical trial is complete and four are ongoing in which infants with SMA type 1 receive a single IV administration of onasemnogene abeparvovec (Table 4). In addition to these trials, LT-002, which will enrol infants treated with onasemnogene abeparvovec (IV or IT) in AveXis clinical trials, is also planned to commence in September 2020. The safety and tolerability of intrathecal administration of onasemnogene abeparvovec is also being investigated in SMA type 2 patients in AVXS-101-CL-102 (STRONG, clinicaltrials.gov link); however, as onasemnogene abeparvovec was administered via intrathecal administration and the patient population was infants with SMA type 2, this clinical trial is outside the scope of the decision problem addressed in this submission and is therefore not described.

Table 4: Summary of clinical studies of onasemnogene abeparvovec included in the submission

Trial no. (acronym, clinicaltrials.gov link)	Intervention	Population	Objectives	Primary study ref.	Justification for inclusion
Completed studies					
AVXS-101-CL-101 (START, link)	Onasemnogene abeparvovec (IV)	SMA type 1 with 2 copies of *SMN2* (n=15; Cohort 1 6.7 x 10^{13} vg/kg, (n=3, low dose) Cohort 2 2.0 x 10^{14} vg/kg† (therapeutic dose, n=12)	The primary objective of the study was safety. Efficacy objectives were secondary objectives with a primary efficacy endpoint of time from birth to either (a) requirement of ≥16-hour respiratory assistance per day (BiPAP) continuously for ≥2 weeks in the absence of an acute reversible illness, excluding perioperative ventilation or (b) death.	Mendell et al. 2017 (2) Al-Zaidy et al. 2019 (24) CSR (25)	Phase I/IIa study
Ongoing studies					
AVXS-101-CL-302 (STR1VE-EU, link)	Onasemnogene abeparvovec (IV)	Patients in Europe with SMA type 1 with 1 or 2 copies of *SMN2*, aged <6 months at the time of gene replacement therapy (enrolled n=33‡) Includes 2 UK sites.	To determine efficacy by demonstrating achievement of developmental milestone of sitting without support up to 18 months of age as assessed by WHO Motor Developmental Milestones.	Protocol (41) Clinical overview (8 Mar 2019 data cut) (42) 120-Day efficacy update (27 Sept 2018) (43) 120-Day safety update (28 Jan 2019) (44)	Phase III study

Trial no. (acronym, clinicaltrials.gov link)	Intervention	Population	Objectives	Primary study ref.	Justification for inclusion
AVXS-101-CL-303 (STR1VE-US, link)	Onasemnogene abeparvovec (IV)	Patients in the US with SMA type 1 with 1 or 2 copies of *SMN2*, aged <6 months at the time of gene replacement therapy (n=22[§])	To determine the efficacy of onasemnogene abeparvovec by demonstrating achievement of developmental milestone of functional independent sitting for at least 30 seconds at the 18 months of age study visit. To determine the efficacy of onasemnogene abeparvovec based on survival at 14 months of age. Survival is defined by the avoidance of combined endpoint of either (a) death or (b) permanent ventilation (considered a surrogate for death).	Protocol (45) Clinical overview (8 Mar 2019 data cut) (42) 120-Day efficacy update (27 Sept 2018) (43) 120-Day efficacy update (31 Dec 2018) (28) 120-Day safety update (28 Jan 2019) (44)	Phase III study
AVXS-101-CL-304 (SPR1NT, link)	Onasemnogene abeparvovec (IV)	Presymptomatic patients with type 1 or 2 SMA with 2 or 3 copies of *SMN2*, ≤6 weeks of age at the time of gene replacement therapy Includes 1 UK site. (planned n = ≥27 evaluable patients [enrolled = 29[¶]]: 2 x *SMN2* = 14 3 x *SMN2* = 15)	To evaluate the safety of onasemnogene abeparvovec through incidence of adverse events and/or serious adverse events. To assess the safety of onasemnogene abeparvovec based on the change from baseline in clinical laboratory parameters. To assess the efficacy of onasemnogene abeparvovec by demonstrating functional independent sitting for at least 30 seconds at any visit up to 18 months of age.	Protocol (46) Clinical overview (8 Mar 2019 data cut) (42) 120-Day efficacy update (27 Sept 2018) (43) 120-Day safety update (28 Jan 2019) (44)	Phase III study

Trial no. (acronym, clinicaltrials.gov link)	Intervention	Population	Objectives	Primary study ref.	Justification for inclusion
LT-001 (link)	Onasemnogene abeparvovec (IV)	Patients treated with onasemnogene abeparvovec in study AVXS-101-CL-101 (n=13††)	To collect long-term safety and efficacy data of patients with SMA type 1 who were treated with onasemnogene abeparvovec in the START gene replacement therapy clinical trial	Al-Zaidy et al. 2019 (24) Protocol (47) 120-Day efficacy update (27 Sept 2018) (43) 120-Day efficacy update (31 Dec 2018) (28) 120-Day safety update (27 Sept 2018) (44)	Observational LT-FU study
LT-002	Onasemnogene abeparvovec (IV or IT)	Patients participating in clinical trials for SMA type 1, 2, or 3 who were treated with onasemnogene abeparvovec	To collect long-term follow-up safety and efficacy data of patients with SMA type 1, 2, or 3 who were treated with onasemnogene abeparvovec in a clinical trial, including but not limited to STR1VE-EU, STR1VE-US, and SPR1NT In addition, patients treated with onasemnogene abeparvovec (intravenous or intrathecal) in future parent studies may be enrolled	Protocol (48) Statistical analysis plan (49)	Observational LT-FU study

Abbreviations: BiPAP, bi-level positive airway pressure; CSR, clinical study report; Dec, December; IMP, investigational medicinal product; LT-FU, long-term follow-up; Sept, September; SMA, spinal muscular atrophy; *SMN*, survival motor neurone; US, United States; WHO, World Health Organization.
† Direct testing of the actual lot of IMP used in START by an improved and more fully qualified analytical method has determined the actual dose received by Cohort 2 to be 1.1 x 10^{14} vg/kg. The same method has been used to establish an equivalent dose for the IMP in all Phase III trials
‡ Enrolment to STR1VE-EU completed in May 2019. At the 8 March 2019 data cut (42), 23/33 infants with SMA type 1 were enrolled in STR1VE-EU.
§ 1/22 patients was initially enrolled as a pre-symptomatic SMA patient, however this patient was reclassified as symptomatic by the Investigator after 31 December 2018.
¶ As of July 2019, 29 patients were enrolled in SPR1NT. At the 8 March 2019 efficacy data cut, 17 patients were enrolled in SPR1NT (42).
†† Number of patients enrolled as of 31 December 2018 data cut-off.

4.2 *If the technology is, or is planned to be, subject to any other form of assessment in the UK, please give details of the assessment, organisation and expected timescale.*

AveXis is submitting an application for onasemnogene abeparvovec to the Scottish Medicines Consortium in [redacted].

5 Equality

NICE is committed to promoting equality of opportunity and eliminating unlawful discrimination on the grounds of age, disability, gender reassignment, race, religion or belief, sex, and sexual orientation, and to comply fully with legal obligations on equality and human rights.

Equality issues require special attention because of NICE's duties to have due regard to the need to eliminate unlawful discrimination, promote equality and foster good relations between people with a characteristic protected by the equalities legislation and others.

Any issues relating to equality that are relevant to the technology under evaluation should be described.

Further details on equality may be found on the NICE website (http://www.nice.org.uk/aboutnice/howwework/niceequalityscheme.jsp).

5.1 *Please let us know if you think that this evaluation:*

- ***could exclude from full consideration any people protected by the equality legislation who fall within the patient population for which [the treatment(s)] is/are/will be licensed;***
- ***could lead to recommendations that have a different impact on people protected by the equality legislation than on the wider population, e.g. by making it more difficult in practice for a specific group to access the technology;***
- ***could lead to recommendations that have any adverse impact on people with a particular disability or disabilities***

There are no special considerations in equality.

5.2 *How will the submission address these issues and any equality issues raised in the scope?*

Not applicable.

Section B – Nature of the condition

6 Disease morbidity

6.1 *Provide a brief overview of the disease or condition for which the technology is being considered in the scope issued by NICE. Include details of the underlying course of the disease, the disease morbidity and mortality, and the specific patients' need the technology addresses.*

6.1.1 SMA type 1

SMA is an ultra-rare, progressive, genetic neuromuscular disease caused by deficient SMN protein, which is required for motor neurone survival (7, 11). The motor neurones most affected by this condition are those that allow walking, crawling, arm movement, head and neck movement, swallowing and breathing (12, 27, 50). In infants with SMA the *SMN1* gene, the telomeric copy of the *SMN* gene responsible for production of the full-length SMN protein, is either deleted or mutated (95% of SMA infants are homozygous for the *SMN1* deletion). The centromeric copy of the *SMN* gene, *SMN2*, provides insufficient salvage expression of the SMN protein; therefore disease severity is related to the *SMN2* gene copy number, with a higher number of copies associated with less severe disease as the absolute amount of SMN protein that is produced is higher (12, 51).

SMA exists on a spectrum of five clinical types (0 through 4), which are historically classified based on the age at onset and motor milestone achievement (Table 5) (7). Advances in the 20th century have unequivocally shown that 5q SMA is one disease, with one underlying genetic aetiology. It is recognised that there is overlap between the historically defined 'types' of SMA; a severe type 2 infant, for example, may have motor function and disability almost equivalent to that of a milder type 1 infant (17, 20).

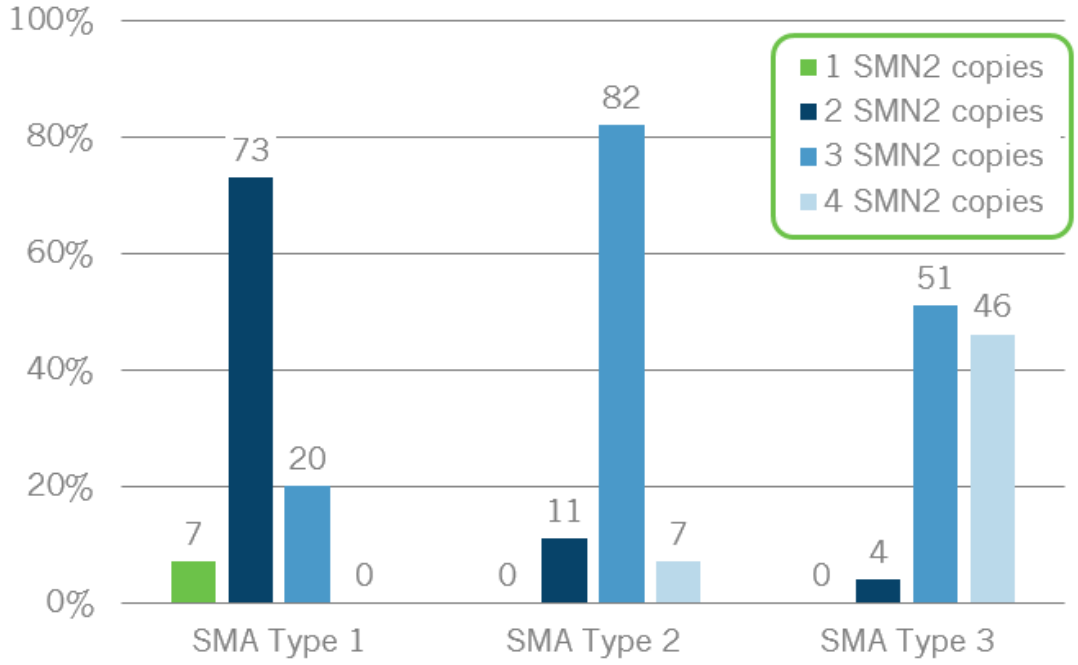
Table 5: Spinal muscular atrophy classification

Type	Age at Symptom Onset	Maximum Motor Function	Life Expectancy	*SMN2* Copy No.
0	Foetal	Nil	Days–Weeks	1
1	<6 months	Never sits	<2 years	1, **2**, 3
2	6–18 months	Never walks	20–40 years	2, **3**, 4
3	1.5–10 years	Walks, regression	Normal	3, **4**, 5
4	>35 years	Slow decline	Normal	4, 5

SMN2 = survival motor neurone 2 gene.
Bold = predominant *SMN2* copy number that defines the SMA type, the other copy numbers represent a small percentage of the designated SMA type.
Source: Adapted from Kolb et al. 2011 (7).

Infants with SMA type 1 show onset of disease at <6 months of age, never achieve the ability to sit, and have 1–3 copies of *SMN2* (7). The majority (73.4%) of infants with SMA type 1 have 2 copies of *SMN2* and >97% of infants with 2 copies of *SMN2* are predicted to develop SMA type 1 (52). The number of copies of *SMN2* varies across the population both in those with and without SMA; low copy number is associated with more severe disease (Figure 3) (52).

Figure 3: Frequency of SMN2 copy number in infants with SMA



Source: Feldkotter et al. 2002 (52).

SMA type 1 is associated with earlier onset, lower maximum motor function achievement, and reduced life expectancy compared with SMA types 2–4 (7). Survival outcomes for infants with SMA type 1 are extremely poor; SMA type 1 typically causes death before 2 years of age (12). Onasemnogene abeparvovec is expected to be indicated for the single treatment of infants with 5q13 SMA type 1 (1); other types of SMA will therefore not be discussed further in this section.

6.1.2 Diagnosis

In the absence of a newborn screening programme, diagnosis of SMA type 1 is prompted by severe muscle weakness, unless there are previous cases of the disease within a family in which case newborn infants may undergo genetic testing (16). Typical symptoms include paradoxical breathing, bulbar dysfunction (swallowing difficulties), failure to thrive, and profound muscle weakness leading to early gross motor delay and loss of transiently achieved function; infants with SMA type 1 are often described as 'floppy' babies (12, 27, 53, 54). The pathway to diagnosis of infants with SMA type 1 depends on where and when the symptoms are noticed. In extremely rare cases symptoms may be first noticed in the hospital setting; children can be in a neonatal intensive care unit or being seen by a pulmonologist/specialist for repetitive infections (18). Infants may be referred to a neuromuscular specialist directly from the neonatal unit (18). For infants at home, symptoms are typically first noticed by health visitors and infants are generally referred to general practitioners (GPs) and then community paediatricians (18). A diagnosis of SMA type 1 is typically made by a paediatric neurologist and confirmed by the application of quantitative genetic testing of *SMN1/SMN2*, with the absence of both functional *SMN1* copies providing a diagnosis of SMA (16). Further molecular genetic testing may be performed to determine *SMN2* copy number (55). There can be a delay to diagnosis (typically 3 months or more)

caused by a lack of disease recognition, differential diagnosis of various conditions, and referral waiting times between primary and specialist care centres (18, 56).

A deficiency in SMN protein results in motor neurone cell death, which leads to progressive muscle weakness and atrophy (7, 11). As a result, SMA type 1 is associated with a decline in motor function, a failure to achieve motor milestones, and the development of pulmonary difficulties which culminate in premature death (12). There is an important early postnatal period in which high levels of SMN protein are required to ensure functional neuromuscular junction development and motor neurone survival. An assessment of the loss of nerve supply in infants with SMA reported rapid motor neurone loss in the first year of life of babies with SMA type 1 (9), highlighting the importance of early intervention to prevent further motor neurone loss. Animal studies have shown that a lack of SMN protein at the early postnatal period results in abnormal development of neuromuscular junctions, resulting in reduced motor neurone function (57, 58). It is consequently vital to diagnose and treat infants with SMA type 1 as early as possible in order to ensure provision of critical levels of the SMN protein to halt disease progression and prevent motor neurone loss in infants with SMA type 1.

6.1.3 Management of SMA type 1

In England, infants with SMA will often have short lives, much of which will be spent in hospital and under 24-hour care. Although infants with SMA type 1 are alert and aware, they are unable to swallow or feed, never gain developmental milestones after initial presentation, and suffer from chronic ventilatory failure, eventually succumbing to complications related to acute respiratory illness which exacerbates the weakened state of the child (12, 27, 50, 54, 59, 60).

The care of infants with SMA type 1 is informed by guidelines from the International Standards of Care for Spinal Muscular Atrophy, described in Section 8.1, which provide recommendations on the management of nutritional, respiratory, and orthopaedic requirements (15, 16). Treatment of SMA type 1 requires a multidisciplinary team of healthcare practitioners (HCPs) including neuromuscular specialists and nurses, respiratory and orthopaedic specialists, nutritionists/dieticians, occupational therapist, community nurses, health visitors, and social workers (18). As the decision-makers, parents play a key role in the care of infants with SMA type 1 (18).

Pulmonary complications such as chest infections or breathing difficulties due to decline in muscle function occur in all infants and contribute to a decline in respiratory function after birth (59). Declining ventilatory function leads to increasing dependence on mechanical ventilation (should it be provided) and risk of respiratory failure and death due to impaired secretion clearance, and insufficient ventilation and oxygenation (11, 12, 61). Infants with SMA type 1 also need assistance to maintain airway clearance and to cough and may benefit from interventions such as oral suctioning or physiotherapy (15, 16). Bulbar-innervated muscle function deterioration prevents children with SMA type 1 from developing the ability to speak (62). In addition, the development of tongue and swallowing weakness increases swallowing and feeding difficulty over time, and leads to weight loss, pulmonary aspiration and the need for mechanical feeding (11, 12, 61).

The provision of ventilatory and nutritional support has been shown to prolong the survival of children with SMA type 1 and changes in clinical practice/parental acceptance of respiratory interventions for infants with SMA type 1 have been observed over time (14, 63). In a retrospective study of the clinical care received by 64 infants with SMA type 1 treated at the Great Ormond Street Hospital, UK between 2007 and 2017, an increase in the use of non-invasive ventilation (NIV) was observed, (14); between 2007 and 2011, 5/27 (18.5%) infants received NIV compared with 36/44 (81.8%) between 2012 and 2017 ($p<0.001$, Fisher's exact test). Cough assist, a device which aids secretion mobilisation and clearance from the lungs, was introduced in 2013; by 2017 11/18 (61%) children were using it. Natural history studies show that 75% of SMA type 1 patients require permanent ventilation by 13.6 months of age, with 100% of patients older than 12 months requiring either nutritional or combined nutritional and ventilation support (12). Despite the available BSC, acquisition of motor developmental milestones over time has not been observed in infants with SMA type 1 (50).

BSC does not halt SMA type 1 disease progression and is primarily palliative. Management of these patients with ongoing intensive supportive care can result in children surviving for years (17), however, this is with significant morbidity and diminished patient and caregiver quality of life (QoL). Some aspects of supportive care may appear to prioritise duration of life over QoL, prolonging suffering instead of easing the burden of disease. Based on this conflict in clinical care goals, consensus exists that there is no moral imperative to any interventional supportive care; a choice for or against interventional supportive care may change over time (64).

Nusinersen was recently (July 2019) granted reimbursement in England for use in all patients with 5q SMA (pre-symptomatic SMA, or SMA types 1, 2 or 3) via a MAA but was not yet considered established standard of care at the time of this submission (19, 20). Due to the recent approval of nusinersen for use in England, limited information on the care pathway including this treatment is currently available. In clinical trials, nusinersen demonstrates an improvement in some clinical outcomes versus supportive care, but only temporarily increases SMN protein expression and requires long-term, multiple dosing (22). Additionally, nusinersen therapy requires chronic intrathecal administration, which incurs ongoing associated healthcare costs, and represents a significant burden to infants with SMA type 1, caregivers and payers.

Despite the advent of nusinersen, significant unmet needs still exist in terms of survival without the need for permanent ventilatory support, speed of treatment effect, the achievement of developmental milestones, and the burden of chronic, life-time invasive therapy.

6.1.4 Onasemnogene abeparvovec for SMA type 1

Infants with SMA lack a functional *SMN1* gene, which produces the SMN protein vital to motor neurone survival (7, 11). Without disease-modifying treatment infants with SMA type 1 experience rapid, significant, and progressive muscle weakness, leading to the inability to breathe or swallow and culminating in death before 2 years of age (12). onasemnogene abeparvovec is a one-time gene replacement therapy, which uses a non-replicating AAV9 vector to deliver a functional copy of the *SMN* gene to patient's cells (Section 2.2). Treatment with onasemnogene abeparvovec delivers a stable, functional human *SMN* gene

which allows rapid and durable production of functional SMN protein and prevents the death of motor neurones, thereby improving neuromuscular function.

The clinical results observed in the START trial show that onasemnogene abeparvovec, the first gene therapy for any neuromuscular condition, is a revolutionary treatment for SMA type 1; 100% of infants were alive and free from permanent ventilation at 24 months, and 92% had achieved the ability to sit without support (2). The onasemnogene abeparvovec clinical data are presented in full in Section 9.

6.2 *Please provide the number of patients in England who will be covered by this particular therapeutic indication in the marketing authorisation each year and provide the source of data.*

SMA (all types) has an annual incidence of approximately 9.4:100,000 live births (4); SMA type 1 accounts for approximately 58% of cases of SMA (5). Due to the high mortality rate of infants with SMA type 1, with few affected children surviving free from permanent ventilation beyond 2 years of age under BSC, the reported prevalence in the literature varies, ranging from 0.04 to 0.28 per 100,000 population (5). In English clinical practice, onasemnogene abeparvovec is expected to be used only in newly diagnosed infants with SMA type 1 as described in Section 8.4. In practice, this will limit the eligible population to incident infants only.

Epidemiological data indicate that approximately 61 people are born with SMA (all types) per year in England (Table 6) (4). Using the estimate that SMA type 1 accounts for approximately 58% of cases of SMA, it is calculated that 35 infants could be eligible for treatment with onasemnogene abeparvovec in England each year, assuming a timely diagnosis (Table 6) (5, 6). These estimates can be relied upon in this appraisal as they are supported by real world evidence (RWE) from:

The nusinersen UK early access programme (EAP) which reports that in its last year of operation, 32 babies were diagnosed with SMA type 1 and treated with nusinersen in England (personal communication; [redacted], Paediatric Neurologist)

- Analysis of England Hospital Episodes Statistics (HES) data indicate that the number of incident SMA type 1 patients (defined as those aged from 0 months to 12 months at point of first coding [ICD-10, G12.0]) in England ranged from 28–32 cases per year between April 2013 – March 2017 (65)

Table 6: Estimated SMA incident cases by region

Region	Live births, n	Incident case		Year†	ONS date‡
		SMA, n	SMA type 1, n		
England	646,794	61	35	2017	18-Jul-18

Abbreviations: ONS, Office for National Statistics; SMA, spinal muscular atrophy; UK, United Kingdom.
Assumptions: Incident rate, SMA = 9.4:100,000 live births (4). Rate of SMA, type 1 = 58% (5).
† Year in which live births were recorded.
‡ Date of Office for National Statistics live birth data publication.
Source: Office for National Statistics, 2018 (6).

6.3 *Please provide information about the life expectancy of people with the disease in England and provide the source of data.*

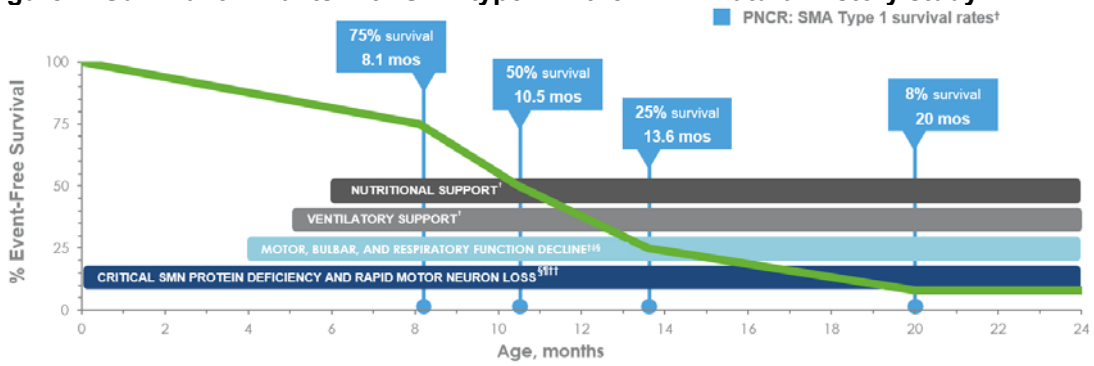
Without disease-modifying treatment, infants with SMA type 1 experience rapid, significant, and progressive muscle weakness, leading to the inability to breathe or swallow and culminating in premature death (12). Life-expectancy data for England-specific SMA type 1 cohorts have been reported in two studies:

- Great Ormond Street Hospital, London (14)
    - Clinical practice and overall survival data were collected retrospectively and analysed for children with genetically confirmed SMA type 1 between 2007 and 2017. In total, 64 infants with SMA type 1 were identified; this cohort had a median survival of 11 months. Overall survival for children with SMA type 1 remains poor with 50% of infants dying before one year of age
- The John Walton Muscular Dystrophy Research Centre, Newcastle (66)
    - An audit was conducted to identify the mortality of infants with SMA in the UK Northeast population over the last 10 years (poster presented April 2019). In total 77 infants were diagnosed with SMA (all subtypes):
        - Twenty-one of 77 infants were diagnosed with SMA type 1
        - Sixteen of 21 infants with SMA type 1 died. Confirmed respiratory failure was the most common cause of death in infants with SMA type 1. Seven of these infants received nusinersen. The five infants still alive were all treated with nusinersen
        - Prior to the introduction of an antisense oligonucleotide intervention (nusinersen) for the treatment of SMA type 1, infants with SMA type 1 died at the mean age of 6 months

The data derived from UK-specific SMA type 1 cohorts are similar to US-centric natural history and life-expectancy estimates reported in studies which provided detailed information of patient characteristics, disease modifiers, and clinical outcomes. In one prospective natural history cohort study (conducted by the Pediatric Neuromuscular Clinical Research Network [PNCR]) the survival of infants with SMA type 1 enrolled between 2005 and 2009 was investigated (12). The study included infants with SMA type 1 drawn from a natural

history study of 337 infants in the US with any form of SMA followed at three internationally recognised tertiary medical centres with significant expertise in the management of SMA. Patients had an age of onset of ≤6 months, bi-allelic deletion of *SMN1* (exon 7/8 common homozygous deletion), and two copies of *SMN2.* A composite endpoint of death or the need for ≥16 hours/day of NIV support for ≥2 weeks was assessed, which accurately captures the milestone of sustained respiratory failure, a surrogate for death. Survival outcomes were very poor for infants with SMA type 1 with 2 copies of *SMN* (n=23) *2;* >90% of infants with SMA type 1 receiving BSC died or required permanent ventilation by 2 years of age. At 8.1 months of age 75% of infants survived free of permanent ventilation, this decreased to 50% at 10.5 months of age and 8% at 20 months of age (Figure 4) (12, 67). Causes of death were acute pulmonary infection, airway obstruction and bradycardic arrest (12).

Figure 4: Survival of infants with SMA type 1 in the PNCR natural history study



Abbreviations: PNCR, Pediatric Neuromuscular Clinical Research database; SMA, spinal muscular atrophy.
Note: Survival was defined as no death, or no need for ≥16-hr/day ventilation continuously for ≥2 weeks, in the absence of an acute reversible illness; n=23 (2 copies of SMN2).
† Source: Finkel et al. 2014a (12).
‡ Source: Kolb et al. 2015 (11).
§ Source: Finkel et al. 2013 (68).
¶ Source: Govoni et al. 2018 (69).
†† Source: Swoboda et al. 2005 (9).

Another US prospective, multicentre, natural history study was performed by the National Network for Excellence in Neuroscience Clinical Trials (NeuroNext) Network (27). The NeuroNext natural history study enrolled 26 SMA infants <6 months of age (and 27 healthy control infants) at 14 centres over 21 months within the National Institute of Neurological Disorders and Stroke (NINDS) -sponsored NeuroNext Network (26, 27); sixteen infants had 2 copies of *SMN2* and the *SMN2* copy number of 4 infants was unknown. Survival within the NeuroNext study was defined as alive without tracheostomy, a somewhat less stringent definition than that used in the PNCR and onasemnogene abeparvovec clinical studies (event defined by death, tracheostomy or requirement of ≥16 hours of ventilatory support for ≥2 weeks, excepting acute reversible illness or perioperative use). Among 20 infants with SMA type 1, including 16 infants with a known *SMN2* copy number of 2, the median age of survival without tracheostomy was 8 months (27, 67).

Despite differences in methodology, geographical location, and study populations, the PNCR and the NeuroNext studies show consistency in mortality, ventilatory requirement, motor function, and milestone achievement with the European experience described in recent

papers by Wadman et al. 2017 (54), De Sanctis et al. 2018 (60), De Sanctis et al. 2016 (50), and Finkel et al. 2017 (22):

- Wadman et al. 2017 (54) reported that in 42 infants with SMA type 1 in the Netherlands, inexorable decline in motor function is universally seen in SMA type 1
- De Sanctis et al. 2018 (60) conducted a retrospective study assessing the phenotypic and functional trajectories of disease progression in 20 infants with SMA type 1 in Italy. Patients were pooled based upon baseline severity of disease; the *SMN2* copy number of individual patients was not identified. The median survival of 16 patients with severe or typical onset was ~13 months, and median survival free of permanent ventilation was ~11.5 months, with 75% of these patients reaching this combined endpoint of death or permanent ventilation by ~14 months. Only 1 of these 16 patients survived alive and free of permanent ventilation beyond 20 months of age. Overall, no child experienced an improvement in motor function from baseline in any follow-up assessment, nor were any advanced milestones (rolling, sitting, etc.) achieved
- De Sanctis et al. 2016 (50) published a comprehensive report detailing the experience of infants with SMA type 1 from multiple centres in the US (the PNCR network for SMA) and Italy treated with BSC care. The study reported that even when current standards of care are applied, developmental milestones are rarely even partially achieved as part of natural history in infants with SMA type I; no infant achieved a major milestone such as rolling over or sitting independently. Of 24 infants with SMA type 1 included in the study, 12 infants died during study follow-up
- Finkel et al. 2017 (22) reported results from a randomised controlled trial (RCT) which assessed the efficacy of intrathecal nusinersen (n=81) and a sham control procedure (n=41) in infants aged <7 months at screening with 2 copies of *SMN2* in Australia, Belgium, Canada, France, Germany, Italy, Japan, Republic of Korea, Spain, Sweden, Turkey, United Kingdom, and the US. Ventilation-free survival was defined as time to death or use of permanent assisted ventilation (tracheostomy or ventilatory support for ≥16 hours per day for ≥21 continuous days in the absence of an acute reversible event). In the control group, 68% of patients had died or required assisted permanent ventilation by 13 months post sham procedure; 48% of patients had received permanent ventilation at 13 months. The median time to death or the use of permanent ventilation was 22.6 weeks

The PNCR and the NeuroNext studies are also in line with studies from the UK (14, 66), Poland and Germany (70), France (71), the US (72), Hong Kong (73), and Australia (8), all of which describe a universally rapid loss of function and progression to death or complete ventilatory dependence by 2 years of age.

7 Impact of the disease on quality of life

7.1 *Describe the impact of the condition on the quality of life of patients, their families and carers. This should include any information on the impact of the condition on physical health, emotional wellbeing and everyday life (including ability to work, schooling, relationships and social functioning).*

7.1.1 Patient quality of life

Infants with SMA type 1 are alert and aware, however, it is not possible to obtain self-reported QoL information from babies with SMA type 1 due to their young age. The profound muscle weakness caused by the disease impacts every aspect of an infant's short life, and consequently has a substantial effect on their health-related quality of life (HRQoL) compared with healthy infants (74, 75). Infants with SMA type 1 will never sit, walk, talk, or achieve any developmental milestones and their short lives are defined by hospital stays and ever-increasing levels of medical interventions. Infants with SMA type 1 will require breathing assistance; a UK HCRU study conducted by AveXis (Section 12.3.1) reported that the majority (>80%) of infants with SMA type 1 seen by health care practitioners in a 12-month period required daily non-invasive ventilation (bi-level positive airway pressure [BiPAP], NIPPY, Breas) and/or required cough assist on a daily basis (18). Patients' respiratory function can decline further requiring invasive ventilation via tracheostomy (12, 59, 60).

Nutritional support, either via a nasogastric or nasojejunal tube, will also be required (15, 16). While this medical support helps keep infants alive, the procedures are often traumatic and invasive, particularly for infants who cannot understand what is happening to them. Assessment of HRQoL is complicated in SMA type 1 by the fact that infants cannot describe the impact of the disease; it must therefore be reported by a parent, caregiver, or medical professional. The difficulties of exploring subjective HRQoL in infants with SMA type 1 means that obtaining utilities which are truly reflective of the patient experience and aspects of the condition that most affect patients' HRQoL is problematic. In addition, quantitative reports of HRQoL and health state utility values in this population are varied and sparse; available data are described in Section 10.

7.1.2 Caregiver burden

SMA has substantial effects on families and carers, including the impact of caring for the patient, the need for specialist equipment and ongoing emotional, financial and social impacts. Caregivers of infants with SMA type 1 undergo a substantial emotional burden. After the initial worry and stress of their child's symptoms, their burden is further compounded by being told that their child has a disease with no cure which means they will die in early infancy; they are then told that their child will require extensive medical care during their short life (13, 31). Diagnosis of SMA type 1 removes any expectations or hope caregivers had for a 'normal' life for their child, and they must make difficult decisions around extending their child's life via interventions which may worsen their QoL (13, 31). Caregivers can consequently feel helpless, guilty, and lost, and may experience anxiety, stress, loss of

sleep, and discomfort around telling friends and family about the diagnosis (13, 18, 31). Following diagnosis, caregivers face a constant physical and emotional burden; they must do everything for their baby while it is not in hospital, are constantly vigilant to problems with breathing which could lead to asphyxiation, are limited in their ability to interact with direct and wider family networks, and face financial pressure due to time off paid employment to attend frequent hospital visits and providing care at home (13, 20, 31). The burden of caregiving can extend to multiple family members and also affect those without caring responsibilities, with grandparents, siblings and family friends often severely affected (13, 20, 31, 76).

Common themes reported in the literature for caregiver burden include confronting premature death; making difficult treatment choices (i.e. whether to pursue an invasive treatment regimen for a child with respiratory function deterioration); feeling sad, fearful, and helpless with the loss of functional abilities; coming to terms with lost expectations; loss of sleep (i.e. awakening multiple times to help the child rollover to prevent bedsores); stress of caring for a child with substantial physical disability requiring high levels of physical care and constant supervision; dealing with uncertainty in the trajectory of decline in functional status or life expectancy; isolation due to limitations in the ability to socialise and engage in activities outside of the home; and pressure on family finances from lost income or changes in career goals or employment related to time spent caring for the extra needs of the child and attending treatment (13, 76, 77).

More than half of the caregivers consequently report feeling that their lives were “hard,” and that they often felt “tied down” (78), and families and caregivers of infants have lower QoL and higher levels of stress compared with families and caregivers of infants without SMA (13, 74). Caregivers also report feeling anticipatory grief, feeling helpless and at fault, and enduring multiple losses (i.e. loss of the typical joys of having a newborn, loss of the future imagined with the affected child, and loss of sibling relationships) (20, 79). The emotional burden of caregivers continues with bereavement as patients succumb to the disease (79).

7.2 *Describe the impact that the technology will have on patients, their families and carers. This should include both short-term and long-term effects and any wider societal benefits (including productivity and contribution to society). Please also include any available information on a potential disproportionate impact on the quality or quantity of life of particular group(s) of patients, and their families or carers.*

Without disease-modifying treatment, infants with SMA type 1 experience rapid, significant, and progressive muscle weakness, leading to the inability to breathe or swallow; only 8% of these infants are alive without the need for permanent ventilatory support at 20 months of age and none achieve any developmental motor milestones such as sitting, standing, swallowing and talking (12). Onasemnogene abeparvovec is the only therapy that provides a functional copy of the *SMN* gene, the primary source of SMN protein production necessary for motor neurone survival, and halts the progression of SMA through durable, continuous, and sustained SMN protein expression (1). In START, SMA type 1 infants treated with

onasemnogene abeparvovec demonstrate unprecedented survival (100% survival as of the latest long-term follow-up data cut [31 December 2018]), improvements in motor function and ability to achieve developmental milestones (e.g. such as sitting, walking, or talking), enabling functional independence and the ability to thrive (2, 24, 25, 28).

Onasemnogene abeparvovec can therefore provide unprecedented and highly meaningful benefits for both infants with SMA type 1 and their caregivers over the short- and long-term. For infants with SMA type 1, the most immediate short-term benefit is surviving beyond the natural life expectancy of their condition (2, 24, 25). In addition, they survive free from permanent ventilation and achieve motor milestones such as sitting, walking, swallowing, and talking which are impossible under BSC (2, 24, 25). Collation of long-term data on the benefits of onasemnogene abeparvovec is ongoing, however, early data from the long-term follow-up study LT-001 show no waning of effect; all patients were alive and free from permanent ventilation as of the latest data cut (31 December 2018) and no patients have lost motor milestones (28, 29). If infants with SMA type 1 can be promptly diagnosed and treated with onasemnogene abeparvovec, patients may do things that no previous infant with SMA type 1 has ever done; they could play with other children, go to school, and may eventually lead a life independent of their caregiver.

For caregivers, onasemnogene abeparvovec offers the immediate short-term benefit of a treatment option for a disease which would otherwise cause premature death of their child in early infancy. The availability of onasemnogene abeparvovec may therefore mean that caregivers of infants with SMA type 1 never again have to be told that their child has no future. Further short-term benefits include relief from the burden that comes with caring for a progressively weakening child, as demonstrated by the achievement of motor milestones and the ability to thrive by patients in the START trial who received the therapeutic dose of onasemnogene abeparvovec (2, 24, 25). Such benefits will reduce both the physical and mental burden of caregivers, and they may never have to make the choice between putting their child on permanent ventilation or allowing them to die. The reduction in short-term burden will also allow caregivers to maintain paid employment which they may otherwise have had to reduce or give up entirely. In the long-term, it is possible that the burden of caring for a child with SMA type 1 would be entirely removed from caregivers. Currently, caregivers must watch their child die in early infancy; with onasemnogene abeparvovec, patients achieve motor milestones and survival outcomes not possible without pharmacological treatment.

8 Extent and nature of current treatment options

8.1 *Give details of any relevant NICE, NHS England or other national guidance or expert guidelines for the condition for which the technology is being used. Specify whether the guidance identifies any subgroups and make any recommendations for their treatment.*

SMA type 1 in England is managed with multidisciplinary BSC in a network of centres with expertise in neuromuscular disorders. BSC does not affect disease progression but aims to minimise the impact of disability, address complications, and improve the QoL of patients. Guidelines from the International Conference on the Standard of Care for Spinal Muscular Atrophy provide recommendations on the management of infants with SMA categorised according to motor function status, with non-sitters analogous to SMA type 1 (15, 16). Guidelines for the care of non-sitters are presented in Table 7.

BSC for SMA type 1 comprises a wide spectrum of options, including respiratory, gastroenterology, and orthopaedic care, as well as nutritional support, physiotherapy, assistive technologies, occupational therapy and social care. Medical care is focused on respiratory and nutritional support, as summarised in Table 7. Pulmonary care includes ventilation support and methods for aiding airway clearance such as manual chest physiotherapy combined with mechanical insufflation–exsufflation and non-invasive ventilator support (15). Tracheostomy is an option in selected patients in whom non-invasive ventilator support is insufficient or fails (15). Nutritional support may require placement of a gastrostomy tube and the administration of supplements, if required, as well as monitoring of growth charts (15). Despite best supportive efforts, disease progression and the decline of motor and respiratory function, and consequent premature death, are unavoidable. Due to the invasive nature of ventilation and gastrostomy tube treatment the burden is likely to outweigh the benefit of extending overall survival by only a few months and the decision to commence treatment should be focused on individual clinical status, prognosis, and quality of life based on discussion with the patients' family (15).

Nusinersen was recently (July 2019) granted reimbursement in England for use in patients with 5q SMA (pre-symptomatic SMA, or SMA types 1, 2 or 3) via a MAA but was not yet considered established standard of care at the time of this submission (19, 20). Recommendations on how nusinersen should be used, are summarised in Table 8. Prior to this, nusinersen was made temporarily available for the treatment of SMA type 1 via an EAP in England (closed October 2018) (80). Special consideration must be given to the invasive intrathecal administration procedure for nusinersen, which requires lumbar puncture and potentially sedation of the patient as indicated by their clinical condition.

Table 7: Clinical management recommendations for patients with SMA (classified as sitters and analogous to patients with SMA type 1) from the consensus statement by the International Conference on the Standard of Care for SMA

Type of care	
Pulmonary care	• Airway clearance o Assisted cough o Oral suctioning o Physiotherapy/respiratory therapy o Manual chest therapy o Cough insufflator/exsufflator • Bilevel NIV • Immunisations • Tracheostomy
Gastrointestinal and nutritional care	• Referral to specialist dietitian for feeding therapy/modification • Placement of a nasogastric or nasojejunal tube or gastrostomy • Avoidance of fasting during acute care • Adequate hydration and electrolyte balance • Use of bowel regulation medications
Managing musculoskeletal system problems and related functional impairments	• Use of thoracic bracing • Use of cervical bracing for head support • Use of postural and positioning supports • Mobile arm supports to assist upper extremity function • Use of orthoses for limb positioning & stretching • Use of seating and mobility systems

Abbreviations: NIV, non-invasive ventilation; SMA, spinal muscular atrophy. Sources: Finkel et al. 2018 and Mercuri et al. 2018 (15, 16).

Table 8: NICE draft guidance on the criteria for administration of nusinersen to infants with 5q SMA (pre-symptomatic SMA, or SMA types 1, 2 or 3) in England

Key criteria	
Starting criteria	• No permanent ventilation (≥16 hours/day for 21 consecutive days in the absence of acute reversible infection)/ tracheostomy requirement at baseline • Intrathecal injection must be technically feasible in the opinion of the treating clinician and not contraindicated • Must not have received spinal fusion surgery following a diagnosis of scoliosis which prohibits safe administration of nusinersen • Must not have severe contractures which in the opinion of the clinician prohibits measurement of motor milestones • If gained independent ambulation prior to initiation of therapy must still be independently ambulant. Independent ambulation is defined as per the WHO definition: patient takes at least 5 steps independently in upright position with the back straight. One leg moves forward while the other supports most of the body weight. There is no contact with a person or object
Stopping criteria	• Total worsening in scale score corroborated by two consecutive measurements†. A scaled equivalent of these losses would apply if a domain was unmeasurable / not suitable‡ o >2 points on horizontal kick or 1 point on other HINE scores excluding voluntary grasp o >4 points on the CHOP-INTEND scale o >3 points on the RHS scale • Permanent ventilation (≥16 hours/day for 21 consecutive days in the absence of acute reversible infection) or requirement of insertion of permanent tracheostomy • Inability to regain ambulation within 12 months of nusinersen initiation • Inability to administer nusinersen by intrathecal administration because of spinal fusion surgery • All patients stop due to mortality
Exclusion criteria	• SMA type 0 or 4

Abbreviations: CHOP-INTEND, Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders; NICE, National Institute of Health and Care Excellence; NIV, non-invasive ventilation; NHSE, National Health Service England; SMA, spinal muscular atrophy; RHS, Revised Hammersmith Scale; SMA, spinal muscular atrophy; SMN, survival motor neurone; World Health Organization.
† In order to allow for confirmation of worsening and not a 'off' assessment day.
‡ If contracture develop or fracture occurs, then the unmeasurable domain of the scale is removed, and the delta change of remaining domains are scaled up to ensure the total achievable score of the scale remains.
Source: NICE Nusinersen Managed Access Agreement July 2019 (19).

8.2 *Describe the clinical pathway of care that includes the proposed use of the technology.*

Until the recent approval of nusinersen by NICE (July 2019) there were no NICE recommended treatments or clinical pathways for disease-modifying treatments for SMA type 1 in England and patients received BSC.

In the UK, a diagnosis of SMA type 1 is usually made in a specialist hospital setting by paediatric neurologists with experience of the condition (18). Diagnosis is confirmed by the application of quantitative genetic testing of *SMN1/SMN2*, with the absence of both

functional *SMN1* copies providing a diagnosis of SMA (16). Infants may be referred to a paediatric neurologist via a neonatal intensive care unit or via health visitors, GPs, and, hospital and community paediatricians (18).

Following diagnosis of SMA type 1, patient care is guided by a MDT including neuromuscular specialists and nurses, paediatricians, physiotherapists, orthopaedic specialists, surgeons, nutritionists, respiratory specialists, community nurses and health visitors (18). Care is coordinated according to where the infant lives; if a child lives close enough to a hospital with a neuromuscular team, care may be led by a hospital-based neuromuscular consultant. For children who do not live near a hospital with a neuromuscular centre, care may be led by a local paediatrician with support from a neuromuscular team at the nearest hospital with such facilities. Infants with SMA type 1 are immediately provided with respiratory support, nutritional treatment, and orthopaedic rehabilitation following diagnosis, as described in Section 8.1.

Due to the recent status of the NICE recommendation to reimburse nusinersen via a MAA (19), information regarding the 'real world' treatment pathway of infants with SMA type 1 treated with nusinersen is lacking.

8.3 *Describe any issues relating to current clinical practice, including any uncertainty about best practice.*

Current best practice for the treatment of infants with SMA type 1 is BSC, which involves multidisciplinary supportive care to address the symptoms of and complications associated with the condition (15, 16). Best supportive care does not halt or delay disease progression or the premature death of infants and therefore there is a significant unmet need for disease modifying interventions.

Nusinersen was recently (May 2019) recommended by NICE for use in all patients with 5q SMA (pre-symptomatic SMA, or SMA types 1, 2 or 3) subject to a MAA but was not yet considered established standard of care at the time of this submission (19, 20). As a result, nusinersen is expected to become part of established clinical practice and offered in addition to BSC to infants with SMA type 1 in England and Wales over the next 6–12 months. Administration of nusinersen requires repeated hospitalisation for intrathecal administration (21). In addition, as infants with SMA type 1 can develop scoliosis and may require spinal fusion surgery, the possibility that long-term administration of nusinersen may not be feasible in all patients should be considered.

8.4 *Describe the new pathway of care incorporating the new technology that would exist following national commissioning by NHS England.*

Onasemnogene abeparvovec has the potential to mark a step change in the treatment of patients with SMA type 1. It is anticipated that onasemnogene abeparvovec will be administered as soon as clinically possible after a diagnosis of SMA type 1 is made. As early intervention is key due to the rapid loss of motor neurones in infants with SMA type 1, onasemnogene abeparvovec is positioned for use in newly diagnosed infants with SMA type 1, or with a genotype predictive of SMA type 1, only.

AveXis is committed to working with neuromuscular centres, including potential infusion centres and regional specialist centres, to scope and design a service delivery that includes onasemnogene abeparvovec. Preliminary advice sought via a recent UK clinical advisory board (17) (see Section 12.2.5) is that care will be regionally led, but with a protocol in place to facilitate the one-time infusion of onasemnogene abeparvovec at highly specialised infusion centres in England. NHS England has indicated to AveXis that it will determine how many, and which, centres will be commissioned to provide the one-time infusion of onasemnogene abeparvovec. Broadly, the clinical care pathway including onasemnogene abeparvovec is expected to include three stages:

1) **Management pre-administration:**
   The management of infants with SMA type 1 prior to infusion of onasemnogene abeparvovec will be conducted at the nearest neuromuscular centre to the patients' home address, as per BSC. An assessment of baseline characteristics will be conducted, including a test for the AAV9 antibody; in clinical trials, confirmation of anti-AAV9 antibody titres ≤1:50 was required prior to onasemnogene abeparvovec infusion (1). AAV9 antibody testing will be initiated at the patients' local neuromuscular centre to inform the discussion of treatment options between clinicians and families. AAV9 antibody testing could potentially be performed at the same time as *SMN1/SMN2* genetic testing. AAV9 testing will be funded and coordinated by AveXis at a central European lab (Viroclinics, The Netherlands) and results produced within 4 days. The exact requirements of AAV9 antibody testing are subject to the final summary of product characteristics (SmPC), which is under development at the time of this submission.

2) **Management in the infusion centre:**
   Whilst there are a number of expert centres in the diagnosis and management of paediatric neuromuscular disorders in England it is expected that there will be a small number of highly-specialised hospital infusion centres in England commissioned by NHS England to handle and deliver onasemnogene abeparvovec according to necessary biosafety standards. Onasemnogene abeparvovec will be prepared and shipped for each individual patient to ensure correct weight-based dosing; therefore, there will need to be close communication between the infusion centre and the manufacturer. The patient will be admitted to an infusion centre for pre-treatment with prednisolone and assessment of baseline characteristics 24 hours prior to administration of onasemnogene abeparvovec. Onasemnogene abeparvovec is administered as a single IV infusion via a peripheral limb over approximately 60 minutes. There are no technical or safety reasons requiring patients to remain in the infusion centre for an extended period (beyond 24 hours) following administration of onasemnogene abeparvovec. Patients will normally be discharged to the care of the referring neuromuscular centre 24 hours post onasemnogene abeparvovec. Total admission time at the infusion centre is expected to be not more than a two-night, three-day elective stay.

3) **Management post-administration**:
   Once the patient is returned home, or to the referring hospital, initial continued care, including ongoing laboratory safety monitoring, will be provided by a multi-disciplinary specialist team with expertise in managing SMA type 1 at patients' local neuromuscular centre on an in-patient or out-patient basis, according to the patient's condition, as per BSC and the product SmPC (1).

Onasemnogene abeparvovec offers a step-change in the treatment pathway of patients with SMA type 1, enabling the achievement of motor milestones (e.g. sitting unassisted and walking unassisted) and prolonging ventilation-free survival past 2 years; outcomes which have never previously been seen in patients treated with BSC (2, 12, 24, 25, 50). As a result of an improved prognosis, the care requirements of patients would be expected to change significantly over time. Patients are expected to continue to be managed by a multidisciplinary team adopting a symptom-led approach to care as required.

As previously mentioned, onasemnogene abeparvovec is positioned for use in newly diagnosed infants with SMA type 1, i.e. the incident population. This population aligns with the cohorts enrolled in our clinical trial programme all of whom were naïve to previous treatment with nusinersen or other pharmacotherapies intended to treat SMA. In a hypothetical scenario, where the EMA licensed indication defines the eligible population more broadly than that enrolled in the trial programme for example, inclusive of patients up to a higher weight or age range, this could include the use of onasemnogene abeparvovec in older SMA type 1 patients, including those who have already received nusinersen. However, no efficacy data are currently available that can be used as a basis for modelling clinical or cost effectiveness in a broader SMA type 1 population. Use of onasemnogene abeparvovec in a broader SMA type 1 population is limited to a real world, pre-launch compassionate use programme in the US where there was no formal requirement to collect outcomes data. Patients participating in this programme were asked if they would enrol in the RESTORE registry of which a small proportion ([redacted]) agreed. To date, enrolment in RESTORE is very limited.

8.5 *Discuss whether and how you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits, and whether and how the technology is a 'step-change' in the management of the condition.*

Onasemnogene abeparvovec is an Advanced Therapeutic Medicinal Product and represents a highly innovative and potentially transformative treatment which may entirely revolutionise the management of infants with SMA type 1.

Firstly, onasemnogene abeparvovec offers innovation in the form of a novel mechanism of action by delivering a fully functioning *SMN* gene, which is absent or mutated in infants with SMA type 1, in a one-time IV administration. Gene replacement therapy is a pioneering approach for monogenic diseases, such as SMA, because it is feasible to deliver a functional gene to address the single-gene deficiency that is the root cause of the disease. The ability of onasemnogene abeparvovec to drive rapid and sustained SMN protein expression is also important for optimal treatment of this rapidly progressing disease.

Secondly, a one-time peripheral IV infusion of onasemnogene abeparvovec offers innovation in terms of clinical outcomes which have never been observed in infants with SMA type 1 under BSC:

- Infants with SMA type 1 have devastatingly poor overall survival with respiratory failure being the main cause of mortality (12). All infants treated with onasemnogene

abeparvovec in the START trial are alive as of the latest long-term follow-up data cut (31 December 2018), a significant departure from natural history (12, 27); the average age of patients treated with the therapeutic dose of onasemnogene abeparvovec was 3.76 years and the oldest patient was 4.6 years (24, 25, 28)

- Infants with SMA type 1 receiving BSC will never achieve any developmental milestones, such as sitting, walking, or talking. Of 12 infants with SMA type 1 treated with the therapeutic dose of onasemnogene abeparvovec in START, 91.7% were able to hold their head erect without support, 75.0% were able to sit alone for ≥30 seconds, 16.7% were able to walk unassisted, and 91.7% were able to speak at 24-months post dosing (12, 24, 25). Ongoing long-term follow-up also shows no waning of effect; as of the latest long-term follow-up data cut (31 December 2018) no patients have lost motor milestones compared with the 24-month post onasemnogene abeparvovec administration time point in START (43)

- The motor function of infants with SMA has been reported to decline rapidly as demonstrated by CHOP-INTEND scores; in the NeuroNext study a decline of >10 points was observed between 6 and 12 months of age in infants with SMA type 1 (23). Onasemnogene abeparvovec provides rapid improvement in motor function as demonstrated by CHOP-INTEND scores: at months 1 and 3 post gene therapy, patients treated with the therapeutic dose of onasemnogene abeparvovec in START had mean increases from baseline of 9.8 and 15.4 points, respectively (n=12, both $p<0.001$). At 24 months post onasemnogene abeparvovec administration the mean change from baseline in CHOP-INTEND score was 30.7 points (n=6)

Patients who would otherwise die in early infancy without ever being able to sit, walk, or talk could therefore have dramatically extended life expectancies following a one-time IV administration of onasemnogene abeparvovec, and may be able to achieve physical independence from their caregivers. Treatment with onasemnogene abeparvovec could have a transformative effect not only for infants with SMA type 1, but also for their caregivers and families, who would otherwise lose their child in early infancy.

Thirdly, onasemnogene abeparvovec offers innovation as a one-time gene therapy, as indicated by the EMA's priority medicine scheme, and has received promising innovative medicine status from the Medicines and Healthcare products Regulatory Agency. There are no other treatments for SMA type 1 which can offer the dramatic improvements seen with onasemnogene abeparvovec following a one-time IV infusion. The transformative clinical outcomes associated with this treatment have a profound impact on the lives of patients and their caregivers.

8.6 *Describe any changes to the way current services are organised or delivered as a result of introducing the technology.*

It is anticipated that the managed network of specialised paediatric neuromuscular services which is already commissioned for the provision and delivery of BSC to infants with SMA type 1 will be able to manage patients over the long term following a single IV infusion with onasemnogene abeparvovec. The expected number of new cases of SMA type 1 per

year is small (35 per year) and the clinical progression for these infants will be far less severe than for those who did not receive gene replacement therapy. However, as the treatment is to be tailored to individual infants and infused in very few highly specialised centres, national highly specialised commissioning and oversight will be essential, for instance coordinated by the Paediatric Neurosciences Clinical Reference Group.

8.7 *Describe any additional tests or investigations needed for selecting or monitoring patients, or particular administration requirements, associated with using this technology that are over and above usual clinical practice.*

The prevalence of antibodies against AAV differs by serotype and increases with age (81-83). Anti-AAV antibody production due to exposure to wild-type AAV generally starts around 2 years of age, becoming increasingly prevalent starting in mid to late adulthood (81). Maternal AAV antibodies have been found in newborn infants, however, the reported prevalence of antibodies against AAV is relatively low, particularly in infants (81, 82). Although no formal studies have been conducted, antibodies against AAV9 are thought to be rare in infants (84).

It has not been established whether onasemnogene abeparvovec administration may represent a risk for an immune response for patients with higher titres of pre-existing anti-AAV9 antibodies. Patients will require a test for the AAV9 antibody prior to treatment; the exact requirements of AAV9 antibody testing are subject to the SmPC, which is being finalised at the time of this submission. An immune response to the AAV9 capsid will occur after infusion of onasemnogene abeparvovec.

To manage a possible increase in liver transaminases, reflective of liver inflammation, all patients should receive oral prednisolone 24 hours prior to one-time onasemnogene abeparvovec IV administration at an initial dose of 1 mg/kg/day (1). It is recommended that prednisolone 1 mg/kg/day (or equivalent) be administered for 30 days following treatment with onasemnogene abeparvovec (1). Following 30 days of prednisolone treatment, the 1 mg/kg/day dose should be tapered over 4 weeks for patients whose ALT and AST values are both below 2 × upper limit of normal (ULN) (1). If both the AST and ALT values remain >2 × ULN after 30 days of prednisolone treatment, prednisolone treatment should be continued at the 1 mg/kg/day dose until the values return to normal range (e.g. 2 weeks at 0.5 mg/kg/day and then 2 weeks at 0.25 mg/kg/day) (1). Following administration of onasemnogene abeparvovec, patients will require monitoring of liver function, platelet, and cardiac troponin I at regular intervals (1). Patients should be monitored for elevated transaminases and troponin levels for 3 months following onasemnogene abeparvovec administration and until levels return to within the normal reference range. Platelet counts should be monitored during the first two weeks post onasemnogene abeparvovec administration or until platelet counts return to within the normal reference range. The exact prednisolone dosing regimen is subject to the SmPC, which is being finalised at the time of this submission

8.8 *Describe any additional facilities, technologies or infrastructure that need to be used alongside the technology under evaluation for the claimed benefits to be realised.*

The diagnosis of SMA type 1 and long-term follow-up of infants' post onasemnogene abeparvovec administration will continue to be the responsibility of the patient's nearest neuromuscular centre, as per the case for BSC pathway of SMA type 1 patients. Health practitioners potentially making a diagnosis of SMA type 1 must be both aware of, and able to, offer a rapid path to onasemnogene abeparvovec treatment. The initiation of testing for AAV9 antibodies as part of the screening of patient eligibility for administration of onasemnogene abeparvovec will be a new responsibility for neuromuscular centres if onasemnogene becomes available in England. However, the AAV9 testing of infants will be funded and coordinated by AveXis at a central European lab (Viroclinics, The Netherlands) and results produced within 4 days. Testing for AAV9 antibodies should be conducted in a timely manner to facilitate the discussion of treatment options between clinicians and families.

The administration of onasemnogene abeparvovec will require specialist infusion centres across England which will be located within current neuromuscular centres with appropriate facilities for the treatment of infants with SMA type 1. Patients and their families may require assistance with travel to specialist infusion centres, depending on the condition of the child. In addition, National highly specialised commissioning and oversight will be essential to ensure timely and effective referral paths between the community, neuromuscular centres and specialist infusion centres are in place. To enable this, a defined protocol is required to support the monitoring and transfer of patients. As mentioned, AveXis is committed to working with NHS England and neuromuscular centres to scope and design a service delivery that includes onasemnogene abeparvovec.

8.9 *Describe any tests, investigations, interventions, facilities or technologies that would no longer be needed with using this technology.*

If infants with SMA type 1 can undergo timely diagnosis and one-time treatment with onasemnogene abeparvovec, it is possible that these infants could achieve survival outcomes and motor milestones seen in normal development. Although collation of long-term data is ongoing, currently available data from the onasemnogene abeparvovec clinical trial programme demonstrate that one-time treatment with onasemnogene abeparvovec at the therapeutic dose eliminates the requirement for permanent ventilation in patients with SMA type 1 (2, 24). In addition, the requirement for assisted ventilation would be expected to be reduced based on the observation that the majority of patients (58.3%) treated with the therapeutic dose of onasemnogene abeparvovec (n=12) in START remained free of ventilatory support for 2 years post-dosing with onasemnogene abeparvovec (24). Stabilisation or improvement in swallowing function leading to patients maintaining independence from nutritional support was also observed for 50% of the patients in START who received the therapeutic dose of onasemnogene abeparvovec (24).

Overall, data from the clinical trial programme show that onasemnogene abeparvovec may reduce the need for invasive and non-invasive pulmonary support and nutritional support. In addition, the significant improvements in permanent ventilation-free survival (100% versus 8% in an external natural history control study) indicate that there would be a decline in the need for time in intensive care units and palliative care, decreasing the burden on caregiver and NHS services (2, 12, 24). Further potential reductions in resource requirements as a result of the improved condition of patients following treatment with onasemnogene abeparvovec include the use of pharmacological treatments such as antibiotics and the need for mobility equipment and devices (18). Onasemnogene abeparvovec is also associated with a less intensive treatment regimen than nusinersen as onasemnogene abeparvovec is administered as a one-time IV infusion in contrast to the chronic intrathecal administration requirements of nusinersen.

Section C – Impact of the new technology

9 Published and unpublished clinical evidence

Section C requires sponsors to present published and unpublished clinical evidence for their technology.

All statements should be evidence-based and directly relevant to the scope. Reasons for deviating from the scope should be clearly stated and explained.

This section should be read in conjunction with NICE's 'Guide to the methods of technology appraisal' section 5.2 available from www.nice.org.uk/guidance/ta.

Summary of clinical efficacy and safety

SMA type 1 infants treated with a one-time peripheral IV infusion of onasemnogene abeparvovec demonstrated unprecedented survival (100% survival free from permanent ventilation in START in Cohort 2), and improvement in motor function and ability to achieve developmental milestones, enabling functional independence and the ability to thrive (2, 24, 25)

- 100% of patients in Cohort 2 in START who received a one-time treatment of onasemnogene abeparvovec are alive and free from permanent ventilation at study end, 24 months, compared with 8% in an external natural history control study (12)
- Patients in START achieved milestones never before observed in patients with SMA type 1 at 24 months post administration of onasemnogene abeparvovec. Of the 12 patients in Cohort 2 treated with the therapeutic dose of onasemnogene abeparvovec:
    - 91.7% of patients were able to hold their head erect without support
    - 75.0% were able to sit alone for ≥30 seconds
    - 16.7% were able to walk unassisted
    - 71.4% of the 7 patients in Cohort 2 who did not require non-oral nutrition prior to AVXS-101 dosing and had a CHOP-INTEND score ≥20 at baseline, maintained the ability to thrive
    - 58.3% were entirely free from daily ventilatory support
    - 91.7% of patients were able to speak
- No patients lost motor milestones gained in START in currently available long-term follow-up data
- In the START study, onasemnogene abeparvovec had a manageable safety profile
- Four patients were reported to have 5 treatment related AE's; in all cases, AEs were transient, clinically asymptomatic elevated serum aminotransferase levels and resolved with prednisolone treatment
- No new treatment related AEs were reported in LT-001

The unprecedented overall survival and motor milestone achievements observed in START have been broadly replicated in ongoing clinical studies. Based on interim data (8 March 2019 data cut (42)):

- Overall survival remains high; of the 77 patients dosed with onasemnogene abeparvovec via a single IV infusion across the clinical trial programme 75 are alive
    - In STR1VE-US one patient died from respiratory arrest that resulted in death and was not deemed related to onasemnogene abeparvovec

- In STR1VE-EU one patient died from severe respiratory infection followed by neurological complications, the event was deemed possibly related to onasemnogene abeparvovec
- Interim analyses from all ongoing studies indicate that no patients have lost motor milestones following treatment with onasemnogene abeparvovec
- Attainment and maintenance of motor milestones is substantially improved compared with natural history cohorts:
  - For STR1VE-US, the ongoing trial for which the longest follow-up data are available, 50% (11/22) of patients achieved the ability to sit independently as of the 8 March 2019 data cut despite a median age of only 14 months at the time of the data cut
  - In line with START, at 6 months post-dosing, 90% of patients in STR1VE-US with Month 6 data had achieved a ≥4-point increase from baseline CHOP-INTEND score and 75% of patients had achieved a CHOP-INTEND score of ≥40 points

9.1 *Identification of studies*

9.1.1 Published studies

9.1.1.1 Describe the strategies used to retrieve relevant clinical data from the published literature. Exact details of the search strategy used should be provided in the appendix.

Systematic literature reviews (SLR) were conducted for 1) the clinical efficacy and safety of onasemnogene abeparvovec versus competing interventions for SMA, 2) HRQoL and utilities for onasemnogene abeparvovec versus competing interventions for SMA, 3) economic burden of onasemnogene abeparvovec versus competing interventions for SMA, and 4) the natural history of SMA type 1 on the 11 March 2019 (85).

Relevant studies were identified by searching the following databases: Medical Literature Analysis and Retrieval System Online (MEDLINE), Excerpta Medica database (EMBASE), EconLit, and Cochrane Central Register of Controlled Trials. The study design filters recommended by the Scottish Intercollegiate Guidelines Network (SIGN) (86) for MEDLINE and EMBASE were used to identify RCTs, economic studies, and observational studies for the SLRs of clinical efficacy and safety, economic burden, and natural history, respectively. The study design filters recommended by the Canadian Agency for Drugs and Technologies in Health (CADTH) (87) were used to identify studies of HRQoL and utilities. All searches included a combination of medical subject headings and key terms for the population of interest. The searches for the clinical efficacy and safety review included additional key terms for the generic and brand names of interventions for SMA, as well as the study design filters recommended by SIGN. The searches for HRQoL and utilities also included additional key terms for the generic and brand names of interventions for SMA, as well as for instruments collecting data on HRQoL and utilities and the study design filters recommended by CADTH. The economic burden review did not use key terms for interventions of interest, but did use the SIGN study design filters for economic studies. Finally, the searches for the natural history review included key terms for natural history, as well as SIGN study design filters. The references of literature reviews identified during the SLRs were hand-searched. Search strategies for each review are included in Appendix 17.1.

The US National Institutes of Health Clinical Trial Registry (88), EU Clinical Trials Registry (89), and additional sources (http://clinicalstudyresults.org, the International Clinical Trials Registry, and the World Health Organization) were also searched to identify completed clinical trials not yet published to identify any completed or ongoing trials with available results that met the criteria.

Further manual searches of the following conference proceedings were conducted for all four reviews:

- World Muscle Society (WMS) – 2018
- American Academy of Neurology (AAN) – 2018[a]
- International Congress on Neuromuscular Diseases (ICNMD) – 2018
- Child Neurology Society – 2017
- American Association of Neuromuscular & Electrodiagnostic Medicine (AANEM) – 2017

For economic evaluations, the following additional online databases were hand-searched (using key population and disease-specific search terms) to identify relevant studies:

- NHS Economic Evaluation Database
- Tufts Cost-Effectiveness Analysis Registry

Health technology assessments (HTAs) of interest that evaluate SMA therapies in the last 10 years were also included, as published by:

- CADTH
- Croatian Agency for the Quality and Accreditation in Healthcare and Social Welfare
- HTA Database of the International Network of Agencies for Health Technology Assessment (INAHTA)
- National Centre for Pharmacoeconomics, Ireland
- National Institute for Health and Care Excellence (NICE)
- Scottish Medicines Consortium (SMC)
- Swedish Dental and Pharmaceutical Benefits Agency (TLV)

Notably, publications were cross-referenced across the four systematic reviews, such that if any article identified by one of the four reviews (e.g. clinical efficacy and safety, HRQoL and utility, economic burden, or natural history of SMA type 1) was also relevant to one of the

[a]The SLR was conducted prior to publication of AAN 2019 abstracts. However, posters presented by AveXis at AAN 2019 are referenced in the submission.

other reviews, it was accounted for in both. For example, a publication identified by and included in the economic burden SLR, which also reported relevant HRQoL data was categorised as a database include within the economic burden SLR and tracked as such within the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) flow diagram. For the HRQoL review, it was also documented as an 'additional material' included within the PRISMA flow diagram (90).

The reference lists of relevant SLRs identified from our review were hand-searched to identify any additionally relevant publications not identified by the database searches. In addition, the reference list of the US Institute for Clinical and Economic Review's (US ICER) final report, which assessed the comparative clinical effectiveness and value of onasemnogene abeparvovec and nusinersen for SMA (32)[b], was hand-searched to identify any additionally relevant publications not identified by the database searches. The US ICER final report itself was not formally included in the SLR as it was published after the date on which the SLR was conducted.

Study selection

Two reviewers, working independently, reviewed all abstracts and proceedings identified by the searches according to the selection criteria, with the exception of outcome criteria, which were only applied during the screening of full-text publications. All studies identified as eligible during abstract screening were then screened at the full-text stage by the same two reviewers. The full-text studies identified at this stage were included for the data extraction. Following reconciliation between the two reviewers, a third reviewer was included to reach consensus on any remaining discrepancies. The process of study identification and selection is summarised with a PRISMA flow diagram (90).

Data extraction

Two reviewers, working independently, extracted data on study characteristics, interventions, patient characteristics, and outcomes for the final list of included studies. Following reconciliation between the two reviewers, a third reviewer was included to reach a consensus on any remaining discrepancies. Data was stored and managed in a Microsoft Excel workbook.

For dichotomous outcomes, the number of patients with the event and the number of patients in each treatment arm were extracted. For continuous outcomes, the change from baseline in all intervention groups was extracted. If the change from baseline was not provided, the score at end of follow-up and the baseline score was extracted. For event rates, the number of events, the number of patients in each treatment arm, and follow-up or exposure time were extracted. For time-to-event outcomes, hazard ratios (HRs) and associated information regarding uncertainty were extracted. Kaplan Meier (KM) curves were extracted in terms of the proportion of patients who had an event over time using DigitizeIt® in addition to the number of patients at risk over time.

[b] The final evidence report published by the US Institute for the Clinical and Economic Review of Spinraza® and Zolgensma® for Spinal Muscular Atrophy (April 3, 2019, Updated May 24, 2019) is available here: https://icer-review.org/wp-content/uploads/2018/07/ICER_SMA_Final_Evidence_Report_052419.pdf

Means were favoured over medians if both were provided. Measures of dispersion were extracted using the following hierarchy: standard error, standard deviation, confidence intervals, interquartile ranges, ranges and p-values. When multiple measurements were available, the highest measurement on the hierarchy was extracted. For example, if standard error and range were both provided, only standard error was extracted. Additionally, details of the study population, the sample size, the unit and definition where applicable, and the measurement type (e.g. observed or least squares mean) were extracted.

When information was available for multiple populations, data was extracted using the following hierarchy: the intention to treat (ITT) population, followed by the full analysis set (FAS), modified intention to treat population (mITT), and the per protocol (PP) population. As with dispersion, only the preferred population was extracted. For safety outcomes, the safety analysis set (SAS) was extracted. Note that the choice of population has an impact on the sample size. In particular, ITT and FAS populations typically include all those randomised and all those having received at least one treatment dose, respectively. Thus, through methods such as last observation carried forward and regression, the sample size stays consistent across time despite loss to follow-up. This does not hold in mITT and per protocol populations.

Study characteristics

The following study characteristics were extracted in all four SLRs:

- Study name
- Study year
- Study author
- Study design (e.g. RCT, non-randomised clinical trial, observational study, number of arms, double blind, open label, etc.)
- Study inclusion criteria (including type of SMA)
- Study exclusion criteria
- Location of study
- Study duration and follow-up period
- Sample size
- Definition of BSC, as available (in the review of natural history)

Intervention characteristics

The following intervention characteristics were extracted in all SLRs except the review of natural history:

- Treatment regimen
- Treatment dose

- Method of administration
- Frequency of administration
- Duration of treatment
- Concomitant/background therapies

Patient characteristics

The following patient characteristics were extracted in all four SLRs:

- Age at symptom onset
- Age at diagnosis
- Age at study start
- Gender
- Race and ethnicity
- Weight
- CHOP-INTEND score (in the review of clinical efficacy and safety)
- Nutritional support
- Ventilation support
- SMA type and subtype (in the reviews of clinical efficacy and safety and natural history)
- *SMN2* copy number (in the reviews of clinical efficacy and safety and natural history)
- Confirmation of bi-allelic deletion of *SMN1* gene (*SMN1*; in the reviews of clinical efficacy and safety and natural history)
- Proportion of pre-symptomatic and symptomatic patients (in the reviews of clinical efficacy and safety and natural history)

Clinical efficacy and safety outcomes collated are detailed in section 9.2.1.

Study quality

Two independent reviewers assessed study quality. Following reconciliation between the two investigators, a third investigator was included to reach consensus on any remaining discrepancies.

The Cochrane Collaboration's Risk of Bias tool was used to assess risk of bias in included clinical trials (Appendix 3) (91). This instrument is used to evaluate six key domains: sequence generation; allocation concealment; blinding of participants, personnel and outcome assessors; incomplete outcome data; selective outcome reporting; and other sources of bias. The risk of bias instrument can be used to assign summary assessments of

within-study bias, low risk of bias (low risk of bias for all key domains), unclear risk of bias (unclear risk of bias for one or more key domains), or high risk of bias (high risk of bias for one or more key domains).

The Newcastle-Ottawa Scale was used to assess the quality of observational studies (Appendix 3) (92). This instrument is used to evaluate the quality of observational studies based on 1) study group and selection, 2) comparability of the groups within studies, and 3) the ascertainment of either the exposure or outcomes of interest for case-control or cohort studies. Studies were ranked using a 'star system' in which a study can be given a maximum of one star for each numbered item within the 'Selection' and 'Exposure' categories and a maximum of two stars for 'Comparability' category. Two independent reviewers assessed study quality. Following reconciliation between the two investigators, a third investigator was included to reach consensus on any remaining discrepancies.

Included economic evaluations were assessed for study quality according to criteria specified by NICE for single technology appraisals (STA) (93). This 36-item checklist was adapted from Drummond and Jefferson and requires reviewers to assess studies on the reporting and quality of study design, data collection, and analysis and interpretation of results (Appendix 3) (94).

As HTA documents are not primary sources of evidence and conference proceedings (e.g. meeting abstracts and posters) provide limited information, these documents did not undergo study quality assessment.

9.1.2 Unpublished studies

9.1.2.1 Describe the strategies used to retrieve relevant clinical data from unpublished sources.

Please see Section 9.1.1.1 which describes a literature review conducted in line with NICE guidance and therefore describes retrieval of both published and unpublished evidence.

9.2 *Study selection*

Published studies

9.2.1 Complete Table 9 to describe the inclusion and exclusion criteria used to select studies from the published literature. Suggested headings are listed in the table below. Other headings should be used if necessary.

Selection criteria used for the review of published clinical efficacy, safety, and natural history studies are presented in Table 9 and Table 10. All SMA types were searched for so as not to miss publications that evaluated mixed SMA populations and reported separate, relevant data for SMA type 1.

Table 9: Selection criteria used for review of clinical efficacy and safety studies

Inclusion criteria	
Population	SMA (type 1, type 2, and type 3; pre-symptomatic and symptomatic)
Interventions	Any of the following interventions used in the treatment of SMA: • Nusinersen • Onasemnogene abeparvovec (ZOLGENSMA; AVXS-101) • Branaplam • CK-2127107 • RO7034067/RG7916 • RO6885247 • Olesoxime • Proactive ventilator use and insufflator/exsufflator use (“cough assist”) • 4-aminopyridine • Anti-cholinesterase therapy/pyridostigmine bromide • Celecoxib • Hydroxyurea • Leuprolide and testosterone • Pyridostigmine • Riluzole • Sodium phenylbutyrate • Somatotropin • Valproic acid • Valproic acid and levocarnitine • Air stacking technique • Assisted standing treatment programme • Exercise • Palliation • Whole body vibration therapy
Comparators	No restrictions

Outcomes	**SMA type 1** • Efficacy outcomes: o Overall survival o Mortality (time-to-event) o Event-free survival o Achievement of motor milestones o CHOP-INTEND response o Time from treatment onset until full-time ventilation (≥16 out of 24 hours, regardless of ventilation type) • Safety outcomes: o Any adverse events o Treatment-related adverse events	**SMA type 2 and 3** • Efficacy outcomes: o Disability score (e.g. Hammersmith Functional Motor Score, Upper Limb Module, Hammersmith Functional Motor Scale Expanded, Motor Function Measure, Gross Motor Function Measure), where possible transformed to Modified Rankin Scale o Muscle strength (e.g. dynamometry, isometric strength testing, manual muscle testing), where possible transformed to Medical Research Council Sum score o Ambulatory status o Forced vital capacity • Safety outcomes: o Any adverse events o Treatment-related adverse events
Study design	• Randomised controlled trials • Single-arm or non-randomised controlled trials	
Language restrictions	Unrestricted	
Search dates	Unrestricted	

Abbreviations: CHOP-INTEND, The Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders; SMA, spinal muscular atrophy.

Table 10: Selection criteria used for review of natural history studies

Inclusion criteria	
Population	SMA (type 1, type 2, and type 3; pre-symptomatic and symptomatic)†
Interventions	No intervention or best supportive care (natural history)
Comparators	No intervention or best supportive care (natural history)
Outcomes	• Overall survival • Event-free survival • Achievement or deterioration of motor milestones (e.g. CHOP-INTEND) • Ventilation support • Nutritional support
Study design	• Prospective cohort studies with ≥12 months of follow-up • Randomised controlled trials
Language restrictions	Unrestricted
Search dates	Unrestricted

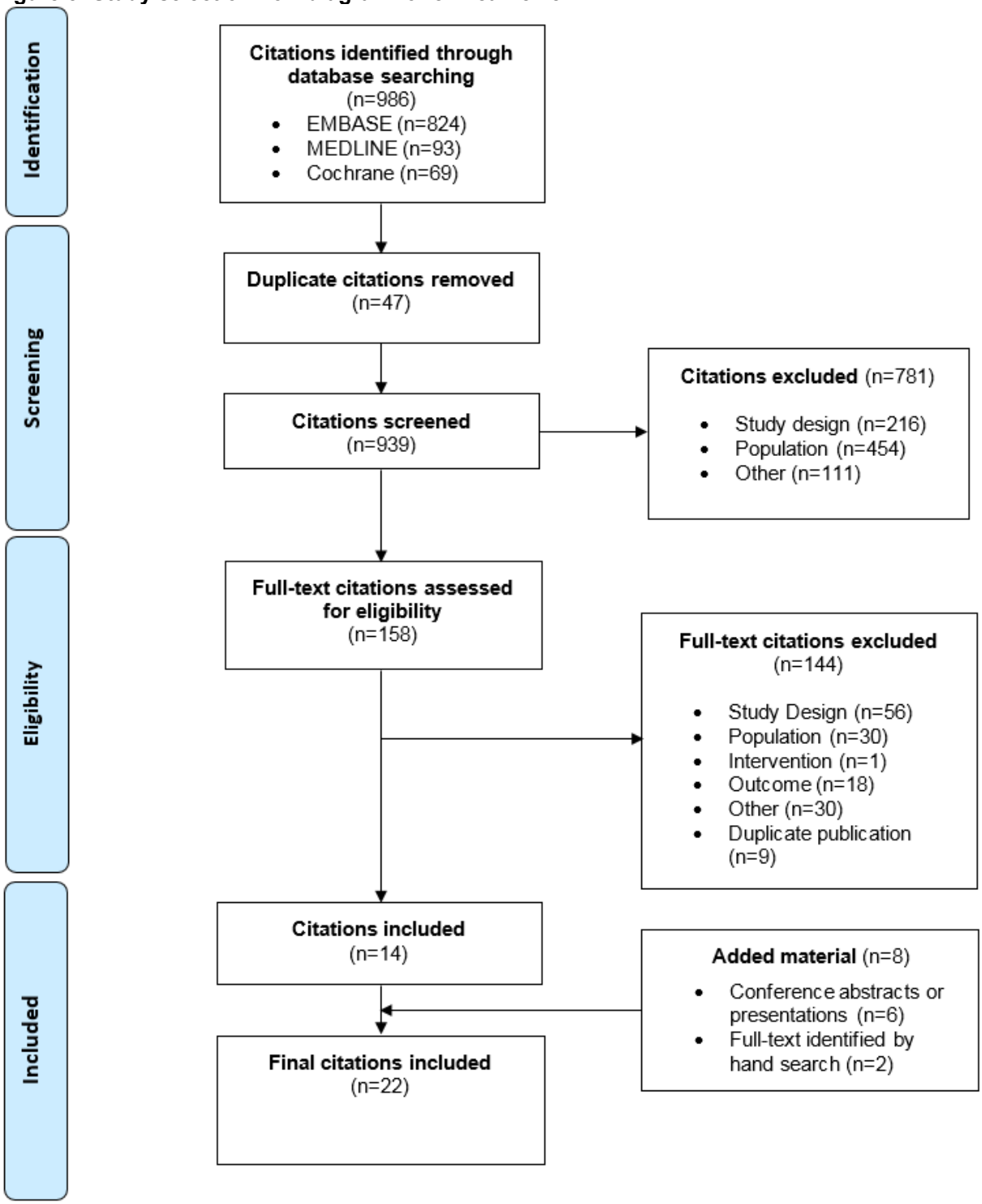
Abbreviations: CHOP-INTEND, The Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders; PICOS, Population, intervention, comparators, outcomes, and study design; SMA, spinal muscular atrophy.
† The search and PICOS criteria allow for the inclusion of all SMA types. While publications describing SMA types 1-3will be flagged separately, ultimately only SMA type 1 will be included in this review

9.2.2 Report the numbers of published studies included and excluded at each stage in an appropriate format.

For the review of clinical efficacy and safety, a total of 986 citations were identified via searches of MEDLINE, EMBASE, and the Cochrane Central Register of Controlled Trials. After title/abstract screening, 158 publications were selected for full-text review. Following review of the full-text articles, a total of 14 publications were identified for inclusion in the review. In addition, six citations were identified via searches of the grey literature, and two additional citations were identified via hand search. Ultimately, a total of 22 publications reporting on 20 unique studies, 14 of which were available as full-text articles and seven as conference proceedings, were included in the review.

Figure 5 presents the PRISMA flow diagram, which outlines the study selection process for the search to identify RCTs and single arm trials of interest for the SLR of clinical efficacy and safety.

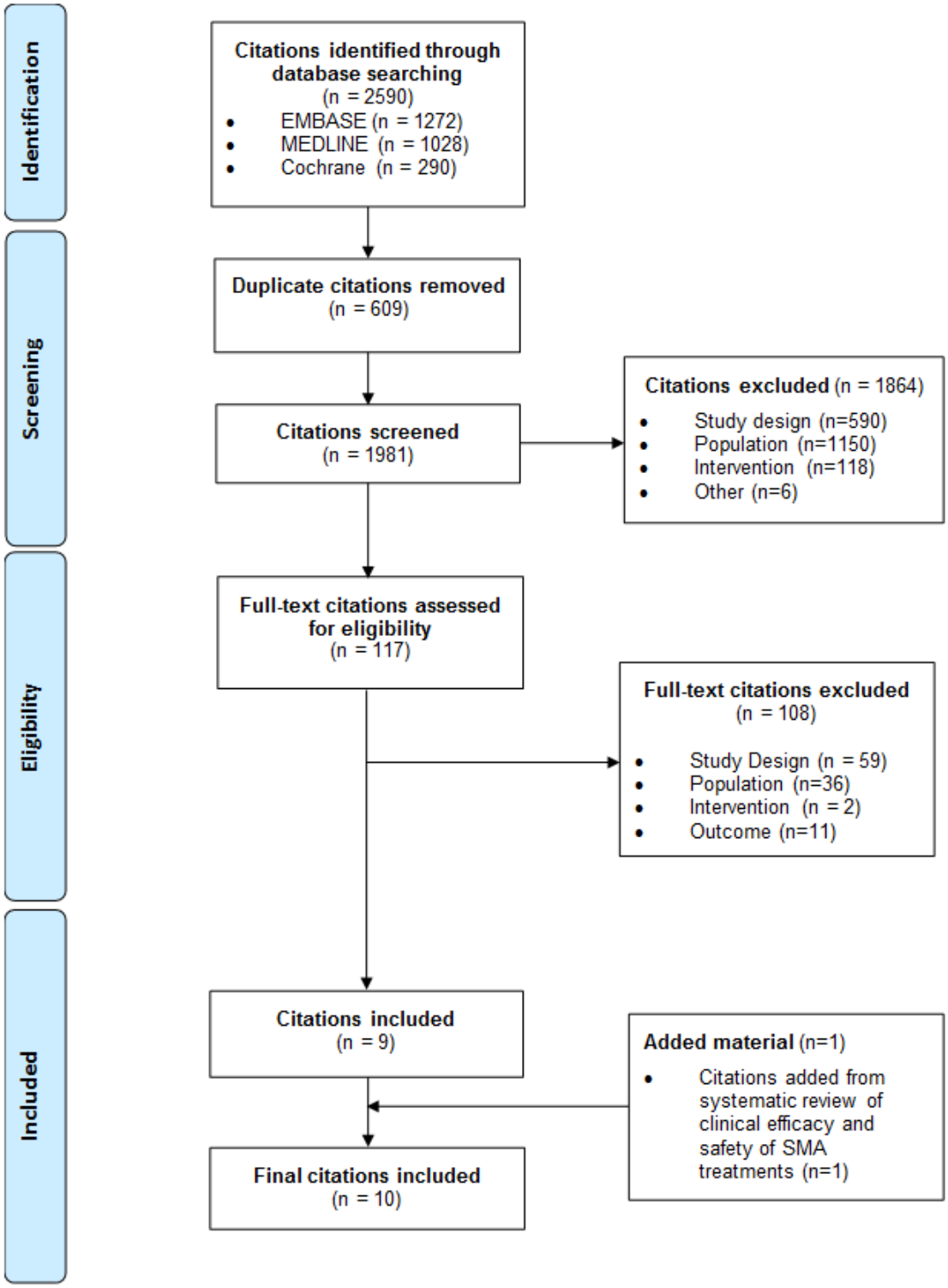
Figure 5: Study selection flow diagram for clinical review



The electronic database searches for natural history studies identified a total of 2,590 citations. After review of the titles/abstracts of citations identified by the searches, 117 publications were selected for further review in full-text. Following review of the full-text articles of these 117 citations, a total of 9 publications were identified for inclusion in the review. Additionally, during the cross-referencing of publications across the four systematic literature review topics (e.g. clinical efficacy and safety, HRQoL and utilities, economic burden, and natural history) a single study (ENDEAR RCT) identified from the separate review of clinical efficacy and safety outcomes was also deemed relevant for inclusion in this natural history SLR. As this study was identified from a separate search, it appears in the PRISMA diagram as 'additional material'. Ultimately, a total of 10 publications reporting on 4 unique studies were included in the review.

Figure 6 outlines the study selection process for the search to identify prospective cohort studies of interest for the SLR of the natural history of SMA type 1.

Figure 6: Study selection flow diagram for natural history review of SMA type 1



Unpublished studies

9.2.3 Complete table C2 to describe the inclusion and exclusion criteria used to select studies from the unpublished literature. Suggested headings are listed in the table below. Other headings should be used if necessary.

Please see Section 9.2.1 which describes the inclusion/exclusion criteria for both published and unpublished evidence.

9.2.4 Report the numbers of unpublished studies included and excluded at each stage in an appropriate format.

Four unpublished studies were identified from the known onasemnogene abeparvovec clinical development programme and included in the evidence review; namely STR1VE-EU, STR1VE-US, SPR1NT, and LT-001.

9.3 *Complete list of relevant studies*

The sponsor should provide a PDF copy of all studies included in the submission. For unpublished studies for which a manuscript is not available, provide a structured abstract about future journal publication. If a structured abstract is not available, the sponsor must provide a statement from the authors to verify the data provided.

9.3.1 Provide details of all published and unpublished studies identified using the selection criteria described in tables Table 9 and Table 10.

Published studies identified in the SLR of clinical efficacy and safety of onasemnogene abeparvovec and other competing interventions for SMA types 1–3 are presented in Table 11 with unpublished studies presented in Table 12. Published studies identified in the SLR of the natural history data for SMA type 1 are presented in Table 13.

Table 11: List of relevant published studies from the SLR of clinical efficacy and safety

Primary study reference	Study name (acronym)	Population	Intervention	Comparator
Al-Zaidy et al. 2019 (24) Mendell et al. 2017 (2)	NCT02122952 (START)	• SMA type 1 possessing 2 copies of *SMN2* without c.859G>c modification in exon 7 • Aged ≤6 months • Symptom onset at ≤6 months	Onasemnogene abeparvovec (one-time IV administration) (n=15: Cohort 1 6.7 x 10^{13} vg/kg, n=3; Cohort 2 2.0 x 10^{14} vg/kg†, n=12)	No comparator‡
Bertini et al. 2017 (95)	NCT01302600	• SMA type 2 or non-ambulatory SMA type 3 with homozygous deletion of *SMN1* exon 7, or a heterozygous deletion accompanied by a point mutation on the other allele • Aged 3–25 years • Symptom onset at ≤3 years	Olesoxime (n=108, OD oral administration, 10 mg/kg)	Placebo (n=57, oral, 10 mg/kg, OD)
Chen et al. 2010 (96)	NCT00485511	• SMA type 2 or 3 with homozygous deletion of *SMN1* • Aged ≥5 years	Hydroxyurea (n=37, OD oral administration, 10 mg/kg)	Placebo (n=20, OD oral administration 20 mg/kg)
Mercuri et al. 2018 (97)	NCT02292537 (CHERISH)	• SMA type 2 or 3, genetic documentation of 5q SMA (a homozygous deletion, mutation, or compound heterozygote in *SMN1*) • Aged of 2–12 years with the ability to sit independently • Symptom onset at ≤6 months • No history of the ability to walk independently, and a HFMSE score of 10–54	Nusinersen (n=84, IT administration of 12 mg on Days 1, 29, 85, and, 274; maintenance dose)	Placebo (n=42, sham IT procedure on Days 1, 29, 85, and 274)

Primary study reference	Study name (acronym)	Population	Intervention	Comparator
Chiriboga et al. 2016 (98)	NCT01494701 and NCT01780246	• Symptomatic SMA type 2 or 3 with homozygous deletion of *SMN1* • Aged 2–14 years • Life expectancy of ≥2 years	Nusinersen (single IT administration of 1 mg n=6, 3 mg n=6, 6 mg n=6, 9 mg n=10)	No comparator
Finkel et al. 2016 (99)	NCT01839656 (CS3A)	• Genetic documentation of 5q SMA • Aged 3 weeks to 7 months old • Symptom onset at ≥21 days and ≤6 months	Nusinersen (IT administration of 6 mg n=4 or 12 mg n=16 on day 1, 15, 85, and 253, followed by every 4 months)	No comparator
Shieh et al. 2018 (100)	NCT02462759 (EMBRACE)	• SMA type 1 or 2 with homozygous *SMN1* gene deletion, mutation, or compound heterozygote • Onset of SMA symptoms at: o ≤6 months with 3 copies of *SMN2* o ≤6 months, >7 months at screening with 2 copies of *SMN2* o >6 months, ≤18 months with 2/3 copies of *SMN2*	Nusinersen (n=14, IT administration of 12 mg)	Placebo (n=7, sham IT procedure)
Finkel et al. 2017 (22)	NCT02193074 (ENDEAR)	• SMA type 1 with homozygous deletion or mutation in the *SMN1* gene and 2 copies of *SMN2* • Aged ≤7 months at screening • Symptom onset at ≤6 months	Nusinersen (n=81, IT administration of 12 mg on day 1, 15, 29, 64, 183, and 203)	Placebo (n=41, sham procedure on days 1, 15, 29, 64, 183, and 203)
Frongia et al. 2014 (101)	NR	• SMA type 2	Salbutamol (n=48)	No comparator

Primary study reference	Study name (acronym)	Population	Intervention	Comparator
Chiriboga et al. 2018 (102)	NCT03032172 (JEWELFISH)	• SMA type 2 or 3 • Age 12–60 years • Previously participated in a study with therapies targeting *SMN2* splicing	RG7916 (n=10, oral OD for a minimum of 2 months as a maximum of 11 months))	No comparator
Kirschner et al. 2014 (103)	NCT00533221	• SMA type 2 or 3 (independent sitting was possible) • Age 6–36 years	Somatropin (n=19, SC administration of 0.015 mg/kg OD over one week followed by an 11-week period of 0.03 mg/kg OD)	Placebo (n=19, SC administration of 0.015 mg/kg OD over one week followed by an 11-week period of 0.03 mg/kg OD)
Kissel et al. 2011 (104)	NCT00227266	• Genetically confirmed diagnosis of 5q SMA type 2 or 3 • Age 3–17 years • Able to stand without braces or other support for up to 2 seconds	VPA + L-carnitine (n=33, oral administration of 125 mg BID or TID)	No comparator
Krosschell et al. 2018 (105)	NCT00661453	• Homozygous deletion of *SMN1* and a phenotype consistent with SMA type 1 • Aged 2 weeks to 12 months • Symptom onset at ≤6 months	VPA + L-carnitine (n=37, oral administration of 10–30 mg/kg OD dose adjusted to a serum trough level of 50–100 µg/mL)	No comparator
Deconinck et al. 2018 (106)	NCT02268552 (LMI070X2201)	• Infants with SMA type 1 possessing 2 copies of *SMN2*	Branaplam (n=13, oral administration)	No comparator
De Vivo et al. 2018 (107)	NCT02386553 (NURTURE)	• Genetically diagnosed pre-symptomatic SMA with 2 or 3 copies of *SMN2* • Age ≤6 weeks at first dose	Nusinersen (n=25, IT administration of 12 mg on day 1, 15, 29, and 64)	No comparator
Muntoni et al. 2018 (108)	NCT02628742 (OLEOS)	• SMA type 2 or non-ambulatory type 3	Olesoxime (n=128, oral administration of 10 mg/kg OD)	No comparator

Primary study reference	Study name (acronym)	Population	Intervention	Comparator
Russman et al. 2003 (109)	NR	• SMA type 1 with a homozygous deletion of *SMN* • Age ≥3 months and ≤18 months at the time of enrolment • Symptom onset at ≤6 months of age and a maximum motor ability no better than sitting with support	Riluzole (n=7, oral administration of 107 mg/m^2)	Placebo (n=3)
Finkel et al. 2018 (110)	NCT02594124 (SHINE)	• Infantile-onset SMA (most likely to develop type I) who transitioned from ENDEAR	Nusinersen (n=89)	No comparator
Swoboda et al. 2010 (111)	NCT00227266 (SMA CARNI-VAL Trial)	• SMA type 2 or non-ambulatory type 3 (able to sit independently for ≥3 seconds without support) with confirmed genetic diagnosis of 5q SMA • Age 2–8 years	VPA + L-carnitine (n=30, oral administration of 125 mg BID or TID)	Placebo (n=31, oral BID or TID)
Swoboda et al. 2009 (112)	NCT00374075	• SMA type 1, 2, or 3 • Age ≥2 years	VPA (n=42, oral administration of 125 mg BID or TID)	No comparator

Abbreviations: BID, twice daily; HFMSE, Hammersmith Functional Motor Scale–Expanded; IT, intrathecal; IMP, investigational medicinal product; IV, intravenous; L-carnitine, levocarnitine; NR, not reported; OD, once daily; PNCR, Pediatric Neuromuscular Clinical Research database; SMA, spinal muscular atrophy; *SMN*, survival motor neurone; TID, three times a day; VPA, valproic acid.

† Direct testing of the actual lot of IMP used in START by an improved and more fully qualified analytical method has determined the actual dose received by Cohort 2 to be 1.1 x 10^{14} vg/kg. The same method has been used to establish an equivalent dose for the IMP in all Phase III trials.

‡ Well characterised external datasets from SMA natural history studies (PNCR and NeuroNext (67)) are used to provide an external control comparator.

Table 12: List of relevant unpublished studies

Data source	Study name (acronym)	Population	Intervention	Comparator[†]
Protocol (41) Clinical overview (8 Mar 2019 data cut) (42) 120-Day efficacy update (27 Sep 2018) (43) 120-Day safety update (28 Jan 2019) (44)	NCT03461289 (STR1VE-EU)	• Symptomatic SMA type 1 with 1 or 2 copies of *SMN2* • <6 months of age at the time of gene replacement therapy • Enrolled n=33[‡]	Onasemnogene abeparvovec (IV)	No comparator
Protocol (45) Clinical overview (8 March 2019 data cut) (42) 120-Day efficacy update (27 Sep 2018) (43) 120-Day efficacy update (31 Dec 2018) (28) 120-Day safety update (28 Jan 2019) (44)	NCT03306277 (STR1VE-US)	• SMA type 1 with 1 or 2 copies of *SMN2* • <6 months of age at the time of gene replacement therapy • n=22[§]	Onasemnogene abeparvovec (IV)	No comparator
Protocol (46) Clinical overview (8 Mar 2019 data cut) (42) 120-Day efficacy update (27 Sep 2018) (43) 120-Day safety update (28 Jan 2019) (44)	NCT03505099 (SPR1NT)	• Pre-symptomatic patients with type 1, or 2 SMA with 2 or 3 copies of *SMN2* • ≤6 weeks of age at the time of gene replacement therapy • Planned n=≥27 evaluable patients, enrolled = 29[¶]: 2 x *SMN2* n=14, 3 x *SMN2* n=15	Onasemnogene abeparvovec (IV)	No comparator

Data source	Study name (acronym)	Population	Intervention	Comparator†
Protocol (47) 120-Day efficacy update (27 Sep 2018) (43) 120-Day efficacy update (31 Dec 2018) (28) 120-Day safety update (28 Jan 2019) (44)	NCT03421977 (LT-001, extension of START)	• Patients treated with onasemnogene abeparvovec in Study AVXS-101-CL-101 (enrolled n=13††)	Onasemnogene abeparvovec (IV)	No comparator
Protocol (48) Statistical analysis plan (49)	LT-002	• Patients treated with onasemnogene abeparvovec in an AveXis clinical trial	Onasemnogene abeparvovec (IV or IT)	No comparator

Abbreviations: EU, Europe; IV, intravenous; SMA, spinal muscular atrophy; *SMN*, survival motor neurone; US, United States.
† Well-characterised external datasets from SMA natural history studies (PNCR and NeuroNext (67)) are used to provide an external control comparator
‡ Enrolment to STR1VE-EU completed in May 2019. At the 8 March 2019 data cut (42), 23/33 infants with SMA type 1 were enrolled in STR1VE-EU.
§ 1/22 patients was initially enrolled as a pre-symptomatic SMA patient, however this patient was reclassified as symptomatic by the Investigator after 31 December 2018.
¶ As of July 2019, 29 patients were enrolled in SPR1NT. At the 8 March 2019 efficacy data cut, 17 patients were enrolled in SPR1NT (42).
†† Number of patients enrolled as of 31 December 2018 data cut.

Table 13: Study characteristics for natural history review of SMA type 1

Data source	Study name (acronym)	Population	Intervention
ENDEAR (22, 100, 113-116)	NCT02193074 (ENDEAR)	• SMA type 1 (n=7) with homozygous deletion or mutation in the *SMN1* gene and 2 copies of the *SMN2* gene • Age ≤7 months at screening • Symptom onset at ≤6 months of age	Sham IT procedure
Finkel et al. 2014a (12)	PNCR	• SMA type 1 and 2 (n=34), including SMA type 1 with *SMN2* x 2 copies (n=23)	No comparator
Finkel et al. 2014b (59)	NA	• SMA type 1 (n=7) with homozygous deletion of exon 7 in the *SMN1* gene and 2 copies of the *SMN2* gene • No known co-morbid medical factors, lung disease, or prematurity	No comparator
NeuroNext (26, 27)	NCT01736553 (NeuroNext)	• SMA type 1 (n=26), including n=16 with *SMN2* x 2 copies • Age ≤6 months at enrolment and born between 36 and 42 weeks of gestation • Asymptomatic subjects who had been genetically tested prior to the enrolment	No comparator

Abbreviations: IT, intrathecal; NA, not available; PNCR, Pediatric Neuromuscular Clinical Research database; SMA, spinal muscular atrophy; *SMN*, survival motor neurone.

9.3.2 State the rationale behind excluding any of the published studies listed in tables Table 11 and Table 12.

As the NICE decision problem includes onasemnogene abeparvovec and the comparators of nusinersen or BSC (natural history) for the treatment of SMA type 1 only, all other trials examining different interventions or different populations (e.g. SMA type 2) were excluded from further analysis. Excluded studies and the reason for exclusion are presented in Table 14.

Table 14: Published studies identified in the clinical efficacy and safety SLR but excluded from further analysis

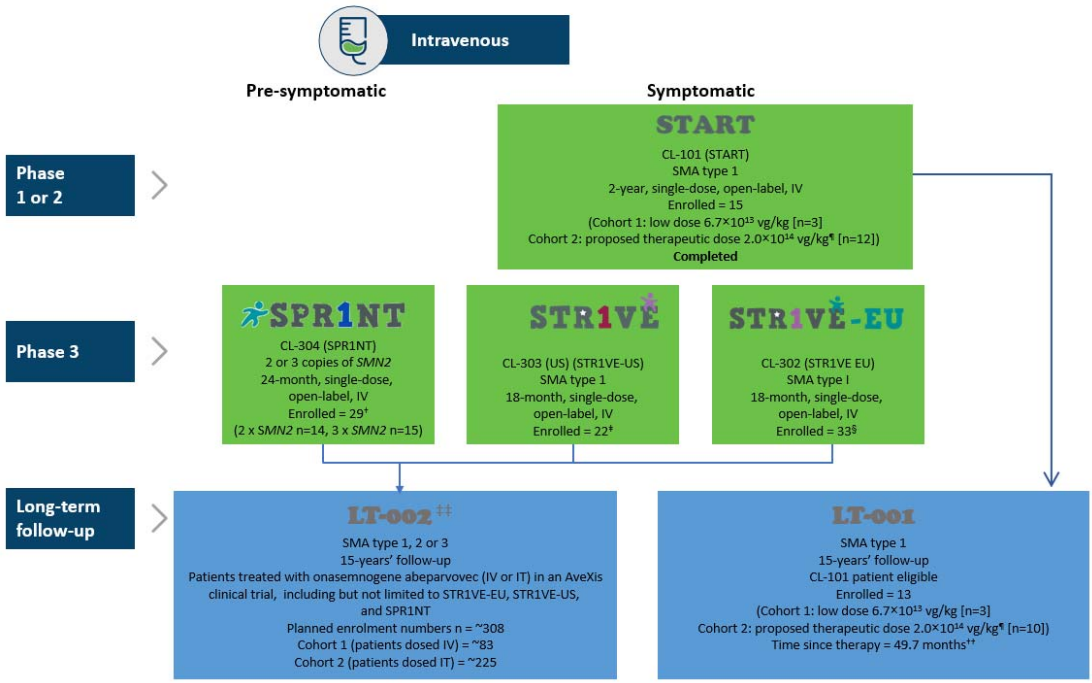
Primary study reference	Study name (acronym)	Interventions	Reason for exclusion
Bertini et al. 2017 (95)	NCT01302600	• Olesoxime • Placebo	Intervention
Chen et al. 2010 (96)	NCT00485511	• Hydroxyurea • Placebo	Intervention
Mercuri et al. 2018 (97)	NCT02292537 (CHERISH)	• Nusinersen • Placebo	SMA population
Chiriboga et al. 2016 (98)	NCT01494701 and NCT01780246	• Nusinersen • No comparator	SMA population
Frongia et al. 2014	NR	• Salbutamol • No comparator	Intervention
Chiriboga et al. 2018 (102)	NCT03032172 (JEWELFISH)	• RG7916 • No comparator	Intervention
Kirschner et al. 2014 (103)	NCT00533221	• Somatropin • Placebo	Intervention
Kissel et al. 2011 (104)	NCT00227266	• VPA + L-carnitine • No comparator	Intervention
Krosschell et al. 2018 (105)	NCT00661453	• VPA + L-carnitine • No comparator	Intervention
Deconinck et al. 2018	NCT02268552 (LMI070X2201)	• Branaplam • No comparator	Intervention
Muntoni et al. 2018 (108)	NCT02628742 (OLEOS)	• Olesoxime • No comparator	Intervention
Russman et al. 2003 (109)	NR	• Riluzole • Placebo	Intervention
Swoboda et al. 2010 (111)	NCT00227266 (SMA CARNI-VAL Trial)	• VPA + L-carnitine • Placebo	Intervention
Swoboda et al. 2009 (112)	NCT00374075	• VPA • No comparator	Intervention

Abbreviations: SMA, spinal muscular atrophy; VPA, valproic acid.

9.4 *Summary of methodology of relevant studies*

The clinical development programme for onasemnogene abeparvovec comprised a number of Phase I–III clinical trials in patients with SMA (Table 11 and Table 12). To date, one study has been completed and four are ongoing (Figure 7); data from the completed study (START) are presented in full, along with interim data cuts from the ongoing studies. The next data cut for ongoing studies is 31 May 2019 and September 2019; the outputs and results of this data cut will be available for sharing with NICE in Q4 2019/Q1 2020. A further long-term follow-up study, LT-002, which will enrol infants treated with onasemnogene abeparvovec (IV or IT) in AveXis clinical trials, is also planned to commence in September 2019.

Figure 7: Overview of completed and ongoing studies in the clinical trial programme for onasemnogene abeparvovec



Abbreviations: IV, intravenous; IMP, investigational medicinal product; SMA, spinal muscular atrophy.
† As of July 2019, 29 patients were enrolled in SPR1NT. At the 8 March 2019 efficacy data cut, 17 patients were enrolled in SPR1NT (4).
‡ One patient in STR1VE-US was initially enrolled as a pre-symptomatic SMA patient, however this patient was reclassified as symptomatic by the Investigator after 31 December 2018.
§ Enrolment to STR1VE-EU completed in May 2019. At the 8 March 2019 data cut (42), 23/33 infants with SMA type 1 were enrolled in STR1VE-EU.
¶ Direct testing of the actual lot of IMP used in START by an improved and more fully qualified analytical method has determined the actual dose received by Cohort 2 as 1.1 x 10^{14} vg/kg. The same method has been used to establish an equivalent dose for the IMP in all Phase III trials.
†† The maximum duration of therapy in LT-001 of patients treated with the proposed therapeutic dose of onasemnogene abeparvovec in START (n=10) as of the 31 December 2018 data cut (28).
‡‡ LT-002 is planned to commence in September 2019.

The initial clinical study, START, was a Phase I/IIa study in which safety was the primary outcome and efficacy was a secondary objective. However, as discussed in Section 9.6.1.1, initial results from START demonstrated unprecedented evidence of efficacy in improving the survival, motor function, and achievement and maintenance of developmental milestones and bulbar function (i.e. swallowing, oral feeding, and speech) of patients with SMA type 1. Given the lethality of SMA, the extremely poor prognosis for patients who do not receive treatment (Section 6), the unprecedented efficacy observed in the START trial, and the favourable safety profile observed in START, it was considered that it would be unethical to include placebo arms in further onasemnogene abeparvovec trials. All interventional studies in the clinical development programme therefore had an open-label design with all patients receiving a one-time dose of onasemnogene abeparvovec; the START study also included a dose comparison evaluation.

To support the open-label design of the onasemnogene abeparvovec studies, well characterised datasets from the SMA natural history studies (the PNCR database and NeuroNext) were identified as appropriate for use as historical controls (12, 27, 67). Despite differences in methodology, geographical location, and study populations, the PNCR and the NeuroNext studies show consistency in mortality, ventilatory requirement, motor function, and milestone achievement with the European experience described in recent papers by Wadman et al. 2017 (54) and De Sanctis et al. 2018 (60), as well as studies from the UK (14, 66), Poland and Germany (70), France (71), the US (72) and Hong Kong (73). Patient level data were available from the PNCR and NeuroNext databases; European privacy rules preclude the publication of patient level from European studies. Therefore, SMA type 1 patients from the PNCR and the NeuroNext datasets were considered to be highly relevant and appropriate comparators for the patients treated with onasemnogene abeparvovec.

Description of clinical assessments

An overview of the outcome measures used in the onasemnogene abeparvovec clinical trial programme is provided below; tests were selected on the basis of the literature and the natural history of SMA (12, 27).

Survival without permanent ventilation

A combined endpoint of survival without permanent ventilation was considered appropriate as, while permanent ventilation can extend the life of infants with SMA type 1, patients will still never achieve developmental milestones such as sitting, walking, or talking. A single endpoint of mortality would therefore underestimate the benefit of treatment, as permanent ventilation can be considered a surrogate for death given that a child who did not receive such intervention would be unlikely to survive.

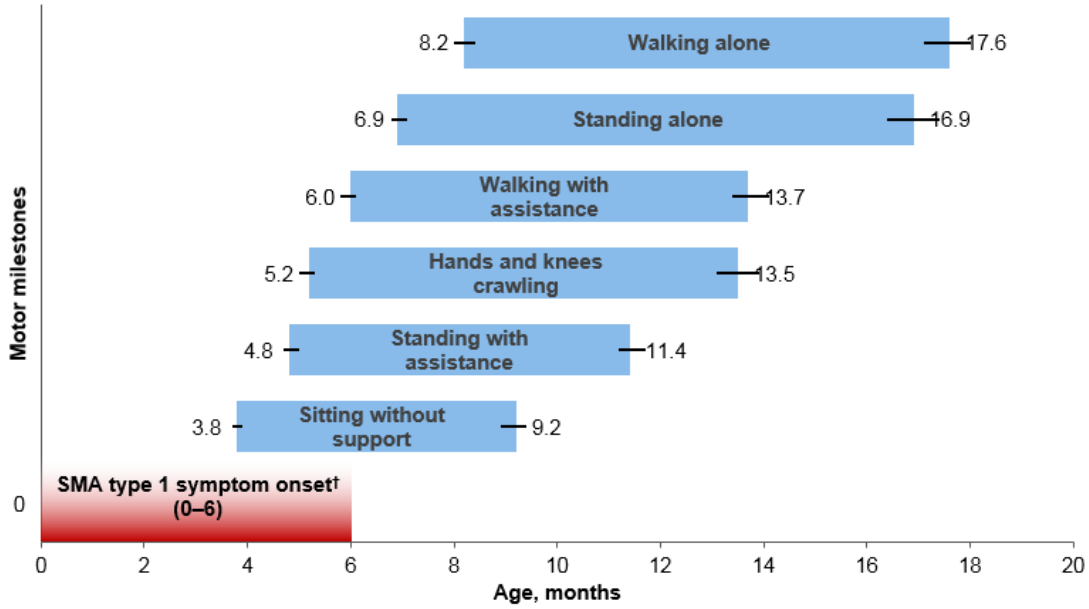
The survival of SMA patients was defined by the avoidance of the combined endpoint of either (a) death or (b) permanent ventilation, defined as tracheostomy or the requirement of ≥16 hours of respiratory assistance per day (via non-invasive ventilatory support) for ≥14 consecutive days in the absence of an acute reversible illness, excluding perioperative ventilation. This was in line with the definition of survival used in the PNCR study (12) and was a more conservative endpoint than that used in the NeuroNext study, in which data reflect tracheostomy-free survival, a less conservative endpoint (a child could receive 24 hours per day of non-invasive support without triggering the combined endpoint, for

example) (27). Independence from ventilatory support and instances and reasons for invasive ventilatory support were also monitored during the onasemnogene abeparvovec clinical development programme.

Development of significant motor function milestones based on video reviews by an external expert

Healthy children typically attain the motor milestones presented in Figure 8 by 24 months of age. However, untreated infants with SMA type 1 fail to achieve any motor milestones (50). Therefore, improvements in motor function and muscle strength as determined by the achievement of significant development milestones by infants treated with onasemnogene abeparvovec were assessed by a central reviewer.

Figure 8: Age of SMA onset compared with the windows of normal motor-milestone achievement



Abbreviations: CI, confidence interval; SMA, spinal muscular atrophy.
Notes: Red shading represents the age of symptom onset for SMA type 1. Blue bars represent windows of normal motor-milestone achievement. Numerical values indicate the left and right borders (1st and 99th percentiles, respectively) of the windows of normal motor-milestone achievement; black lines represent the 95% CI for the left and right borders (1st and 99th percentiles, respectively) of the windows of normal motor-milestone achievement.
† The underlying disease pathology is present before SMA type 1 symptom onset. Although the age range for SMA type 1 symptom onset overlaps with the lower end of some of the windows of normal motor-milestone achievement, these motor-milestones are not attained as the underlying disease process is already underway.
Source: Prior and Finanger 1993 (55); Farrar et al. 2017 (117); WHO Multicentre Growth Reference Study Group (118).

Compiled video recordings of the CHOP-INTEND, Bayley Scales (119), submitted home videos, and physical examinations were sent to an independent reviewer for confirmation of development milestones.

The motor milestones assessed included:

- Head control: Child holds head erect for at least 3 seconds without support (Bayley Scales Gross Motor subset item #4)
- Rolls over: Child turns from back to both right and left sides (Bayley Scales Gross Motor subset item #20)
- Sits with support: Child sits with slight support for at least 30 seconds (Bayley Scales Gross Motor subset item #19)
- Sits without support
    - Sits without support for ≥30 seconds (Bayley Scales Gross Motor subset item #26)
    - Sitting without support is defined by the World Health Organization Multicentre Growth Reference Trial (WHO MGRS) as sitting up with back straight and head erect for at least 10 seconds; child does not use arms or hands to balance body or support position (120)
    - Sitting without support for ≥5 seconds – defined by Bayley Scales Gross Motor Subset item #22 – child sits alone without support for ≥5 seconds

<u>The Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders</u>

The CHOP-INTEND is a motor function scale developed and validated for use specifically to monitor motor function status and decline amongst children with SMA type 1, and is administered by a qualified clinical evaluator (121, 122). The CHOP-INTEND scale (range 0 to 64, with higher score indicating better functional status) examines several aspects of motor function, including head control, righting reactions, and trunk movements in supported sitting, supine, and prone positions. Anti-gravity movements in assisted rolling, ventral suspension, and supported standing are also measured.

In the START study, if a patient achieved 2 consecutive CHOP-INTEND scores of ≥62, a teleconference was conducted between the principal investigator, the physical therapist, and the sponsor to review the patient status and determine whether or not continued CHOP-INTEND assessments were necessary. If it was decided that no further assessments were necessary, the physical therapist ceased completion of the CHOP-INTEND assessment at subsequent visits; otherwise, CHOP-INTEND assessments continued monthly during Year 1 and quarterly during Year 2 in the START trial. In the STR1VE-EU, STR1VE-US, and SPR1NT studies, patients who achieved 3 consecutive CHOP-INTEND scores ≥58 did not undergo any additional CHOP-INTEND examinations.

The proportion of patients who achieved CHOP-INTEND thresholds of ≥40, ≥50, and ≥60 (START) or 58 (STR1VE-EU, STR1VE-US, and SPR1NT) was assessed in the

onasemnogene abeparvovec clinical development programme. The rationale for selecting these thresholds is as follows:

- A score ≥40 is beyond that reported in the literature for maximum function amongst symptomatic patients with SMA type 1 beyond 6 months of age (12)
- A score ≥50 - achieving this score would suggest the potential to gain milestones such as independent sitting
- A score ≥60 (START) or ≥58 (STR1VE-EU, STR1VE-US, and SPR1NT) marks the effective ceiling using the CHOP-INTEND

Bayley Scales

The Bayley Scales of Infant and Toddler Development (Version 3) are a standardised, norm-referenced infant assessment of developmental functioning across 5 domains: cognitive, language, motor, social-emotional, and adaptive behaviour (119). The Bayley Scales are administered by a physical therapist. A scaled score ≥8 on the Bayley Scales would be considered the low end of normal (25).

In START, the gross and fine motor subtests were administered monthly until patients reached 15 months of age or 12 months post-dose, whichever was later, if a patient reached or exceeded a score of 60/64 on the CHOP-INTEND. The language (receptive communication and expressive communication) and cognition subtests were administered every 3 months if a patient reached or exceeded a score of 60/64 on the CHOP-INTEND. The CHOP-INTEND assessment was to be discontinued and only the Bayley was to be administered for patients who achieved 2 consecutive CHOP-INTEND scores of ≥62. In STR1VE-EU, the full and gross and fine motor subsets of the motor domain were administered at each monthly visit. In STR1VE-US the full Bayley Scales was administered at screening, every 6 months starting at Month 6, and at End of Study when the patient reaches 18 months of age (or early termination), whereas the gross and fine motor subtests of the motor domain were administered at each monthly visit. For patients for whom English is not their first language, the language subtests and cognitive scale portions of the Bayley were not performed. In SPR1NT, the Bayley Scales gross and fine motor subtests were administered to all patients at screening, Day 30, Day 60 (Month 2), Day 90 (Month 3), every 3 months starting at 6 months of age, and at End of Study when the patient reached 18 or 24 months of age (or early termination). The language and cognition subtests of the Bayley Scales are not evaluated in STR1VE-EU or SPR1NT.

Exploratory efficacy endpoints

Maintaining ability to thrive: The ability to thrive was defined as meeting the following:

1. The ability to tolerate thin liquids as demonstrated through a formal swallowing test
2. Not requiring nutrition through mechanical support such as a feeding tube
3. Maintained weight within expected ranges based upon age and gender norms at time of primary efficacy data cut-off

Nutritional status and swallowing function

The number (%) of patients who used non-oral feeding at any time from baseline to the efficacy analysis time points was summarised by cohort and type of feeding tube (gastrostomy with Nissen fundoplication, gastrostomy without Nissen fundoplication, nasogastric, or nasojejunal). Swallowing function, determined through video-fluoroscopic swallowing studies, was assessed at baseline and every 6 months during the follow-up period.

Motor neurone function

Compound muscle action potential (CMAP) amplitude is an indicator of motor neurone health and denervation severity. SMA infants have substantially reduced CMAP and motor unit number estimation (MUNE) responses compared with reference data from neonate to 2 years of age (CMAP: 1,800–5,000 mV; MUNE: 100–250). (12, 27). The CMAP size is found using supramaximal stimulation of the motor nerve to a defined muscle or muscle group. It is recorded using surface electrodes, and is representative of the sum of the surface detected motor unit action potentials from muscles innervated by that nerve. The MUNE is a technique that uses electromyography to estimate the number of motor units in a muscle. MUNE uses a general formula of:

$$Number\ of\ motor\ unites = \frac{compound\ muscle\ action\ potential\ size}{mean\ surface - detected\ motor\ unit\ action\ potential\ size}$$

Both CMAP and MUNE were recorded from surface electrodes at baseline and every 6 months after onasemnogene abeparvovec infusion in START. CMAP was assessed in STR1VE-US and SPR1NT; neurophysiology assessments were not performed in STR1VE-EU.

9.4.1 Describe the study design and methodology for each of the published and unpublished studies using tables C5 and C6 as appropriate. A separate table should be completed for each study.

The methodologies for the trials in the clinical development programme of onasemnogene abeparvovec are presented in Table 15 to Table 20.

9.4.1.1 Methods of the completed studies in the onasemnogene abeparvovec clinical trial programme

Table 15: Summary of methodology for START (AVXS-1010-CL-101)

Study name	Phase I gene transfer clinical trial for spinal muscular atrophy type 1 delivering AVXS-101
Objective	To assess the safety of onasemnogene abeparvovec
Location	US
Design	Phase I, open-label, one-time infusion, ascending-dose, single-centre study
Duration of study	Start date: 5 May 2014 Date of completion: 15 December 2017
Patient population	Patients with SMA type 1 possessing 2 copies of *SMN2* without c.859G>c modification in exon 7
Sample size	15 patients
Inclusion criteria	Six months of age[†] and younger at day of vector infusion with SMA type 1 as defined by the following features: • Bi-allelic *SMN1* gene mutations (deletion or point mutation) with 2 copies of *SMN2* (no more and no fewer) • Patients 6 months of age and younger with disease onset up to 6 months of age • Hypotonia by clinical evaluation with delay in motor skills, poor head control, round shoulder posture, and hypermobility of joints
Exclusion criteria	• Active viral infection (included HIV or serology positive for hepatitis B or C) • Use of invasive ventilatory support (tracheostomy with positive pressure) or pulse oximetry <95% saturation at the screening visit • Non-invasive ventilator support (e.g. BiPAP) for >16 hours/day • Concomitant illness that in the opinion of the Investigator created unnecessary risks for gene transfer • Concomitant use of: drugs for treatment of myopathy or neuropathy, agents used to treat diabetes mellitus, or ongoing immunosuppressive therapy or immunosuppressive therapy within 3 months of starting the study (e.g. corticosteroids, cyclosporine, tacrolimus, methotrexate, cyclophosphamide, IV immunoglobulin, rituximab) • Antibody to anti-AAV9 titres >1:50 • Abnormal laboratory values considered clinically significant (GGT >3 × ULN, bilirubin ≥3.0 mg/dL, creatinine ≥1.8 mg/dL, haemoglobin <8 or >18 g/dL; white blood cells >20,000/mm^3)

	• Participation in a recent SMA treatment clinical trial or receipt of an investigational or commercial compound, product or therapy administered with the intention to treat SMA (e.g. nusinersen, valproic acid) that in the opinion of the Investigator created unnecessary risks for gene transfer • Patient with signs of aspiration based on a swallowing test and unwilling to use an alternative method to oral feeding • Patients with c.859G>C modification in exon 7, based on predicted mild phenotype
Intervention(s) (n =) and comparator(s) (n =)	Onasemnogene abeparvovec (IV) • Cohort 1 received a low dose 6.7×10^{13} vg/kg (n=3) • Cohort 2 received a therapeutic dose 2.0×10^{14} vg/kg‡ (n=12) Comparator: natural history cohort§
Baseline differences	See full details of baseline characteristics in Section 9.4.3
Duration of follow-up, participants lost to follow-up information	During the first year of the 2-year safety follow-up period, patients returned for post-dose follow-up visits on Days 7, 14, 21, and 30, followed by monthly visits through Month 12 During the second year, patients with CHOP-INTEND scores ≥62 were assessed with the Bayley Scales and completed visits every 3 months; all other patients completed monthly visits (subsequently changed to quarterly visits)
Statistical tests	Efficacy analyses conducted for START were considered descriptive by agreement with FDA and were performed without a statistical analysis plan The following analysis sets were used for the statistical analyses: SAS, ITT, FAS, EES, mITT, per protocol set, and ability to thrive ITT population Changes from baseline to each study visit were analysed with the use of a mixed-effects model for repeated measurements. The mixed model included the fixed effects of cohort and visit and a covariate of baseline score. Statistical analyses were performed with the use of SAS software, version 9.4. All hypothesis testing was conducted at the 0.05 level of significance except for the endpoint of survival, which was conducted at the 0.025 level of significance. Tests were 1-sided or 2-sided, as appropriate, and were considered descriptive. Categorical measures, such as percent surviving event-free, were summarised using counts and percentages.

Primary outcomes (including scoring methods and timings of assessments)	Primary Objective: Safety (AEs, laboratory evaluations, DILI, vital signs, ECGs, physical examinations, and immunologic response) Primary efficacy endpoint: Survival, defined as time from birth to either (a) requirement of ≥16-hour respiratory assistance per day (includes BiPAP) continuously for ≥2 weeks in the absence of an acute reversible illness, excluding perioperative ventilation or (b) death Efficacy analyses were conducted at the following time points: • The date at which all patients had completed a study visit after reaching 13.6 months of age • When the last enrolled patient had a study visit after reaching 20 months of age • When all patients completed 24 months of post-dose follow-up
Secondary outcomes (including scoring methods and timings of assessments)	Secondary efficacy endpoints • Change in CHOP-INTEND from baseline score • Demonstration of improvement of motor function and muscle strength as determined by achievement of significant development milestones including but not limited to the ability to sit alone and roll over unassisted

Exploratory efficacy endpoints	• Maintain ability to thrive defined as meeting the following criteria at the each of the 3 efficacy data time points: o The ability to tolerate thin liquids as demonstrated through a formal swallowing test o Did not receive nutrition through mechanical support (e.g. feeding tube) o Maintained weight (>3rd percentile for age and gender as defined by WHO guidelines) at the time of the primary efficacy data cut-off ▪ A patient was defined as not requiring non-oral nutrition at baseline if the patient 1) did not use non-oral nutrition of any kind and 2) demonstrated intact swallowing at the baseline assessment such that the patient did not receive a recommendation for non-oral nutrition prior to onasemnogene abeparvovec administration • Independence from ventilatory support defined as requiring no daily ventilator support/usage at the 3 efficacy analysis time points, in the absence of acute reversible illness and excluding perioperative ventilation • Achievement of CHOP-INTEND threshold scores of ≥40, ≥50, and ≥60 by the time of the primary efficacy data cut-off and at 24 months post-infusion • Development of significant motor function milestones per gross motor skills checklist • Achievement of functional independent sitting (≥30 seconds) based on video reviews by an external expert • Change from baseline in fine and gross motor components of the Bayley Scales of Infant and Toddler Development • Motor neurone function assessed through CMAP and MUNE • The proportion of patients who used non-oral feeding (gastrostomy with Nissen fundoplication, gastrostomy without Nissen fundoplication, nasogastric, or nasojejunal) • The types of and reasons for invasive ventilatory support required by patients • Hospitalisations during the study

Abbreviations: AAV9, adeno-associated virus serotype 9; AE, adverse event; BiPAP, bi-level positive airway pressure; CHOP-INTEND, Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders; CMAP, compound motor action potential; DILI, drug-induced liver injury; ECG, electrocardiogram; EES, efficacy evaluable set; FAS, full analysis set; GGT, gamma-glutamyl transferase; HIV, human immunodeficiency virus; IMP, investigational medicinal product; ITT, intention-to treat; IV, intravenous; MUNE, motor unit number estimation; mITT, modified ITT; PNCR, Pediatric Neuromuscular Clinical Research database; SAS, safety analysis set; SMA, spinal muscular atrophy; *SMN*, survival motor neurone; ULN, upper limit of normal; WHO, World Health Organization.

† This inclusion criterion was revised to allow enrolment of patients 6 months of age or younger. The first 9 patients were enrolled under previous version(s) of the protocol, which allowed an age range of 9 months or younger.

‡ Direct testing of the actual lot of IMP used in START by an improved and more fully qualified analytical method has determined the actual dose received by Cohort 2 to be 1.1×10^{14} vg/kg. The same method has been used to establish an equivalent dose for the IMP in all Phase III trials.

§ Well characterised external datasets from SMA natural history studies (PNCR and NeuroNext (67)) are used to provide an external control comparator.

9.4.1.2 Ongoing studies in the onasemnogene abeparvovec clinical trial programme

The methods of the ongoing studies in the onasemnogene abeparvovec clinical trial programme are outlined in Table 16 to Table 20.

Table 16: Summary of methodology for STR1VE-EU (AVXS-101-CL-302)

Study name	Phase III, open-label, single-arm, single-dose gene replacement therapy clinical trial for patients with spinal muscular atrophy type 1 with one or two *SMN2* copies delivering AVXS-101 by intravenous infusion
Objective	To assess the efficacy of onasemnogene abeparvovec
Location	12−16 European investigative sites located in the following countries: Belgium, France, Germany, Italy, Netherlands, Spain, UK (2 sites), Sweden
Design	Phase III open-label, single-arm, one-time infusion trial investigating the efficacy and safety of onasemnogene abeparvovec in patients with SMA type 1
Duration of study	Estimated start date: Q2 2018. Estimated date of completion: Q3 2020
Patient population	Symptomatic SMA type 1 patients genetically defined by no functional *SMN1* as well as 1 or 2 copies of *SMN2* who are ≤6 months of age at time of gene replacement therapy infusion
Sample size	Planned: up to 30 patients (enrolled n=33[†])
Inclusion criteria	• Patients with SMA type 1 as determined by diagnosis of SMA based on gene mutation analysis with biallelic *SMN1* mutations (deletion or point mutations) and one or two copies of *SMN2* (inclusive of the known *SMN2* gene modifier mutation [c.859G>C]) • Aged <6 months (<180 days) at the time of onasemnogene abeparvovec infusion • Patients must have a swallowing evaluation test performed prior to administration of gene replacement therapy • Up-to-date on childhood vaccinations
Exclusion criteria	• Previous, planned or expected scoliosis repair surgery/procedure prior to 18 months of age • Use of invasive ventilatory support (tracheostomy with positive pressure) or pulse oximetry <95% saturation at screening (saturation must not decrease ≥4 percentage points between screening and dosing with confirmatory oximetry reading), patients may be put on non-invasive ventilatory support for <12 hours per day at the discretion of their physician or trial staff) • Use or requirement of non-invasive ventilatory support for ≥12 hours daily in the 2 weeks prior to dosing • Patient with signs of aspiration based on a swallowing test or whose weight-for-age falls below the third percentile based on WHO Child Growth Standards, and unwilling to use an alternative method to oral feeding • Active viral infection (includes HIV or positive serology for hepatitis B or C, or known Zika virus infection)

	• Serious non-respiratory tract illness requiring systemic treatment and/or hospitalization within 2 weeks prior to screening • Upper or lower respiratory infection requiring medical attention, medical intervention, or increase in supportive care of any manner within 4 weeks prior to screening. • Severe non-pulmonary/respiratory tract infection (e.g. pyelonephritis, or meningitis) within 4 weeks before administration of gene replacement therapy or concomitant illness that, in the opinion of the Investigator, creates unnecessary risks for gene replacement • Known allergy or hypersensitivity to prednisolone or other glucocorticosteroids or their excipients • Concomitant use of any of the following: drugs for treatment of myopathy or neuropathy, agents used to treat diabetes mellitus, or ongoing immunosuppressive therapy, plasmapheresis, immunomodulators such as adalimumab, or immunosuppressive therapy within 3 months prior to gene replacement therapy • Anti-AAV9 antibody titre >1:50. Should a potential patient demonstrate anti-AAV9 antibody titer >1:50, he or she may receive retesting within 30 days of the screening period and will be eligible to participate if the anti-AAV9 antibody titer upon retesting is ≤1:50 • Biological mother refuses anti-AAV9 antibody testing prior to dosing o The mothers of enrolled patients were also screened for anti-AAV9 antibodies. If AAV9 antibodies were identified, the investigator discussed with the mother whether to continue or to stop breastfeeding. Biological mothers who tested positive for antibodies to AAV9 were asked to refrain from further feedings with breast milk until at least 1 month after the onasemnogene abeparvovec administration. Patients consuming banked breast milk from donor sources that could not be tested for anti-AAV9 antibodies were transitioned to formula prior to participation • Clinically significant abnormal laboratory values prior to gene replacement therapy (GGT, ALT, and AST >3x ULN; bilirubin ≥3.0 mg/dL; creatinine ≥1.0 mg/dL; Hgb <8 or >18 g/dL; WBC >20,000/cmm) • Participation in recent SMA treatment clinical trial (with the exception of observational cohort studies or non-interventional studies) or receipt of an investigational or commercial compound, product or therapy administered with the intention to treat SMA (e.g. nusinersen, valproic acid) at any time prior to screening for this trial. Oral beta-agonists must be discontinued ≥30 days prior to dosing • Expectation of major surgical procedures during the trial assessment period (e.g. spinal surgery or tracheostomy) • Patients <35 weeks gestational age at time of birth
Intervention(s) (n =) and comparator(s) (n =)	Intervention: peripheral IV infusion of 1.1 X 10^{14} vg/kg‡ onasemnogene abeparvovec (enrolled n=33†) Comparator: natural history cohort§
Baseline differences	See full details of baseline characteristics in Section 9.4.3

Duration of follow-up, participants lost to follow-up information	Patients will return for follow-up visits on Days 7, 14, 21, and 30. Patients will return monthly thereafter, following the Day 30 visit, for 18 months from dose administration.
Statistical tests	Primary efficacy endpoint: The number and percent of patients whom, through video evidence, exhibit the milestone achievement of sitting without support at any visit up to and including 18 months of age study visit will be summarised for the ITT population. A one-sided Exact Binomial Test will be used to test the null hypothesis of p=0.1% at significance level of 0.025. Furthermore, the corresponding 95% confidence intervals will be estimated by the exact method for binomial proportions. Secondary efficacy endpoint: The observed proportion surviving in the current study was compared with the natural history data of the matching cohort using a two-sample Fisher's exact test, along with the corresponding 95% confidence intervals.
Primary outcomes (including scoring methods and timings of assessments)	The primary objective was to demonstrate efficacy by achievement of the developmental milestone of sitting without support for at least 10 seconds up to 18 months of age (as assessed by WHO Motor Development Milestones)
Secondary outcomes (including scoring methods and timings of assessments)	To determine efficacy based on survival at 14 months of age, defined by the avoidance of combined endpoint of either (a) death or (b) permanent ventilation (defined by tracheostomy or by the requirement of ≥16 hours of respiratory assistance per day [via non-invasive ventilatory support] for ≥14 consecutive days in the absence of an acute reversible illness, excluding perioperative ventilation)

Exploratory efficacy endpoints	• Achievement of the ability to: o hold head erect without support o roll over o sit with support (121) o achieve functional independent sitting for at least 30 seconds (121) o crawl as defined by WHO Motor Developmental Milestones (120) o pull to stand o stand with assistance as defined by WHO Motor Developmental Milestones (120) o stand alone as defined by WHO Motor Developmental Milestones (120) o walk with assistance as defined by WHO Motor Developmental Milestones (120) o walk alone as defined by WHO Motor Developmental Milestones (120) • Change from baseline in fine and gross motor components of the Bayley Scales of Infant and Toddler Development • Change from baseline in gross motor function as determined by improvement CHOP-INTEND score • Ability to remain independent of ventilator support, defined as requiring no daily ventilator support/usage at 18 months of age • Maintain ability to thrive defined as meeting the following criteria at the each of the 3 efficacy data time points: o The ability to tolerate thin liquids as demonstrated through a formal swallowing test o Did not receive nutrition through mechanical support (e.g. feeding tube) o Maintained weight (>3rd percentile for age and gender as defined by WHO guidelines) at the time of the primary efficacy data cut-off

Abbreviations: AAV9, adeno-associated virus serotype 9; ALT, alanine aminotransferase; AST, aspartate aminotransferase; CHOP-INTEND, Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders ; GGT, gamma-glutamyl transpeptidase; Hgb, haemoglobin; HIV, human immunodeficiency virus; IMP, investigational medicinal product; ITT, intention-to-treat; IV, intravenous; PNCR, Pediatric Neuromuscular Clinical Research database; SMA, spinal muscular atrophy; *SMN*, survival motor neurone; UK, United Kingdom; ULN, upper limit of normal; WBC, white blood cell; WHO, World Health Organization.

† Enrolment to STR1VE-EU completed in May 2019 (N=33). At the 8 March 2019 data cut (42), 23/33 infants with SMA type 1 were enrolled in STR1VE-EU.

‡ Equivalent to the dose received by the Cohort 2 in START as determined by direct product testing with improved analytical methods. Direct testing of the actual lot of IMP used in START by an improved and more fully qualified analytical method has determined the actual dose received by Cohort 2 to be 1.1×10^{14} vg/kg. The same method has been used to establish an equivalent dose for the IMP in all Phase III trials.

§ Well characterised external datasets from SMA natural history studies (PNCR and NeuroNext (67)) are used to provide an external control comparator.

Table 17: Summary of methodology for STR1VE-US (AVXS-101-CL-303)

Study name	Phase III, open-label, single-arm, single-dose gene replacement therapy clinical trial for patients with spinal muscular atrophy type 1 with one or two *SMN2* copies delivering onasemnogene abeparvovec by intravenous infusion
Objective	To determine the efficacy of onasemnogene abeparvovec
Location	US
Design	Phase III, open-label, single-arm, one-time infusion gene replacement study
Duration of study	Start date: Q2 2017 Completion date: Q4 2019
Patient population	Patients with SMA type 1 with 1 or 2 copies of *SMN2* <6 months of age at the time of gene replacement therapy
Sample size	21 (enrolled n=22[†])
Inclusion criteria	• Diagnosis of SMA based on gene mutation analysis with bi-allelic *SMN1* mutations (deletion or point mutations) and 1 or 2 copies of *SMN2* (inclusive of the known *SMN2* gene modifier mutation [c.859G>C]) • Patients must be <6 months (<180 days) of age at the time of onasemnogene abeparvovec infusion • Patients must have a swallowing evaluation test performed prior to administration of gene replacement therapy • Up-to-date on childhood vaccinations
Exclusion criteria	• Previous, planned or expected scoliosis repair surgery/procedure during the study assessment period • Pulse oximetry <96% saturation at screening while the patient is awake or asleep without any supplemental oxygen or respiratory support, or for altitudes >1,000 m, oxygen saturation <92% awake or asleep without any supplemental oxygen or respiratory support. Pulse oximetry saturation may decrease to <96% after screening provided that the saturation does not decrease by ≥4 percentage points • Tracheostomy or current use or requirement of non-invasive ventilatory support averaging ≥6 hours daily over the 7 days prior to the screening visit; or ≥6 hours/day on average during the screening period or requiring ventilatory support while awake over the 7 days prior to screening or at any point during the screening period prior to dosing • Patients with signs of aspiration/inability to tolerate non-thickened liquids based on a formal swallowing test performed as part of screening. Patients with a gastrostomy tube who pass the swallowing test will be allowed to enrol in the study • Patients whose weight-for-age is below the third percentile based on WHO Child Growth Standards (123) • Active viral infection (includes HIV or positive serology for hepatitis B or C, or Zika virus) • Serious non-respiratory tract illness requiring systemic treatment and/or hospitalisation within 2 weeks prior to screening

	• Upper or lower respiratory infection requiring medical attention, medical intervention, or increase in supportive care of any manner within 4 weeks prior to screening • Severe non-pulmonary/respiratory tract infection (e.g. pyelonephritis, or meningitis) within 4 weeks before administration of gene replacement therapy or concomitant illness that, in the opinion of the Principal Investigator, creates unnecessary risks for gene replacement therapy • Known allergy or hypersensitivity to prednisolone or other glucocorticosteroids or their excipients • Concomitant use of any of the following: drugs for treatment of myopathy or neuropathy, agents used to treat diabetes mellitus, or ongoing immunosuppressive therapy, plasmapheresis, immunomodulators such as adalimumab, immunosuppressive therapy within 3 months prior to gene replacement therapy (e.g. corticosteroids, cyclosporine, tacrolimus, methotrexate, cyclophosphamide, IV immunoglobulin, rituximab) • Anti-AAV9 antibody titre >1:50. Should a potential patient demonstrate anti-AAV9 antibody titer >1:50, he or she may receive retesting within 30 days of the screening period and will be eligible to participate if the anti-AAV9 antibody titer upon retesting is ≤1:50 o The mothers of enrolled patients were also screened for anti-AAV9 antibodies. Mothers who tested positive for antibodies to AAV9 were be asked to refrain from further feedings with breast milk. If AAV9 antibodies were identified, the patient stopped consuming breast milk from the biological mother. Patients consuming banked breast milk from donor sources that could not be test for anti-AAV9 antibodies were transitioned to formula prior to participation • Clinically significant abnormal laboratory values (GGT, ALT, and AST >3 × ULN, bilirubin ≥3.0 mg/dL, creatinine ≥1.0 mg/dL, Hgb <8 or >18 g/dL, WBC >20,000/cmm) prior to gene replacement therapy • Participation in recent SMA treatment clinical study (with the exception of observational cohort studies or non-interventional studies) or receipt of an investigational or commercial compound, product, or therapy administered with the intention to treat SMA (e.g. nusinersen, valproic acid) at any time prior to screening for this study. Oral β-agonists must be discontinued at least 30 days before gene replacement therapy dosing. Inhaled albuterol specifically prescribed for the purposes of respiratory (bronchodilator) management is acceptable and not a contraindication at any time prior to screening for this study • Expectation of major surgical procedures during the study assessment period (e.g. spinal surgery or tracheostomy) • Gestational age at birth <35 weeks (245 days)
Intervention(s) (n =) and comparator(s) (n =)	Onasemnogene abeparvovec at 1.1 X 10^{14} vg/kg‡ will be administered as a one-time peripheral IV infusion over approximately 30–60 minutes (enrolled n=22†) Comparator: natural history cohort§
Baseline differences	See full details of baseline characteristics in Section 9.4.3

Duration of follow-up, participants lost to follow-up information	During the outpatient follow-up period (Day 4 to End of Study at 18 months of age), patients returned at regularly scheduled intervals for efficacy and safety assessments. Missed visits were rescheduled as soon as possible, but within 7 days and still within the required visit window. For the 14 and 18 months of age visits, the patient will return within 0 to 14 days after the date on which the patient reaches 14 and 18 months of age, respectively. The 18 months of age visit will also serve as the End of Study visit. After the End of Study visit, eligible patients may roll over into the long-term follow-up study
Statistical tests	<u>Primary efficacy endpoints:</u> The number and percent of patients whom, through video evidence, exhibit the milestone achievement of sitting without support at any visit up to and including 18 months of age study visit will be summarised for the ITT population. A one-sided Exact Binomial Test will be used to test the null hypothesis of p=0.1% at significance level of 0.025. Furthermore, the corresponding 95% confidence intervals will be estimated by the exact method for binomial proportions. The observed proportion surviving in the current study was compared with the natural history data of the matching cohort using a two-sample Fisher's exact test, along with the corresponding 95% confidence intervals
Primary outcomes (including scoring methods and timings of assessments)	<u>Co-primary outcomes:</u> • Proportion of patients who achieved functional independent sitting for ≥30 seconds at the 18 months of age study visit • Survival, defined as avoidance of either (a) death or (b) permanent ventilation, at 14 months of age. Permanent ventilation is defined by tracheostomy or by the requirement of ≥ 16 hours of respiratory assistance per day (via non-invasive ventilatory support) for ≥ 14 consecutive days in the absence of an acute reversible illness, excluding perioperative ventilation.
Secondary outcomes (including scoring methods and timings of assessments)	<u>Co-secondary outcomes:</u> • Proportion of patients maintaining the ability to thrive, defined as the ability to tolerate thin liquids (as demonstrated through a formal swallowing test) and to maintain weight (>3rd percentile based on WHO Child Growth Standards (123) for age and gender) without need of gastrostomy or other mechanical or non-oral nutritional support at 18 months of age • Proportion of patients who are independent of ventilatory support, defined as requiring no daily ventilator support/usage at 18 months of age, excluding acute reversible illness and perioperative ventilation, as defined above through assessment of actual usage data captured from the device (Phillips Trilogy)

Exploratory efficacy endpoints	• Achievement of the ability to: o hold head erect without support o roll from back to both sides o sit with support o sit independently (>10 seconds; WHO Motor Developmental Milestones (120)) o crawl o pull to stand o stand with assistance o stand alone o walk with assistance o walk alone • Change from baseline in fine and gross motor components of the Bayley Scales of Infant and Toddler Development • Change from baseline in gross motor function as determined by improvement CHOP-INTEND score • Proportion of patients achieving CHOP-INTEND score ≥40 • Proportion of patients achieving CHOP-INTEND score ≥50 • Proportion of patients achieving CHOP-INTEND score ≥58 • Improvement in peroneal nerve CMAP amplitude • Age at which independent sitting (30 seconds) is first achieved

Abbreviations: AAV9, adeno-associated virus serotype 9; CMAP, compound motor action potential; GGT, gamma glutamyl- transpeptidase; Hgb, haemoglobin; HIV, human immunodeficiency virus; IMP, investigational medicinal product; ITT, intention-to-treat; IV, intravenous; PNCR, Pediatric Neuromuscular Clinical Research database; SMA, spinal muscular atrophy; *SMN*, survival motor neurone; US, United States; WBC, white blood cell; WHO, World Health Organization.

† As of 31 December 2018 data cut (28) 22 patients enrolled; 1/22 patients was initially enrolled as a pre-symptomatic SMA patient, however this patient was reclassified as symptomatic by the Investigator after 31 December 2018.

‡ Equivalent to the dose received by the Cohort 2 in START as determined by direct product testing with improved analytical methods. Direct testing of the actual lot of IMP used in START by an improved and more fully qualified analytical method has determined the actual dose received by Cohort 2 to be 1.1×10^{14} vg/kg. The same method has been used to establish an equivalent dose for the IMP in all Phase III trials.

§ Well characterised external datasets from SMA natural history studies (PNCR and NeuroNext (67)) are used to provide an external control comparator.

Table 18: Summary of methodology for SPR1NT (AVXS-101-CL-304)

Study name	A global study of a single, one-time dose of AVXS-101 delivered to infants with genetically diagnosed and pre-symptomatic spinal muscular atrophy with multiple copies of *SMN2*
Objective	To evaluate the safety and efficacy of onasemnogene abeparvovec in infants with genetically diagnosed and pre-symptomatic spinal muscular atrophy
Location	15–25 global centres in the US, Australia, Belgium, Canada, Germany, Israel, Japan, Spain, Taiwan, and the UK (1 site)
Design	Phase III, open-label, single-arm study of a one-time infusion of onasemnogene abeparvovec in patients with spinal muscular atrophy
Duration of study	Estimated start date: Q1 2018 Estimated date of completion: *SMN2* 2 copies: Q4 2020; *SMN2* 3 copies: Q2 2021
Patient population	Pre-symptomatic patients with type 1 or 2 SMA genetically defined by bi-allelic deletion of *SMN1* with 2 or 3 copies of *SMN2* and ≤6 weeks of age at the time of gene replacement therapy who meet enrolment criteria
Sample size	Planned: ≥27 (enrolled n=29[†])
Inclusion criteria	**All patients** • Age ≤6 weeks (≤42 days) at time of dose • Ability to tolerate thin liquids as demonstrated through a formal bedside swallowing test • CMAP ≥2 mV at baseline; centralised review of CMAP data will be conducted • Gestational age of 35 to 42 weeks • Genetic diagnosis as described below, obtained from an acceptable newborn or pre-natal screening test method **Patients with 2 copies of *SMN2* (n≥15)** • Patients with pre-symptomatic SMA type 1 as determined by 2 copies of *SMN2* **Patients with 3 copies of *SMN2* (n≥12)** • Patients with pre-symptomatic SMA type 2 as determined by 3 copies of *SMN2*
Exclusion criteria	• Weight at screening visit <2 kg • Hypoxaemia (oxygen saturation <96% awake or asleep without any supplemental oxygen or respiratory support) at the screening visit or for altitudes >1,000 m, oxygen saturation <92% awake or asleep without any supplemental oxygen or respiratory support at the screening visit • Any clinical signs or symptoms at screening or immediately prior to dosing that are, in the opinion of the Investigator, strongly suggestive of SMA (e.g. tongue fasciculation, hypotonia, areflexia)

	• Tracheostomy or current prophylactic use or requirement of non-invasive ventilatory support at any time and for any duration prior to screening or during the screening period • Patients with signs of aspiration/inability to tolerate non-thickened liquids based on a formal swallowing test performed as part of screening or patients receiving any non-oral feeding method • Clinically significant abnormalities in haematology or clinical chemistry parameters as determined by the investigator or medical monitor • Treatment with an investigational or commercial product, including nusinersen, given for the treatment of SMA. This includes any history of gene replacement therapy, prior antisense oligonucleotide treatment, or cell transplantation. • Patients whose weight-for-age is below the third percentile based on WHO Child Growth Standards (123) • Biological mother with active viral infection as determined by screening laboratory samples (includes HIV or positive serology for hepatitis B or C) • Serious non-respiratory tract illness requiring systemic treatment and/or hospitalisation within 2 weeks prior to screening • Upper or lower respiratory infection requiring medical attention, medical intervention, or increase in supportive care of any manner within 4 weeks prior to dosing • Severe non-pulmonary/respiratory tract infection (e.g. pyelonephritis, or meningitis) within 4 weeks before administration of gene replacement therapy or concomitant illness that, in the opinion of the Investigator or Sponsor medical monitor, creates unnecessary risks for gene replacement therapy • Known allergy or hypersensitivity to prednisolone or other glucocorticosteroids or their excipients • Previous, planned or expected major surgical procedure including scoliosis repair surgery/procedure during the study assessment period • Concomitant use of any of the following: drugs for treatment of myopathy or neuropathy, agents used to treat diabetes mellitus, or ongoing immunosuppressive therapy, plasmapheresis, immunomodulators such as adalimumab, immunosuppressive therapy within 4 weeks prior to gene replacement therapy (e.g. corticosteroids, cyclosporine, tacrolimus, methotrexate, cyclophosphamide, IV immunoglobulin, rituximab) • Anti-AAV9 antibody titre >1:50 • Biological mother refuses anti-AAV9 antibody testing prior to dosing o The mothers of potential participants were screened for anti-AAV9 antibodies. Patient samples for anti-AAV9 screening were collected if biological mother's titer result was positive. If AAV9 antibodies were identified, the investigator discussed with the mother whether to continue or to stop breastfeeding. Patients consuming banked breast milk from donor sources that could not be tested for anti-AAV9 antibodies were transitioned to formula prior to participation. Patients who do not have a biological mother available to screen for antibodies to AAV9 will have blood drawn for screening of anti-AAV9 antibodies.

Intervention(s) (n =) and comparator(s) (n =)	Onasemnogene abeparvovec at 1.1 X 10^{14} vg/kg[‡] will be administered as a one-time peripheral IV infusion over approximately 60 minutes (planned n=30, enrolled n=29[†]) Comparator: natural history cohort[§]
Baseline differences	See full details of baseline characteristics in Section 9.4.3
Duration of follow-up, participants lost to follow-up information	During the outpatient follow-up period (Days 3 to End of Study at 18 or 24 months of age, dependent upon respective *SMN2* copy number), patients will return at regularly scheduled intervals for efficacy and safety assessments until the End of Study when the patient reaches 18 months of age (*SMN2* = 2), 24 months of age (*SMN2* = 3)
Statistical tests	Primary efficacy endpoint in patients with 2 copies of *SMN2*: The proportion of patients who exhibit the milestone achievement of sitting without support for at least 30 seconds up to 18 months of age will be summarised for the ITT population. A one-sided Exact Binomial Test will be used to test the null hypothesis of p=0.1% at significance level of 0.025 Primary efficacy endpoint in patients with 3 copies of *SMN2*: The proportion of patients who achieve the ability to stand without support for at least three seconds up to 24 months of age will be compared with the natural history data of the matching cohort using a two sample 2-sided superiority Fisher exact test with a significance level of 0.05
Primary outcomes (including scoring methods and timings of assessments)	Safety: • Incidence of AEs and/or serious AEs • Change from baseline in clinical laboratory parameters Primary efficacy: • **2 copies of *SMN2*:** Proportion of patients achieving the ability of functional independent sitting for at least 30 seconds up to 18 months of age • **3 copies of *SMN2*:** Proportion of patients achieving the ability to stand without support for at least 3 seconds up to 24 months of age

Secondary outcomes (including scoring methods and timings of assessments)	<u>Secondary efficacy:</u> **2 copies of *SMN2*:** • Proportion of patients that have survived and have not required permanent ventilation in the absence of acute illness and perioperatively, assessed at 14 months of age. Permanent ventilation is defined as tracheostomy or the requirement of ≥16 hours of respiratory assistance per day (via non-invasive ventilatory support) for ≥14 consecutive days in the absence of an acute reversible illness, excluding perioperative ventilation • Proportion of patients that have achieved the ability to maintain weight at or above the third percentile without need for non-oral/mechanical feeding support at any visit up to 18 months of age **3 copies of *SMN2*:** • Proportion of patients demonstrating the ability to walk alone defined as the ability to take at least five steps independently displaying coordination and balance at any visit up to 24 months of age
Exploratory efficacy endpoints	**2 copies of *SMN2*:** • Achievement of motor milestones as assessed by WHO Multicentre Growth Reference Study (120) criteria at any visit up to 18 months of age: o Sitting without support o Hands and knees crawling o Standing with assistance o Walking with assistance o Standing alone o Walking alone • Time to respiratory intervention • Requirement for respiratory intervention at 18 months of age • Avoidance of death or the requirement of permanent ventilation in the absence of acute illness or perioperatively as assessed at 18 months of age • Proportion of patients alive and without tracheostomy at 18 months of age • Proportion of patients achieving an improvement over baseline of ≥15 points on Bayley V.3 Gross and Fine Motor Subsets (raw score) at any visit up to 18 months of age • Ability to achieve a scaled score on Bayley V.3 Gross and Fine Motor Subtests within 1.5 standard deviations of a chronological development reference standard at any visit up to 18 months of age • Achievement of a CHOP-INTEND motor function scale score ≥40 at any visit up to 18 months of age

	• Achievement of CHOP-INTEND score >50 at any visit up to 18 months of age • Achievement of CHOP-INTEND score ≥58 at any visit up to 18 months of age • Maintenance of achieved milestones at visits up to 18 months of age in the absence of acute illness or perioperatively **3 copies of *SMN2*:** • Achievement of motor milestones as assessed by WHO Multicentre Growth Reference Study (120) criteria at any visit up to 24 months of age: o Standing with assistance o Walking with assistance • Time to respiratory intervention • Proportion of patients requiring respiratory intervention at 24 months of age • Survival, defined as avoidance of death or the requirement of permanent ventilation in the absence of acute illness or perioperatively as assessed at 24 months of age • Improvement over baseline of ≥15 points on Bayley V.3 Gross and Fine Motor Subsets (raw score) at any visit up to 24 months of age • Achievement of a scaled score on Bayley V.3 Gross and Fine Motor Subtests within 1.5 standard deviations of a chronological development reference standard as assessed at any visit up to 24 months of age • Ability to maintain weight at or above the third percentile without need for non-oral/mechanical feeding support at any visit up to 24 months of age • Maintenance of achieved milestones at visits up to 24 months of age in the absence of acute illness or perioperatively

Abbreviations: AAV9, adeno-associated virus serotype 9; AE, adverse event; CMAP, compound muscle action potential; HIV, human immunodeficiency virus; IMP, investigational medicinal product; IV, intravenous; ITT, intention-to-treat; PNCR, Pediatric Neuromuscular Clinical Research database; SMA, spinal muscular atrophy; *SMN*, survival motor neurone; UK, United Kingdom; US, United States; WHO, World Health Organization.

† As of July 2019, 29 patients were enrolled in SPR1NT. At the 8 March 2019 efficacy data cut, 17 patients were enrolled in SPR1NT (4).

‡ Equivalent to the dose received by the Cohort 2 in START as determined by direct product testing with improved analytical methods. Direct testing of the actual lot of IMP used in START by an improved and more fully qualified analytical method has determined the actual dose received by Cohort 2 to be 1.1×10^{14} vg/kg. The same method has been used to establish an equivalent dose for the IMP in all Phase III trials.

§ Well characterised external datasets from SMA natural history studies (PNCR and NeuroNext (67)) are used to provide an external control comparator.

Table 19: Summary of methodology for LT-001 (extension of START)

Study name	A long-term follow-up safety study of patients in the AVXS-101-CL-101 gene replacement therapy clinical trial for spinal muscular atrophy type 1 delivering AVXS-101
Objective	To collect long-term follow-up safety data of patients with SMA type 1 who were treated with onasemnogene abeparvovec in START
Location	US
Design	Long-term, safety follow-up study
Duration of study	Estimated start date: Q2 2017 Estimated date of completion: Q4 2033
Patient population	Patients with SMA type 1 who were treated with onasemnogene abeparvovec in START
Sample size	Planned: up to 15 (enrolled n=13[†])
Inclusion criteria	• Patient who received onasemnogene abeparvovec in the START gene replacement therapy clinical trial for SMA type 1 • Parent/legal guardian willing and able to complete the informed consent process and comply with study procedures and visit schedule
Exclusion criteria	• Parent/legal guardian unable or unwilling to participate in the long-term follow-up safety study
Intervention(s) (n =) and comparator(s) (n =)	Study drug was not administered in LT-001 they were dosed in START
Baseline differences	See full details of baseline characteristics in Section 9.4.3
Duration of follow-up, participants lost to follow-up information	The study will consist of an initial 5-year phase, during which subjects will be seen annually for evaluation of long-term safety, followed by a 10-year observational phase. Upon completion of the initial five years of follow-up visits, patients will be contacted via phone annually for the remaining 10-year follow-up period. During the 10-year observational phase, caregivers and patients will be contacted at least once a year and site staff will review a yearly questionnaire designed to elicit information regarding medical history, adverse events, and other clinical conditions. Additionally, patient record transfers from their local physician and/or neurologist will be requested in conjunction with the annual phone contacts for review by the investigator
Statistical tests	This is a long-term follow-up study with safety as the primary measure. Sample size was not determined through statistical justification

Primary outcomes (including scoring methods and timings of assessments)	<u>Safety assessments:</u> • Medical history and record review • Physical examinations, including height, weight, vital signs, ventilation, nutritional support, and developmental milestone assessments • Clinical laboratory evaluations • Pulmonary assessments • Echocardiograms, holter monitoring, electrocardiograms <u>Efficacy assessments:</u> • Physical examinations to assess developmental milestones o New milestones demonstrated by patients which were not documented during START must be supported by video evidence
Secondary outcomes (including scoring methods and timings of assessments)	N/A

Abbreviations: N/A, not applicable; SMA, spinal muscular atrophy.
† Number of patients enrolled as of 31 December 2018 data cut (28).

Table 20: Summary of methodology for LT-002 (long-term extension study)

Study name	A long-term follow-up study of patients in the clinical trials for spinal muscular atrophy receiving AVXS-101
Objective	To collect long-term follow-up safety and efficacy data of patients with SMA type 1, 2, or 3 who were treated with onasemnogene abeparvovec in an onasemnogene abeparvovec clinical trial, including but not limited AVXS-101-CL-302 (Phase III), AVXS-101-CL-303 (Phase III), and AVXS-101-CL-304 (Phase III) In addition, patients treated with onasemnogene abeparvovec (intravenous or intrathecal) in future parent studies may be enrolled
Location	Studies may be conducted in any location worldwide
Design	Long-term, safety and efficacy follow-up study
Duration of study	Estimated start date: Q4 2019 Estimated date of completion: Q4 2034
Patient population	Patients participating in clinical trials for SMA type 1, 2, or 3 who were treated with onasemnogene abeparvovec
Sample size	Planned: approximately 308 • Cohort 1 (patients dosed IV): approximately 83 • Cohort 2 (patients dosed IT): approximately 225
Inclusion criteria	• Patients with SMA (with 1, 2 or 3 copies of survival motor neuron gene 2) who received onasemnogene abeparvovec gene replacement therapy in an AveXis clinical study • Patient/parent/legal guardian willing and able to complete the informed consent process and comply with study procedures and visit schedule
Exclusion criteria	• Patient/parent/legal guardian unable or unwilling to participate in the long-term follow-up study
Intervention(s) (n =) and comparator(s) (n =)	Study drug was not administered in LT-002
Baseline differences	N/A

Duration of follow-up, participants lost to follow-up information	Monitoring will continue for up to 15 years from the date of onasemnogene abeparvovec dosing. The number of study visits required in LT-002 will depend on the length of participation in the parent study. For example, patients followed 1 year in the parent study will participate in LT-002 for 14 years, patients followed 2 years in the parent study will participate for 13 years, and patients followed for 3 years in the parent study will participate for 12 years. If the HFMSE was performed during the parent study, within 6 months of the baseline visit in LT-002, it does not need to be repeated (parent study HMFSE may serve as the baseline for LT-002). If not done as part of the last visit in the parent study, or if the last HMFSE was conducted >6 months prior to the initial visit in LT-002, the HMFSE evaluation may be performed at the initial visit of LT-002. Patients will then return bi-annually for follow-up study visits for 2 years. Thereafter, in-person annual follow-up visits will be conducted for years 3 to 5. Patients will then be contacted via phone annually for the remainder of the study, until 15 years from the date of onasemnogene abeparvovec dosing
Statistical tests	The primary analysis of evaluating safety and efficacy data will be conducted when the last patient has completed the initial 5-year phase annual safety follow-up study visit or has discontinued study follow-up. Since less data will be collected during the 10-year observational phase which is based on annual telephone contact, analyses on serious adverse events, adverse events of special interest and pulmonary assessment will be implemented at the end of study using data collected during the 10-year observational phase Descriptive statistical methods will be used to summarise the data from this study. Continuous data, such as lab values, will be summarised using count, mean, median, standard deviation, minimum, and maximum. For continuous data specified to be analysed using parametric procedures, non-parametric procedures will be used if the parametric procedure is felt to be inappropriate
Primary outcomes (including scoring methods and timings of assessments)	<u>Safety assessments:</u> • Medical history and record review • Physical examinations, including height, weight, vital signs, ventilatory and nutritional support • Clinical laboratory evaluations • Pulmonary assessments • Cardiac assessments • Observational phase questionnaire <u>Efficacy assessments:</u> • Physical examinations to assess developmental milestones • New milestones demonstrated by patients which were not documented during onasemnogene abeparvovec study must be supported by video evidence • HFMSE to be performed during first 2 years of study in all patients • Pulmonary assessments • Swallowing questionnaire

Secondary outcomes (including scoring methods and timings of assessments)	N/A

Abbreviations: HFMSE, Hammersmith Functional Motor Scale - Expanded; N/A, not applicable; SMA, spinal muscular atrophy.

9.4.2 Provide details on data from any single study that have been drawn from more than one source (for example a poster and unpublished report) and/or when trials are linked this should be made clear (for example, an open-label extension to randomised controlled trial).

An overview of the clinical development programme for onasemnogene abeparvovec in SMA type 1 which consists of one completed Phase I/IIa trial (START), three ongoing Phase III trials (SPR1NT, STR1VE-EU and STR1VE [US]), and one ongoing long-term, follow-up study (LT-001) is provided in Section 9.4. To date, START is the only trial to have reached completion. Data for the START study reported in the submission have been drawn from two publications where possible, Mendell et al. 2017 (2) and Al-Zaidy et al. 2019 (24), and the clinical study report (CSR) where additional detail is necessary (25). At the end of the START study, patients were invited to enrol in the ongoing observational long-term, single-centre study LT-001 to obtain a long-term data set. LT-001 involves evaluation of the efficacy of onasemnogene abeparvovec by a single annual assessment of whether the highest milestone attained in START has been maintained (or improved) up to 15 years post administration.

9.4.3 Highlight any differences between patient populations and methodology in all included studies.

The key differences between the included studies are as follows:

- Efficacy is a primary objective in the ongoing STR1VE-US, STR1VE-EU and SPR1NT studies and a secondary objective in the completed START study
- The STR1VE-US, and STR1VE-EU studies include symptomatic patients with SMA type 1, as did the START study.
- SPR1NT includes pre-symptomatic SMA patients with 2 or 3 copies of *SMN2*
- START enrolled patients with SMA type 1 with two copies of *SMN2*. The STR1VE studies (US and EU) have a slightly broader inclusion criteria, enrolling SMA type 1 patients with 1 or 2 copies of *SMN2;* however, patients with 1 copy of *SMN2* will be excluded from the ITT efficacy analyses and assessed as part of an all enrolled population only. The SPR1NT study is enrolling patients with 2 or 3 copies of *SMN2*; both *SMN2* copy number populations will form part of the ITT population in SPR1NT and patients will be followed in discrete cohorts based upon *SMN2* copy number, and analysed separately based upon genotype-specific primary endpoints (sitting independently, walking independently)
- START excluded patients with SMA type 1 who had the *SMN2* [c.859G>C] modification in exon 7 (which increases the amount of full-length mRNA transcripts produced, thus resulting in, and predictive of, a less severe SMA phenotype). The STR1VE (US and EU) and SPR1NT studies allow enrolment of SMA patients inclusive of this known *SMN2* gene modifier mutation [c.859G>C]; however, patients with this *SMN2* gene modifier mutation [c.859G>C] will be excluded from the ITT

efficacy analysis, and assessed as part of additional analyses only. As of the 8 March 2019 data cut (42), no infants with the *SMN2* gene modifier mutation [c.859G>C] have been enrolled in the clinical development programme for the IV administration of onasemnogene abeparvovec

- START included two different onasemnogene abeparvovec dosing cohorts; Cohort 1 received a one-time peripheral IV infusion of 6.7 x 10^{13} vg/kg (low dose) and Cohort 2 received a one-time peripheral IV infusion of 2.0 x 10^{14} vg/kg (therapeutic dose), when measured initially by an early development stage quantitative polymerase chain reaction (qPCR) assay. Direct testing of the actual lot of investigational product used in START by an improved and more fully qualified analytical method (droplet digital PCR [ddPCR]) has determined the actual dose received by Cohort 1 to be 3.7 x 10^{13} vg/kg and the actual dose received by Cohort 2 to be 1.1 x 10^{14} vg/kg. It is important to note that the ddPCR value is a more accurate measurement of the vector genome content than the qPCR value, and does not represent a reduction in the dose administered. The therapeutic IV dose of the onasemnogene abeparvovec manufactured by AveXis and used in the STR1VE-US, STR1VE-EU and SPR1NT studies is determined by the ddPCR assay and is 1.1 X 10^{14} vg/kg

- To address the need for long-term data, patients receiving onasemnogene abeparvovec in START were enrolled in the ongoing observational long-term LT-001, that includes a single annual assessment of whether the highest milestone attained in START has been maintained up to 15 years post administration. To date (31 December 2018 data cut), the median time since one-time onasemnogene abeparvovec administration in patients treated with the therapeutic dose in START (Cohort 2) was 44.8 months; with longest duration of therapy recorded at 49.7 months since dosing in START

- To provide further long-term data AveXis also plan to introduce a patient registry (RESTORE). The registry will follow approximately 500 patients with SMA in clinical practice in the US, UK, France, Germany, Italy, Spain, and other countries, including 100 patients treated with existing or upcoming approved treatments. The demographics, genetic status, family and medical history of patients will be collated as will details of treatments received. The output from the registry will include long-term effectiveness and safety outcomes in a real-world observational setting, including the pulmonary and nutritional requirements of patients, hospitalisations, AEs, and caregiver burden and QoL. The registry will collate data for patients every 6 months until the 24 month visit and then annually for up to 15 years or until death, whichever is sooner

- To allow development of an appropriate natural history comparator cohort for START, a control population was drawn from external sources, namely the PNCR and NeuroNext studies (12, 27, 67). Details of the PNCR and NeuroNext patient populations, and their comparison to the START cohort, are described in Section 9.4.3.1

The key baseline characteristics of the patients included in each trial are shown in Table 21 to Table 25.

Table 21: Baseline characteristics of START

Characteristic	Cohort 1 6.7×10^{13} vg/kg (N=3)	Cohort 2 2.0×10^{14} vg/kg (N=12)	All patients (N=15)
SMN2 copy number	2	2	2
Age at treatment[†], months Mean (SD) Min, Max	 6.3 (0.75) 5.9, 7.2	 3.4 (2.06) 0.9, 7.9	 4.0 (2.21) 0.9–7.9
Sex Female, % Male, %	 66.7 33.3	 58.3 41.7	 60.0 40.0
Race, % White Other	 100 0	 91.7 8.3	 93.3 6.7
Ethnicity, % Not Hispanic or Latino Hispanic or Latino	 100 0	 83.3 16.7	 86.7 13.3
Weight, mean (SD), kg	6.6 (0.56)	5.7 (1.34)	5.9 (1.27)
Gestational age at birth, weeks n Mean (SD)	 2 39.0 (1.41)	 10 38.5 (1.43)	 12 38.6 (1.38)
Mean age at symptom onset, months (SD)	1.7 (1.15)	1.4 (1.0)	1.5 (0.99)
Mean age at genetic diagnosis, days (range)[§]	33 (4–85)	60 (0–136)	–
Mean CHOP-INTEND score (SD)[¶]	16.3 (10.5)	28.2 (12.3)	25.8 (12.6)[††]

Characteristic	Cohort 1 6.7×10^{13} vg/kg (N=3)	Cohort 2 2.0×10^{14} vg/kg (N=12)	All patients (N=15)
Swallowing thin liquid, n (%)			
Yes	0 (0.0)	4 (33.3)	4 (26.7)
No	3 (100)	8 (66.7)	11 (73.3)
Non-oral feeding support, n (%)			
Yes	3 (100)	5 (41.7)	8 (53.3)
No	0	7 (58.3)	7 (46.7)
Ventilatory support (invasive/non-invasive), n (%)			
Yes	3 (100)	1 (8.3)‡	4 (26.7)‡
No	0	11 (91.7)	11 (73.3)
Familial history of SMA including affected siblings or parent carriers, n (%)			
Yes	1 (33.3)	3 (25.0)	4 (26.7)
No	2 (66.7)	8 (66.7)	10 (66.7)
Unknown	0	1 (8.3)	1 (6.7)
Total number of days of prednisolone administration, mean (SD)	47.7 (14.1)‡‡	73.8 (33.0)	68.6 (31.7)

Abbreviations: CHOP-INTEND, Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders; SD, standard deviation; SMA, spinal muscular atrophy.
† On day of onasemnogene abeparvovec administration. ‡ Does not include one additional patient in Cohort 2 who was receiving BiPAP at baseline but for whom data was mis-entered at the clinical site. § In one patient in Cohort 2, the diagnosis was made prenatally, so an age of 0 was reported at the time of genetic diagnosis. ¶ Scores on the CHOP-INTEND scale of motor function range from 0 to 64, with higher scores indicating better function. †† Data for 'All patients' were calculated using CHOP-INTEND data for all patients (Listing 16.2.6.4-24). ‡‡ Includes one patient who did not receive prednisolone prophylactically but the corticosteroid began on Day 27.

Table 22: Baseline characteristics of STR1VE-EU (Day 120 update [8 March 2019], study ongoing)

Characteristic	N=23[†]
SMN2 copy number	2
Mean (range) age at treatment, months[‡]	3.8 (2–6)
Mean (range) age at symptom onset, months	1.4 (0–4)
Mean (range) age at genetic diagnosis[§¶], days	71 (0–147)
Mean (range) weight at baseline, kg	5.8 (4–8)
Mean (range) length/height at baseline, cm	61.9 (55–68)
Sex, n (%)	
Female	13 (57)
Male	10 (43)
Patients with clinical support, n (%)	
Nutritional support prior to or within 1 week of dosing	8 (35)
Ventilatory support prior to dosing	4 (17)
Ventilatory support prior to or within 1 week of dosing	7 (30)
Ventilatory support prior to 6 months of age	8 (35)
Swallowing test, n (%)[††]	
Safely swallows thin liquids	20 (87)
Safely swallows allowing for oral feeding	21 (91)
Exclusively fed by mouth	17 (74)
Mean (range) score on CHOP-INTEND scale[‡‡]	26 (14–38)

Abbreviations: SD, standard deviation; SMA, spinal muscular atrophy.
† Enrolment to STR1VE-EU completed in May 2019. At the 8 March 2019 data cut (31), 23/33 infants with SMA type 1 were enrolled in STR1VE-EU.
‡ Age = (dose date - date of birth + 1).
§ Age at genetic diagnosis is missing for 4 patients, therefore n=19 for this entry.
¶ Patients diagnosed prenatally are standardised to 0 days.
†† Swallowing function was assessed via video fluoroscopic swallow test.
‡‡ Scores on CHOP-INTEND scale of motor function range from 0 to 64, with higher scores indicating better function.
Source: Mercuri et al. 2019 (124), 8 March 2019 efficacy data cut (data on file) (42).

Table 23: Baseline characteristics of STR1VE-US (Day 120 update [8 March 2019], study ongoing)

Characteristic	N=22
SMN2 copy number	2
Mean (range) age at treatment, months†	3.7 (1–6)
Mean (range) age at symptom onset, months	1.9 (0–4)
Mean (range) age at genetic diagnosis‡, days	78 (0–162)
Mean (range) weight at baseline, kg	5.8 (4–8)
Mean (range) length/height at baseline, cm	61 (51–70)
Sex, n (%)	
Female	12 (55)
Male	10 (45)
Patients with clinical support, n (%)	
Nutritional support prior to or within 1 week of dosing	0
Ventilatory support prior to dosing	0
Ventilatory support prior to or within 1 week of dosing	1 (5)
Ventilatory support prior to 6 months of age	2 (9)
Swallowing test, n (%)§	
Safely swallows thin liquids	22 (100)
Safely swallows allowing for oral feeding	22 (100)
Exclusively fed by mouth	22 (100)
Mean (range) score on CHOP-INTEND scale¶	32 (17–52)

Abbreviations: CHOP-INTEND, Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders.
† Age = (dose date - date of birth + 1).
‡ Age at genetic diagnosis is missing for 4 patients, therefore n=19 for this entry.
§ Swallowing function was assessed via video fluoroscopic swallow test.
¶ Scores on CHOP-INTEND scale of motor function range from 0 to 64, with higher scores indicating better function.
Source: Mercuri et al. 2019 (124), 8 March 2019 efficacy data cut (data on file) (42).
Note: 1/22 patients was initially enrolled as a pre-symptomatic SMA patient, however this patient was reclassified as symptomatic by the Investigator after 31 December 2018.

Table 24: Baseline characteristics of SPR1NT (Day 120 update [8 March 2019], study ongoing)

Characteristic	*SMN2* x 2 (n=8)	*SMN2* x 3 (n=9)
Mean age† ± SD (range) at study day 1 visit, days	18.3 ± 9.5 (8.0–34.0)	25.6 ± 12.2 (9.0–40.0)
Mean age ± SD (range) at genetic diagnosis, days	-54.9 ± 84.6‡ (-177.0–14.0)	9.4 ± 8.2 (2.0–26.0)
Sex		
Female, %	75.0	55.6
Male, %	25.0	44.4
Race, %		
White	62.5	66.7
Other	37.5	33.3
Ethnicity, %		
Not Hispanic or Latino	75.0	88.9
Hispanic or Latino	25.0	11.1
Weight, kg (SD)	3.5 (0.4)	4.0 (0.6)
CHOP-INTEND (SD)	44.0 (8.4)	–
Patients with ≥1 affected siblings, n (%)§	6 (86)	6 (75)
Modality of diagnosis, n (%)		
Prenatal testing	3 (38)	0
Targeted perinatal screening¶	5 (63)	9 (100)

Abbreviations: CHOP-INTEND, Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders; SD, standard deviation; SMA, spinal muscular atrophy.
† Age = (dose date - date of birth + 1), expressed in days.
‡ Age of diagnosis is negative for patients diagnosed in utero.
§ Data were only available for 15 patients; n=7 for 2 copies of *SMN2*; n=8 for 3 copies of *SMN2*.
¶ Four patients were identified via carrier testing followed by molecular screening of umbilical cord blood.
Source: Strauss et al. 2019a (125); 8 March 2019 efficacy data cut (data on file) (42).

Table 25: Baseline characteristics of LT-001 (Day 120 update [27 September 2018], study ongoing)

Characteristic	All patients (N=13)
Mean age† (SD), years	2.5 (0.52)
Sex	
Female, %	53.8
Male, %	46.2
Race, %	
White	92.3
Other	7.7
Ethnicity, %	
Not Hispanic or Latino	92.3
Hispanic or Latino	7.7
Weight, mean (SD), kg	12.2 (1.4)

Abbreviations: CHOP-INTEND, Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders; SD, standard deviation; SMA, spinal muscular atrophy.
† Age = (Visit Date - Date of Birth + 1) / 365.25.
Source: 27 September 2018 efficacy data cut (data on file) (43).

9.4.3.1 Natural history cohorts (NeuroNext and PNCR)

PNCR

The PNCR Natural History dataset (67) was drawn from a natural history study of 337 patients in the US with any form of SMA followed at three internationally recognised tertiary medical centres with significant expertise in the management of SMA (i.e. Harvard University/Boston Children's Hospital, Columbia University, and the University of Pennsylvania/Children's Hospital of Philadelphia). The study enrolled both previously identified patients followed in PNCR site clinics and newly diagnosed patients. All eligible patients were offered participation in the PNCR study. Study visits were scheduled at Baseline, 2, 4, 6, 9, and 12 months, and every 6 months thereafter. The SMA standard of care guidelines published in 2007 (64) were used as a basis for providing uniform care among the study sites. For the purposes of this study, the ability to sit unsupported (to distinguish and differentiate infants with SMA type 1 and 2) was defined as being able to sit independently for >10 seconds (the World Health Organization-Multicentre Growth Reference Study criteria) (126); infants who were unable at any point to achieve this milestone were classified as SMA type 1.

To allow development of an appropriate comparator cohort for START, a natural history control population was drawn from this PNCR Natural History Dataset (67) consisting of patients with age of onset ≤6 months, bi-allelic deletion of *SMN1* (exon 7/8 common homozygous deletion) and two copies of *SMN2* for whom enrolment data (retrospective and prospective) were available. All patients with SMA type 1 in the PNCR natural history study were affected by bi-allelic deletions of *SMN1*.

The *SMN2* modifier mutation (c.859G>C) described by Prior et al. 2009 (127) was not assessed in the PNCR study cohort. Because this positive modifier is associated with lesser

clinical severity, and patients with this modifier were excluded from the intention-to-treat (ITT) population in START, this potential difference in study populations could result in some bias against detecting efficacy of onasemnogene abeparvovec if the PNCR included some patients with this modifier.

Based on these criteria, the control population consists of 23 patients from the PNCR dataset. As demonstrated in Table 27 below, the overall demographics of these patients are similar to the START Cohort 2 group (those treated with the therapeutic dose of onasemnogene abeparvovec).The mean age of onset of SMA was 3.0 months and half of patients required both nutrition and ventilation support at baseline; the majority of patients (91.3%) required ventilation before 6 months of age. Comparative details reflective of the course of disease in the PNCR cohort are presented versus START in Section 9.6.1.1.

Both the natural history populations reported by Finkel et al. 2014a (12) and the PNCR external control group for START (67) were selected from the PNCR natural history database for SMA. Each population has 23 patients with SMA type 1 and 2 copies of *SMN2,* but one patient differs between these control groups. Finkel et al. 2014a (12) selected patients enrolled from May 2005 until April 2009 in the PNCR database, while the START PNCR external control group was selected using the entire PNCR database. As a result, one patient was included in the START PNCR control group and one other patient was excluded; see Table 26. All other 22 patients in the control groups reported by Finkel et al. 2014a (12) and the START PNCR external control group (67) are the same. As a result, the population reported by Finkel et al. 2014a (12) had 19 events (death or permanent ventilation) but the START PNCR control group has 18 events (death or permanent ventilation) (67).

Table 26: Demographic and baseline characteristics START, NeuroNext and PNCR

Patient ID	Status for Finkel et al. 2014a PNCR control group	Status for START PNCR control group	Patient status for composite event
[redacted]	Excluded because enrolment date was after April, 2009	Included because all entry criteria were met	No events
[redacted]	Included	Excluded because did not meet entry criterion for age of SMA onset ≤6 months (7 months)	Event of permanent ventilatory support at 8.3 months of age

Abbreviations: CHOP-INTEND, Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders; PNCR, Pediatric Neuromuscular Clinical Research database; SD, standard deviation.

NeuroNext

A population drawn from the NeuroNext natural history study was used as a supplementary control cohort (67). The NeuroNext natural history study was a longitudinal, multi-centre, prospective, natural history study that enrolled 26 SMA infants <6 months of age (and 27 healthy control infants) at 14 centres over 21 months within the National Institute of Neurological Disorders and Stroke (NINDS) -sponsored NeuroNext Network, designed to mimic a clinical study (26, 27).

Enrolment was restricted to infants who were 6 months of age or younger and were born between 36 and 42 weeks of gestation. The study, which was designed to mimic the inclusion and timing of future SMA clinical trials targeting treatment to SMA infants, closely resembled the entry criteria for START with respect to age, genetic criteria (SMN2 copy number) and baseline function. The diagnosis of SMA was made by study investigators or community neurologists and confirmed with clinical genetic testing prior to enrolment. Asymptomatic (pre-symptomatic) patients who had been genetically tested prior to the enrolment were also permitted entry into the study. Patients were excluded if they required non-invasive ventilatory support (i.e. BiPAP) for ≥12 hours/day, had a comorbid illness or were enrolled in an SMA therapeutic clinical trial. The study excluded SMA infants taking any therapies thought to increase SMN expression, such as valproic acid.

Survival within the NeuroNext study was defined as alive without tracheostomy, a somewhat less stringent definition than that used in the PNCR and onasemnogene abeparvovec clinical studies (event defined by death, tracheostomy or requirement of ≥16 hours of ventilatory support for ≥2 weeks, excepting acute reversible illness or perioperative use). Infant motor function as measured by the CHOP-INTEND was assessed prior to 6 months of age and at 6, 9, 12, 18, and 24 months of age.

SMA was confirmed by genetic testing prior to enrolment. All patients had bi-allelic deletions of SMN1 exon 7. SMN2 copy number was measured in all patients except for four who died before confirmation samples were obtained but who were presumed to have 2 copies of SMN2 based upon disease course. Sixteen infants had 2 copies of *SMN2*, 5 infants had 3 copies, and 1 infant had 4 copies. Exclusion of the *SMN2* gene modifier mutation c.859G>C was confirmed in all but the 4 patients who died.

The NeuroNext cohort of 16 patients with *SMN2* copy number of 2 was therefore selected as a secondary natural history control population. As demonstrated in Table 27, the overall demographics of these patients are similar to the START Cohort 2 group (those treated with the therapeutic dose of onasemnogene abeparvovec). Comparative details reflective of the course of disease in the NeuroNext cohort are presented versus START in Section 9.6.1.1.

Table 27: Demographic and baseline characteristics START, NeuroNext and PNCR

Characteristic	START, Cohort 2 (N=12)	NeuroNext control (N=16)	PNCR control (N=23)
Age at enrolment†, months			
Mean (SD)	3.5 (2.1)	4.1 (1.7)	29.0 (41.7)
Min, Max	0.9, 7.9	0,6	2, 171
Sex, %			
Female	58.3	50.0	52.2
Male	41.7	50.0	47.8
Race, %			
White	91.7	93.8	69.6
Other	8.3	6.2	30.4
Ethnicity, %			
Not Hispanic or Latino	83.3	68.7	87.0
Hispanic or Latino	16.7	31.3	13.0
Mean age at symptom onset, months (SD)	1.4 (1.0)	N/A	3.0 (1.6)
CHOP-INTEND scale, score‡			
Mean (SD)	28 (12.3)	20.3 (7.3)	24.6 (11.6)
Min, Max	12, 50	10, 33	5, 40
Did not require support of, n (%):			
Nutrition	7 (58.3)	9 (56.3)	5 (21.7)
Ventilation	10 (83.3)	10 (62.5)	11 (47.8)
Both nutrition and ventilation	10 (83.3)	14 (87.5)	11 (47.8)
Ventilation before 6 months of age	10 (83.3)	10 (62.5)	21 (91.3)

Abbreviations: CHOP-INTEND, Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders; N/A, not applicable; PNCR, Pediatric Neuromuscular Clinical Research database; SD, standard deviation.
† At baseline (Study 101 and NeuroNext) or enrolment (PNCR).
‡ Scores on the CHOP-INTEND scale of motor function range from 0 to 64, with higher scores indicating better function.

9.4.3.2 Natural history controls comparison with START population

The PNCR and NeuroNext datasets provide valid patient-level data that thoroughly describes the natural history of SMA type 1 without the use of a disease-modifying therapy (67). Both datasets are internally consistent and consistent with other studies from Europe and the US that have detailed the course of the disease (54, 60, 70, 71). Therefore, SMA type 1 patients from the PNCR dataset and the NeuroNext dataset were considered to be appropriate comparators for the patients treated with onasemnogene abeparvovec (67). Details of the START population are provided in Sections 9.4.3 and 9.6.1.1. All patients in all three cohorts (PNCR, NeuroNext, and START) were classified as SMA type 1 based upon clinical characteristics and age of onset. Additionally, all patients had 2 copies of *SMN2*, indicating a consistent genetic profile across the patient pool.

Motor function at baseline (START) and enrolment (PNCR) was similar between patients in both studies, despite the older age of the PNCR cohort at the time of screening. A greater proportion of the PNCR cohort required ventilator and non-oral feeding support at the time of the initial evaluation, reflecting the different nature of the datasets. However, the comparison considers age at the initiation and escalation of ventilatory and nutritional support, which in many cases occurred prior to the enrolment of patients into the PNCR. A more relevant comparison is the ventilation support status at 6 months of age in the PNCR dataset, the age at which almost all patients in START had been enrolled. At 6 months of age, the majority of the PNCR cohort (91.3%) remained free of ventilator support, a higher percentage than were free of such support at baseline in the START cohort (83.3%). This suggests that the START cohort had more severe pulmonary dysfunction prior to dosing than the PNCR cohort at similar ages.

The NeuroNext and START cohorts had similar baseline ventilatory and nutritional support requirements, and a similar age of enrolment and baseline motor function, although the NeuroNext cohort was enrolled at a slightly older age and had slightly lower motor function at the time of enrolment. The generalisability of the extracted PNCR and NeuroNext natural history control cohorts to the UK SMA patient population treated with BSC was confirmed by the UK Clinical Advisory Board (May 2019) (17).

9.4.4 Provide details of any subgroup analyses that were undertaken in the studies included in section 9.4.1. Specify the rationale and state whether these analyses were pre-planned or post-hoc.

Whilst no formal subgroup analyses were pre-planned in START, an explorative post-hoc analysis was completed to assess time to independent sitting based on age at treatment. Results should be interpreted with an understanding of the caveats of the small sample size and that the analysis was conducted post-hoc.

9.4.5 If applicable, provide details of the numbers of patients who were eligible to enter the study(s), randomised, and allocated to each treatment in an appropriate format.

Details of patients who were screened but did not receive treatment in each trial are presented in Table 28. In total, of 94 infants screened for inclusion in the clinical trial programme for IV administration of onasemnogene abeparvovec, of which 5 infants were excluded due to elevated AAV9 titres (>1:50).

In START, 3 of the 16 (18.8%) patients screened for AAV9 antibodies had titers >1:50 at first testing. Two patients were retested following cessation of breast-feeding and reported to have titres of <1:50 and both were enrolled in the study. The remaining patient was excluded due to elevated AAV9 antibody titers.

In STR1VE-EU, 6/29 infants failed screening: 4 patients had elevated AAV9 titres, [redacted] Twenty-three infants with SMA type 1 or 2 genetically defined by bi-allelic deletion of *SMN1* with 2 or 3 copies of *SMN2* were screened for inclusion in SPR1NT. [redacted]

Table 28: Screening failures in the onasemnogene abeparvovec clinical trial programme

Study name	Number of patients screened	Reason for screening failure								Total number of patients excluded	Patients treated as of 8 March 2019
		Elevated AAV9 titres	Withdrew consent	Died	Respiratory infection within 4 weeks of screening	CMAP <2 mV	Symptomatic at screening	Weight below the WHO 3% limit	Failed swallowing test		
Newborns											
SPR1NT	23	–	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	5	17†
Total	**23**	–	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**5/23 (21.7%)**	**17**
Infants											
START	16	1	–	–	–	–	–	–	–	1	15
STR1VE-EU	29	4	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	6	23
STR1VE-US	26	–	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	4	22
Total	**71**	**5/71 (7.0%)**	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**11/71 (15.5%)**	**60**
All trials total	**94**	**5/94 (5.3%)**	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**16/94 (17.0%)**	**77**

Abbreviations: AAV-9, adeno-associated virus; N/A, not applicable.
Source: AveXis data on file; data extracted 8 March 2019.
† One additional patient originally included in SPR1NT was excluded as in protocol amendment 27 September 2018, pre-symptomatic patients with 4 copies of *SMN2* were removed from inclusion (46).

9.4.6 If applicable provide details of and the rationale for, patients that were lost to follow-up or withdrew from the studies.

No patients withdrew from START or were lost to follow-up. Of the 15 patients enrolled in START, 13 patients enrolled in the long-term follow-up study, LT-001. The parents/carers of the 2 patients from START who were not enrolled in LT-001 were not required to provide a reason for the decision not to enrol.

As of the latest available data cut (8 March 2019), 1 patient had died (Section 9.7.2.4) and 1 patient had withdrawn consent for inclusion in STR1VE-US. One patient enrolled in STR1VE-EU had also died (Section 9.7.2.3).

9.5 *Critical appraisal of relevant studies*

9.5.1 Complete a separate quality assessment table for each study. A suggested format for the quality assessment results is shown in tables C7 and C8.

A critical appraisal of START is presented in Table 29. Quality assessments of STR1VE-EU, STR1VE-US, SPR1NT, or LT-001 are not provided as the studies are ongoing.

Table 29: Critical appraisal of START

Study name	Mendell et al. 2017 (2) (NCT02122952)	
Study question	**Response yes/no/not clear/N/A)**	**How is the question addressed in the study?**
Was the cohort recruited in an acceptable way?	Yes	The cohort was representative of the relevant targeted population. Clear inclusion/exclusion criteria were described in the publication and protocol
Was the exposure accurately measured to minimise bias?	Yes	Details of interventions for each of the two cohorts were fully described
Was the outcome accurately measured to minimise bias?	Yes	Measurements for primary and secondary outcomes were clearly described. Safety was determined on the basis of the occurrence of any one Grade III or higher treatment-related toxicity. Secondary outcomes were time until death and the need for permanent ventilatory assistance defined as ≥16 hours of respiratory assistance per day continuously for at least 14 days in the absence of an acute, reversible illness or a perioperative state
Have the authors identified all important confounding factors?	Yes	The inclusion criteria were carefully considered by investigators with regards confounding factors. Investigators '*restricted enrolment to include only symptomatic patients with SMA1 who had biallelic SMN1 mutations and two SMN2 copies and did not enrol patients with the c.859G→C genetic modifier in exon 7 of SMN2, since this genetic modifier predicts a milder phenotype of the disease*'

Have the authors taken account of the confounding factors in the design and/or analysis?	Yes	See above
Was the follow-up of patients complete?	Yes	All 15 patients were alive and event-free at 24 months of age as of the data cut off
How precise (for example, in terms of confidence interval and p values) are the results?	N/A	
Adapted from Critical Appraisal Skills Programme (CASP): Making sense of evidence 12 questions to help you make sense of a cohort study		

9.6 *Results of the relevant studies*

9.6.1 Complete a results table for each study with all relevant outcome measures pertinent to the decision problem. A suggested format is given in table C9.

9.6.1.1 START

The efficacy analysis of onasemnogene abeparvovec was carried out in the following SMA type 1 populations:

- ITT analysis set – included all 15 patients who underwent gene replacement therapy via a one-time peripheral IV infusion of onasemnogene abeparvovec
- Full analysis set (FAS) – included all 15 patients who underwent gene replacement therapy via a one-time peripheral IV infusion of onasemnogene abeparvovec and had at least 1 post-infusion visit
- Ability to thrive ITT population – included all 7 patients with bi-allelic deletion of *SMN1* and a baseline CHOP-INTEND score of ≥20 who received an infusion of onasemnogene abeparvovec at 2.0 x 10^{14} vg/kg[c] (therapeutic dose) and who did not require non-oral nutrition prior to gene replacement therapy via a one-time peripheral IV infusion of onasemnogene abeparvovec
- SAS – included any patient who underwent gene replacement therapy via a one-time peripheral IV infusion of onasemnogene abeparvovec

Efficacy analyses were conducted at the following time points:

- The date at which all patients had completed a study visit after reaching 13.6 months of age

[c] Direct testing of the actual lot of IMP used in START by an improved and more fully qualified analytical method has determined the actual dose received by Cohort 2 to be 1.1 x 10^{14} vg/kg. The same method has been used to establish an equivalent dose for the IMP in all Phase III trials.

- When the last enrolled patient had a study visit after reaching 20 months of age
- When all patients completed 24 months of post-dose follow-up

The first two time points were selected to allow a comparison with the external PNCR natural history study of SMA type 1 patients (12), in which it was estimated that only 25% of SMA type 1 patients with 2 copies of *SMN2* would survive ventilation-free to 13.6 months of age and that only 8% would survive ventilation-free to 20 months of age.

Results of the outcomes relevant to the decision problem are presented in Table 30.

Table 30: START efficacy results

Outcome	13.6 months of age			24 months post-dose		
	Cohort 1 (N=3)	Cohort 2 (N=12)	All patients (N=15)	Cohort 1 (N=3)	Cohort 2 (N=12)	All patients (N=15)
Survived without permanent ventilation, ITT set, % (95% CI[†]; p value[‡])	100 (29.2, 100; 0.016)	100 (73.5, 100; <0.001)	100 (78.0, 100; <0.001)	66.7 (9.4, 99.2; 0.018)	100 (73.54 100; <0.001)	93.3 (68.1, 99.8; <0.001)
Change from baseline in CHOP-INTEND score, FAS	+7.7	+24.6	–	–	+30.7	–
Proportion of patients in the FAS who achieved CHOP-INTEND scores:						
≥40, % (p value[¶])	0	91.7 (<0.001)	–	–	91.7 (<0.001)	–
≥50, % (p value[¶])	0	83.3 (<0.001)	–	–	91.7 (<0.001)	–
≥60, % (p value[¶])	0	25.0 (<0.001)	–	–	33.3 (<0.001)	–
Bayley score, mean (SD)	–	–	–	–	40.3 (3.10)	–
Functional independent sitting (≥30 seconds), % 95% CI[†]; p value[¶])	0	41.7 (15.2, 72.3; <0.001)	33.3 (11.8, 61.6; <0.001)	0	75 (42.8, 94.5; <0.001)	60.0 (32.3, 83.7; <0.001)
Developed significant motor function milestones based on video reviews by external expert, %						
Rolling (back to side from both sides)	0	75.0	60.0	0	75.0	60.0
Hold head erect ≥3 seconds, unsupported	0	91.7	73.3	0	91.7	73.3
Sits with support	0	91.7	73.3	0	91.7	73.3
Sits alone ≥5 seconds[§††]b	0	75.0	60.0	0	91.7	73.3
Sits alone ≥10 seconds[§]	0	58.3	46.7	0	83.3	66.7
Sits alone ≥15 seconds[§]	0	50.0	40.0	0	75.0	60.0
Sits alone ≥30 seconds[§]	0	41.7	33.3	0	75.0	60.0
Stands with assistance	0	16.7	13.3	0	16.7	13.3
Stands alone	0	16.7	13.3	0	16.7	13.3
Walks with assistance	0	16.7	13.3	0	16.7	13.3
Walks alone	0	16.7	13.3	0	16.7	13.3
Independent of ventilatory support, FAS, % (95% CI[†]; p value[¶])	0	58.3 (27.7, 84.8; <0.001)	46.7 (21.3, 73.4; <0.001)	0	50.0[¶¶] (21.1, 78.9; <0.001)	40.0[¶¶] (16.3, 67.7; <0.001)

Outcome	13.6 months of age			24 months post-dose		
	Cohort 1 (N=3)	Cohort 2 (N=12)	All patients (N=15)	Cohort 1 (N=3)	Cohort 2 (N=12)	All patients (N=15)
Maintained the ability to thrive, Ability to thrive ITT set, % (95% CI†; p value¶)	0	85.7 (42.1, 99.64; <0.001)	85.7 (42.1, 99.6; <0.001)	0	71.4 (29.0, 96.3; <0.001)	71.4 (29.0, 96.3; <0.001)
Proportion of patients in the SAS receiving non-oral feeding support‡‡, %						
Gastrostomy with Nissen fundoplication	100	33.3	46.7	100	33.3	46.7
Gastrostomy without Nissen fundoplication	0	0	0	0	8.3	6.7
Nasogastric	0	0	0	0	8.3	6.7
Nasojejunal	0	25.0	20.0	0	25.0	20.0
Gastrostomy with a jejunostomy tube threaded for feeds	0	8.3	6.7	0	8.3	6.7

Abbreviations: CI, confidence interval; CHOP-INTEND, Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders; FAS, full analysis set; IMP, investigational medicinal product; ITT, intention-to-treat; SAS, safety analysis set.

Note: Cohort 1 received the low dose onasemnogene abeparvovec (6.7 x 10^{13} vg/kg) and Cohort 2 received the therapeutic dose of onasemnogene abeparvovec (2.0 x 10^{14} vg/kg). Direct testing of the actual lot of IMP used in START by an improved and more fully qualified analytical method has determined the actual dose received by Cohort 2 to be 1.1 x 1014 vg/kg. The same method has been used to establish an equivalent dose for the IMP in all Phase III trials.

† Confidence interval from the superiority 1-sided exact binomial test.

‡ Compared with the external natural history estimates of 25% for 13.6 months of age and 8% for 24 months post-dose (12) using a 1-sample exact binomial test.

¶ Compared with zero using a 1-sided exact binomial test. To make computation of the p-value possible, the value of 0.1% was used in place of a literal zero.

§ Patients are included in multiple categories for the "sits alone" milestone. Patients sitting ≥30 seconds are included in the totals for ≥15 seconds, ≥10 seconds, and ≥5 seconds.

†† The source table and listing include a milestone identified as "Sits alone <10 seconds". The external reviewer confirmed that this milestone was defined as "Sits alone ≥5 seconds" and that is how it is labelled here.

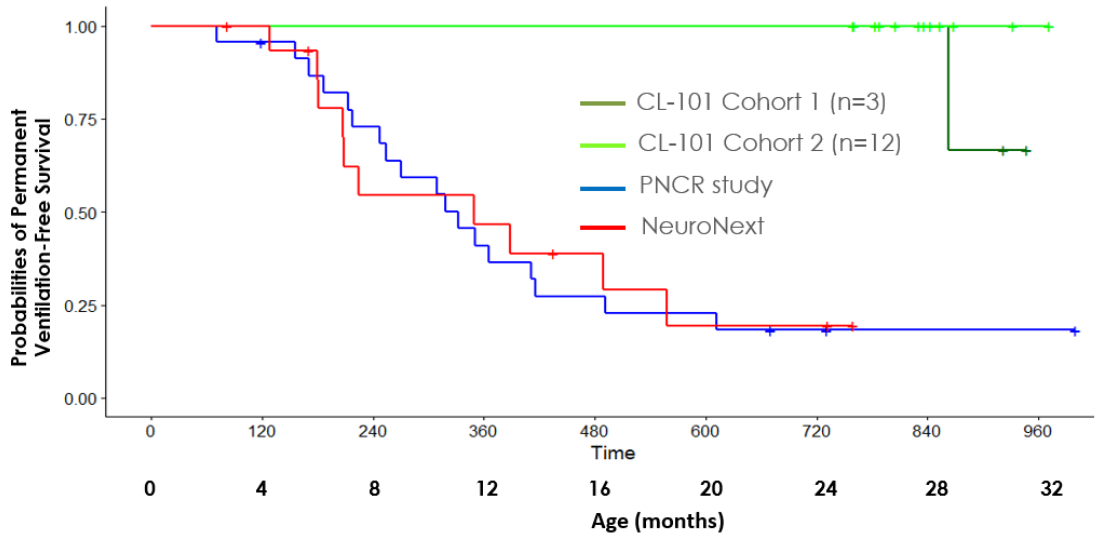
‡‡ patients may be counted more than once in a non-oral feeding category due to changes in non-oral feeding support apparatus or mechanism

¶¶ Does not include 1 additional patient in Cohort 2 who only used BiPAP during illness.

Sustained improvements from baseline to last observation across a range of clinical outcomes were observed in both patient cohorts following treatment with onasemnogene abeparvovec in the START study. It should be noted that patients in Cohort 1 received a lower dose of onasemnogene abeparvovec than those in Cohort 2 (6.7×10^{13} vg/kg versus 2.0×10^{14} vg/kg[d]). Patients in Cohort 1 were also older at the time of administration (6.3 months [range 5.9 to 7.2] versus 3.4 months [range 0.9 to 7.9]), and had greater nutritional and ventilatory support requirements at baseline indicating that they suffered from more advanced disease. As the catastrophic loss of motor neurones in SMA is irreversible, disease progression results in permanent disability and the differences in baseline variables could therefore have favoured better outcomes in Cohort 2. However, the substantially greater efficacy observed across a broad number of the endpoints in Cohort 2, including CHOP-INTEND, developmental milestones, and respiratory support, suggest that these baseline differences are unlikely to fully account for the readily apparent greater efficacy of the 2.0×10^{14} vg/kg observed in this study.

Primary efficacy endpoint – survival without permanent ventilation

Onasemnogene abeparvovec administration increased survival for patients with SMA type 1, the primary efficacy endpoint, across all time-points assessed (**Error! Reference source not found.**). Survival and survival free of permanent ventilation (alive, without tracheostomy, and not requiring ≥16 hours of ventilatory support per day for ≥2 weeks, absent an acute reversible illness or perioperative) was markedly improved for patients in START compared with patients in natural history cohorts. All patients in START were alive and without permanent ventilation at the final assessment time point of 24 months after dosing, a statistically significant difference compared with the natural history rates estimated from the PNCR and NeuroNext database cohorts (67) (**Error! Reference source not found.**) and



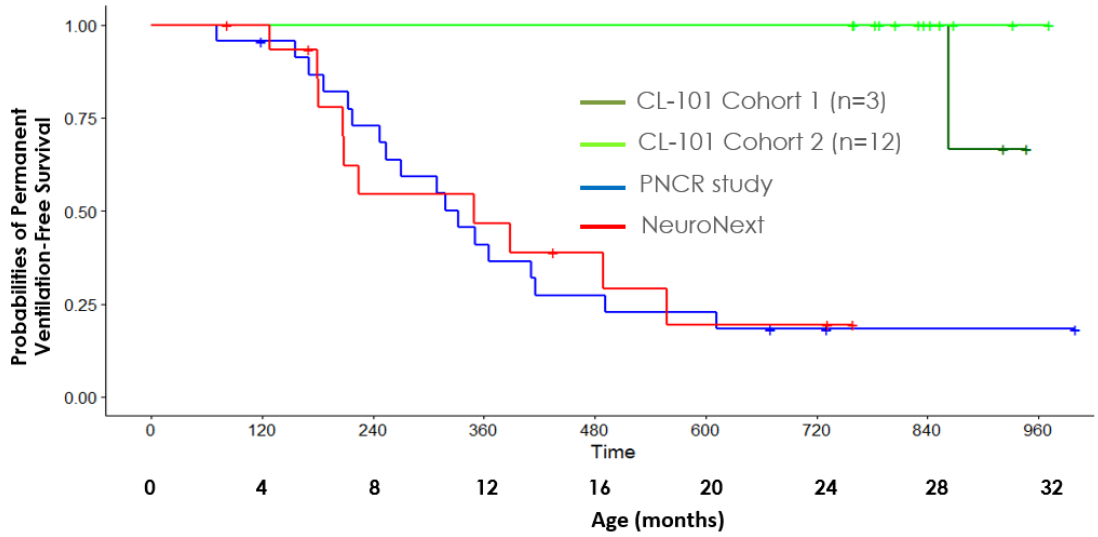
Data cut on August 7, 2017.
Natural history: The percentages of patients who were event-free in a study of SMA conducted by the PNCR network included ventilation-free survival measured as time until death or the need for ventilation for at least

[d] Direct testing of the actual lot of IMP used in START by an improved and more fully qualified analytical method has determined the actual dose received by Cohort 2 to be 1.1×10^{14} vg/kg. The same method has been used to establish an equivalent dose for the IMP in all Phase III trials.

16 hours per day for at least 14 consecutive days. In the NeuroNext study, a prospective natural history study in SMA infants with 2 copies of *SMN2*, survival as defined as alive without tracheostomy.

Table 31 and Table 32). One patient in Cohort 1 required permanent ventilation at approximately 29 months of age (22 months post-dose) for hypersalivation, thus meeting the survival endpoint. Following surgical ligation of the salivary glands, the child's ventilatory requirement subsequently reduced by 25% to below the 16 hours/day threshold.

Figure 9: Ventilation-free survival in START versus PNCR and NeuroNext natural history control



Abbreviations: PNCR, Pediatric Neuromuscular Clinical Research; SMA, spinal muscular atrophy.
Data cut on August 7, 2017.
Natural history: The percentages of patients who were event-free in a study of SMA conducted by the PNCR network included ventilation-free survival measured as time until death or the need for ventilation for at least 16 hours per day for at least 14 consecutive days. In the NeuroNext study, a prospective natural history study in SMA infants with 2 copies of *SMN2*, survival as defined as alive without tracheostomy.

Table 31: Time to event (death or permanent ventilation) for START and PNCR

	LIFETEST Procedure		
	START, Cohort 2 (N=12)	**PNCR (N=23)†**	**Total (N=35)**
Number of censored and uncensored values			
Reached an event, n	0	18	18
Censored, n (%)	12 (100)	5 (21.74)	17 (48.57)
Statistics for Time to Event (Months)			
Mean (SE)	--	11.9 (1.21)	--
Median	--	11.1	--
Homogeneity of Survival Curves for Time to Event			
Log-Rank Test	Ch-Square= 18.19	p<0.0001	--

Abbreviations: PNCR, Pediatric Neuromuscular Clinical Research; SE, standard error.
† Both the natural history populations reported by Finkel et al. 2014a (12) and the START PNCR external control group (67) were from the PNCR natural history database for SMA. Each population has 23 patients with SMA

type 1 and 2 copies of *SMN2,* but one patient differs between these control groups. As a result, the population reported by Finkel et al. 2014a had 19 events but the START PNCR external control group has 18 events.

Table 32: Time to event (death or permanent ventilation) for START and NeuroNext

	LIFETEST Procedure		
	START, Cohort 2 (N=12)	**NeuroNext (N=16)**	**Total (N=28)**
Number of censored and uncensored values			
Reached an event, n	0	10	10
Censored, n (%)	12 (100)	6 (37.50)	18 (64.29)
Statistics for Time to Event (Months)			
Mean (SE)	--	11.8 (1.59)	--
Median	--	11.6	--
Homogeneity of Survival Curves for Time to Event			
Log-Rank Test	Ch-Square= 15.94	p<0.0001	--

Abbreviations: SE, standard error.

Secondary efficacy endpoints

Motor function assessments

The Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders

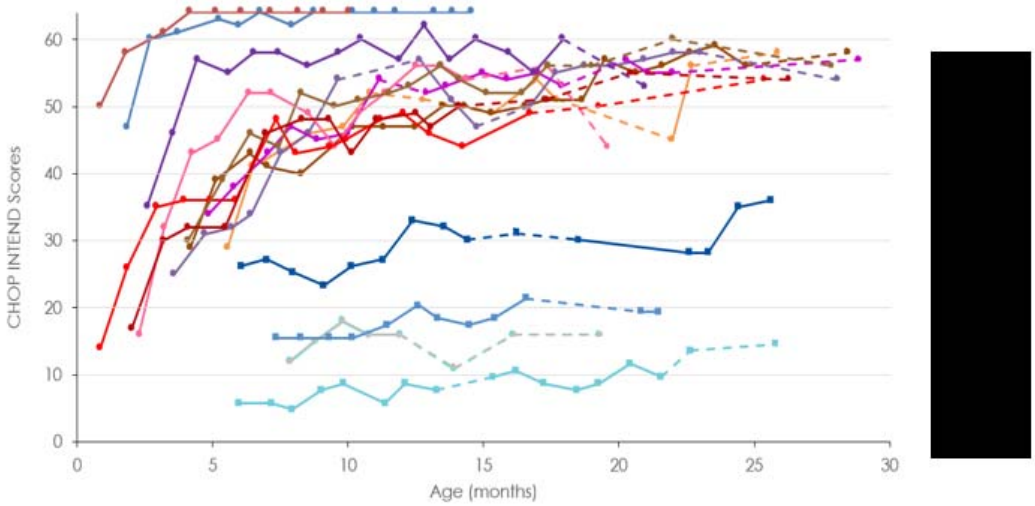
The absolute and change from baseline in CHOP-INTEND score over time by patient and by cohort through 24 months post-dose is presented in Figure 10 and Figure 11.

The mean (SD) CHOP-INTEND score of patients in Cohort 2 at baseline was 28.2 (12.3) points.

The change from baseline in the CHOP-INTEND score, an assessment of motor function, was assessed as a secondary efficacy endpoint in START. The mean CHOP-INTEND scores improved (increased) from baseline and were sustained over time; all the patients in Cohorts 1 and 2 had increased scores from baseline on the CHOP-INTEND scale of at least 4 points at their last observation. This 4-point increase is considered a clinically meaningful response to treatment and is a clear deviation from natural history, where, as documented in the NeuroNext natural history study, CHOP-INTEND scores decline after initial diagnosis (27). Further, the average CHOP-INTEND improvement in Cohort 2 patients was substantially greater than 4 points.

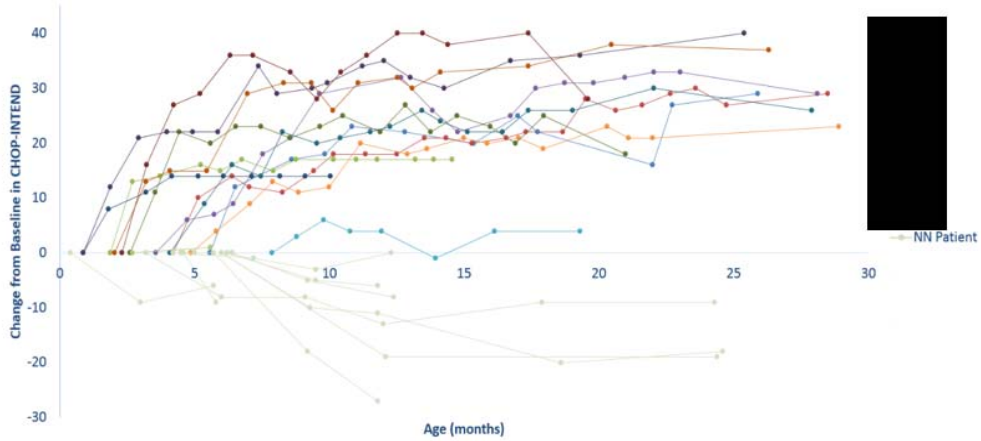
Mean increases from baseline of 9.8 and 15.4, were reported at 1 and 3 months post gene therapy, respectively (n=12, both p<0.001). At 24 months post onasemnogene abeparvovec administration a mean increase from baseline CHOP-INTEND score of 30.7 was reported (n=6; p value not reported). These results reflect rapid and sustained improvement in motor function and were in stark contrast to a decline of a mean of more than 10 points between 6 and 12 months of age in the NeuroNext study (27).

Figure 10: CHOP-INTEND response in START (full analysis set)



Note:
Cohort 1 received the low dose of onasemnogene abeparvovec (6.7 x 1013 vg/kg) and Cohort 2 received the therapeutic dose of onasemnogene abeparvovec (2.0 x 1014 vg/kg).
Abbreviations: CHOP-INTEND, Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders.
Data cut on August 7, 2017

Figure 11: CHOP-INTEND change from baseline by patient in Cohort 2 up to 24 months after onasemnogene abeparvovec infusion (full analysis set) in START and in the NeuroNext natural history control cohort



Abbreviations: CHOP-INTEND, Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders; NN, NeuroNext.
Data cut on August 7, 2017.

In terms of the achievement of selected CHOP-INTEND threshold scores, nearly all Cohort 2 patients (91.7%) achieved a score ≥40 at 13.6 months of age and 83.3% achieved a score ≥50, surpassing a threshold effectively never seen amongst patients with SMA type 1 beyond 6 months of age (26). Three patients (25%) achieved CHOP-INTEND scores of ≥60, approaching the ceiling of the CHOP-INTEND scale. At 24 months post-dosing, 91.7% of patients from Cohort 2 achieved CHOP-INTEND scores of ≥50 and 4 scored ≥60; 2 patients (16.7%) achieved the maximum score of 64, indicating normal functional status.

The significant milestone achievements observed in START are in contrast with the complete absence of milestone achievement in natural history cohorts. In the PNCR cohort,

no patient achieved a CHOP INTEND score >40 at or after the 6-month visit (with one transient exception) (67). In the NeuroNext cohort, no patient achieved a CHOP INTEND score >33 at or after the 6-month visit, and no patient had an increase in score from Baseline (27). Amongst patients with 2 copies of *SMN2*, a mean decline of 10.7 points was observed between the 6 and 12 months of age visit (67).

Bayley Scales

Four patients from Cohort 2 scored ≥60 on the CHOP-INTEND and Bayley Scales assessments were initiated per protocol (initial assessments ranging from Day –1 to 24 months post-dosing). Mean (SD) Bayley scores increased from [redacted] between the first and final visit (Figure 12).

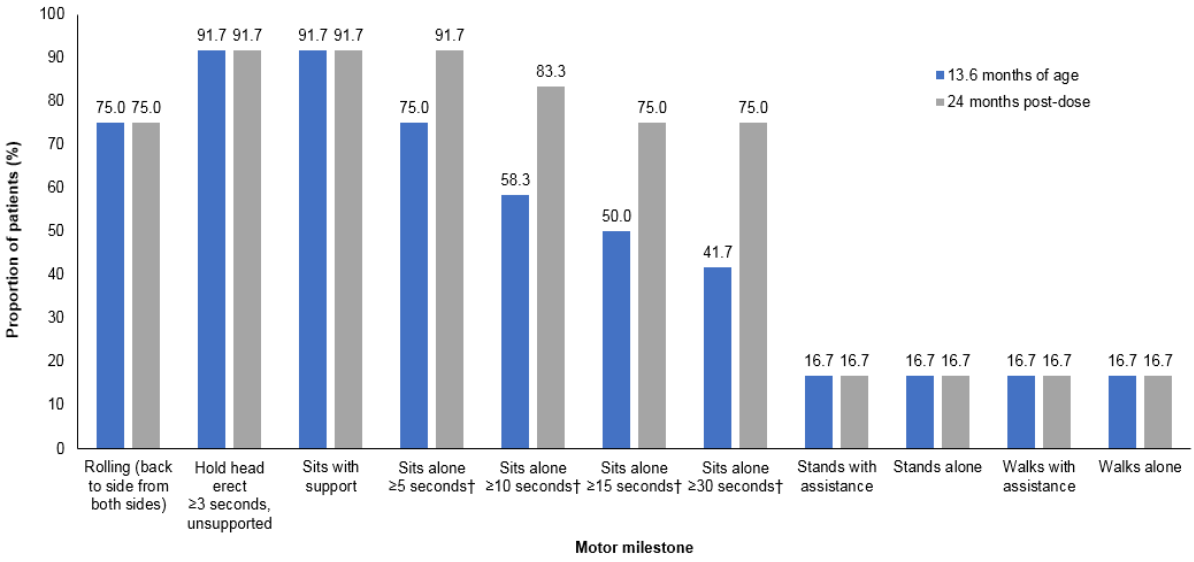
Figure 12: Change from baseline in Bayley score by patient and cohort 24 months after onasemnogene abeparvovec infusion (full analysis set)

Significant motor function milestones based on independent central review

The development of significant motor function milestones was assessed based on video reviews by an external expert. Compiled video recordings of the CHOP-INTEND, Bayley Scales, submitted home videos, and physical examinations were sent to a central reviewer for independent confirmation of development milestones.

At the 24 months post-dose time point, 91.7% of patients in Cohort 2 were able to hold their head erect without support for ≥3 seconds and sit with support, 75% of patients were able to sit alone for ≥30 seconds, and 16.7% of patients were able to walk alone (Figure 13, Table 33). No patients in Cohort 1 achieved a significant motor milestone, reflecting the more advanced disease of patients in Cohort 1 compared with Cohort 2 prior to onasemnogene abeparvovec administration and the greater efficacy of the therapeutic dose. Data from both the PNCR and NeuroNext natural history studies report that no patients with SMA type 1 were able to control head, roll over, sit with or without support, stand with assistance or alone, or walk with assistance or alone (67).

Figure 13: Motor milestones achieved by patients with SMA type 1 in Cohort 2 in START



† Patients are included in multiple categories for the “sits alone” milestone. Patients sitting ≥30 seconds are included in the totals for ≥15 seconds, ≥10 seconds, and ≥5 seconds.

Table 33: START: motor milestones and other achievements in Cohort 2 at 24 months post onasemnogene abeparvovec administration versus historical cohorts

Endpoint	Cohort 2 (n=12)	Historical cohorts
Motor milestone achievements, n (%)		
Brings hand to mouth	12 (100)	NR
Controls head	11 (91.7)	0‡
Rolls over†	9 (75.0)	0‡
Sits with assistance	11 (91.7)	0‡
Sits unassisted§		
≥5 seconds	11 (91.7)	0‡
≥10 seconds	10 (83.3)	0‡
≥30 seconds	9 (75.0)	0‡
Stands with assistance	2 (16.7)	0‡
Stands unassisted	2 (16.7)	0‡
Walks unassisted	2 (16.7)	0‡

Abbreviations: n/N, number of patients meeting the criterion/number of patients in the group; NR, not reported; SMA, spinal muscular atrophy; WHO, World Health Organization.
At baseline, none of the patients in Cohort 2 had achieved any of the listed motor milestones, except for bringing a hand to the mouth. During the 24-month study period, the majority of these patients had reached ≥1 major motor milestone. No patients in Cohort 1 are listed, since none attained any motor milestones.
† According to item 20 on the Bayley-III assessment tool, rolling over is defined as movement of ≥180 degrees both left and right from a position of lying on the back.
‡ Data are from De Sanctis et al. 2016 (50).
§ Sitting unassisted for ≥5 seconds is in accordance with the criteria of item 22 on the Bayley-III assessment tool gross motor subtest. Sitting unassisted for ≥10 seconds is in accordance with the criteria used in the WHO Multicentre Growth Reference Study. Sitting unassisted for ≥30 seconds defines functional independent sitting and is in accordance with the criteria of item 26 on the Bayley-III assessment tool gross motor subtest.
Sources: Al-Zaidy et al. 2019 (24); Mendell et al. 2017 (2).

Effect of Age at Dosing on Motor Milestone Development

In a post-hoc analysis of the effect of age at onasemnogene abeparvovec administration on the motor milestone development of patients treated with the therapeutic dose (n=12), patients treated with onasemnogene abeparvovec at ≤3 months of age achieved the motor milestone of sitting unassisted for ≥5 seconds at a younger median age than patients treated at >3 months of age (12.5 versus 21.6 months, respectively; p=0.0087), even with poor baseline motor function (Table 34) (128). All 3 patients treated with onasemnogene abeparvovec at ≤3 months of age who had baseline CHOP-INTEND scores >20 (35, 47 and 50) experienced early motor milestone achievement. All 3 patients treated with onasemnogene abeparvovec at ≤3 months of age who had low baseline CHOP-INTEND scores of <20 (14, 16 and 17) and would therefore generally be expected to have the most severe and rapid disease progression, still experienced profound motor milestone achievement. Among the 6 patients treated with onasemnogene abeparvovec at >3 months of age, 5 patients achieved motor milestones. This exploratory post-hoc analysis suggests that early treatment is key to maximising the efficacy outcomes possible following treatment with onasemnogene abeparvovec.

Table 34: START Phase I/IIa trial: motor milestones in Cohort 2 by age at dosing and baseline CHOP-INTEND scores

	Onasemnogene abeparvovec dosing at <3 months of age		Onasemnogene abeparvovec dosing at >3 months of age (n=6)
	High baseline CHOP-INTEND scores† (n=3)	Low baseline CHOP-INTEND scores† (n=3)	
Age at dosing, months, mean	1.8	1.8	5.1
Motor milestone achievements			
None, n	0	0	1‡
Sits unassisted for ≥5 seconds, n	3	3	5
Age achieved			
Mean	9.4	17.0	22.0
Median (range)	8.2 (8.0–11.9)	17.6 (13.0–20.5)	21.6 (17.9–27.4)
Sits unassisted for ≥30 seconds, n	3	3	3§
Age achieved			
Mean	10.0	21.2	23.1
Median (range)	10.0 (8.0–11.9)	22.1 (19.1–22.5)	24.4 (20.3–24.7)
Walks unassisted	2	0	0

Abbreviations: CHOP-INTEND, Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders. The CHOP-INTEND scale ranges from 0 to 64, with higher scores indicating better motor function.
† High baseline CHOP-INTEND scores were >20 points and low baseline CHOP-INTEND scores were <20 points.
‡ Patient had a baseline CHOP-INTEND score of 12 and was dosed at 7.9 months of age.
§ Overall, 5 patients achieved the ability to sit unassisted for ≥30 seconds, including 2 patients who achieved this milestone during long-term follow-up post-24 months at the ages of 3.8 and 3.1 years.
Source: Alfano et al. 2018 (128).

Exploratory efficacy endpoints

Pulmonary status

Seven of 15 patients (46.7%) in START required the use of temporary, reversible, invasive ventilatory support (endotracheal tube via mouth/nose) during the study. All were single instances, with the duration of use ranging from 1 to 9 days. Two patients were in Cohort 1 (2/3, 66.7%) and 5 patients were in Cohort 2 (5/12, 41.7%). Thus, 7 patients in Cohort 2 (58.3%) required no use of invasive ventilatory support during the study. Temporary invasive ventilatory support was provided either electively when patients had an upper respiratory illness or pneumonia (3/15 patients), or, was planned and used during a procedure or elective evaluation (4/15 patients). In all cases, invasive ventilatory support was temporary and reversed following resolution of the acute reversible illness or after the conclusion of the procedure or evaluation. No patient received a tracheostomy.

At baseline, 5 patients (33.3%) required non-invasive ventilatory support (all 3 patients [100%] in Cohort 1 and 2/12 patients [16.7%] in Cohort 2) while 10 of 12 patients in Cohort 2 (83.3%) were independent of ventilatory support. Of the 10 patients in Cohort 2 who did not require non-invasive ventilatory support before dosing with onasemnogene abeparvovec, seven completed the study without requiring any daily ventilatory support (Table 35). The 3 patients who required non-invasive ventilatory support post-dosing but not at baseline had early onset of symptoms in the first month of life and a rapid disease progression characterised by diffuse muscle weakness, respiratory insufficiency, and inability to swallow. The non-invasive ventilatory support was required in the context of viral illnesses and was maintained thereafter.

Table 35: Decreased pulmonary support in patients in Cohort 2 of START

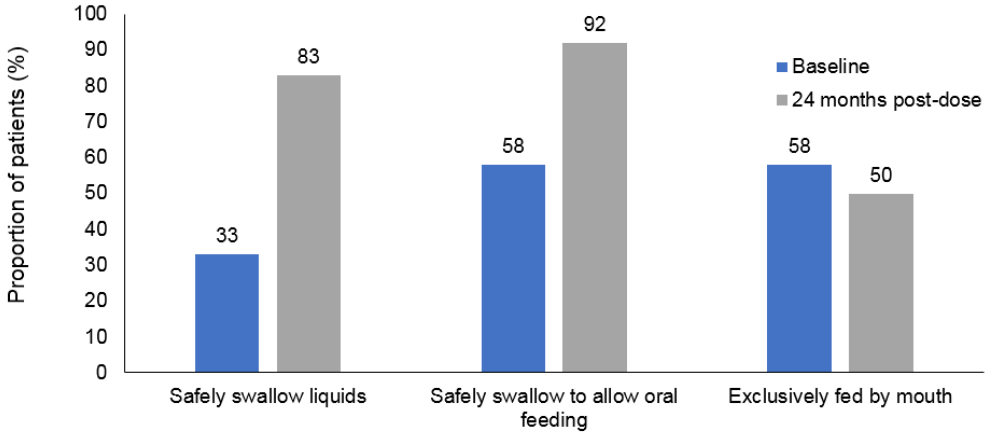
Patients	BiPAP use prior to dosing	Age at last pulmonary assessment (months)	BiPAP use post-dosing	Pulmonary event reached
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

BiPAP, Bi-level positive airway pressure.
† BiPAP was needed in these infants because of hospitalisations for respiratory infections

Nutritional status and swallowing function

At baseline, 53.3% of all patients required non-oral feeding support. At 13.6 months of age, 60% of patients required non-oral feeding support, including all 3 patients in Cohort 1 and 6 patients in Cohort 2. Video-fluoroscopic swallowing studies showed that the proportion of patients in Cohort 2 who achieved safe swallowing function using thin liquids increased from 33% at baseline to 83% at 24 months post-dosing (Figure 14). The proportion of patients in Cohort 2 able to safely swallow to allow for at least partial oral feeding increased from 58% at baseline to 92% at the end of the follow-up period.

Figure 14: Stabilisation or improvement in swallowing function in patients in Cohort 2 in START



Ability to thrive

Patients' ability to thrive was defined by the following: the ability to tolerate thin liquids (as demonstrated through a formal swallowing test), was not receiving nutrition through mechanical support (i.e. feeding tube), and had maintained weight (>3rd percentile for age and gender). Of the 7 patients in Cohort 2 who did not require non-oral nutrition prior to onasemnogene abeparvovec dosing, 85.7% and 71.4% maintained the ability to thrive at 13.6 months of age and 24 months post-dosing, respectively.

Ability to speak

The ability of infants treated with onasemnogene abeparvovec to speak was not formally assessed as part of START, however, clinician observations have been reported (24). Of the 12 patients in Cohort 2, 11 (92%) achieved the ability to speak at 24 months post-dosing (24).

Motor neurone function assessment

Motor neurone assessments were conducted at baseline and every 6 months after infusion of onasemnogene abeparvovec.

CMAP

Measurement of CMAP provides information on motor neurone health and the severity of denervation of infants with SMA (Section 9.4). In healthy infants, CMAP values rise during development before plateauing at adult levels by the end of the first decade; in natural history studies of SMA, CMAP is reduced relative to reference data (12). Changes from baseline in CMAP responses from tibialis anterior-peroneal nerve (peroneal CMAP) and abductor digiti minimi-ulnar nerve (ulnar CMAP) were assessed. At baseline, mean (SD) peroneal and ulnar CMAP amplitude values of [redacted] and 0.74 (1.059) were reported for Cohort 1 and 2 , respectively. At 24 months post-dose, patients in Cohort 2 achieved sustained improvements in both peroneal CMAP amplitude (mean change [redacted] increase) and ulnar CMAP amplitude (mean change 0.84 mV, 142% increase). Patients in Cohort 1 also showed improvements in CMAP; at 24 months post-dose, patients in Cohort 1 ([redacted]) achieved an improvement in peroneal CMAP amplitude of [redacted] from a mean (SD) baseline of [redacted]. Ulnar CMAP amplitude decreased from a baseline value of 0.30 (n=1) both at the 12- and 24-month time points (both –0.10 mV, –33%). The observed increases in CMAP amplitudes may be indicative of improved muscle fibre innervation, consistent with the improved motor function observed clinically.

MUNE

MUNE is an electrophysiologic method used to estimate the number of motor neurones innervating a muscle group and to help understand the time course of motor neurone loss in SMA (129) (Section 9.4). At baseline, MUNE values of [redacted] and [redacted] were reported for patients in Cohort 1 and Cohort 2, respectively. Patients in Cohort 2 achieved improvements in MUNE of [redacted] at 24 months post-dose, indicating no motor neurone loss. Patients in Cohort 1 showed a [redacted] decline from baseline at 24 months after dosing. As MUNE is considered to be an exploratory measure, the physiological relevance to the effects of onasemnogene abeparvovec are currently unknown.

Cognitive function

An assessment of the cognitive function of 7 infants treated with the intended therapeutic dose of onasemnogene abeparvovec reported that all patients scored in the typically developing range on the Bayley-III cognitive subtest composite score (score range: patients treated with onasemnogene abeparvovec, 90–105; typically developing infants, 90–109) (130). These results indicate that infants with SMA type 1 who received onasemnogene abeparvovec performed similarly to healthy children of the same age (130).

Comparison of clinical outcomes in START versus natural history

Compared with the patients in START who received the therapeutic dose of onasemnogene abeparvovec (Cohort 2, n=12), a greater proportion of the PNCR natural history control cohort required nutritional (69.6% versus 50.0%) or ventilatory support (78.3% versus 41.7%) over the course of follow-up, indicative of the impact of therapeutic intervention in START (Table 36) (67). Similarly, a greater proportion of the NeuroNext cohort required

nutritional and ventilatory support over the course of follow-up (67), an additional indication of the strong impact of therapeutic intervention in START.

In both the PNCR and NeuroNext natural history control cohorts, no child achieved the milestone of sitting with or without support, hands and knees crawling, standing with assistance, walking with assistance, standing alone or walking alone. Within the PNCR cohort, no patient achieved a CHOP-INTEND score of >40 at or after the 6-month visit (with one transient exception). In the NeuroNext cohort, no patient achieved a CHOP-INTEND score of >33 at or after the 6-month visit, and no patient had an increase in score from baseline (67). Amongst patients with 2 copies of *SMN2*, a mean decline of 10.7 points was observed between the 6 and 12 months of age visit (67). The significant milestone achievements observed in START in patients who received the proposed therapeutic dose cohort, contrast sharply with the complete absence of milestone achievement in the PNCR and NeuroNext natural history control cohorts.

Table 36 illustrates the markedly improved survival and survival free of permanent ventilation (alive, without tracheostomy, and not requiring ≥16 hours of ventilatory support per day for ≥2 weeks, absent an acute reversible illness or perioperative) in START compared with the PNCR and NeuroNext natural history control cohorts. All 12 patients in the START proposed therapeutic dose cohort remained alive, and none met the definition of requiring permanent ventilation over the course of the 24-month study. Sixteen patients (69.6%) in the PNCR cohort reached the combined endpoint of death or the need for a minimum of 16 hours/day of NIV support for a minimum of 14 continuous days by 13.6 month of age. The data for the NeuroNext cohort reflect tracheostomy-free survival, a less conservative endpoint (a child could receive 24 hours per day of non-invasive support without triggering the combined endpoint, for example). Table 36 also presents the range of ages for death and for reaching the composite survival endpoint (survival free of permanent ventilation) for the PNCR and NeuroNext cohorts.

Table 36: Summary of disease course in the PNCR and NeuroNext natural history cohorts

Variable	Cohort 2 (N=12)	NeuroNext control (N=16)	PNCR control (N=23)
Gastrostomy and ventilation support, n (%)			
Experimental SMA medication used (non-onasemnogene abeparvovec)	0	0	4 (17.4)
Gastrostomy tube placed	6 (50.0)	N/A	16 (69.6)
Ventilation support	5 (41.7)	N/A	18 (78.3)
Motor milestone and motor function achievements, n (%)			
Ever sit without support for ≥5 seconds	11 (91.7)	0	0
Ever sit without support for ≥10 seconds	10 (83.3)	0	0
Ever sit without support for ≥30 seconds	9 (75.0)	0	0
Ever stand without support	2 (16.7)	0	0
Ever walk alone	2 (16.7)	0	0
CHOP-INTEND score >40 at any time >6 months of age n (%)	11 (91.7)	0	1 (4.3)
BiPAP or intubation (for ≥16 hours/day and ≥14 days), n (%)	0	N/A	13 (56.5)
Age reached, months, mean (SD)			10.2 (4.9)
Intubation, n (%)	0	2 (12.5)	NA
Age reached, months, mean (SD)		12.1 (8.8)	
Mortality or ventilation outcome at 14 months			
Mortality, n (%)	0	7 (43.8)	7 (30.4)
Age at death, months, mean (SD)		7.9 (3.1)	7.7 (3.5)
Composite of mortality or ventilation, n (%)	0	8 (50.0)	16 (69.6)
Age at composite of mortality or ventilation, months, mean (SD)		7.7 (2.3)	8.8 (3.3)
Mortality or ventilation outcome – all data			
Mortality, n (%)	0	8 (50.0)	11 (47.8)
Age at death, months, mean (SD)		8.9 (4.1)	33.1 (53.1)
Composite of mortality or ventilation, n (%)	0	10 (62.5)	18 (78.3)
Age at composite of mortality or ventilation, months, mean (SD)		9.6 (4.8)	9.8 (4.4)

Abbreviations: BiPAP, bi-level positive airway pressure; CHOP-INTEND, Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders; NA, not available; SMA, spinal muscular atrophy; PNCR, Pediatric Neuromuscular Clinical Research; SMA, spinal muscular atrophy.
Sources: PNCR NeuroNext report (67).

9.6.1.2 LT-001

As of the latest data cut (31 December 2018), all patients administered IV onasemnogene abeparvovec in the START study who enrolled in LT-001 (n=13) are alive. For those patients who received the therapeutic dose of onasemnogene abeparvovec (Cohort 2) in the START study and were then enrolled in LT-001 (n=10), at the 31 December 2018 data cut the median age of patients was 4 years; with oldest patient aged 4.6 years old (28). The median time since onasemnogene abeparvovec administration was 44.8 months; with longest duration of therapy recorded at 49.7 months since dosing. These results indicate that a single IV infusion of onasemnogene abeparvovec at the therapeutic dose in START has continued to provide prolonged and durable efficacy after 33.9 to 53.3 months (2.8 to 4.4 years), (mean 41.7 months [3.5 years]) of follow-up post-dose.

The available long-term data in LT-001 demonstrated that no patients have lost motor milestones since the completion of START. The assessment of new motor milestone achievements was not originally conducted as part of the long-term follow-up study after the end of START. However, as additional new motor milestone achievements were observed by clinical investigators in LT-001, motor milestone data are now being collated. Al-Zaidy et al. 2019 reported that, based on video evidence of patients abilities following completion of START, 4 patients achieved new motor milestones compared with the video-confirmed milestones captured at the end of START (24). Two children developed the ability to sit unassisted for ≥30 seconds, and 2 children were able to stand with support in LT-001 (24). These observations of new milestones are not yet formally recorded as part of the LT-001 database due to timings of clinical visits/data cuts and the way milestone data are recorded (e.g. the LT-001 database currently does not distinguish between sitting unassisted for >5 seconds versus >30 seconds). Patients also maintained or improved ventilatory status, aside from in the context of acute reversible illness. Of the 4 patients in Cohort 2 who used BiPAP at the start of long-term follow-up, 2 no longer required regular BiPAP as of the latest data cut (29).

LT-001 is an open-label, long-term follow-up study in which the use of nusinersen is not excluded. Data on the use of nusinersen by patients enrolled in the LT-001 study were reported at the latest data cut (31 December 2018). In total, 4/10 patients treated with the therapeutic dose of onasemnogene abeparvovec in START were documented as taking nusinersen during LT-001. Two patients were taking nusinersen at the LT-001 baseline visit and three patients were taking nusinersen at the 1-year follow-up visit; of the two patients taking nusinersen at the baseline visit, one was documented as taking nusinersen at the 1-year follow-up visit and data were not available for the other patient.

Onasemnogene abeparvovec is not intended or expected to be indicated for use in combination with nusinersen in patients with 5q13 SMA type 1. As no patients treated with onasemnogene abeparvovec in START exhibited loss of motor milestone achievements or disease progression prior to initiation of nusinersen therapy in LT-001, there is no evidence that the administration of nusinersen to patients who had received onasemnogene abeparvovec was in any way due to a loss of motor milestones. Similarly, per communication from the investigator, there is no indication of any clinical decline or perceived loss of effectiveness for patients treated with onasemnogene abeparvovec. For the two patients with nusinersen use at LT-001 baseline, initiation of nusinersen was per

parental request to see if they could achieve additional benefit from combination therapy. As the patients had only received an investigational therapy at the time (onasemnogene abeparvovec), they were immediately eligible for nusinersen under the US policy at the time.

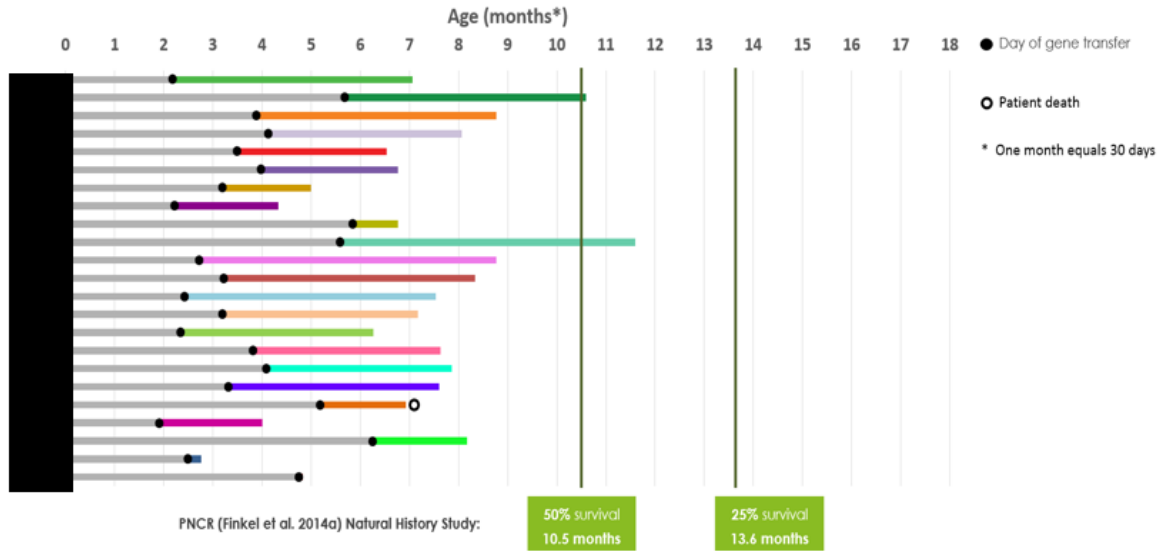
9.6.1.3 STR1VE-EU

Survival and permanent ventilation

STR1VE-EU is an ongoing study for which enrolment completed in May 2019 (n=33). As of the efficacy data cut date of 8 March 2019 (42), 23/33 patients had enrolled in STR1VE-EU.

One patient ([redacted]) had died, and this case is summarised in Section 9.7.2.3. The other 22 patients had all survived without invasive ventilation and were continuing in the study. The patients ranged in age from 1.9 to 6.3 months at the time of treatment and from 2.8 to 11.6 months at the 8 March 2019 data cut (Figure 15). The time since onasemnogene abeparvovec administration ranged from 0.1 to 6.4 months as of the 8 March 2019 data cut. Two of the 22 patients reached more than 10.5 months of age, the age at which only 50% of untreated SMA type 1 patients survived without permanent ventilation in the external PNCR natural history study (12).

Figure 15: Ventilation-free survival in STR1VE-EU (8 March 2019) (ITT population)



Motor function assessments

Milestones based on video review

As shown in Table 37, as of the 8 March 2019 data cut, one patient ([redacted]) met the WHO-MGRS guidelines (120) criteria for sitting without support for more than 10 seconds and achieved the Bayley definition (Bayley Scales Gross Motor Subset item #26) (119), 'sitting alone without support for at least 30 seconds', which constitutes functional independent sitting. The patient achieved this milestone prior to 18 months of age and therefore met the primary efficacy endpoint for STR1VE-EU.

The achievement of these endpoints in this patient is remarkable as in natural history studies, untreated patients with SMA type 1 never sit alone without support (7, 50, 67).

Table 37: Video confirmed developmental milestones in STR1VE-EU (8 March 2019) (ITT population)

Milestone achieved	n (%) (N=22)
Holds head erect for ≥3 seconds without support	4 (18.2)
Sits independently without support for ≥30 seconds	1 (4.5)
Sits independently for ≥10 seconds	1 (4.5)

The Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders

The mean baseline CHOP-INTEND score of patients enrolled in STR1VE-EU was 26.5 (6.9) with a median of 28. As of the 8 March 2019 data cut, improvements in motor function were observed early after treatment with onasemnogene abeparvovec (Figure 16). Nineteen (19) patients had Day 30 visit data, 17 patients had Month 2 visit data, and 15 patients had Month 3 visit data. CHOP-INTEND scores improved by a mean (SD) of 5.5 (6.10), 7.8 (8.65), and 9.4 (8.85) points by Day 30, Month 2, and Month 3, respectively. At Month 6 post onasemnogene abeparvovec administration, the mean change from baseline was 16.0 (1.41) points for the 2 patients for whom data was available. At the 8 March 2019 data cut, 8 (36.4%) patients had scored ≥40 on the CHOP-INTEND, and 1 (4.5%) patient had scored ≥50. No patients had scored ≥60 on the CHOP-INTEND at the 8 March 2019 data cut.

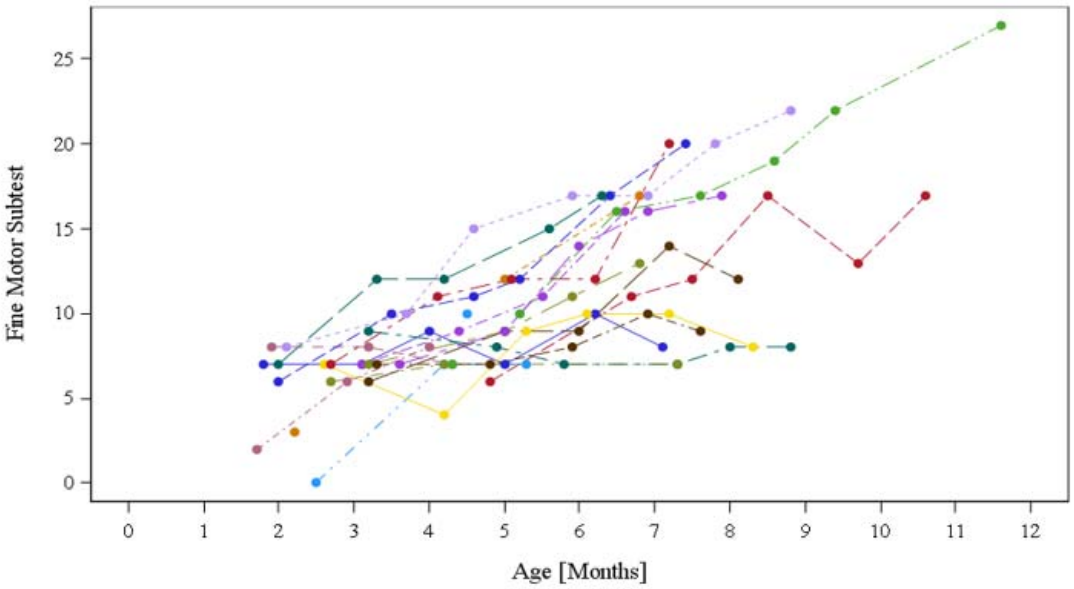
Figure 16: CHOP-INTEND response in STR1VE-EU (8 March 2019) (ITT population) and START Cohort 2

Bayley Scales

Early improvement in fine and gross motor function as assessed by the Bayley Scales has been seen across patients in STR1VE-EU. As of the 8 March 2019 data cut, 19 patients had up to Month 1 visit data, 17 patients had Month 2 visit data, and 15 patients had Month 3 visit data. Bayley Scales fine motor subtest scores improved by a mean (SD) of 2.5 (2.61), 4.0 (2.81), and 6.0 (3.80) points from baseline to the Month 1, 2, and 3 visits after

onasemnogene abeparvovec administration, respectively (Figure 17). The two patients for whom data was available for the Month 6 visit improved by a mean (SD) of 15.5 (2.12) points.

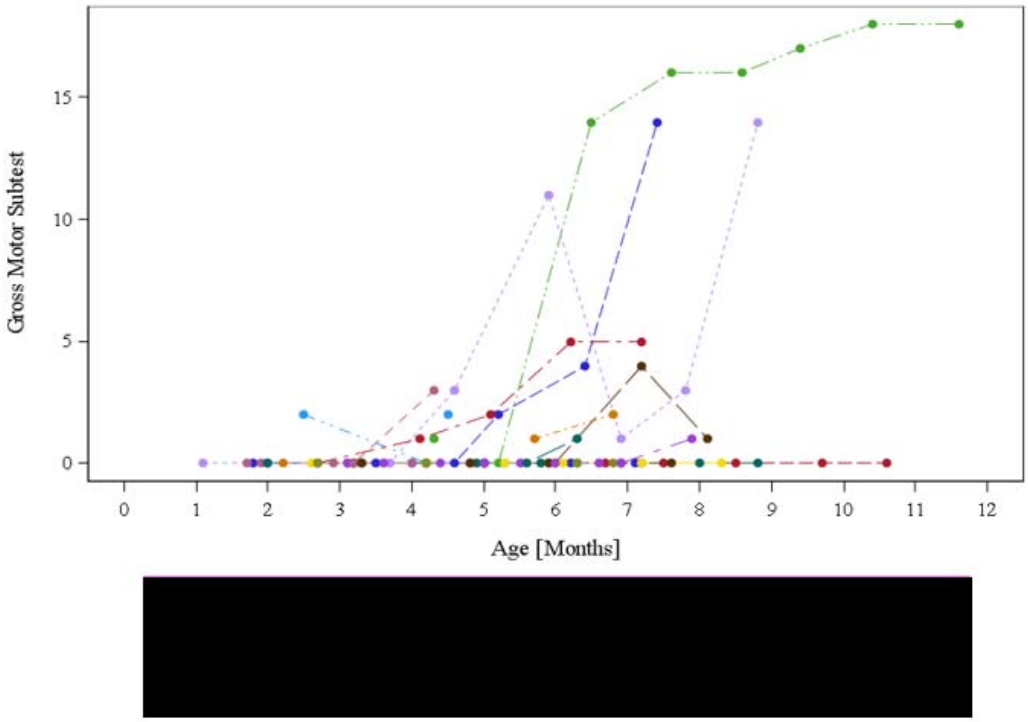
Figure 17: Bayley fine motor subset score over time in STR1VE-EU (8 March 2019) (ITT population)



[redacted]

Bayley Scales gross motor subtest scores improved by a mean (SD) of 0.7 (3.26), 1.3 (3.98), and 2.5 (4.82) points from baseline to the Month 1, 2, and 3 visits post onasemnogene abeparvovec administration, respectively (Figure 18). Twelve patients had data available beyond the Month 3 visit (range Month 4 to Month 6). The two patients for whom data was available for the Month 6 visit improved by a mean (SD) of 16.0 (2.83) points.

Figure 18: Bayley gross motor subset score over time in STR1VE-EU (8 March 2019)) (ITT population)



9.6.1.4 STR1VE-US

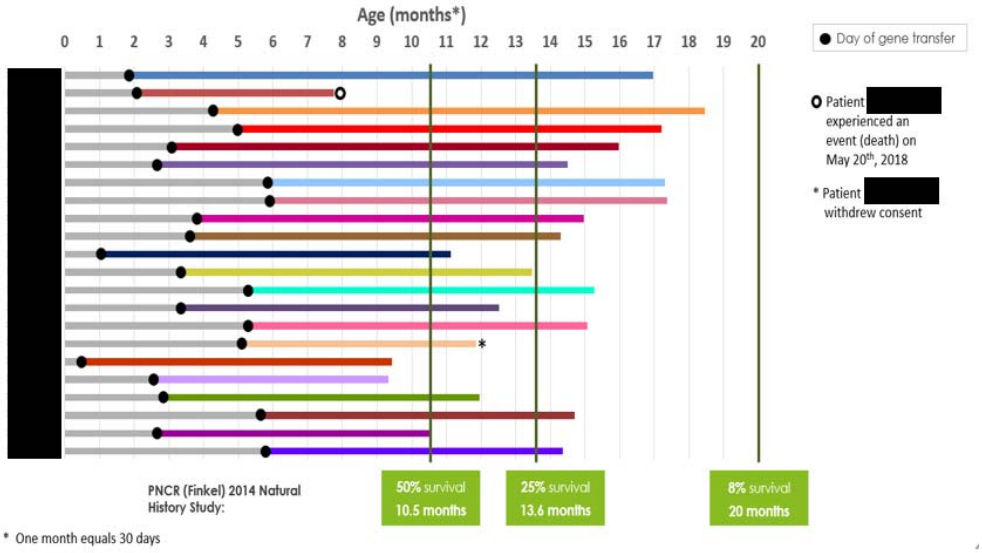
Survival and permanent ventilation

STR1VE-US is an ongoing study. As of the efficacy data cut of 8 March 2019 (42), 22 patients had enrolled in STRIVE-US. As described in Section 9.7.2.4, one patient ([redacted]) had died and one patient ([redacted]) withdrew from the study. Twenty-one of the 22 patients had all survived without invasive ventilation and 20 patients were continuing in the study.

While 2 patients are currently reported to require permanent invasive ventilation, this is believed to be incorrect by AveXis and reflective of a data coding error. In the protocol, permanent ventilation is defined as tracheostomy or the requirement of ≥16 hours of respiratory assistance per day (via non-invasive ventilatory support) for ≥14 consecutive days in the absence of an acute reversible illness, excluding perioperative ventilation. Permanent ventilation, so defined, is considered a surrogate for death. Temporary endotracheal intubation as part of perioperative management does not qualify under this definition. There have been no reports of permanent ventilation to the sponsor that would meet this definition. For the two patients currently listed as requiring 'permanent, invasive ventilation' ([redacted] and [redacted]), the reasons for invasive ventilation are recorded as peri-operative use and respiratory syncytial virus (RSV) bronchiolitis ([redacted]) and upper respiratory illness and pneumonia ([redacted]). Both are reported as 'not ongoing' and from the serious adverse event (SAE) reports, both patients were successfully extubated and would not meet the definition of requiring permanent ventilation (requiring tracheostomy). The two patients' data are included on Figure 19.

The patients ranged in age from 0.5 to 5.9 months at the time of onasemnogene abeparvovec administration. As of the 8 March 2019 data cut, patients in STR1VE-US ranged in age from 9.4 to 18.5 months and the mean (median) time since onasemnogene abeparvovec administration was 10.2 (10.1) months (42, 131). At the time of the data cut (8 March 2019), 19 of the 22 patients were ≥10.5 months of age, the age at which only 50% of SMA type 1 patients survived without permanent ventilation in the PNCR natural history study (12) (Figure 19). Patient [redacted], who discontinued the study, had also met the milestone of being ≥10.5 months of age at the time of discontinuation. With 19/20 (95%) patients surviving ventilation-free to 10.5 months, and 13/14 (93%) patients who survived to 13.6 months (13/15 or 87% including one patient withdrawal with unknown outcome) surviving without permanent ventilation. Onasemnogene abeparvovec compares favourably to the external PNCR natural history study, where 50% of patients survived at 10.5 months and 25% survived at 13.6 months (12).

Figure 19: Ventilation-free survival in STR1VE-US (8 March 2019)



Motor milestones

Milestones based on video review

As of the 8 March 2019 data cut, 11/22 patients (50.0%) had achieved sitting alone without support for ≥30 seconds (Bayley definition - Bayley Scales Gross Motor Subset item #26) (119), constituting functional independent sitting (Table 38). Nine of 22 (40.9%) patients met the WHO-MGRS guidelines (120) criteria for sitting without support for ≥10 seconds. The WHO definition for sitting without support for ≥10 seconds (child sits up straight with head erect for ≥10 seconds; child does not use hands or arms to balance body or support position) differs sufficiently from the Bayley definition, which simply states 'child sits alone without support for ≥30 seconds,' (119) therefore, the proportion of patients achieving this motor milestone may vary between these two measures. Of note, two patients achieved sitting for ≥30 seconds (Bayley definition) but not sitting for ≥10 seconds (WHO). All patients who achieved sitting for ≥10 seconds (WHO) also achieved sitting for ≥30 seconds (Bayley). These patients achieved this milestone prior to 18 months of age and therefore met the primary efficacy endpoint for STR1VE-US, a remarkable achievement as in the PNCR natural history control (67) patients with SMA type 1 never achieved the ability to sit alone

without support. One patient in STR1VE-US achieved the ability to stand with assistance, crawl, and pull to stand.

Table 38: Video confirmed developmental milestones in STR1VE-US (8 March 2019) (ITT population)

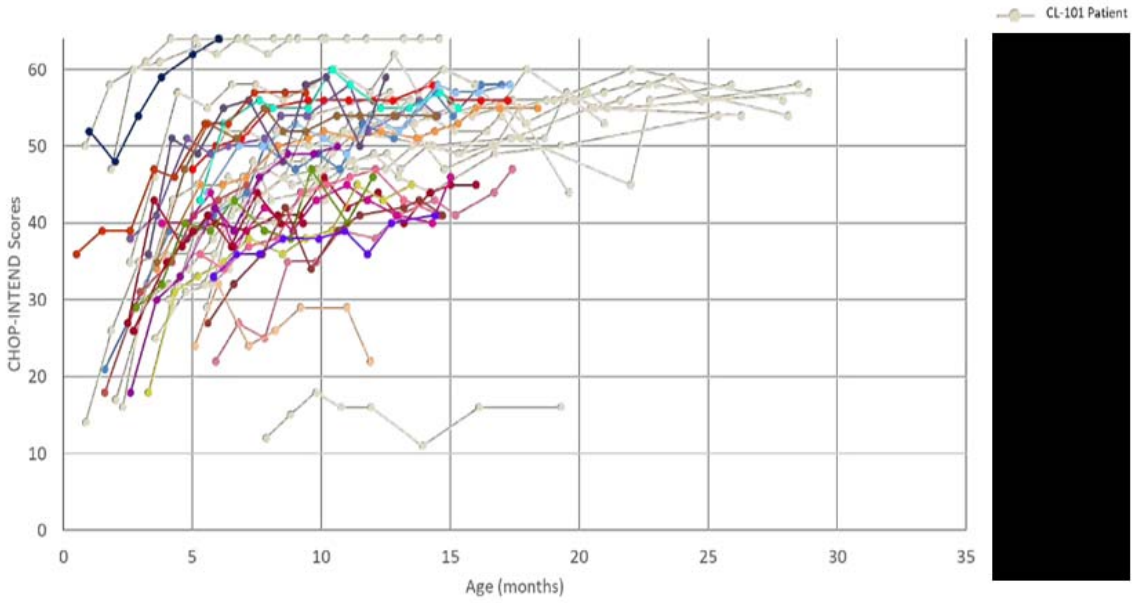
Milestone achieved	n/N (%)
Holds head erect for ≥3 seconds without support†	17/20 (85.0)
Turns from back to both right and left sides	9/22 (40.9)
Sits alone without support for ≥30 seconds	11/22 (50.0)
Stands with assistance‡	1/22 (4.5)
Crawls	1/22 (4.5)
Pulls to stand	1/22 (4.5)
Sits independently for ≥10 seconds	9/22 (40.9)

† Patient [redacted] was able to hold head erect for ≥3 seconds without support at screening visit.
‡ Bayley Scales Gross Motor Subtest Item #33: Child supports his or her own weight for ≥2 seconds.

Change in CHOP-INTEND score from baseline

As of the 8 March 2019 data cut, rapid improvements in motor function were observed following treatment with onasemnogene abeparvovec, as demonstrated by improvements in the CHOP-INTEND scores (Figure 20). Mean (SD) baseline CHOP-INTEND score was 32.0 (9.7) with a median of 34. All 22 patients had Day 30, Month 2 and Month 3 post onasemnogene abeparvovec administration data. CHOP-INTEND scores improved from baseline by a mean (SD) of 6.9 (5.35), [redacted], and 11.7 (6.40) points at Day 30, Month 2, and Month 3, respectively. At Month 6 post onasemnogene abeparvovec administration, the mean change from baseline [redacted] points for the 20 patients for whom data was available. [redacted] At the 8 March 2019 data cut, 21/22 patients (95.5%) had scored ≥40 on the CHOP-INTEND, 11 (50.0%) patients had scored ≥50, and 2 patients had scored ≥60. Broadly, the CHOP-INTEND trajectories in STR1VE-US appear to be showing the same marked improvement in the first months following onasemnogene abeparvovec administration as observed in START, with many patients achieving a ≥4-point increase from baseline CHOP-INTEND score (18/20, 90%) or reaching a score of ≥40 points (15/20, 75%) by Month 6.

Figure 20: CHOP-INTEND response in STRIVE-US (8 March 2019) and START Cohort 2



Bayley scales

Improvements in the fine and gross motor function of infants with SMA type 1 treated with onasemnogene abeparvovec in STR1VE-US as assessed by the Bayley Scales [redacted]

Figure 21: Bayley fine motor subset score over time in STR1VE-US (8 March 2019) (ITT population)

Figure 22: Bayley gross motor subset score over time in STR1VE-US (8 March 2019) (ITT population)

9.6.1.5 SPR1NT

SPR1NT is an ongoing study in pre-symptomatic infants; efficacy results obtained to date are presented separately for Cohort 1 (infants with 2 copies of *SMN2* that meet the ITT criteria) and Cohort 2 (infants with 3 copies of *SMN2* that meet the ITT criteria).

Cohort 1 (2 copies of *SMN2)*

Combined Survival Endpoint (Cohort 1)

As of the efficacy data cut of 8 March 2019 (42), 8 patients had enrolled in Cohort 1 of SPR1NT and all had survived without invasive ventilation and were continuing in the study. The median age at last follow-up was 6.1 months (Figure 23); median time since treatment was 5.4 months (42, 132).

Figure 23: Ventilation-free survival in Cohort 1 (2 copies of *SMN2*) in SPR1NT (8 March 2019) (ITT population)

Video confirmed motor milestones (Cohort 1)

As shown in Table 39 as of the 8 March 2019 data cut, 3 of 8 patients met the WHO-MGRS guideline (120) criteria for sitting without support for ≥10 seconds. Four of 8 enrolled patients in Cohort 1 had achieved the motor milestone of 'sitting alone without support for ≥30 seconds', which constitutes functional independent sitting. These 4 patients achieved this milestone prior to 18 months of age (at visit Month 9, Month 8, Month 5, and Month 6 post onasemnogene abeparvovec administration, respectively, which is within the window for achievement of motor milestones of healthy developing children (120)); therefore, all 4 patients met the primary efficacy endpoint for SPR1NT. In addition, one patient achieved standing with assistance according to both the Bayley and WHO definitions.

The achievement of these endpoints is remarkable as in the PNCR natural history control cohort (12, 67), patients with SMA type 1 never achieved the ability to sit alone without support.

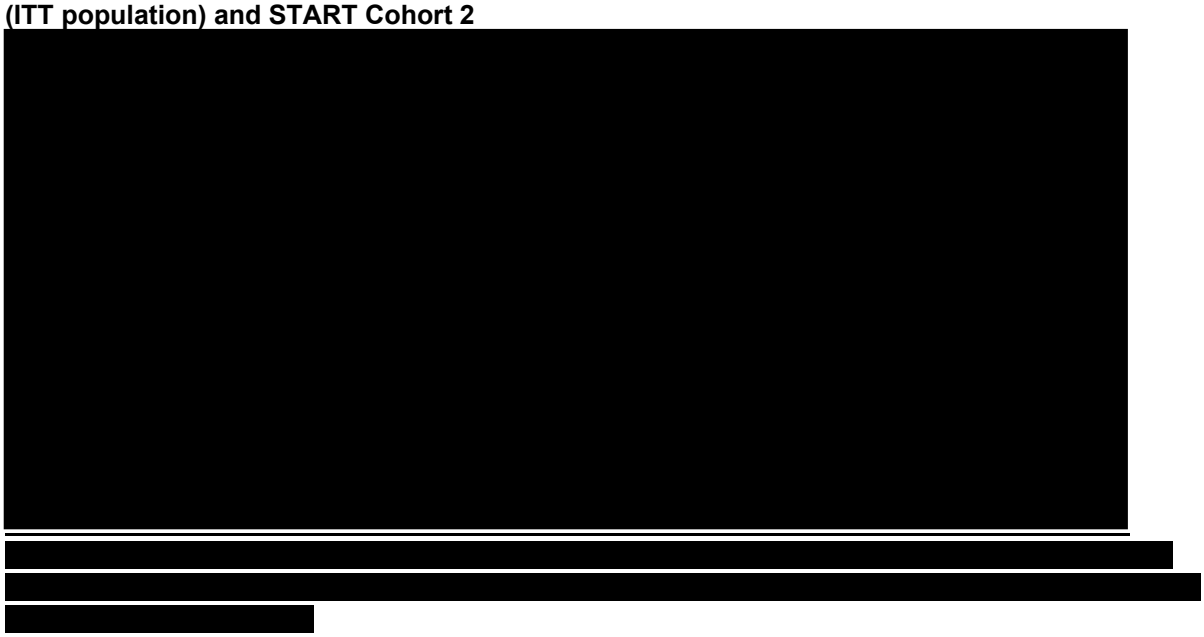
Table 39: Video confirmed developmental milestones (ITT population) in Cohort 1 (2 copies of *SMN2*) in SPR1NT (8 March 2019 data cut)

Milestone achieved	n (%) (N=8)
Holds head erect for ≥3 seconds without support*	5 (62.5)
Turns from back to both right and left sides	3 (37.5)
Sits alone without support for ≥30 seconds	4 (50.0)
Sits alone without support for ≥10 seconds	3 (37.5)
Supports own weight for ≥2 seconds	1 (12.5)
Stands with assistance	1 (12.5)

CHOP-INTEND (Cohort 1)

CHOP-INTEND scores for all 8 of the infants enrolled in Cohort 1 of SPR1NT were available as of the data cut (8 March 2019) and are presented in Figure 24. The mean (SD) CHOP-INTEND score at baseline was 44.0 (8.4). Eight patients had Day 30 visit data, 7 patients had Month 2 visit data, and 6 patients had Month 3 visit data. CHOP-INTEND scores improved by a mean (SD) of 8.9 (5.67), 11.6 (9.66), and 12.0 (15.94) points by Day 30, Month 2, and Month 3, respectively. At Month 6 post onasemnogene abeparvovec administration, the mean (SD) change from baseline was 19.3 (14.98) points for the 3 patients for whom data was available. At the 8 March 2019 data cut, all 8 patients (100%) had scored ≥50 on the CHOP-INTEND, and 6 (75.0%) patients had scored ≥60, approaching the ceiling of the CHOP-INTEND scale.

Figure 24: CHOP-INTEND response in Cohort 1 (2 copies of *SMN2*) in SPR1NT (8 March 2019) (ITT population) and START Cohort 2



Bayley Scales (Cohort 1)

Early improvement in fine and gross motor function as assessed by the Bayley Scales has been seen across Cohort 1. As of the 8 March 2019 data cut, 8 patients had Month 1 visit data, 5 patients had Month 2 visit data, and 6 patients had Month 3 visit data (Figure 25).

Bayley Scales fine motor subtest scores improved by a mean (SD) of 1.3 (1.70), 3.3 (2.22), and 4.8 (0.75) points from baseline to the Month 1, 2, and 3 visits after onasemnogene abeparvovec administration, respectively. The 3 patients for whom data was available for the Month 6 visit improved by a mean (SD) of 12.0 (6.08).

Using the same 8 March 2019 data cut, Bayley Scales gross motor subtest scores improved by a mean (SD) of 1.9 (1.73), 4.2 (3.96), and 8.0 (3.22) points from baseline to the Month 1, 2, and 3 visits post onasemnogene abeparvovec administration, respectively (Figure 26). Three patients for whom data was available for the Month 6 visit improved by a mean of 10.0 (7.94) points by the Month 6 visit.

Figure 25: Bayley fine motor subtest score over time in cohort 1 of SPR1NT (*SMN2 2 copies*) (8 March 2019) (ITT population)

*

Figure 26: Bayley Gross Motor Subtest score over time in cohort 1 of SPR1NT (*SMN2 2 copies*) (8 March 2019) (ITT population)

Cohort 2 (3 copies of *SMN2*)

The number of copies of *SMN2* varies across the SMA population; a higher copy number is associated with less severe disease and the majority (82%) of infants with 3 copies of *SMN2* have been reported to develop SMA type 2 (52, 54). Since individuals with SMA type 2 typically live beyond 2 years of age (11), the results presented for Cohort 2 in SPR1NT, while promising, should be considered preliminary.

Combined Survival Endpoint (Cohort 2)

As of the efficacy data cut of 8 March 2019 (42), 9 patients had enrolled in Cohort 2 of SPR1NT and all had survived without invasive ventilation and were continuing in the study. The patients ranged in age from 24 days to 6 months as of the 8 March 2019 data cut and were 0.4 to 4.8 months post onasemnogene abeparvovec administration (Figure 27) (42, 133).

Figure 27: Event free survival in Cohort 2 (3 copies of *SMN2*) in SPR1NT (8 March 2019 data cut) (ITT population)

Video confirmed motor milestones (Cohort 2)

As of the 8 March 2019 data cut, 4 of the 9 patients in Cohort 2 achieved the developmental motor milestone of head control as defined by the Bayley Scales Gross Motor Subset (Item #20, 'Child holds head erect for at least 3 seconds without support' (119)). This was the most advanced Bayley Scales Gross Motor developmental motor milestone met by Cohort 2.

It should be noted that the patients in Cohort 2 are very early in their post-treatment course and time is required to achieve developmental motor milestones.

CHOP-INTEND (Cohort 2)

Given the expectation that children with 3 copies of *SMN2* would not develop symptoms of SMA type 1 nor develop symptoms within the first months of life, the SPR1NT study protocol did not include the assessment of CHOP-INTEND scores in individuals with 3 copies of *SMN2*. Therefore, at the 8 March 2019 data cut, no CHOP-INTEND data had been reported for patients in Cohort 2.

Bayley Scales (Cohort 2)

Early improvement in fine and gross motor function as assessed by the Bayley Scales was observed in Cohort 2 in SPR1NT. Baseline data was available for 8 patients, 7 patients had Month 1 visit data, 6 patients had Month 2 visit data, and one patient each had data from the Month 3 and Month 5 visits as of the 8 March 2019 data cut. Bayley Scales fine motor subtest scores improved by a mean (SD) of 2.3 (1.51) and 4.3 (2.07) points from baseline to the Month 1 and Month 2 visits post onasemnogene abeparvovec administration, respectively. Patient [redacted] improved by 8 points from baseline to the Month 3 visit, and patient [redacted] improved by 15 points from baseline to the Month 5 visit (Figure 28).

Bayley Scales gross motor subtest scores improved by a mean (SD) of 1.7 (2.25) and 5.5 (3.21) points from baseline to the Month 1 and Month 2 visits post onasemnogene abeparvovec administration, respectively. Patient [redacted] improved by 11 points from baseline to the Month 3 visit, and patient [redacted] improved by 12 points from baseline to the Month 5 visit (Figure 29).

Figure 28: Bayley fine motor subtest (raw score) score over time in cohort 2 (3 copies of *SMN2*) in SPR1NT (8 March 2019) (ITT population)

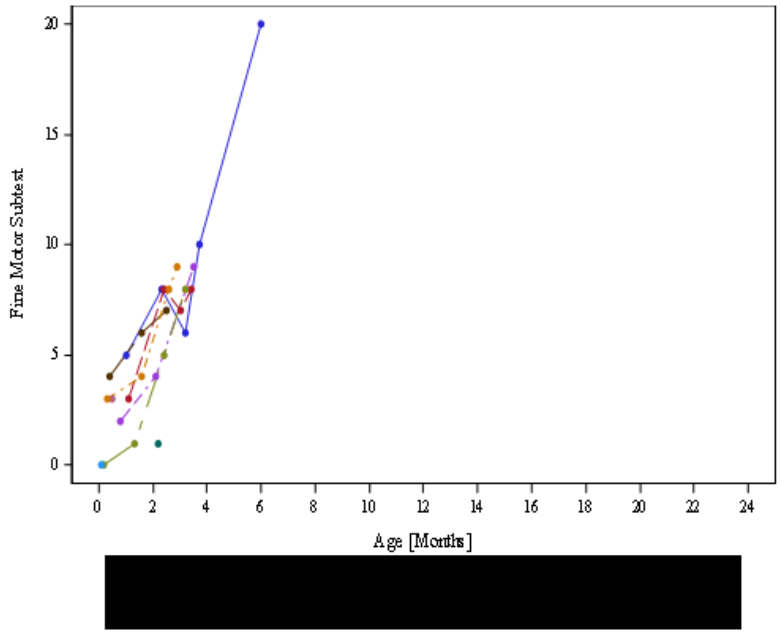
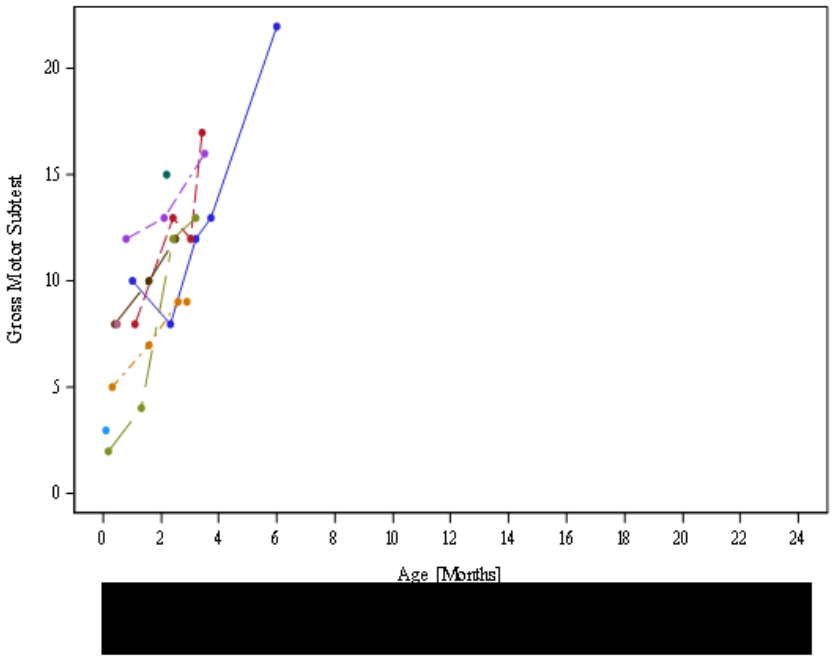


Figure 29: Bayley gross motor subtest (raw score) score over time in cohort 2 (3 copies of *SMN2*) in SPR1NT (8 March 2019) (ITT population)



9.6.1.6 Conclusions

One-time administration of onasemnogene abeparvovec to patients with SMA type 1 in START resulted in unprecedented survival rates and the achievement of developmental milestones not possible without disease modifying treatment. Improvement in motor function was further evidenced at the proposed therapeutic dose by the rapid (as early as 1-month post dosing) and statistically significant increase in mean CHOP-INTEND scores. In addition, the majority of patients without supportive care at study enrolment were free of nutritional (6/7) and ventilatory (7/10) support at end-of-study, indicating a significant decrease in the burden of illness at the patient level, as all of these patients were expected to require supportive care under natural history trajectory. The START results support persistence of efficacy of onasemnogene abeparvovec for a period of 2 years after dosing across multiple endpoints. Persistence of efficacy was further supported by the continued survival and lack of functional decline of patients who received the low dose of onasemnogene abeparvovec (Cohort 1), and Patient E08-208, who responded less well to the therapeutic dose than other Cohort 2 patients, outcomes which are drastically different from the motor decline and death associated with the natural history of SMA (12, 27, 50).

The durability of response to onasemnogene abeparvovec has been demonstrated in the long-term follow-up study LT-001. The results of LT-001 to date indicate that a one-time IV administration of onasemnogene abeparvovec at the proposed therapeutic dose provides prolonged and durable efficacy in infants with SMA type 1 for durations longer than 3 years post gene therapy administration (up to and including 49.7 months). For those patients enrolled in LT-001 who received the therapeutic dose of onasemnogene abeparvovec in START (n=10), at the 31 December 2018 data cut-off (28) all patients were alive with no loss of previously attained milestones or worsening of ventilatory or nutritional function compared with the end of START.

Results from ongoing studies continue to demonstrate the rapid and substantial clinical efficacy of onasemnogene abeparvovec across multiple endpoints: survival, developmental motor milestones and motor function. The data from ongoing studies also support the use of onasemnogene abeparvovec in other patient populations than that investigated in the START study, for example, in European populations and in pre-symptomatic patients with different *SMN2* copy numbers in SPR1NT. Patients in SPR1NT achieved higher (maximal or near maximal) CHOP-INTEND scores more quickly than patients in STR1VE-EU and STR1VE-US, who were dosed at an older age, further supporting the hypothesis that early intervention has the greatest potential to achieve maximum therapeutic benefit.

In conclusion, based on the consistent evidence of rapid and substantial efficacy across endpoints and clinical trials and the continuing high unmet medical need in the severe and life-threatening disease, onasemnogene abeparvovec provides an opportunity to significantly improve the clinical outcomes of infants with SMA type 1.

9.6.2 Justify the inclusion of outcomes in table C9 from any analyses other than intention-to-treat.

For the START study, the FAS was used for:

- Assessment of change from baseline in CHOP-INTEND score

- Proportion of patients who achieved specified CHOP-INTEND thresholds
- Proportion of patients independent of ventilatory support
- Proportion of patients who required invasive ventilatory support

The SAS was used for the assessment of the proportion of patients receiving non-oral feeding support. However, all ITT patients received onasemnogene abeparvovec and no patients discontinued from the study. The ITT, FAS, and SAS analysis sets are therefore equivalent.

For STR1VE-EU, STR1VE-US, and SPR1NT, all efficacy analyses reported as of the 8 March 019 data cut (42) were conducted using the ITT populations of each study as the primary population. The SAS in each study was used for safety analyses.

9.7 *Adverse events*

In section 9.7 the sponsor is required to provide information on the adverse events experienced with the technology being evaluated in relation to the scope. For example, post-marketing surveillance data may demonstrate that the technology shows a relative lack of adverse events commonly associated with the comparator.

9.7.1 Using the previous instructions in sections 9.1 to 9.6, provide details of the identification of studies on adverse events, study selection, study methodologies, critical appraisal and results.

Adverse events (AE) were recorded throughout the onasemnogene abeparvovec clinical development programme; the identification, study details, methodologies and results of the onasemnogene abeparvovec trials are presented in Sections 9.1–9.6. For ongoing trials (STR1VE-US, STR1VE-EU, SPR1NT, and LT-001) safety data are currently only available from the 27 September 2018 data cut (44). The safety data for ongoing trials as of the 8 March 2019 data cut will become available in the timeframe of this submission (estimated Q3 2019).

9.7.2 Provide details of all important adverse events reported for each study. A suggested format is shown in table C10.

9.7.2.1 START

All AEs were collected from the time at which informed consent was signed until 30 days following the last study visit. All 15 treated patients (100%) in the START study experienced at least one AE (Table 40). Thirteen patients (87%) had a SAE during the study and four patients (27%) had an AE considered by the investigator to be related to onasemnogene abeparvovec. No AE resulted in death or study discontinuation.

The most frequently reported AEs (frequency ≥40% overall) were upper respiratory tract infection (73%), pyrexia (53%), vomiting (53%), constipation (47%), pneumonia (46.7%), gastroesophageal reflux disease (40.0%), and nasal congestion (40.0%). The majority of

these events resolved during the observation period and none of the most frequently reported treatment-emergent AEs (TEAE) were considered to be related to onasemnogene abeparvovec. There were no statistically significant differences between cohorts in the frequency of any specific TEAEs.

Four patients (27%) had a total of 5 AEs considered by the investigator to be definitely related to onasemnogene abeparvovec. Increased transaminases were reported in three patients and increased aspartate aminotransferase and increased transaminases were reported in one patient. All TEAEs considered definitely related to onasemnogene abeparvovec resolved within the observation period.

Hospitalisations during the study

Hospitalisations during the study were summarised by patient and included start and end dates as well as the reason(s) for hospitalisation. In addition, a post hoc summarisation was conducted so that the results could be standardised per year.

At the final assessment, 13/15 patients (86.7%) had had at least one hospitalisation during the study, including all three patients (100%) in Cohort 1 and 10/12 patients (83.3%) in Cohort 2. The mean (standard error) annualised hospitalisation rates were 0.81 (0.17) for Cohort 1, 2.08 (0.68) for Cohort 2, and 1.83 (0.53) for both cohorts combined. The hospitalisation rates of infants with SMA type 1 in natural history studies have been reported to range from 4.210 to 7.611 hospitalisations/year (134, 135). For Cohort 2, the mean proportion of study time hospitalised was 4.4% (range, 0–18.3%); 10 (83%) patients were hospitalised <10% of the time, and none were hospitalised for ≥20% of the time. In addition, the mean length of stay per hospitalisation was 6.7 days (range, 3–12.1) for the 10 patients who were hospitalised after treatment with onasemnogene abeparvovec.

Table 40: START – treatment-emergent adverse events (safety analysis set)

Event	Cohort 1 (N=3), n (%)	Cohort 2 (N=12), n (%)	All patients (N=15), n (%)
Any adverse event	3 (100)	12 (100)	15 (100)
Any serious adverse event	3 (100)	10 (83.3)	13 (86.7)
Treatment-emergent adverse events associated with onasemnogene abeparvovec[†]	1 (33.3)	3 (25.0)	4 (26.7)
Treatment-emergent adverse events reported in ≥2 patients			
Cardiac disorders			
Tachycardia	0	2 (16.7)	2 (13.3)
Gastrointestinal disorders			
Vomiting	0	8 (66.7)	8 (53.3)
Constipation	1 (33.3)	6 (50.0)	7 (46.7)
Gastroesophageal reflux disease	1 (33.3)	5 (41.7)	6 (40.0)
Diarrhoea	0	3 (25.0)	3 (20.0)
General disorders and administration site conditions			
Pyrexia	1 (33.3)	7 (58.3)	8 (53.3)
Infections and infestations			
Upper respiratory tract infection	1 (33.3)	10 (83.3)	11 (73.3)
Pneumonia	0	7 (58.3)	7 (46.7)
Enterovirus infection	1 (33.3)	4 (33.3)	5 (33.3)
Gastroenteritis viral	0	5 (41.7)	5 (33.3)
Rhinovirus infection	1 (33.3)	4 (33.3)	5 (33.3)
Otitis media	2 (66.7)	2 (16.7)	4 (26.7)
Parainfluenza virus infection	1 (33.3)	3 (25.0)	4 (26.7)
Bronchiolitis	0	3 (25.0)	3 (20.0)
Ear infection	1 (33.3)	2 (16.7)	3 (20.0)
Pharyngitis streptococcal	1 (33.3)	2 (16.7)	3 (20.0)
Pneumonia respiratory syncytial viral	1 (33.3)	2 (16.7)	3 (20.0)
Respiratory syncytial virus bronchiolitis	1 (33.3)	2 (16.7)	3 (20.0)
Viral upper respiratory infection	0	3 (25.0)	3 (20.0)
Adenovirus infection	0	2 (16.7)	2 (13.3)
Conjunctivitis	0	2 (16.7)	2 (13.3)
Influenza	1 (33.3)	1 (8.3)	2 (13.3)
Urinary tract infection	0	2 (16.7)	2 (13.3)
Injury, poisoning and procedural complications			
Fall	0	3 (25.0)	3 (20.0)

Event	Cohort 1 (N=3), n (%)	Cohort 2 (N=12), n (%)	All patients (N=15), n (%)
Investigations			
Transaminases increased	1 (33.3)	3 (25.0)	4 (26.7)
Human rhinovirus test positive	0	3 (25.0)	3 (20.0)
Enterovirus test positive	0	2 (16.7)	2 (13.3)
Metabolism and nutrition disorders			
Dehydration	0	2 (16.7)	2 (13.3)
Respiratory, thoracic and mediastinal disorders			
Nasal congestion	0	6 (50.0)	6 (40.0)
Cough	0	5 (41.7)	5 (33.3)
Atelectasis	0	4 (33.3)	4 (26.7)
Respiratory failure	1 (33.3)	3 (25.0)	4 (26.7)
Rhinorrhoea	0	3 (25.0)	3 (20.0)
Pneumonia aspiration	0	2 (16.7)	2 (13.3)
Respiratory distress	0	2 (16.7)	2 (13.3)
Wheezing	0	2 (16.7)	2 (13.3)
Skin and subcutaneous tissue disorders			
Rash	0	5 (41.7)	5 (33.3)
Decubitus ulcer	0	2 (16.7)	2 (13.3)
Erythema	1 (33.3)	1 (8.3)	2 (13.3)

† Included in this category are all the adverse events (including elevations in aminotransferase levels) that were definitely related to gene replacement therapy, according to investigator assessment.
Source: START CSR (data on file) (25).

9.7.2.2 Ongoing studies

A summary of AEs and Grade 3 or 4 AEs in ongoing studies as of the most recent safety data cut (27 September 2018) is provided in Table 41.

Table 41: Ongoing onasemnogene abeparvovec studies – summary of safety

Event	STR1VE-EU (N=5)	STR1VE-US (N=22)	SPR1NT (N=7)	LT-001 (N=13)
Any adverse event	[redacted]	[redacted]	[redacted]	[redacted]
Any serious adverse event	[redacted]	[redacted]	[redacted]	[redacted]
Treatment-emergent adverse events associated with onasemnogene abeparvovec†	[redacted]	[redacted]	[redacted]	[redacted]
Adverse event leading to discontinuation of study	[redacted]	[redacted]	[redacted]	[redacted]

Event	STR1VE-EU (N=5)	STR1VE-US (N=22)	SPR1NT (N=7)	LT-001 (N=13)
Adverse event leading to death	[redacted]	[redacted]	[redacted]	[redacted]
Grade 3 or 4 adverse events				
Pneumonia	[redacted]	[redacted]	[redacted]	[redacted]
Atelectasis	[redacted]	[redacted]	[redacted]	[redacted]
Acute respiratory failure	[redacted]	[redacted]	[redacted]	[redacted]
Respiratory failure	[redacted]	[redacted]	[redacted]	[redacted]
Transaminases increased	[redacted]	[redacted]	[redacted]	[redacted]
Aspartate aminotransferase increased	[redacted]	[redacted]	[redacted]	[redacted]
Enterovirus infection	[redacted]	[redacted]	[redacted]	[redacted]
Human rhinovirus test positive	[redacted]	[redacted]	[redacted]	[redacted]
Parainfluenza virus infection	[redacted]	[redacted]	[redacted]	[redacted]
Pneumonia aspiration	[redacted]	[redacted]	[redacted]	[redacted]
Pneumonia respiratory syncytial viral	[redacted]	[redacted]	[redacted]	[redacted]
Respiratory distress	[redacted]	[redacted]	[redacted]	[redacted]
Respiratory syncytial virus bronchiolitis	[redacted]	[redacted]	[redacted]	[redacted]
Rhinovirus infection	[redacted]	[redacted]	[redacted]	[redacted]
Upper respiratory tract infection	[redacted]	[redacted]	[redacted]	[redacted]
Abnormal weight gain	[redacted]	[redacted]	[redacted]	[redacted]
Alanine aminotransferase increased	[redacted]	[redacted]	[redacted]	[redacted]
Dysphagia	[redacted]	[redacted]	[redacted]	[redacted]
Failure to thrive	[redacted]	[redacted]	[redacted]	[redacted]
Feeding disorder	[redacted]	[redacted]	[redacted]	[redacted]
Hypercalcaemia	[redacted]	[redacted]	[redacted]	[redacted]
Sleep apnoea syndrome	[redacted]	[redacted]	[redacted]	[redacted]
Dehydration	[redacted]	[redacted]	[redacted]	[redacted]
Cardiac arrest	[redacted]	[redacted]	[redacted]	[redacted]
Gastroenteritis	[redacted]	[redacted]	[redacted]	[redacted]
Hypoglycaemia	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: AE, adverse event.
†Included in this category are all the adverse events (including elevations in aminotransferase levels) that were definitely related to gene replacement therapy, according to investigator assessment.
Source: 27 September 2018 safety data cut (data on file) (44)

9.7.2.3 STR1VE-EU

As of the 27 September 2018 data cut, five patients were enrolled in STR1VE-EU and had received a peripheral IV infusion of onasemnogene abeparvovec. Of the enrolled patients, [redacted] experienced at least 1 TEAE and [redacted] were reported to have a TEAE considered by the investigator to be related to onasemnogene abeparvovec. To date, 1 patient has died during the STR1VE-EU study; the patient died from severe respiratory infection followed by neurological complications, the event was deemed possibly related to onasemnogene abeparvovec.

9.7.2.4 STR1VE-US

As of the data 27 September 2018 cut, 22 patients were enrolled in STR1VE-US and had received a peripheral IV infusion of onasemnogene abeparvovec. [redacted] had at least one SAE. [redacted] experienced at least 1 TEAE and [redacted] had at least 1 TEAE that was severe (Grade 3 or higher). [redacted] were reported to have a TEAE considered by the investigator to be related to onasemnogene abeparvovec. One patient was discontinued from the study due to a respiratory arrest that resulted in death and was not deemed related to onasemnogene abeparvovec.

9.7.2.5 SPR1NT

As of the 27 September 2018 data cut, 7 patients were enrolled in SPR1NT and had received a peripheral IV infusion of onasemnogene abeparvovec. [redacted] experienced at least 1 TEAE. [redacted] experienced a single episode of hypercalcemia, which was both a SAE and a severe TEAE (Grade 3 or higher). [redacted] were reported to have a TEAE considered by the investigator to be related to onasemnogene abeparvovec. No patient had a TEAE resulting in death or discontinuation from the study.

9.7.2.6 LT-001

A total of [redacted] were reported in LT-001 as of the 27 September 2018 data cut; [redacted] enrolled in Study LT-001 were reported to have at least 1 SAE. Reported SAEs have included events of pneumonia, respiratory distress, acute or chronic respiratory failure, cardiac arrest, gastroenteritis, hypoglycaemia, and dehydration. Each of these SAEs was assessed as not related to onasemnogene abeparvovec.

9.7.3 Provide a brief overview of the safety of the technology in relation to the scope.

Onasemnogene abeparvovec has been shown to has been shown to have a manageable safety profile in the treatment for of type 1, both in the START trial and in the ongoing clinical studies. Safety outcomes noted in the NICE scope were mortality and adverse effects of treatment. Two patients have died in the onasemnogene abeparvovec clinical trial programme; it should be noted that natural history studies show that greater than 90% of patients in populations comparable to those in the onasemnogene abeparvovec clinical trial programme die or are on permanent ventilation by 20 months (12).

In START, four patients (27%) had a total of 5 AEs considered by the investigator to be definitely related to onasemnogene abeparvovec (increased transaminases [N=3] and increased aspartate aminotransferase [N=1] and increased transaminases [N=1]). All TEAEs considered definitely related to onasemnogene abeparvovec resolved within the observation period. To date, two patients have died during the onasemnogene abeparvovec clinical development programme. One patient has died during STRIVE-US due to a respiratory arrest that resulted in death and was not deemed related to onasemnogene abeparvovec. One patient has died during STR1VE-EU; the patient died from severe respiratory infection followed by neurological complications, the event was deemed possibly related to onasemnogene abeparvovec.

9.8 *Evidence synthesis and meta-analysis*

When more than one study is available and the methodology is comparable, a meta-analysis should be considered.

Section 9.8 should be read in conjunction with the 'Guide to the Methods of Technology Appraisal', available from www.nice.org.uk/guidance/ta

9.8.1 Describe the technique used for evidence synthesis and/or meta-analysis. Include a rationale for the studies selected, details of the methodology used and the results of the analysis.

Nusinersen was recently recommended by NICE (July 2019) for the treatment of patients with 5q SMA (including SMA type 1) via an MAA but was not yet considered established standard of care at the time of this submission (19, 20). As nusinersen is the only disease-modifying therapy licensed for the treatment of SMA type 1 in England, AveXis performed an exploratory assessment of the relative efficacy and safety of onasemnogene abeparvovec versus nusinersen for the treatment of patients with SMA type 1 with 2 copies of *SMN2* gene based on currently available data (30).

In the absence of head-to-head trials of onasemnogene abeparvovec and nusinersen a matching-adjusted indirect comparison (MAIC) was attempted, but deemed infeasible to complete (see below, with full details provided in the ITC report (30)). As a consequence an unanchored ITC is presented as this was the best remaining approach given the data constraints.

9.8.1.1 Methods

Literature review

Study identification

A search was conducted in PubMed and ClinicalTrials.gov on 5 March 2018 to identify trials assessing nusinersen or onasemnogene abeparvovec in patients with SMA type 1. Keywords included "spinal muscular atrophy", "SMA", "type 1", and "trial". The current analysis was focused on the 24-month results data from two trials, START (24) and SHINE (31) (open-label, extension of ENDEAR (22)), evaluating onasemnogene abeparvovec and nusinersen, respectively, as the updated trial results became available. Data from ongoing

Phase III studies in the onasemnogene abeparvovec clinical trial programme and LT-001, the long-term extension study of START, were not included in the analysis as the interim results available did not have sufficient follow-up at the time of the analysis, and the Phase III ongoing trials had incomplete enrolment.

Publications were evaluated according the Population, Intervention, Comparators, Outcomes, and Study design (PICOS) criteria shown in Table 42. A single researcher reviewed the title and abstract of each retrieved citation; publications deemed relevant were reviewed in full-text by the same researcher. In addition, reference lists of reviews identified in a topical search were reviewed to identify any additional trial publications.

Table 42: PICOS criteria for selection of studies

Domain	Inclusion criteria
Population	Spinal muscular atrophy type 1
Interventions	Onasemnogene abeparvovec (AVXS-101) Nusinersen
Comparators	No restrictions
Outcomes	Efficacy outcomes: • Overall survival • Event-free survival • Achievement of motor milestones • CHOP-INTEND change from baseline • CHOP-INTEND response rate • HINE-2 score • CMAP response • Permanent ventilation rate Safety outcomes: • Mortality rate • Overall adverse events • Treatment-related adverse events • Severe adverse events • Specific adverse events
Study design	• Randomised controlled trials • Single-arm non-randomised comparative trials
Other	No other restrictions

Abbreviations: CHOP-INTEND, Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders; HINE-2, Hammersmith Infant Neurological Examination-2; PICOS, Population, Intervention, Comparators, Outcomes, and Study design.

Data extraction

A single reviewer extracted data on study characteristics, interventions, patient characteristics, and outcomes for the final list of included studies. A second reviewer conducted a quality assessment of the data extraction process. Following reconciliation

between the two reviewers, a third reviewer was included to reach consensus for any remaining discrepancies. Data was stored and managed in a Microsoft Excel workbook.

The following study characteristics were extracted: study name, study year, study authors, study design, study inclusion criteria, study exclusion criteria, year of study initiation and study close, location of study, follow-up period, sample size, and outcome definitions.

The following intervention characteristics were extracted: treatment regimen, treatment dose, method of administration, frequency of administration, duration of treatment, and concomitant/background therapies.

The following patient characteristics were extracted: sample size at baseline, age at symptom onset, age at diagnosis, age at study start, gender, race and ethnicity, Hammersmith Infant Neurological Examination (HINE-2) score, CHOP-INTEND score, CMAP (peroneal and ulnar).

The following outcomes were extracted: event-free survival (EFS), overall survival (OS), CHOP-INTEND score, HINE-2 score, motor milestone response, CMAP response, permanent ventilation rate, mortality rate, overall adverse event, and individual adverse events.

For dichotomous outcomes, the number of patients with the event and the number of patients in each treatment arm was extracted. For continuous outcomes, the change from baseline in all intervention groups was extracted. If the change from baseline was not provided, the score at end of follow-up and the baseline score was extracted. For event rates the number of events, the number of patients in each treatment arm and follow-up or exposure time were extracted. Kaplan Meier curves were extracted in terms of the proportion of patients who had an event over time using DigitizeIt® in addition to the number of patients at risk over time. Full details of the decision rules that were applied to the extracted data in order to generate the necessary data set for the analysis for the trials included in the feasibility assessment can be found in the ITC report (30).

MAIC feasibility

In order to perform the MAIC, a logistic propensity score model was constructed. This model included all variables for which individual-patients data (IPD) are available in the index trial, START, and are reported in other studies identified from the SLR (SHINE, an extension of ENDEAR) to obtain a pairwise comparison between onasemnogene abeparvovec and nusinersen. Patient related factors, confirmed by AveXis's clinical team, that were considered for inclusion in the MAIC, are listed from highest to least importance:

(1) Mean CHOP-INTEND score at baseline

(2) Proportion with nutritional support

(3) Proportion with ventilator support

(4) Age at symptom onset

(5) Age at study start (first dose)

(6) Baseline weight

(7) *SMN2* copy number

(8) Gender

Patient characteristics for SHINE were used for the MAIC; where these were missing, values from ENDEAR (nusinersen arm) were used. The onasemnogene abeparvovec IPD from START contained 12 individuals and the MAIC produced weights for these individuals using the method of moments such that the weighted mean of START patient characteristics (the index trial) matched those of nusinersen. The MAIC weights were then applied to each outcome of interest (overall survival, event-free survival, CHOP-INTEND response, and CHOP-INTEND change from baseline, motor milestone achievement: head control, motor milestone achievement: independent sitting, and motor milestone achievement: independent walking) in the START IPD data and compared to those of nusinersen. In cases where the algorithm used to estimate the weights did not converge using the full set of baseline characteristics, included variables were removed in a stepwise fashion until convergence was achieved. Due to the small sample size of START, convergence was reached when including only one covariate: CHOP-INTEND score at baseline.

Based on the small sample size as well as 100% overall survival, event-free survival, and CHOP-INTEND response in START, the MAIC had no impact on the outcomes of interest. With no variation in overall survival, event-free survival, and CHOP-INTEND response in START, MAIC-weighted IPD yielded the treatment effect/outcomes as unweighted IPD as provided in the index trial (START). Although, the CHOP-INTEND change from baseline was variable across the 12 patients included in START, the MAIC weighting yielded the same result as the unweighted IPD. For outcomes where no re-weighting was observed between the original IPD and the MAIC weighting for the index trial (START) and treatment of interest (onasemnogene abeparvovec), an MAIC is not feasible because re-weighting IPD based on clinically relevant covariates is necessary to execute an MAIC. Another underlying reason preventing re-weighting of START data is only one covariate converging, and therefore only one covariate being used to re-weight START data. Mean CHOP-INTEND at baseline for START was similar to the pooled average from trials evaluating nusinersen (28.2 versus 26.7). Without other covariates to re-weight onasemnogene abeparvovec, due to non-convergence as a result of sample size, it is likely that the similar values for CHOP-INTEND mean at baseline further prevented re-weighting of the START data. Based on the aforementioned conclusions, it was deemed unfeasible to execute a MAIC for all outcomes of interest. Full details of the MAIC feasibility can be found in the ITC report (30).

Indirect treatment comparison versus nusinersen

Based on the length of follow up, only START (24) and SHINE (31) studies were included in the ITC analysis, as they provide outcomes at 24 months post dose. The patient populations assessed in the ITC included 12 infants treated with the therapeutic dose of onasemnogene abeparvovec in START and 81 infants treated with nusinersen in ENDEAR and SHINE (n=80/81 were treated with nusinersen in ENDEAR; one infant in the nusinersen group was withdrawn from the ENDEAR trial before treatment but subsequently was dosed with nusinersen in SHINE). As a MAIC was deemed unfeasible and given that the available studies for the interventions of interest do not include RCTs to facilitate a standard anchored indirect comparison, a naïve, or unanchored, indirect comparison was performed to compare efficacy of these treatments.

In the unanchored ITC, treatment effects of onasemnogene abeparvovec were compared with nusinersen in patients with SMA type 1 with 2 copies of the *SMN2* gene. The outcomes considered in the ITC were those that were assessed in both clinical trials, namely, EFS; OS; CHOP-INTEND change from baseline; CHOP-INTEND response rate and motor milestones. Differences in the definition of outcomes are described below. As updated safety outcomes at 24 months were not reported for SHINE, only efficacy outcomes were analysed. The safety outcomes from clinical trials of onasemnogene abeparvovec are presented in Section 9.7. The safety outcomes from clinical trials of nusinersen are reported in the SmPC of nusinersen (21).

Event-free survival was defined as alive without a requirement for permanent assisted ventilation and was evaluated at last visit. In addition death and the need for permanent assisted ventilation were analysed separately. There were minor differences between studies in the definition of endpoints. In START, permanent assisted ventilation was defined as ≥16 hours of respiratory assistance per day continuously for ≥14 days in the absence of an acute, reversible illness or a perioperative state whereas in SHINE it was defined as tracheostomy or ventilatory support for ≥16 hours per day continuously for >21 days in the absence of an acute reversible event.

The effect of treatment on motor function was assessed by a CHOP-INTEND response, defined as an increase ≥4 points from baseline, and was recorded at the last study visit. For the nusinersen clinical trial, the CHOP-INTEND response was only reported among patients who were enrolled for ≥6 months. For the START trial, the CHOP-INTEND response was calculated from the patient-level data adopting the same definition of response as in the nusinersen trials.

The definition of motor milestones differed in the two trials. START defined the achievement of motor milestones as per the Bayley Scales Gross Motor Subtest (119). SHINE defined the achievement of motor milestones using the HINE-2 score scale (136) (note: the definition of motor milestones are taken from the definitions described in the ENDEAR publication, as these were not reported in the interim analysis of SHINE). The time required for the assessment of motor milestones using the HINE-2 score scale depends on the age, understanding and co-operation of the children.

All outcomes were assessed at 24 months post onasemnogene abeparvovec or nusinersen administration/initiation with the exception of CHOP-INTEND response, CHOP-INTEND change from baseline and motor milestones:

1. CHOP-INTEND response (defined as ≥4 point improvement from baseline) was reported at 24 months post administration for onasemnogene abeparvovec and at the last available assessment for nusinersen
2. CHOP-INTEND change from baseline was reported at 2 months for both onasemnogene abeparvovec and also at 24 months and at Day 698 post administration for onasemnogene abeparvovec and nusinersen, respectively
3. Motor milestones were reported at the last available assessment for each patient post administration of onasemnogene abeparvovec or nusinersen

9.8.1.2 Results

Quality assessments for the START, ENDEAR and SHINE studies can be found in Appendix 4.

The patient populations assessed in the ITC included 12 infants treated with the therapeutic dose of onasemnogene abeparvovec in START and 81 infants treated with nusinersen in ENDEAR and SHINE (n=80/81 were treated with nusinersen in ENDEAR; one infant in the nusinersen group was withdrawn from the ENDEAR trial before treatment but subsequently was dosed with nusinersen in SHINE). Patient baseline characteristics are presented in Table 43.

Table 43: Baseline characteristics of infants in START and SHINE assessed in the ITC

	START (n=12)	SHINE (extension of ENDEAR) (n=81†)
SMN2 copy number	2	2
Mean age at study start (first dose), days (range)	103.4 (27.4–240.3)	164.3 (60.8–456.3)¶
Mean age at onset of symptoms, days (range)	42.6 (0–91.3)	48.7 (0–121.7)††
Mean age at genetic diagnosis, days (range)	60 (0–136)	88.2 (0-203)§
N (%) female	7 (58%)	44 (54%)
Mean weight, kg (range)	5.7 (3.6–8.4)	NR
Mean CHOP-INTEND score (range)	28 (12–50)	26.7 (8.1‡)
Nutritional support, N (%)	5 (42%)	7 (9%)§
Ventilator support, N (%)	2 (17%)	21 (26%)§

Abbreviations: CHOP-INTEND, Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders; NR, not reported.
† One infant randomized to receive nusinersen in ENDEAR was not dosed, but was dosed in SHINE.
‡ Standard deviation.
§ Values imputed from ENDEAR, nusinersen arm.
¶ Reported in source document in months: 5.4 (2–15).
†† Reported in source document in months: 1.6 (0-4).

Given the available data, an unanchored ITC was performed for the following efficacy outcomes: EFS, OS, CHOP-INTEND change from baseline, CHOP-INTEND response rate and motor milestones. As updated safety outcomes at 24 months were not reported, only efficacy outcomes were analysed.

Findings from the unanchored ITC suggest an efficacy advantage for onasemnogene abeparvovec relative to nusinersen; the outcomes reported for onasemnogene abeparvovec and nusinersen are presented in Table 44.

Table 44: Outcomes reported in the ITC of onasemnogene abeparvovec and nusinersen in infants with SMA type 1

Outcome (timepoint†)	Outcome definition	Timepoint†	Onasemnogene abeparvovec	Nusinersen
Overall survival, % (n/N)	Alive at the time of assessment	24 months	100 (12/12)	54.1 (20/37)
Survival free of permanent ventilation, % (n/N)	START: alive without a requirement for permanent assisted ventilation defined as ≥16 hours of respiratory assistance per day continuously for ≥14 days in the absence of an acute, reversible illness or a perioperative state whereas SHINE: alive without a requirement for permanent ventilation defined as tracheostomy or ventilatory support for ≥16 hours per day continuously for >21 days in the absence of an acute reversible event	24 months	100 (12/12)	20.0 (10/50)
CHOP-INTEND response, % (n/N)	≥4 point improvement from baseline	START: 24 months SHINE: last available assessment‡	100 (12/12)	67.9 (55/81)
CHOP-INTEND change from baseline	N/A	START: 24 months SHINE: Day 698	30.7	16.9
Achieved head control, % (n/N)	START: holds head erect for at least 3 seconds without support as per the Bayley Scales Gross Motor subset item #4 SHINE: achieved head control as used in the HINE-2 score scale	START: last available assessment SHINE: last available assessment‡	91.7 (11/12)	28.4 (23/81)
Sitting unassisted, % (n/N)	START: sitting unassisted for ≥30 seconds as per item 26 in the Bayley Scales Gross Motor Subtest SHINE: stable sitting and pivoting as used in the HINE-2 score scale	START: last available assessment SHINE: last available assessment‡	91.7 (11/12)	14.8 (12/81)

Outcome (timepoint†)	Outcome definition	Timepoint†	Onasemnogene abeparvovec	Nusinersen
Walking unassisted, % (n/N)	START: walking alone as per item 42 in the Bayley Scales Gross Motor Subtest SHINE: stable walking without assistance as used in the HINE-2 score scale	START: last available assessment SHINE: last available assessment‡	16.7 (2/12)	0 (0/81)§

Abbreviations: CHOP-INTEND, Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders; HINE, Hammersmith Infant Neurological Examination; NA, not applicable.

† Time post treatment administration (onasemnogene abeparvovec)/ initiation (nusinersen).

‡ As SHINE is subject to loss to follow up, only 17 out of 81 patients had follow up data at the latest available timepoint (698 days). Therefore, the last available assessment for each patient was used for analysis.

§ No patients had yet achieved standing unaided or walking independently, although patients were gaining HINE sub-milestones in both categories (31).

Conclusion

The unanchored ITC indicates that onasemnogene abeparvovec may have better clinical effectiveness in preventing death and use of permanent ventilation and in improving motor function in SMA type 1 patients relative to nusinersen. Despite the small sample sizes in all clinical trials used, the analysis performed was the best feasible with the data available at the time. Although no adjustment has been made for differences (known or unknown) in trial populations, it should be noted that the eligibility criteria for START and SHINE (extension of ENDEAR) were very similar with respect to the genetic profile of the SMA type 1 patients enrolled (age at symptom onset <6 months, 2 x *SMN2* copy number) and respiratory function (oxygen saturation levels ≥95 or 96% in START and SHINE, respectively). However, as a naïve comparison does not preserve within-study randomisation or take into account differences in study effects, all results should be interpreted with methodological limitations in mind. Any findings from such a comparison could be potentially misleading if there are significant differences in the distributions of prognostic factors or effect modifiers between the included trials. Although this does not invalidate the appropriateness of the results for decision-making; caution is nevertheless required in any interpretation of results.

9.8.2 If evidence synthesis is not considered appropriate, give a rationale and provide a qualitative review. The review should summarise the overall results of the individual studies with reference to their critical appraisal.

As described, only an unanchored ITC of onasemnogene abeparvovec to BSC based on data sourced from natural history studies in infants with SMA type 1 was performed and results are presented throughout Section 9.6.1.1.

The control groups from the natural history databases included 23 patients from the PNCR network and 16 from the NeuroNext database who met the criteria for eligibility similar to those used for START, i.e. patients with age of onset ≤6 months, bi-allelic deletion of *SMN1* (exon 7/8 common homozygous deletion) and 2 copies of *SMN2*. As the generalisability of the selected natural history cohorts, to the infants enrolled in START, was confirmed by clinical experts (17) these infants were selected as a population-matched control group rather than individual matched controls.

To further demonstrate the appropriateness of the natural history control cohorts, additional analyses were performed to examine individual patient matching between the PNCR and NeuroNext datasets and START. Sub-cohorts of individually-matched subjects from the described PNCR and NeuroNext natural history cohorts were selected to explore the extent to which the characteristics of PNCR and NeuroNext patients match those in START. All patients were matched by genotype (patients in both cohorts had bi-allelic *SMN1* deletions, 2 copies of *SMN2*), age at disease onset, nutritional and ventilatory support at 6 months of age, and baseline motor function (described by score on the CHOP-INTEND scale). These factors are broadly understood to be predictive of the rate of disease progression (12, 137).

Full details of the matched analysis are presented in Appendix 6. Patients were reasonably well-matched and the overall demographics were very similar between individually-matched natural history control patients and those in START. As seen in the population-matched

cohorts, no patients in either the PNCR or NeuroNext individually-matched patient cohorts achieved any motor milestones.

Minor differences in mortality outcomes were observed between natural history subgroups. For the PNCR natural history dataset, mortality at 14 months of age mortality was 41.67% and 30% in the individually- and population-matched subgroups, respectively, and the proportion of patients meeting the composite endpoint (mortality or permanent assisted ventilation) was 66.67% and 69.6%, respectively.

Mortality data at the end of follow-up were 50% and 47.8% in the individually- and population-matched PNCR subgroups, respectively, and the composite endpoint (mortality or permanent assisted ventilation) was 66.67% and 78.3%, respectively. For the NeuroNext natural history dataset, mortality at 14 months of age was 41.7% and 43.8% in the individually- and population-matched subgroups, respectively, and the proportion of patients meeting the composite endpoint (mortality or ventilation) was 50.0% in both subgroups. All data mortality was 50.0% in the individually- and population-matched NeuroNext subgroups, and the composite endpoint (mortality or ventilation) was 66.7% and 62.5%, respectively.

The clear benefit of onasemnogene abeparvovec was apparent irrespective of the data set used for comparison.

Table 45: Comparison of mortality outcomes between START, population-matched and individually-matched natural history control subgroups

Variable	START Cohort 2 (n=12)	Population-matched PNCR control (n=23)	Individually-matched PNCR control (n=12)	Population-matched NeuroNext control (n=16)	Individually-matched NeuroNext control (n=12)
Mortality at 14 months, n (%)	0	7 (30.4)	5 (41.67)	7 (43.8)	5 (41.7)
Composite (mortality or ventilation) at 14 months, n (%)	0	16 (69.6)	8 (66.67)	8 (50.0)	6 (50.0)
Mortality all data, n (%)	0	11 (47.8)	6 (50.0)	8 (50.0)	6 (50.0)
Composite (mortality or ventilation) all data, n (%)	0	18 (78.3)	8 (66.67)	10 (62.5)	8 (66.7)

9.9 *Interpretation of clinical evidence*

9.9.1 Provide a statement of principal findings from the clinical evidence highlighting the clinical benefit and any risks relating to adverse events from the technology. Please also include the Number Needed to Treat (NNT) and Number Needed to Harm (NNH) and how these results were calculated.

The current clinical evidence base shows that SMA type 1 infants treated with onasemnogene abeparvovec in START have unprecedented survival (100% survival to date) (2, 24). All patients in START who received a one-time treatment of onasemnogene abeparvovec were alive and free from permanent ventilation at the end of the study (24 months) (24, 25). This outcome is in contrast to the survival rates reported in a UK natural history study that 50% of patients with SMA type 1 die before 1 year of age and also that reported in a US natural history study that only 8% of infants with SMA type 1 were alive without permanent ventilation at 20 months of age (12, 14). In addition, patients in START achieved unprecedented improvements in motor function and developmental milestones that were never previously observed in patients with SMA type 1. At the end of START, 91.7% of patients were able to hold their head erect without support, 75.0% were able to sit alone for ≥30 seconds, 16.7% were able to walk unassisted, 71.4% maintained the ability to thrive, 58.3% were entirely free from ventilation support, and 91.7% of patients were able to speak by 24 months post dosing (24, 25).

In currently available long-term follow-up, there is no evidence that patients have lost motor milestones gained in START (43). The rapid and statistically significant increase from baseline in mean CHOP-INTEND scores in babies treated with the proposed therapeutic dose of onasemnogene abeparvovec, provide further evidence of improvement in motor function. In addition, START included observations of substantial benefits in survival, motor function, and developmental milestone achievements relative to natural history cohorts (67), which were particularly striking for several patients treated at younger ages (Section 9.6.1.1). This is consistent with the theory that administration of a gene replacement therapy that can rapidly restore SMN protein expression before extensive neurodegeneration has occurred may achieve optimal outcomes.

Improvements in bulbar function were also observed in START 24 months after onasemnogene abeparvovec infusion. Of the 7 patients in Cohort 2 who did not require non-oral nutritional support prior to onasemnogene abeparvovec dosing, 71.4% maintained the ability to thrive and 91.7% could swallow effectively enough to feed orally. In comparison with the natural history (12, 137), all untreated patients with SMA type 1 are expected to lose the ability to swallow and fail to thrive by 1 year of age. Results of the cognitive assessment of infants treated with the therapeutic dose of onasemnogene abeparvovec suggest that these children have cognitive skills similar to healthy children. In START, onasemnogene abeparvovec had a manageable safety profile (2, 25). The unprecedented outcomes observed in START provided a basis for AveXis to make a regulatory submission for onasemnogene abeparvovec, though subsequent Phase III trials to confirm the efficacy and safety results observed are ongoing.

The outcomes observed in START have been broadly replicated in the interim results from the ongoing clinical studies in infants with SMA type 1. (STRIVE-US, STRIVE-EU and SPRINT). A total of 77 patients have been dosed with onasemnogene abeparvovec via a single IV infusion, as part of the clinical trial programme (8 March 2019 data cut) (42). Overall survival remains high with 75 remaining alive, in stark contrast to natural history data (12, 27). In addition, rapid and substantial clinical improvements in motor milestones and motor function have been observed. STR1VE-US is the ongoing Phase III trial for which the longest follow-up data are available; 50% (11/22) of patients achieved the ability to sit independently as of the 8 March 2019 data cut, achievement of this milestone was identified in patients between 5 and 13 months post onasemnogene abeparvovec administration (42). Data from ongoing studies demonstrate that the efficacy of onasemnogene abeparvovec is generalisable to European healthcare systems. A range of SMA type 1 patients than those in START, including pre-symptomatic patients and patients with different *SMN2* copy numbers in SPR1NT. In addition, patients in the ongoing multi-centre SPR1NT study achieved higher (maximal or near maximal) CHOP-INTEND scores more quickly than patients in STR1VE-EU and STR1VE-US, who were dosed at an older age, supporting the hypothesis that early intervention is key to achieve maximum therapeutic benefit.

The ability to sit independently (and potentially stand and walk), breathe without ventilatory requirement, swallow, and speak are critical functional needs that would potentially allow a child affected by SMA type 1 to attend school, maintain functional and social independence, and participate more fully in society. Onasemnogene abeparvovec represents an innovative and potentially transformative treatment which will not only represent a step-change in the management of SMA type 1, but may entirely revolutionise the treatment of infants with this disease. Infants who would otherwise die under BSC and who would never be able to sit, walk, or talk could have dramatically extended life expectancies and may be able to achieve physical independence from their caregivers. This is particularly true for children diagnosed at the pre-symptomatic stage of the disease, for whom the prospect of dramatic gains is greatest. Treatment with onasemnogene abeparvovec could also have a transformative effect for caregivers, who would otherwise have reduced QoL as a result of the burden of caring for a severely ill child with SMA type 1 and then losing their child in early infancy

An unanchored ITC was performed to estimate the relative efficacy of onasemnogene abeparvovec and nusinersen (as measured by EFS, OS, change from baseline in CHOP-INTEND, and CHOP-INTEND response). Despite the significant limitations of the current analysis, which includes a small sample size, and potential for differences in prognostic and predictive factors between studies, the relative treatment effects in EFS (100% versus 54.1%), OS (100% versus 20%), and CHOP-INTEND response (100% versus 67.9%) outcomes indicate that onasemnogene abeparvovec offers continued benefit compared with nusinersen throughout 24 months follow up. When considering motor function milestones achieved, the proportion of the cohort sitting unassisted was 75.0% (9/12 at 24 months) for onasemnogene abeparvovec versus 24.0% (at Day 689) for nusinersen. The numbers needed to treat for onasemnogene abeparvovec (START) versus nusinersen (SHINE) were 1.26, 2.27, and 3.24 for EFS, OS, and CHOP-INTEND response, respectively, at 24 months or last visit. Onasemnogene abeparvovec appears to induce a rapid improvement in motor function, as measured by CHOP INTEND scores in the first months post treatment, relative to nusinersen.

9.9.2 Provide a summary of the strengths and limitations of the clinical-evidence base of the technology.

The clinical development programme for onasemnogene abeparvovec comprises a series of Phase I–III clinical trials in patients with SMA type 1. To date, one study has been completed and four are ongoing. The current clinical evidence for onasemnogene abeparvovec has demonstrated the important benefits of this disease-modifying treatment versus BSC on several clinically and patient-relevant outcomes including survival without permanent ventilation and achievement of motor milestones.

In START, the primary efficacy endpoint was survival without permanent ventilation; onasemnogene abeparvovec demonstrated a clear and unequivocal benefit for this outcome, with 100% of patients alive and free from permanent ventilation at 24 months post onasemnogene abeparvovec administration, compared with 8% in external natural history PNCR study (12). The secondary efficacy endpoint in START was another highly relevant outcome to infants with SMA type 1: achievement of motor milestones (e.g. sitting and walking) which are never achieved without treatment (50). Onasemnogene abeparvovec demonstrated a clear benefit in motor milestone achievement, with 91.7%, 75.0%, and 16.7% of patients treated with the expected therapeutic dose of onasemnogene abeparvovec in START able to talk, sit, or walk by the end of the study (24, 25).

While results from the START trial are limited to 24 months following a one-time administration of onasemnogene abeparvovec, the follow-up study LT-001 provides long-term evidence, which demonstrates the durable effects of this disease-modifying treatment. The results of LT-001 to date indicate that a one-time IV administration of onasemnogene abeparvovec at the proposed therapeutic dose provides prolonged efficacy for durations longer than 3 years (up to 49.7 months) post gene therapy administration (28). Although the long-term efficacy of onasemnogene abeparvovec beyond this time-frame is currently unknown, long-term efficacy and safety follow-up will be performed for LT-001 until 15 years after treatment or until death, whichever is sooner (28). AveXis is establishing a patient registry to follow patients who receive onasemnogene abeparvovec in clinical practice, which will provide further long-term data. This registry will also address the long-term persistence of the onasemnogene abeparvovec transgene; data on this are currently limited to the survival and sustained motor milestone response of patients in LT-001 and preclinical data. In a mouse model of SMA, gene therapy resulted in survival of greater than 250 days, compared with control-treated animals who did not survive past 22 days; this suggests continued expression (138). In addition, gene therapy vector-derived DNA and RNA were detected in tissues from mice examined at 24 weeks post-injection, indicating persistence of expression (139).

While the evidence base for onasemnogene abeparvovec clearly demonstrates the clinical value of this treatment in infants with SMA type 1, it has some limitations. In START, the small number of patients treated with onasemnogene abeparvovec (N=15) assessed in a single centre is a limitation which may raise concerns about the generalisability of results to a wider population of patients with SMA type 1. However, START was designed as a Phase I/IIa trial, where an open-label dose-escalation design in a small patient population is typical, and despite the small size of the patient population, a clear and unequivocal benefit of

treatment with onasemnogene abeparvovec was demonstrated compared with natural history controls. To further support the robustness of clinical evidence from START, a greater number of patients are enrolled in the ongoing Phase III trials (STR1VE-EU, STR1VE-US, SPR1NT), with a total of 77 patients now dosed with a one-time IV infusion of onasemnogene abeparvovec. The evidence available from ongoing trials demonstrates that the survival and motor milestone efficacy outcomes originally shown in START are reproducible in larger, multicentre trials (Section 9.6.1). The results from SPR1NT also provide confirmation of the efficacy of onasemnogene abeparvovec in a broader infant population than that included in START, including pre-symptomatic patients and patients with different copy numbers of *SMN2*.

A second limitation of the evidence base is the single arm open-label trial design for START and the ongoing Phase III trials. However, given the extremely poor prognosis of patients who did not receive treatment in natural history studies (see Section 6) and the unprecedented efficacy and the safety profile observed in the START trial, it was considered unethical to include placebo patients in further onasemnogene abeparvovec trials. In addition, as nusinersen was not widely available when the clinical development programme for onasemnogene abeparvovec was designed, no head-to-head study has been conducted.

Due to the single arm design of the trials, well characterised datasets from the SMA natural history studies (i.e. the PNCR and NeuroNext) were identified as appropriate for use as historical controls (67). Comparisons with historical controls may be considered as a limitation as perceived treatment effects can be overestimated, particularly when standards of care improve over time or when there is a variable natural history (140). Despite differences in methodology, geographical location, and study populations, the PNCR and the NeuroNext studies show striking consistency in mortality, ventilatory requirement, motor function, and milestone achievement with the European experience described in recent papers by Wadman et al. 2017 (54) and De Sanctis et al. 2018 (60), as well as studies from the UK (14, 66), Poland and Germany (70), France (71), the US (72) and Hong Kong (73). Therefore, SMA type 1 patients from the PNCR and NeuroNext datasets are considered to be the most appropriate comparators for the patients treated with onasemnogene abeparvovec. The generalisability of the extracted PNCR and NeuroNext natural history control cohorts to the UK SMA type 1 patient population treated with BSC was confirmed at the UK Clinical Advisory Board (May 2019) (17). In addition, the efficacy of onasemnogene abeparvovec was evident in analyses versus the sub-cohorts of PNCR and NeuroNext historical control datasets, when using a matched-subject approach.

A further potential limitation of the START study is the greater range in baseline CHOP-INTEND scores (Cohort 1: 6–27; Cohort 2: 12–50) compared with those reported in the PNCR (5–40) and NeuroNext (10–33) natural history control cohorts. These differences may indicate that some infants in the START study had less severe disease than infants in the natural history controls. However, as the infants included in START were proactively identified for the study, they were likely to have been diagnosed at an earlier stage of disease progression than those in natural history controls, explaining the differences in baseline CHOP-INTEND scores. This is supported by the observation that the range of baseline CHOP-INTEND scores for patients in START were similar to those of infants recruited to STR1VE-EU (14–38), STR1VE-US (18–52), and SPR1NT (28–53). In addition, baseline CHOP-INTEND scores in START were in line with those reported for the sham-

control group in ENDEAR (presented in graph format only: approximate range of 10 to 50) (22). As clinical practice in England is moving towards earlier symptom recognition and earlier diagnosis due to the increasing awareness of SMA (in part due to the recent licensing of treatment options), the patient population in the onasemnogene abeparvovec clinical trial programme is expected to be representative of the infants that would receive this gene therapy in clinical practice in England.

Another uncertainty pertinent to onasemnogene abeparvovec relates to the duration of expression of the transgene. Preclinical data support the expectation of long-term gene expression following administration of onasemnogene abeparvovec. In a mouse model of SMA, gene therapy resulted in survival of greater than 250 days, compared with control-treated animals who did not survive past 22 days; this suggests continued expression (138). Gene therapy vector-derived DNA and RNA were detected in tissues from mice examined at 24 weeks post-injection, indicating persistence of expression (139). An opportunity to assess SMN expression following administration of onasemnogene abeparvovec was provided by the unfortunate death of one patient in the ongoing STR1VE-US trial (Section 9.7.2.4) and one patient in STR1VE-EU (Section 9.7.2.3) (42, 141). Widespread biodistribution of the onasemnogene abeparvovec genome and expression of the construct across the CNS and in the peripheral tissues and organs, including the heart and liver, was demonstrated (42, 142). These human data support that onasemnogene abeparvovec traverses the blood brain barrier following systemic administration, with substantial targeting and expression of SMN protein in key cellular targets such as CNS and muscle cells (42, 142). Intravenous administration of onasemnogene abeparvovec is able to restore *SMN* expression to motor neurons that lack a functional *SMN1* gene, thereby addressing the root cause of SMA (42, 142).

While no head-to-head trials are currently available for onasemnogene abeparvovec versus nusinersen, an ITC estimating the relative efficacy of the two treatments in infants with SMA type 1 suggested relative benefits, albeit with limitations, of onasemnogene abeparvovec on a number of outcomes relevant to this patient population (30) (Section 9.8.1). A limitation of ITC's is that a naïve comparison does not preserve within-study randomisation or take into account differences in study effects (143). This suggests that any findings from such a comparison could be potentially misleading if there are significant differences in the distributions of prognostic factors or effect modifiers between the included trials. The treatment arms in START and ENDEAR/SHINE (extension of ENDEAR) differed in terms of sample size, the proportions of patients requiring nutritional support at baseline, and the proportion of patients requiring ventilator support. In addition, there were differences in the definitions of permanent ventilation. Further, patients in START had a lower mean age at study start (first dose) and mean age of symptom onset. While the differences in study design and patient populations between START and ENDEAR/SHINE do not necessarily invalidate the appropriateness of the results for decision-making, a high level of caution is nevertheless required in any interpretation of results.

9.9.3 Provide a brief statement on the relevance of the evidence base to the scope. This should focus on the claimed patient- and specialised service-benefits described in the scope.

The onasemnogene abeparvovec evidence base directly addresses the following outcomes set out in the NICE scope: mortality, need for non-invasive or invasive ventilation, motor function, respiratory function, complications of SMA, and adverse effects of treatment.

HRQoL was included in the NICE scope but is not considered in the current clinical evidence base. Quality of life utilities for infants are extremely difficult to gain a consensus on due to difficulties in receiving reliable feedback from infants or parents regarding the quality of life. HRQoL cannot be directly measured in infants with SMA type 1 and would rely on proxy reported measures. While HRQoL was not included in the onasemnogene abeparvovec clinical trial programme, AveXis has sourced values from the literature to estimate the HRQoL of infants with SMA type 1 and conducted an exploratory UK utilities elicitation study (presented in Section 10.1.9). Given the extreme difficulties in obtaining reliable HRQoL data in SMA type 1 patients, and their caregivers, it may be appropriate to place more consideration to other, more robust outcomes from the clinical evidence base including the unprecedented survival outcomes observed.

9.9.4 Identify any factors that may influence the external validity of study results to patients in routine clinical practice.

It is likely that increasing awareness of SMA and the availability of new treatments will incentivise rapid diagnosis and treatment. The key factor which may influence results in clinical practice is how early treatment is administered, as the loss of motor neurones and resulting muscle atrophy is irreversible, therefore, the earlier patients are diagnosed and treated, the lower the burden of symptoms and the better the expected clinical outcomes. The average age of SMA type 1 diagnosis in the nusinersen EAP, which provides an approximation of UK clinical practice, was 2.6 months (144). In START, the mean age at genetic diagnosis, was 33 days (range: 4–85) and 60 days (range: 0–136) for Cohort 1 and Cohort 2, respectively (2). AveXis is committed to working with HCPs to improve education and awareness of SMA type 1 and available treatments to ensure rapid diagnosis and optimisation of clinical outcomes for babies with this condition.

9.9.5 Based on external validity factors identified in 9.9.4 describe any criteria that would be used in clinical practice to select patients for whom the technology would be suitable.

There are no additional factors which may be used to identify suitable patients for onasemnogene abeparvovec beyond those stated in the indication; the eligible patient population is all newly diagnosed patients with SMA type 1. However, due to the progressive and irreversible damage which SMA type 1 causes, it is likely to be beneficial to identify and treat patients as early as possible.

10 Measurement and valuation of health effects

Patient experience

10.1.1 Please outline the aspects of the condition that most affect patients' quality of life.

The aspects of the condition that affect the QoL of babies with SMA type 1 are discussed in Section 7.1. The profound muscle weakness caused by SMA imposes a substantial burden on every aspect of an infant's short life, and consequently has a substantial impact on their HRQoL compared with healthy infants (74, 75). Babies with SMA type 1 are unable to achieve developmental milestones such as sitting, standing, or walking and disease progression leads to increasing needs for ventilatory (non-invasive or invasive) and nutritional intervention (12, 50). Such intensive supportive care, while necessary to keep patients alive, may be traumatic as although cognition is preserved in babies with SMA type 1 (16, 145), very young children cannot understand what is happening to them.

As SMA type 1 afflicts very young infants, the condition also severely affects the QoL of a patient's parents, caregivers and their families. Babies with SMA type 1 need constant support, requiring caregivers to be constantly vigilant for breathing problems which could lead to asphyxiation and make difficult decisions regarding the extensive medical care needed by their child. Such constant care can cause stress, anxiety, emotional distress and loss of sleep for parents and caregivers. Caring for an infant with SMA type 1 can also have ongoing emotional, financial and social impacts, affecting carers employment due to time spent attending treatment or providing care, as well as straining relationships, which can detrimentally impact parents' and extended families' HRQoL.

10.1.2 Please describe how a patient's health-related quality of life (HRQL) is likely to change over the course of the condition.

Infants with SMA type 1 do not typically survive beyond 2 years of age without significant therapeutic intervention and permanent assisted ventilation (12). During their brief lifespan, the HRQoL of SMA type 1 patients under BSC is expected to deteriorate as the disease progresses due to the development of severe immobility and reduced breathing and swallowing ability (12, 50). The need for increasing levels of invasive intervention to keep patients alive as the disease worsens and having to spend more time in hospital is also expected to reduce the HRQoL of a baby with SMA type 1 over time.

HRQL data derived from clinical trials

10.1.3 If HRQL data were collected in the clinical trials identified in section 9 (Impact of the new technology), please comment on whether the HRQL data are consistent with the reference case. The following are suggested elements for consideration, but the list is not exhaustive.

- ***Method of elicitation.***

- ***Method of valuation.***
- ***Point when measurements were made.***
- ***Consistency with reference case.***
- ***Appropriateness for cost-effectiveness analysis.***
- ***Results with confidence intervals.***

HRQoL data were not collected in any of the onasemnogene abeparvovec trials for SMA type 1. In addition, HRQoL data were not captured in the nusinersen SMA type 1 trials identified (CS3A, ENDEAR or SHINE (22, 99, 110)) or the SMA type 1 natural history studies (PNCR, NeuroNext and Finkel 2014b (12, 26, 27, 59)) identified in the clinical effectiveness SLR.

Mapping

10.1.4 If mapping was used to transform any of the utilities or quality-of-life data in clinical trials, please provide the following information.

- ***Which tool was mapped from and onto what other tool? For example, SF-36 to EQ-5D.***
- ***Details of the methodology used.***
- ***Details of validation of the mapping technique***.

Not applicable.

HRQL studies

10.1.5 Please provide a systematic search of HRQL data. Consider published and unpublished studies, including any original research commissioned for this technology. Provide the rationale for terms used in the search strategy and any inclusion and exclusion criteria used. The search strategy used should be provided in appendix 17.1.

A systematic literature review was performed to gather evidence of HRQoL for onasemnogene abeparvovec and competing interventions for the treatment of SMA types 1–3. The methods used for the SLR of HRQoL data are provided in Section 9.1. Selection criteria used for the review of published HRQoL studies are presented in Table 46. The full search strategies used in the searches are shown in Appendix 1, Section 17.1.2. Although SMA type 1 is the focus of this dossier and the population on which decision-making is sought, the approach to the economic modelling requires utility values to be sourced for SMA health states from proxy populations (e.g. SMA type 2 and SMA type 3), hence the search included a broader SMA population.

Table 46: Selection criteria used for review of HRQoL and utilities

Inclusion criteria	
Population	SMA (type 1, type 2, and type 3; pre-symptomatic and symptomatic[†])
Interventions	Any of the following interventions used in the treatment of SMA: • Nusinersen • Onasemnogene abeparvovec (ZOLGENSMA; AVXS-101) • Branaplam • CK-2127107 • RO7034067/RG7916 • RO6885247 • Olesoxime • Proactive ventilator use and insufflator/exsufflator use (“cough assist”) • 4-aminopyridine • Anti-cholinesterase therapy/pyridostigmine bromide • Celecoxib • Hydroxyurea • Leuprolide and testosterone • Pyridostigmine • Riluzole • Sodium phenylbutyrate • Somatotropin • Valproic acid • Valproic acid and levocarnitine • Air stacking technique • Assisted Standing Treatment Program • Exercise • Palliation • Whole body vibration therapy
Comparators	No restrictions
Outcomes	**HRQoL measures:** • EQ-5D • PedsQL • For SMA types 2–3, other relevant QoL scales are also included • Caregiver QoL scales are also included **Health state utility values:** • HUI-2 • HUI-3S • SF-6D • SF-36

Study design	• RCTs or single-arm or non-randomised controlled trials, including subsequent trial publications reporting on HRQoL outcomes/utilities • Economic evaluations reporting utility values • Mapping algorithms • Observational studies reporting HRQoL/utility • Literature reviews summarizing results of primary research studies†
Language restrictions	Unrestricted
Search dates	Unrestricted

Abbreviations: EQ-5D, EuroQoL 5 Dimension; HRQoL, health-related quality of life; HUI, Health Utility Index; PedsQL, Pediatric Quality of Life Inventory; RCT, randomised controlled trial; SF-6D, Short-form six-dimension; SF-36, Short-form survey with 36 items; SMA, spinal muscular atrophy.
† All SMA types were searched for so as not to miss publications that evaluated mixed SMA populations and reported separate, relevant data for SMA type 1.
‡ Literature reviews that involve some kind of methodology for study identification and study selection will be of interest. This will include systematic literature reviews, structured literature reviews, scoping reviews, and landscape reviews. Narrative reviews that did not involve study identification via databases and are primarily summarize an author's viewpoints are not of interest.

10.1.6 Provide details of the studies in which HRQL is measured. Include the following, but note that the list is not exhaustive.

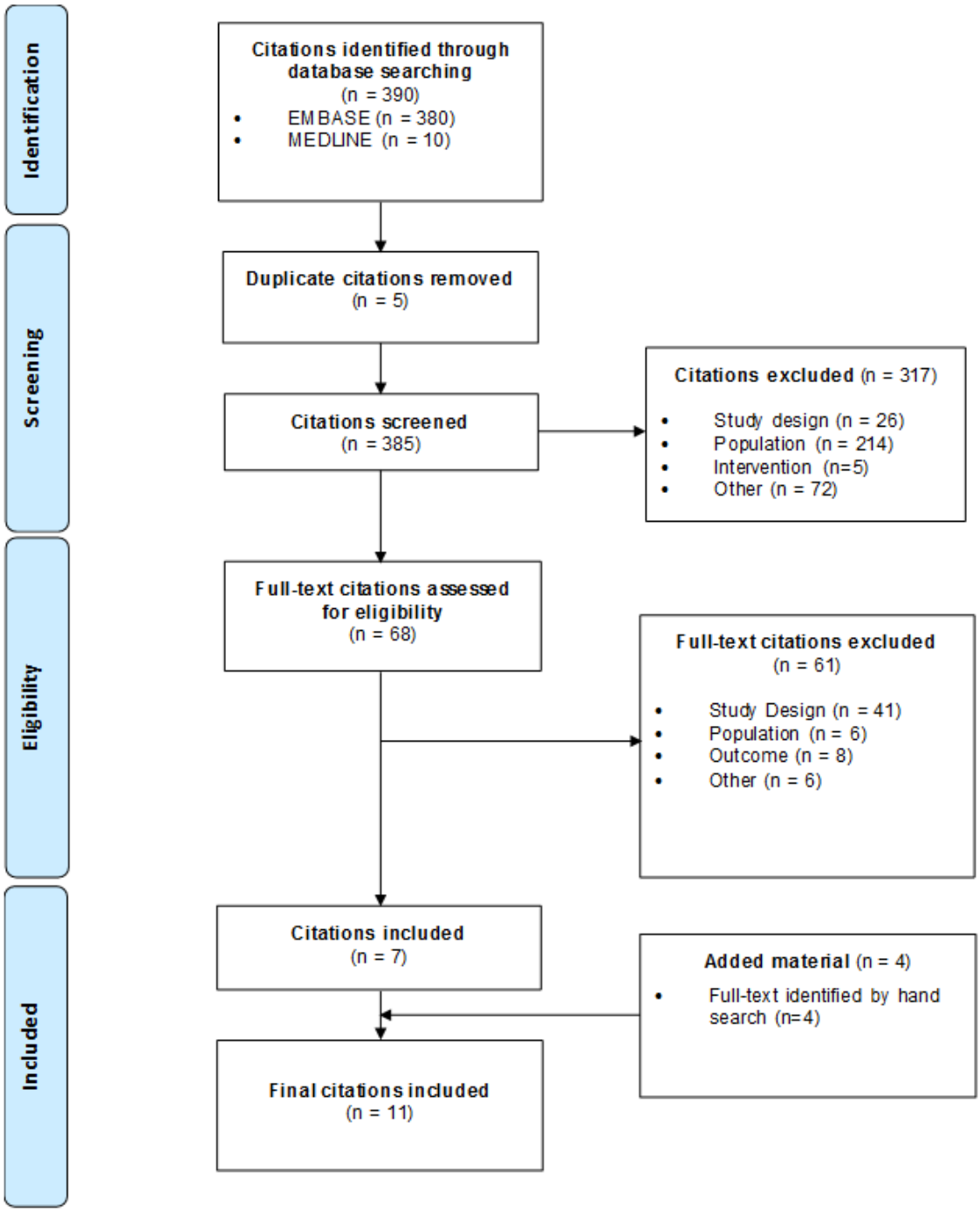
- ***Population in which health effects were measured.***
- ***Information on recruitment.***
- ***Interventions and comparators.***
- ***Sample size.***
- ***Response rates.***
- ***Description of health states.***
- ***Adverse events.***
- ***Appropriateness of health states given condition and treatment pathway.***
- ***Method of elicitation.***
- ***Method of valuation.***
- ***Mapping.***
- ***Uncertainty around values.***
- ***Consistency with reference case.***
- ***Results with confidence intervals.***

10.1.6.1 Study selection

The electronic database searches for HRQoL studies identified a total of 390 citations. After title/abstract screening, 68 publications were selected for further review in full-text. Following review of the full-text articles of these 68 citations, a total of 7 publications were identified for inclusion in the review. Four additional publications were identified via hand searches. A total of 11 publications, were included in the review.

Figure 30 presents the PRISMA flow diagram, which outlines the study selection process for the search to identify studies which described the humanistic burden of SMA.

Figure 30: Study selection flow diagram for HRQoL review



Although the US ICER's final report itself was not formally included in the above PRISMA diagram as a standalone included HRQoL study, the US ICER report's reference list was searched to identify any additionally relevant publications not identified by the database searches[e]. Furthermore, in a recent evaluation (published in April 2019) of SMA therapies – for which a UK academic institution (School of Health and Related Research, University of Sheffield) developed the cos-effectiveness model – it was considered appropriate to draw on the approach used by the US ICER to select patient utilities.

10.1.6.2 Results

The current review included a total of 11 publications (74, 77, 95, 98, 104, 111, 146-150). The baseline characteristics and key findings of these studies are presented in Appendix 2 (Section 17.2.2). In total, 2 RCTs, 2 open-label studies, and 2 cross-sectional studies were included in the full review in addition to five studies including a case study, a clinician survey, a prospective cohort study, a mixed methods, and a vignette study.

The Pediatric Quality of Life Inventory (PedsQL) was the most frequently reported HRQoL measure (77, 95, 98, 104, 111, 146, 148, 150). Results for infants with SMA type 1 were included in 4 studies (74, 77, 147, 150); the remaining studies reported HRQoL results for SMA type 2–3 (95, 98, 104, 111, 146, 148, 149). Worse clinical phenotype was associated with lower HRQoL (77, 147) and infants with SMA were reported to have lower quality of life compared with the general population (74). In addition, the HRQoL of infants with SMA was reported to worsen over time (104, 111).

The US ICER cost-effectiveness model draws on utilities reported by Thompson et al. 2017 (149) – a study reporting on three methods – as identified as part of the conducted HRQoL review and by Tappenden et al. 2018 (the Evidence Review Group [ERG] report associated with the nusinersen NICE STA) (151). Further details of the utilities reported in the US ICER report and the included HRQoL studies are described in Section 10.1.9.

10.1.7 Please highlight any key differences between the values derived from the literature search and those reported in or mapped from the clinical trials.

Not applicable as no HRQoL data were reported in the SMA type 1 clinical trials for onasemnogene abeparvovec, nusinersen or natural history cohorts identified as part of the clinical effectiveness SLR.

Adverse events

10.1.8 Please describe how adverse events have an impact on HRQL.

Disutilities associated with AEs were not included in the model. Given the nature of SMA, it is difficult to separate utilities due to treatment from the complications associated with SMA, which are already accounted for in the health state utility values. For example, with respect to the AEs reported for onasemnogene abeparvovec in START, the most frequently reported

[e] The final evidence report published by the US Institute for the Clinical and Economic Review of Spinraza® and Zolgensma® for Spinal Muscular Atrophy (April 3, 2019, Updated May 24, 2019) is available here: https://icer-review.org/wp-content/uploads/2018/07/ICER_SMA_Final_Evidence_Report_052419.pdf

AEs (frequency ≥40% overall) were upper respiratory tract infection (73%), pyrexia (53%), vomiting (53%), constipation (47%), pneumonia (46.7%), gastroesophageal reflux disease (40.0%), and nasal congestion (40.0%); all such AEs could be plausibly linked to the disease itself. None of the most frequently reported TEAEs were considered to be related to onasemnogene abeparvovec. Four patients (27%) had a total of 5 AEs considered by the investigator to be definitely related to onasemnogene abeparvovec (n=3 had increased transaminases; n=1 had increased aspartate aminotransferase and increased transaminases). All TEAEs considered definitely related to onasemnogene abeparvovec resolved within the observation period.

As such, separate disutilities for AEs are not included in the model. There are precedents for this in that the impact of AEs on HRQoL was also not included in the cost-utility model appraised as part of the nusinersen NICE assessment (31) or the recent US ICER assessment of SMA therapies (32).

Quality-of-life data used in cost-effectiveness analysis

10.1.9 Please summarise the values you have chosen for your cost-effectiveness analysis in the following table. Justify the choice of utility values, giving consideration to the reference case.

10.1.9.1 Base case – health state utility values

The base case patient health state utility values used in the de novo cost-effectiveness model are the same values as those used in the base case of the recent US ICER assessment of SMA therapies (excluding the application of any on-treatment utilities) and are presented in Table 47. These utilities were derived from multiple sources:

- The utilities reported by Thompson et al. 2017 (149) were from a cross-sectional study of individuals with SMA in Europe; investigators collected parent-proxy–assessed quality of life using the EuroQol-5 Dimensions (EQ-5D) 3-level version. The mean utility value for patients with SMA type 1 in the UK was 0.190 (n=7 parent-proxy assessments). As the health states observed in the natural history of SMA type 1 are permanent assisted ventilation and not sitting, this utility value (0.190) was applied to both the E state and D state in the base case analysis
- The utility value (0.600) for the C state (sits unassisted) was sourced from the ERG report evaluating the nusinersen submission for NICE. Tappenden et al. 2018 (151) reported utilities elicited (these estimates were described as ‘not preference-based’) from the clinical experts who advised the ERG, who were asked to provide plausible utility estimates for the different health states
- The utility for the B state (walks unassisted) and A state (within broad range of normal development) are sourced from general population utilities presented in Table 48, as per the well-established methodology of Ara and Brazier (152) using the equation below. Table 49 presented the age bands, mid points and sex coefficients used.

Utility (EQ-5D) = 0.9508566 + (0.0212126 x male) – (0.0002587 x age) – (0.0000332 x age^2)

These utility values have been chosen for the base case as:

- They were considered most appropriate by the US ICER independent assessment group
- All health states, except the C state, use utilities sourced via EQ-5D, which is the preferred measure of HRQoL in the NICE reference case
- They were deemed plausible according to a UK clinical advisory board (May 2019); noting that the experts consulted stated there should be a differentiation between the values for E and D states (i.e. the E state should be a lower value than the D state)
- Measuring robust utility values in babies and young children is exceptionally challenging, even more so in the rare disease setting. The NICE reference case states when it is not possible to obtain measurements of HRQoL directly from patients, data should be obtained from the person who acts as their carer (typically parents in the case of SMA type 1) in preference to healthcare professionals; in the base case parent-proxy EQ-5D values were sourced for the E state and D state

Table 47: Summary of patient utility values used in the base case cost-effectiveness analysis

State	Description	Utility value	Reference	Justification
E state	Permanent assisted ventilation	0.190	Thompson et al. 2017 (149)	• Approach taken by US ICER • Uses parent-proxy via EQ-5D-3L for UK-specific SMA type 1 population
D state	Not sitting	0.190		
C state	Sits unassisted	0.600	Tappenden et al. 2018 (151)	• Approach taken by US ICER • Informed by UK expert clinical advice, sourced by an independent research group (NICE ERG)
B state	Walks unassisted	General population	Ara and Brazier 2010 (152)	• Approach taken by US ICER, adapted to UK general population
A state	Broad range of normal development			

Abbreviations: ERG, Evidence Review Group; NICE, National Institute for Health and Care Excellence; EQ-5D-3L, 3-level EuroQol 5-dimension; SMA, spinal muscular atrophy; UK, United Kingdom; US ICER, United States Institute for Clinical and Economic Review.

Table 48: General population utilities used for A state and B state

Description	Utility value	Reference	Justification
Age 0–24 years	0.954	Calculation as reported in Ara and Brazier 2010 (152)	Walking unassisted by 2 years of age is reflective of normal development, as per the WHO reported windows of motor milestone achievement in healthy children. Therefore, general population utility values are applied for the B state and A state
Age 25–34 years	0.925		
Age 35–44 years	0.899		
Age 45–54 years	0.867		
Age 55–-64 years	0.829		
Age 65–74 years	0.783		
Age ≥75 years	0.685		

Abbreviations: WHO, World Health Organization.

Table 49: Calculations used for age-adjusted general population utilities

Description	Age band low	Age band high	Age midpoint	Sex coefficient	Utility value
Age 0–24 years	0	24	12	0.5	0.954
Age 25–34 years	25	34	29.5	0.5	0.925
Age 35–44 years	35	44	39.5	0.5	0.899
Age 45–54 years	45	54	49.5	0.5	0.867
Age 55-–64 years	55	64	59.5	0.5	0.829
Age 65–74 years	65	74	69.5	0.5	0.783
Age ≥75 years	75	100	87.5	0.5	0.685

10.1.9.2 Scenario analysis – health state utility values

Alternative published sources

Utilities from three alternative studies identified as part of the HRQoL SLR were assessed for incorporation as scenario analyses:

1) PedsQL from CHERISH (nusinersen later-onset SMA clinical trial) mapped to EQ-5D-Y (149). PedsQL data was mapped to the EQ-5D-Y using a published algorithm by Khan et al. 2014 (153)

2) A case vignette study that assessed clinician-proxy–assessed (n=5) EQ-5D-Y (149)

3) A cross-sectional study of individuals with SMA in European countries collected parent-proxy–assessed EQ-5D-3L. Values from UK respondents (n=7) are used only (149)

Further details of each study and a justification for why these were not use in the base case are provided in Table 52 below.

UK *de novo* utilities study

Prior to the publication of the US ICER report there was a lack of robust utility values, with face validity, which could be used to populate the *de novo* cost-effectiveness model, hence AveXis undertook a *de novo* UK utilities elicitation study (154). Further details of this study are in the UK utilities elicitation report (154).

Methods

Four health state vignettes were developed, which reflected the health states in the cost-effectiveness model: permanent assisted ventilation (PAV), non-sitting, sitting unassisted and walking unassisted. These health states reflect the natural history of the disease (off-treatment states), i.e. the patient described is not receiving ‘SMA-targeted’ pharmacotherapy (e.g. nusinersen or onasemnogene abeparvovec) and is receiving BSC only. The vignettes described: developmental milestones (e.g. ability to talk), motor milestones (e.g. able to sit unassisted), treatment requirements (non-invasive ventilation, tracheostomy, physiotherapy, hospital attendance), and intellectual and cognitive capacity of a child, in one of these four health states.

The participant sample recruited comprised of adults aged 18 to 86 (n=100) who participated in face-to-face interviews, between 3 April 2019 – 15 April 2019. Two elicitation methods for valuation of the health state vignettes were selected. Initially participants were presented with a visual analogue scale (VAS) with anchors at -100 and +100 and informed that values less than zero represented a state worse than dead (SWD). Following this, participants were then presented with the time-trade off (TTO).

Participants were asked to complete the VAS and TTO for two different scenarios:

1. "Parent vignettes" – Imagining being a parent valuing the state of their child with SMA
2. "Adult vignettes" – Imagining themselves as an adult with SMA

For the "Adult vignettes" the health state descriptions were modified accordingly; thus, in total eight vignettes were developed: four vignettes reflecting the health states for use in the "Parent vignettes" scenario and four vignettes reflecting the health states for use in the "Adult vignettes" scenario.

Results

The overall health state utilities are shown in Table 50 for the vignettes in which participants were asked to imagine they were the parent of a child with the condition ("Parent vignettes") and Table 51 for the vignettes in which participants were asked to imagine themselves as adults with the disease ("Adult vignettes") by each elicitation method VAS and TTO.

Table 50: Mean overall health utilities – Parent vignettes

TTO	**PAV**	**Non-sitting**	**Sitting Unassisted**	**Walking Unassisted**
Mean	[redacted]	[redacted]	[redacted]	[redacted]
SD	[redacted]	[redacted]	[redacted]	[redacted]
SE	[redacted]	[redacted]	[redacted]	[redacted]
95%CIL	[redacted]	[redacted]	[redacted]	[redacted]
95%CIH	[redacted]	[redacted]	[redacted]	[redacted]
VAS	**PAV**	**Non-sitting**	**Sitting Unassisted**	**Walking Unassisted**
Mean	[redacted]	[redacted]	[redacted]	[redacted]
SD	[redacted]	[redacted]	[redacted]	[redacted]
SE	[redacted]	[redacted]	[redacted]	[redacted]
95%CIL	[redacted]	[redacted]	[redacted]	[redacted]
95%CIH	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: CIL, confidence interval lower; CIH, confidence interval higher; PAV, permanent assisted ventilation; SE, standard error; SD, standard deviation, TTO, time trade off; VAS, visual analogue scale.

As may be seen from Table 50, for the "Parent vignettes", there is a clear improvement (increase) in the mean health utilities moving from the lowest to the highest functioning state. These differences are observed for both elicitation methods and are statistically significant: ($F [1,99] = 268.35$, $p<0.0001$ for TTO; $F [1,99] = 270.53$, $p<0.0001$, for VAS). The 95%CIs suggest that there were no differences between the two worst states, i.e. PAV and non-

sitting. Furthermore, sitting unassisted and walking unassisted states differed from these worst states, as well as from each other.

The same pattern of results was observed for the “Adult vignettes”. Again the differences between the lowest and highest functioning states were statistically significant (F [1,99] = 129.36, p<0.0001 for TTO; F[1,99] = 293.48, p<0.0001, for VAS).

Table 51: Mean overall health utilities – Adult vignettes

TTO	**PAV**	**Non-sitting**	**Sitting Unassisted**	**Walking Unassisted**
Mean	[redacted]	[redacted]	[redacted]	[redacted]
SD	[redacted]	[redacted]	[redacted]	[redacted]
SE	[redacted]	[redacted]	[redacted]	[redacted]
95%CIL	[redacted]	[redacted]	[redacted]	[redacted]
95%CIH	[redacted]	[redacted]	[redacted]	[redacted]
VAS	**PAV**	**Non-sitting**	**Sitting Unassisted**	**Walking Unassisted**
Mean	[redacted]	[redacted]	[redacted]	[redacted]
SD	[redacted]	[redacted]	[redacted]	[redacted]
SE	[redacted]	[redacted]	[redacted]	[redacted]
95%CIL	[redacted]	[redacted]	[redacted]	[redacted]
95%CIH	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: CIL, confidence interval lower; CIH, confidence interval higher; PAV, permanent assisted ventilation; SE, standard error; SD, standard deviation, TTO, time trade off; VAS, visual analogue scale.

Discussion and conclusions

The results showed, in general, that participants did not discriminate between the two worst health states, i.e. “PAV” and “non-sitting”, whereas “sitting unassisted” and “walking unassisted” were rated higher than the other two states. The “walking unassisted” health state had consistently the highest mean utility value.

The vignettes were lengthy in an attempt to capture all the different aspects of the health states beyond motor milestones alone. As a consequence, participants may have found it more difficult to readily identify the key differences between the health states, and hence this may have contributed to the more severe health states being rated similarly.

The overall results for the “Adult vignettes” were generally lower than those of the “Parent vignettes”. Some participants struggled to imagine themselves as adults having SMA. Furthermore, it is possible they were influenced by consideration of what it would be like to lose function and enter into an SMA state i.e. they may have valued the SMA state from the point of view of an adult who was previously healthy and lost function rather than a person who had never achieved significant motor milestones in their earlier life.

Participants found it easier to imagine the scenario in which the parent/caregiver evaluated the state of the child with SMA – i.e. the “Parent Vignettes” scenario. This scenario also more closely corresponds to the population in the trials and entering the cost-effectiveness

model. For these reasons the parent vignettes were preferred over the “Adult vignettes” in this setting.

It is established that the VAS does not reflect any trade-off that a subject may be willing to make in order to obtain better health, neither in terms of risk nor in years of life (155). As the VAS give only “scores” rather than “utilities,” the TTO values are preferred over the VAS scores.

Utility elicitation for rare diseases affecting infants is inherently problematic, as it may naturally be difficult for the general population to imagine themselves as parents of children with a serious life-limiting condition or to imagine themselves as an adult having a life-limiting condition (that started when they were very young) themselves.

In conclusion, the “Parent vignettes” valued using TTO, although deemed to be the most appropriate results to select from this de novo study, are used as an exploratory scenario analysis only, and not included in the base case. It is highlighted that the use of these utility values would give the standard of care (BSC) and recently approved treatment for SMA (nusinersen) an overall negative QALY, which may be considered to lack face validity.

On-treatment utility

Notably, the base case cost-effectiveness model adopted by US ICER also included additional utility benefits – often referred to as ‘on-treatment utility’ – in the treatment arms (onasemnogene abeparvovec and nusinersen) for achieving interim milestones such as head control, rolling, standing, crawling, etc. The US ICER implemented these on-treatment utilities as an additional utility of 0.1 and 0.05 compared to BSC in the non-sitting and sitting health states, respectively. The interim milestones (i.e. head control, rolling, crawling and standing with/without assistance) and other non-motor milestone features that may be achieved with pharmacotherapy (e.g. improvements in talking and non-verbal communication, fine motor control and learning etc.) are also not modelled as explicit health states in the *de novo* cost-effectiveness model presented in this submission. Exploratory additional scenario analyses including an on-treatment utility benefit assumed in the treatment arms to account for achieving such ‘intra-health state’ benefits of treatment. A range of on-treatment utilities increments are modelled in these scenario analyses:

- D state: on treatment utility of 0.05 to 0.15
- C state: on treatment utility of 0.025 to 0.075

Although the US ICER included on-treatment utilities as part of their base case, a more conservative approach has been taken here, and we include on-treatment utilities as additional scenario analyses only, with results presented in Section 12.5.11.

Caregiver disutilities

Due to substantial physical disability resulting from SMA type 1, babies with this disease require high levels of physical support and constant supervision from carers. The carers of babies with SMA type 1 have to make difficult treatment choices (i.e. whether to pursue an invasive treatment regimen for a child with respiratory function deterioration) and deal with uncertainty in the life expectancy or functional status of the infant (13, 76, 77). In addition,

carers experience isolation due to limitations in their ability to socialise and engage in activities outside of the home; and pressure on family finances from lost income or changes in career goals or employment related to time spent attending treatment and caring for the extra needs of the child (13, 76, 77). Whilst it is well accepted that SMA has a substantial effect on the HRQoL of parents, caregivers and families, robust UK quantitative caregiver utility data for the SMA population are lacking.

Methods for performing economic evaluations including caregiver burden are still under development, and currently there are no formally accepted mechanisms of including caregiver disutilities due to bereavement and loss of a child. Furthermore, learnings from other recent evaluations of SMA therapies indicate that incorporating caregiver HRQoL into economic evaluations has limitations, for example:

- US ICER did not include HRQoL burden associated with caregivers in their base case or scenario analyses, stating that incorporating caregiver burden may lead to counter-intuitive results due to prolonged negative productivity effects and unknown HRQoL effects on caregivers when children who need care live longer
- Committee discussions in the nusinersen STA concluded that caregiver utility should be considered in decision making but that quantifying it was extremely difficult

Due to the lack of robust SMA-specific UK caregiver utility data, and for the methodological limitations described, we assess the impact of caregiver HRQoL as an explorative scenario only. This explorative scenario applies a disutility for caregivers that varies by the health state of the patient, drawing data from a proxy, but related, disease – spina bifida. Spina bifida was chosen as an appropriate proxy disease as it shares several characteristics with SMA, for example, it afflicts very young babies and severely impacts the motor function and ambulation of patients. A study by Tilford et al. 2005 (156) compared Quality of Well-Being (QWB) scale data from the primary caregivers of children aged 0–17 years (n=98) with spina bifida versus a control sample of parents of non-disabled/unaffected children (n=49). Spina bifida children were categorised into three disability levels according to the location of the child's lesion: 1) sacral, 2) lower lumbar and 3) thoracic. When comparing caregivers of spina bifida patients to the control caregiver sample, the 'spill over' disutility of spina bifida caregivers are reported as: -0.03, -0.03 and -0.08 for the sacral, lower lumbar and thoracic lesion groups respectively. Values were calculated using the method described by Wittenberg et al. 2013 (157). These caregiver disutilities are incorporated into the exploratory scenario analysis as follows: -0.08 for caregivers of a child in the E state (permanent assisted ventilation) or D state (not sitting) and -0.03 for a child in the C state (sits unassisted).

Table 52: Summary of alternative patient utility values

Health state†	CHERISH: PedsQL mapped to EQ-5D-Y (Thompson et al. 2017)		Lloyd: Clinician-proxy Case Vignette EQ-5D-Y (Lloyd et al. 2017)		European study: Parent-proxy EQ-5D-3L, UK reports only (Thompson et al. 2017)		UK utilities elicitation study using TTO (AveXis, UK utilities report)	
	Health state	**Utility value**	**Health state**	**Utility value**	**Health state**	**Utility value**	**Health state**	**Utility value**
E state	SMA type 2: Worsened (from baseline)	0.730	SMA type 1: Requires ventilation	-0.33	SMA type 1	0.190	Permanent assisted ventilation	-0.2634
D state	SMA type 2: Stabilisation of baseline function	0.756	SMA type 1: Baseline	-0.12	SMA type 1	0.190	Not sitting	-0.2367
C state	SMA type 2: Moderate improvement	0.764	SMA type 1: Reclassified as SMA type 2†	-0.04	SMA type 2	0.100	Sits unassisted	0.2628
B state	SMA type 2: Walks unaided	0.878	SMA type 1: Reclassified as SMA type 3‡	0.71	SMA type 3	0.540	Walks unassisted	0.7898
A state	N/A	General pop.§	N/A	General pop.‡§	N/A	General pop.§	N/A	General pop.§
Justification for exclusion from the base case	The mapping described by Kahn et al 2014 has several methodological limitations: for example, it was conducted in a population that differed considerably (school children aged of 11 to 15 years) to SMA type 1 babies. In addition, the values seem implausibly high; for example, it seems unlikely that for an individual who requires PAV would be considered as being three quarters of that of an individual in perfect health		The study uses clinician-proxy assessment, which is less preferred to parent-proxy assessments, as per the NICE reference case. In addition, the study reported a negative utility (a health state worse than death) for 'reclassified SMA type 2'. A negative utility value for the C state (sits unassisted) lacks face validity and was deemed implausible by UK clinical experts (UK advisory board, May 2019)		Whilst this study uses parent-proxy assessment, which is preferred to clinician-proxy assessments, the results for the SMA type 2 group (used as proxy for the C state [sit unassisted]) lack face validity, as they are lower than the utility value reported for SMA type 1 patients who fail to achieve any milestones. Due to this lack of face validity, a scenario using values reported for SMA type 2 and 3 groups from this study is also not formally modelled		When using the utility values from this study, the overall estimates of discounted QALYs for both the BSC arm (-0.87 QALYs) and nusinersen ([redacted] QALYs) are negative – see Section 12.5.11. This result lacks face validity, in that this suggests that both UK standard of care (BSC) and a recently approved pharmacotherapy (nusinersen) results in patients losing QoL despite receiving treatment	

Abbreviations: BSC, best supportive care; EQ-5D-3L, 3-level EuroQol-Five Dimension; EQ-5D-Y, EuroQol-Five Dimension youth; N/A, not applicable; NICE, National Institute of Health and Care Excellence; PAV: permanent assisted ventilation; pop., population; QALY, quality-adjusted life-year; SMA, spinal muscular atrophy; TTO, ; UK, United Kingdom.
† Where possible, it was decided to use available utility data of type 1 patients behaving as type 2, rather than type 2 has a proxy. These are patients that have been treated, so type 1 patients who can sit, which is similar to our model. ‡ Where possible, it was decided to use available utility data of type 1 patients behaving as type 3, rather than type 2 proxy walkers. These are patients that have been treated, so type 1 patients who can walk, which is similar to our model. Baseline is D state and they can transition to B state.
§ Identified studies did not included an A state. The A state (within broad range of normal development) is assumed to have HRQoL equivalent to the UK general population.

10.1.10 If clinical experts assessed the applicability of values available or estimated any values, please provide the following details:

- ***the criteria for selecting the experts***
- ***the number of experts approached***
- ***the number of experts who participated***
- ***declaration of potential conflict(s) of interest from each expert or medical speciality whose opinion was sought***
- ***the background information provided and its consistency with the totality of the evidence provided in the submission***
- ***the method used to collect the opinions***
- ***the medium used to collect opinions (for example, was information gathered by direct interview, telephone interview or self-administered questionnaire?)***
- ***the questions asked***
- ***whether iteration was used in the collation of opinions and if so, how it was used (for example, the Delphi technique).***

The utility value for the C state (sits unassisted) in the base case analysis was from elicited expert estimates from clinical advisors to the NICE ERG (nusinersen STA appraisal; ERG report (151)).

As described in Section 12.2.5, UK expert clinicians and patient advocacy experts assessed the different options for utilities, reporting the following consensus:

- It is plausible for the D and E health states to be associated with negative health state utility values (i.e. considered worse than death)
- It is implausible for the C state to be associated with a negative health state utility value
- The concept of an average QoL score for each health state in the model is nonsensical as SMA is a heterogeneous disease that impacts very young infants and the impact on the patient, caregiver and family is very individual/environment-specific
- Of the health state utility values options shown, the US ICER values were the most plausible but there should be a differentiation between the values for E and D states (i.e. the E state value should be lower than the D state value)

10.1.11 Please define what a patient experiences in the health states in terms of HRQL. Is it constant or does it cover potential variances?

HRQoL changes over time as patients transition between different model health states. Potential variances with respect to ‘intra-health state’ benefits that patients may incur as a

result of treatment in the D state and C state are explored via an 'on-treatment' utility scenario analysis, as described in Section 10.1.9.2.

As the values used for the base case patient utilities values are sourced from published studies external to AveXis, that employed parent-proxy (149) (E state and D state) or clinician-proxy (151) (C state) assessments, details of the full questions/elicitation technique/vignettes used are lacking to be able assess whether the assessments captured a single timepoint 'snap shot' or also accounted for the potential variation that may occur to a patient in a given health state over time. Due to a lack of robust quantitative data informing how HRQoL may change over time on an 'intra-health state' basis, patient health state utilities remain constant for the lifetime horizon of the model.

10.1.12 Were any health effects identified in the literature or clinical trials excluded from the analysis? If so, why were they excluded?

Reasons for why the other studies reporting HRQoL identified in the SLR are excluded from the cost-effectiveness analysis are presented in Table 53.

Table 53: HRQoL studies identified in SLR excluded from the cost-effectiveness analysis

Study (reference) Study design Country	Rationale for exclusion
Bertini et al. 2017 (95) • Phase 2 RCT of olesoxime • Belgium, France, Germany, Italy, Netherlands, Poland, and the UK	• Did not include all health states (included only SMA type 2 or non-ambulatory SMA type 3 patients, aged 3–25 years) • Used PedsQL, which would require use of mapping that is associated with methodological limitations
Chiriboga et al. 2016 (98) • Open label of nusinersen • USA	• Did not include all health states (included only SMA type 2 or SMA type 3 patients, aged 2–14 years) • Used PedsQL, which would require use of mapping that is associated with methodological limitations
Swoboda et al. 2010 (111) • RCT (SMA CARNI-VAL Part 1) • USA	• Did not include all health states (included only SMA type 2 or non-ambulatory SMA type 3 patients, aged 2–8 years) • Used PedsQL, which would require use of mapping that is associated with methodological limitations
Kissel et al. 2011 (104) • Open label (SMA CARNI-VAL Part 2) • USA	• Did not include all health states (included SMA type 3 patients, aged 3–17 years) • Used PedsQL, which would require use of mapping that is associated with methodological limitations
Kirschner et al. 2018 (146) • Case series of infants treated with 12 mg nusinersen	• Did not include all health states (included SMA type 3 patients only) • Used PedsQL, which would require use of mapping that is associated with methodological limitations
Strauss et al. 2018 (148)	• HRQoL is not reported by motor function status or SMA type, but by *SMN2* copy number only

Study (reference) Study design Country	Rationale for exclusion
• Prospective cohort study of infants treated with 3 sequential doses of nusinersen (12 mg) • USA	• Used PedsQL, which would require use of mapping that is associated with methodological limitations
Lopez-Bastida et al. 2017 (74) • Cross sectional study • Spain	• Reporting the Spanish parent-proxy cohort of the European study described by Thompson et al 2017 (149); it was deemed more appropriate to use the UK parent-proxy cohort only
Klug et al. 2016 (77) • Cross sectional study • Germany	• Used PedsQL, which would require use of mapping that is associated with methodological limitations
Zuluaga et al. 2017 (150) • Clinician-proxy (n=5) vignette study	• Duplicate; used method reported in Lloyd et al 2017

10.1.13 If appropriate, what was the baseline quality of life assumed in the analysis if different from health states? Were quality-of-life events taken from this baseline?

Not applicable.

10.1.14 Please clarify whether HRQL is assumed to be constant over time. If not, provide details of how HRQL changes with time.

Only the general population utilities for the B state and A state vary by age; all other utilities stay constant for the lifetime horizon of the model. General population utilities were adjusted by age, using published methods as described in Section 10.1.9.1.

10.1.15 Have the values been amended? If so, please describe how and why they have been altered and the methodology.

Not applicable.

Treatment continuation rules

10.1.16 **Please note that the following question refers to clinical continuation rules and not patient access schemes. Has a treatment continuation rule been assumed? If the rule is not stated in the (draft) SPC/IFU, this should be presented as a separate scenario by considering it as an additional treatment strategy alongside the base-case interventions and comparators. Consideration should be given to the following.**

- ***The costs and health consequences of factors as a result of implementing the continuation rule (for example, any additional monitoring required).***
- ***The robustness and plausibility of the endpoint on which the rule is based.***
- ***Whether the 'response' criteria defined in the rule can be reasonably achieved.***
- ***The appropriateness and robustness of the time at which response is measured.***
- ***Whether the rule can be incorporated into routine clinical practice.***
- ***Whether the rule is likely to predict those patients for whom the technology constitutes particular value for money.***
- ***Issues with respect to withdrawal of treatment from non-responders and other equity considerations.***

No stopping rules exist for onasemnogene abeparvovec, as it is a one-time treatment administered via a single IV infusion.

The stopping rule for the modelled comparator – nusinersen – is not described in the nusinersen SmPC, but instead the associated NICE MAA (19) (detailed in Section 8.1). As adoption of this stopping rule is a condition of nusinersen reimbursement by NHS England, the following stopping rule is applied in the base case analysis for the nusinersen arm:

- Patients discontinue nusinersen in the E state (permanent assisted ventilation)
- Patient discontinue due to an annual risk of withdrawal (3%) in the D state and C state
    - The annual risk of withdrawal accounts for discontinuation due to reasons of patient/caregiver preferences [e.g. decision to avoid further hospital attendance], inability to administer nusinersen by intrathecal administration because of spinal fusion surgery or a worsening in motor function

- The rate of annual risk of withdrawal (3%) is from ENDEAR (proportion achieving a 4-point worsening in CHOP-INTEND) and reported withdrawal rates (n=3/95 withdrew treatment) from the nusinersen UK/Ireland EAP

Section D – Value for Money and cost to the NHS and personal social services

Section D requires sponsors to present economic evidence for their technology. All statements should be evidence-based and directly relevant to the decision problem.

11 Existing economic studies

11.1 *Identification of studies*

The review of the economic evidence should be systematic and transparent and a suitable instrument for reporting such as the PRISMA statement (www.prisma-statement.org/statement.htm).

A PDF copy of all included studies should be provided by the sponsor.

11.1.1 Describe the strategies used to retrieve relevant health economics studies from the published literature and to identify all unpublished data. The search strategy used should be provided as in section 17.3.

A SLR was undertaken to identify previous cost-effectiveness analyses relevant to the decision problem. The same SLR was used to identify cost and resources use associated with SMA.

The methods used for the SLR of health economic studies are provided in Section 9.1. The full search strategies used in the searches are shown in Appendix 1, Section 17.3.

11.1.2 Describe the inclusion and exclusion criteria used to select studies from the published and unpublished literature. Suggested headings are listed in table D1 below. Other headings should be used if necessary.

Table 54: Selection criteria used for published studies for review of economic evaluations

Inclusion criteria	
Population	Spinal muscular atrophy (type 1, type 2, and type 3; pre-symptomatic and symptomatic)
Interventions	Any of the following interventions used in the treatment of SMA: • Nusinersen • Onasemnogene abeparvovec (ZOLGENSMA; AVXS-101) • Branaplam • CK-2127107 • RO7034067/RG7916 • RO6885247 • Olesoxime • Proactive ventilator use and insufflator/exsufflator use (“cough assist”) • 4-aminopyridine • Anti-cholinesterase therapy/pyridostigmine bromide • Celecoxib • Hydroxyurea • Leuprolide and testosterone • Pyridostigmine • Riluzole • Sodium phenylbutyrate • Somatotropin • Valproic acid • Valproic acid and levocarnitine • Air stacking technique • Assisted Standing Treatment Program • Exercise • Palliation • Whole body vibration therapy
Comparators	No restrictions
Outcomes	• Resource utilisation • Direct costs • Indirect costs • Costs combined with clinical endpoints (e.g. clinical outcomes, utilities, life-years, quality-adjusted life-years, resource use, burden of illness)
Study design	Include: • Primary research studies:

	o Observational studies (e.g. controlled before-and-after studies, interrupted time series studies, historically controlled studies, prospective and retrospective cohort studies, time and motion studies, case-control studies, cross-sectional studies, controlled and uncontrolled longitudinal studies) o Randomised controlled trials and non-randomised clinical trials o Single arm studies o Full economic evaluations (e.g. cost-effectiveness analyses, cost-utility analyses, and cost-benefit analyses) o Partial economic evaluations/cost analyses (e.g. cost-of-illness analyses, cost-minimisation, cost-consequence, and budget impact analyses) • Pooled analysis presenting cost or resource use estimates • Health technology assessment documents • Literature reviews summarising results of primary research studies and/or economic evaluations†
Language restrictions	Unrestricted
Search dates	Unrestricted
Exclusion criteria	
Study design	• Studies with no relevant outcomes • Publication type not of interest (i.e. comment, editorial, letter, case report, animal study, pharmacokinetic-pharmacodynamics study, dose estimation/ dose-escalation studies without cost data)

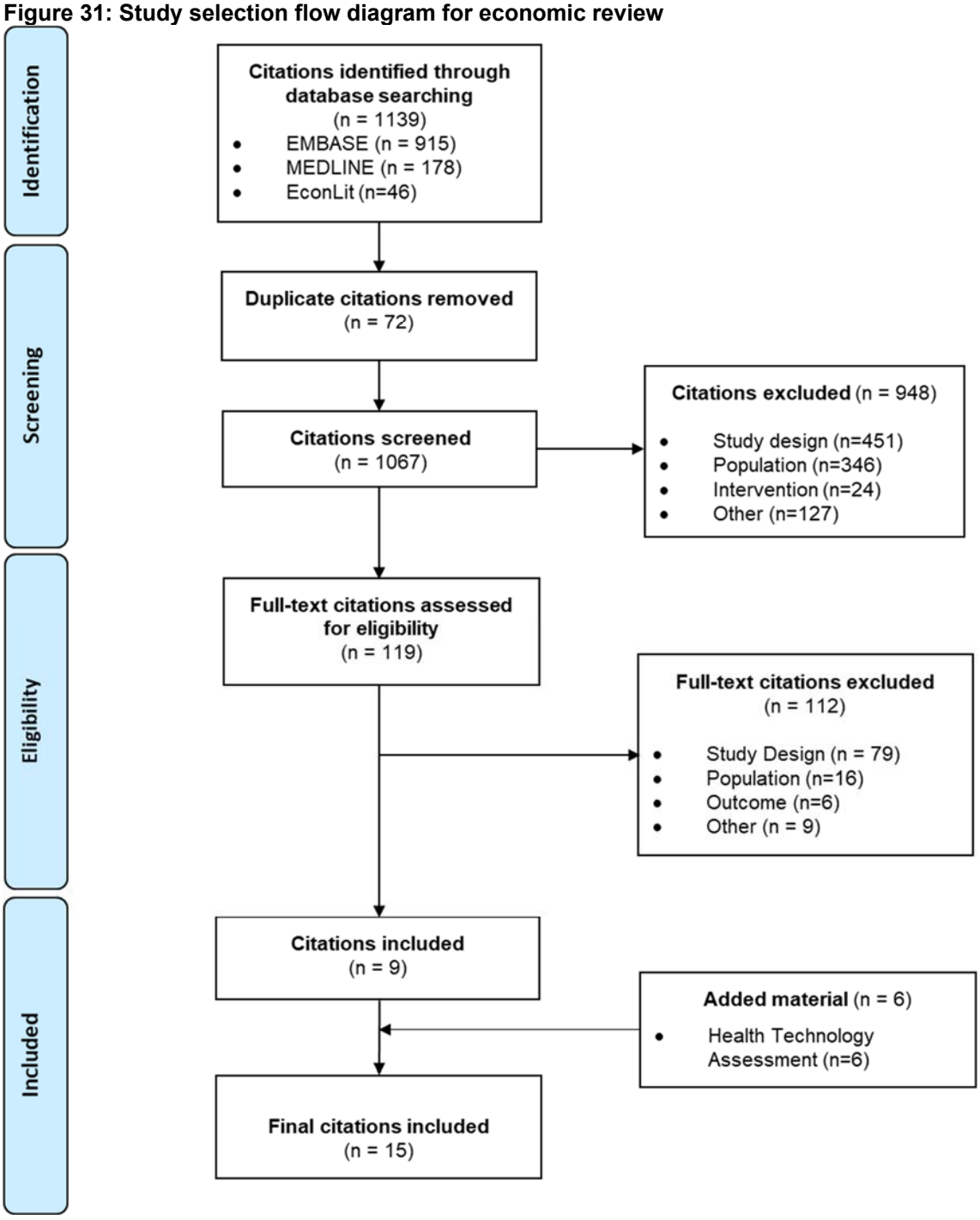
† Literature reviews that involve some kind of methodology for study identification and study selection will be of interest. This will include systematic literature reviews, structured literature reviews, scoping reviews, and landscape reviews. Narrative reviews that did not involve study identification via databases and are primarily summarise an author's viewpoints are not of interest.

11.1.3 Report the numbers of published studies included and excluded at each stage in an appropriate format.

The electronic database searches identified a total of 1,142 citations. After title/abstract screening, 119 publications were selected for further review in full-text. Following review of the full-text articles of these 119 citations, a total of nine publications were identified for inclusion in the review. In the supplementary search of the grey literature, six HTAs, two of which were published only in Croatian and Swedish language, were also identified; for these two non-English HTA publications (the Swedish Dental and Pharmaceutical Benefits Agency and the Agency for the Quality and Accreditation in Health Care and Social Welfare (Croatia) HTAs of nusinersen) no information was extracted. Thus, a total of fifteen publications were included in the review.

Figure 31 presents the PRISMA flow diagram, which outlines the study selection process for the search to identify studies of interest in the SLR of economic burden.

Figure 31: Study selection flow diagram for economic review



11.2 *Description of identified studies*

11.2.1 Provide a brief review of each study, stating the methods, results and relevance to the scope. A suggested format is provided in table D2.

Of the 15 studies included in the full review, 8 were cost evaluations (74, 77, 158-163) and 7 were economic evaluations (31, 164-169). A brief review and summary of the methods and results of included studies is presented in Appendix 2 Section 17.2.3.

11.2.2 Provide a complete quality assessment for each health economic study identified. A suggested format is shown in table D3.

The systematic literature review of economic burden identified several publications –HTA documents and conference proceedings – that were not eligible for quality assessment. However, the included studies that were eligible for a quality assessment were generally considered to have low risk of bias; results of the quality assessment are presented in Appendix 3 Section 17.4.1.3.

12 Economic analysis

Section 12 requires the sponsor to provide information on the de novo cost-effectiveness analysis.

The de novo cost-effectiveness analysis developed should be relevant to the scope.

All costs resulting from or associated with the use of the technology should be estimated using processes relevant to the NHS and personal social services.

12.1 *Description of the de novo cost-effectiveness analysis*

Patients

12.1.1 What patient group(s) is (are) included in the cost-effectiveness analysis?

The patient group included in the cost-effectiveness analysis is infants with a diagnosis of 5q13 SMA type 1, as per the expected licensed indication for onasemnogene abeparvovec. Based on the enrolled cohorts of the available clinical trials used to inform the cost-effectiveness analysis (see Section 12.2) the SMA type 1 population modelled include those:

- with two copies of the *SMN2* gene
- with the onset of symptoms at age ≤6 months
- who are symptomatic at baseline

A cost-effectiveness analysis in a broader symptomatic SMA type 1 population including those with >2 *SMN2* copy number is not possible for the pharmacotherapy treatment arms, as all the available clinical trials for onasemnogene abeparvovec and nusinersen are in symptomatic SMA type 1 patients with two copies of *SMN2;* therefore, an equivalent genetic profile (including only SMA type 1 patients with two copies of *SMN2*) was also used for modelling the BSC arm in the base case. The use of an SMA type 1 natural history cohort for the BSC arm reflective of a broader genetic profile with respect to *SMN2* copy number is provided as a scenario analysis.

Data from ongoing Phase III and long-term follow-up studies in the onasemnogene abeparvovec clinical trial programme were not included in the model as at the time of the analysis follow-up times for ongoing trials were shorter than the 24-months post-dose data available from START. As the model is based on observed milestones and on an extrapolation of CHOP-INTEND scores, mature and completed data are required, preventing the use of data from ongoing trials at this stage.

Technology and comparator

12.1.2 Provide a justification if the comparator used in the cost-effectiveness analysis is different from the scope.

In line with the final scope for this HST, BSC and nusinersen are used as comparators in the cost-effectiveness analysis.

Intervention

- Onasemnogene abeparvovec: one-time dose by IV infusion over approximately 60 minutes at a dose of $1.1x10^{14}$ vg/kg[f], in addition to BSC

[redacted]

Comparators

- BSC: standard respiratory, gastrointestinal, and nutritional care for patients with SMA, delivered via an MDT
- Nusinersen, in addition to BSC: intrathecal use by lumbar puncture. The recommended dosage is 12 mg per administration in 4 loading doses (on Days 0, 14, 28 and 63), followed by a maintenance dose administered once every 4 months thereafter (21).[g] Patients receive six injections in the first year and three injections in subsequent years.

The comparison against nusinersen is considered explorative only, as:

- The comparison is based on published list prices only; however, there is a confidential discount for nusinersen (19) as part of the nusinersen MAA
- The NICE guidance recommending nusinersen for commissioning via an MAA has only recently been published (July 2019) and hence nusinersen was not yet considered established standard of care at the time of this submission (19)

Model structure

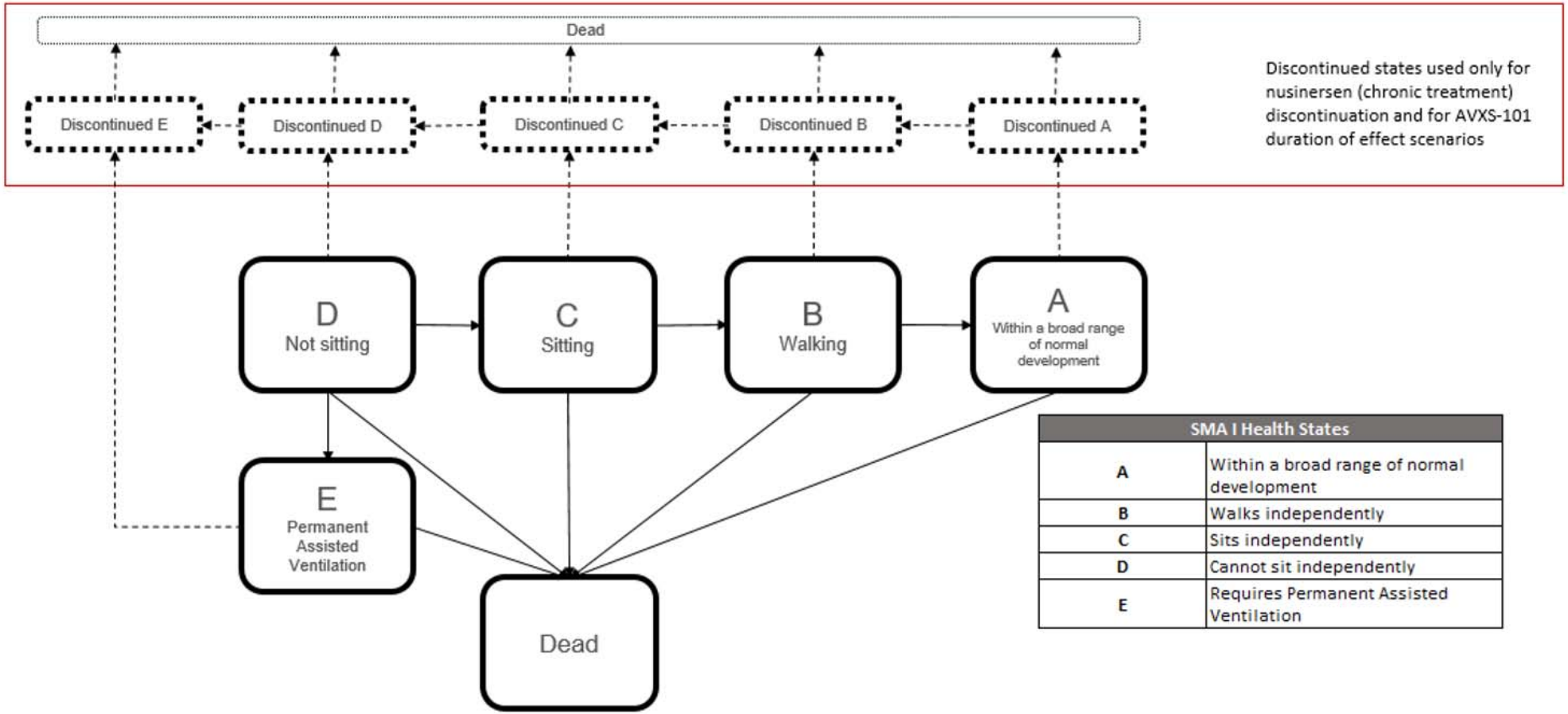
12.1.3 Provide a diagram of the model structure you have chosen.

The cost-effectiveness model is a cohort Markov state-transition model. The structure of the model is shown in Figure 32.

[f] Equivalent to the dose received by Cohort 2 in START as determined by direct product testing with improved analytical methods. Direct testing of the actual lot of IMP used in START by an improved and more fully qualified analytical method has assigned a value of 1.1×10^{14} vg/kg to the actual dose received by Cohort 2. The same method has been used to establish an equivalent dose for the IMP in all ongoing Phase III trials.

[g] In the ENDEAR trial the nusinersen dose was adjusted according to the estimated volume of cerebrospinal fluid for the infant's age on the day of dosing, such that the infant received a dose that was equivalent to a 12-mg dose in a person 2 years of age or older; thus, younger infants were injected with smaller volumes that contained lower doses of the drug. In the nusinersen group, doses were administered on days 1, 15, 29, and 64 and maintenance doses on days 183 and 302.

Figure 32: Model schematic



SMA I Health States	
A	Within a broad range of normal development
B	Walks independently
C	Sits independently
D	Cannot sit independently
E	Requires Permanent Assisted Ventilation

Health states

The model health states differ based on the motor function milestones achieved by the patient, the need for permanent assisted ventilation, and time to death. The model includes two health states that reflect the natural history of SMA type 1: D state (not sitting) and E state (permanent assisted ventilation). Three higher functioning health states are possible for patients in the pharmacotherapy-treated arms: C state (sits unassisted), B state (walks unassisted), and A state (within a broad range of normal development) (Table 55). Whilst the health states are broadly defined by the motor function milestone achieved, each health state also captures the likely associated symptoms and complications of SMA, which are described in Section 12.1.6.

Table 55: Functional status across health states

State	Clinical features
A	Within a broad range of normal development
B	Walks unassisted
C	Sits unassisted
D	Not sitting
E	Requires permanent assisted ventilation

Abbreviations: SMA, spinal muscular atrophy.

Other motor function milestones such as head control, rolling, crawling, and standing with/without assistance were not modelled as explicit health states as these data were not available for all model arms; as such, these milestones represent potential 'intra-health state' clinical benefits or disease progression, if gained or lost, respectively. In addition, other 'intra-health state' clinical benefits that may be achieved as a result of pharmacotherapy treatment are not formally modelled via explicit health or tunnel states, such as:

- an improvement in an attained motor milestone (e.g. ability to sit, stand or walk unassisted for longer period prior to fatigue)
- reduction in time spent on ventilatory support
- improvements in talking and non-verbal communication (e.g. smiling and eye contact)
- improvements in fine motor control (e.g. ability/strength to operate a joystick on a wheelchair, use of a tablet computer or use of utensils for feeding)
- learning to write or being able to go through the education system
- greater independence and self-care ability

However, health benefits associated with such 'intra-health state' improvements are explored through additional sensitivity analyses to examine the potential impact of making allowances for different on-treatment utilities that may be associated with better functioning within the D state and C state.

Transitions

The model consists of two parts: 1) a short-term model concordant with observed clinical trial data, and 2) a long-term extrapolation model. Observed clinical outcomes are captured in the model by moving treated patients into higher functioning health states; higher functioning health states are associated with longer survival, higher QoL, and lower HCRU costs. Patients can only be in one state at a time (mutually exclusive) and all patients must be captured in a state (mutually exhaustive).

At model baseline, all patients are in the D state (not sitting). At the end of each model cycle (every 6 months for the first 3 years, then annually), patients can transition into a new health state or stay in the same health state. A 6-monthly model cycle was chosen in the first three years, to allow changes in childhood development and milestone achievement to be adequately captured. Patients transition to higher health states when they attain motor milestones (sits unassisted or walks unassisted). Transition to the E state (permanent assisted ventilation) in the model was only possible for patients who did not have any motor function milestones (i.e. those in the D state [not sitting]). For E state patients, both overall survival and permanent ventilation-free survival (described as event-free survival) were modelled. Patients who achieved motor function milestones (sits unassisted, walks unassisted or within broad range of normal development) were not considered to be at risk of transitioning to permanent assisted ventilation, and as such, could only transition to death.

In the base case analysis, it is assumed that the motor function milestones achieved at the end of follow-up in the clinical trials were sustained until death (i.e. patients stay in the same motor function milestone-based health state at the end of the short-term model until death). Backwards transitions, i.e. regression from higher functioning health states to worse functioning health states are only applicable for:

- Patients that discontinue nusinersen (discontinuation does not apply to onasemnogene abeparvovec as it requires a one-time, single IV administration)
- Scenario analyses where it is assumed onasemnogene abeparvovec patients begin to lose milestones and regress back through the model, to reflect a pessimistic waning effect (it should be noted that no patients treated with onasemnogene abeparvovec have since lost a milestone that they have attained from treatment, according to interim analysis from completed and ongoing clinical trials)

12.1.4 Justify the chosen structure in line with the clinical pathway of care.

The model framework was conceptualised with clinical experts (see Section 12.1.5), drawing on frameworks developed for other SMA pharmacotherapies and models for similar rare genetic neuromuscular disorders, such as Duchenne's muscular dystrophy. In addition, using a five functioning health state model framework (from permanent assisted ventilation [E state] to within broad range of normal development [A state]) that applies a short-term (observed data) and a long-term (extrapolation) modelling period, is broadly aligned to the model structure chosen by the US ICER model, who recently published an assessment of SMA therapies (32).

Prior to the development of disease-modifying therapies for SMA type 1, patients would never achieve motor milestones, such as sitting unassisted, and would experience rapid, progressive deterioration and mortality without permanent assisted ventilation, typically by the age of 2 years. With the development innovative therapies, children with SMA type 1 now have the potential to attain motor milestones, which correlate with improved functionality, HRQoL and survival. Treatment with onasemnogene abeparvovec in START resulted in all patients surviving free from death or permanent ventilation at 24 months, with 75% and 17% of patients able to sit unassisted and walk unassisted, respectively. The economic model consequently considers these outcomes by including health states aligned with motor milestone development.

The model structure captures the main drivers of costs, mortality and HRQoL associated with SMA type 1 to ensure that the natural history of SMA type 1 is modelled accurately. In addition, the model uses untreated SMA type 2 and SMA type 3 populations as proxies for SMA type 1 pharmacotherapy-treated patients' resource utilisation, survival and outcomes in higher functioning health states (C state [sits unassisted] and B state [walks unassisted]), as under BSC, SMA type 1 patients would never reach such health states.

A de novo UK HCRU study with n=16 UK clinical experts (see Section 12.3.1), was conducted by AveXis to determine the HCRU costs associated with BSC, to ensure the model accurately captured the current UK clinical pathway of care for SMA patients (18). Aligned to the expert advice provided and literature searched, the model structure accounts for the following costs associated with BSC:

- Consultations with the MDT responsible for the care of SMA patients (e.g. neuromuscular specialists, pulmonologists, physiotherapists, nutritionists, nurses [community and hospital based] etc.)
- Hospitalisations (accident and emergency department [A&E] and overnight admissions)
- Pharmacotherapies for treatment of SMA-related symptoms and comorbidities
- Tests, devices and surgeries – including those required for ventilatory and nutritional support
- Community and social care services (including personal and respite care)
- Patient and caregiver out of pocket costs (via an additional scenario analysis only)

12.1.5 Provide a list of all assumptions in the model and a justification for each assumption.

The model is underpinned by three foundational assumptions:

1. **Onasemnogene abeparvovec will have a lifelong duration of effect**

    a. The missing/dysfunctional *SMN1* gene is replaced and normal gene biology is restored, which results in long-term motor neuron survival for innervation and the development functioning neuromuscular junctions and skeletal muscles

    Justification: The results of LT-001 to date indicate that a one-time IV administration of onasemnogene abeparvovec at the proposed therapeutic dose provides prolonged efficacy for durations longer than 3 years (up to 49.7 months) post gene therapy administration (28). In addition, the mechanism of action of onasemnogene abeparvovec results in the delivery of a stable, functioning *SMN* gene that remains in non-mitotic cells indefinitely and enables continuous and sustained SMN protein expression, eliminating the need for repeat administration of onasemnogene abeparvovec. Evidence from animal models also support the prolonged duration of effect of onasemnogene abeparvovec. In a mouse model of SMA, gene therapy resulted in survival of greater than 250 days, compared with control-treated animals who did not survive past 22 days; this suggests continued expression (138). In addition, gene therapy vector-derived DNA and RNA were detected in tissues from mice examined at 24 weeks post-injection, indicating persistence of expression (139)

2. **Survival is improved in correlation with motor function milestone achievement, and life expectancy can be estimated using proxies**

    a. The model uses long-term survival data (observed and extrapolated) for untreated SMA patients who sit unassisted (SMA type 2 used as proxy) and walk unassisted (SMA type 3 used as proxy) to predict survival for pharmacotherapy-treated SMA type 1 patients who achieve motor milestones

    Justification: The use of proxy long-term survival data in the model was the approach adopted in the US ICER independent analysis of the comparative clinical effectiveness and value of onasemnogene abeparvovec and nusinersen for SMA (32) and was considered appropriate by participants in the UK clinical advisory board (17)

3. **Costs and utilities for each motor milestone group can be estimated using proxies**

    a. The model base case uses UK HCRU costs and utilities for untreated SMA patients who sit unassisted (SMA type 2 used as proxy) and walk unassisted (SMA type 3 used as proxy) to predict the costs and utilities of pharmacotherapy-treated SMA type 1 patients who achieve motor milestones

Justification: The use of proxy long-term survival data in the model was the approach adopted in the US ICER independent analysis of the comparative clinical effectiveness and value of onasemnogene abeparvovec and nusinersen for SMA (32) and was considered appropriate by participants in the UK clinical advisory board (17)

These assumptions were considered acceptable by key opinion leader (KOL) expert advisors consulted during model conceptualisation (Section 12.2.5). In addition, these underpinning assumptions were accepted for use by the independent US ICER in their recent assessment of SMA pharmacotherapies (32). A full list of assumptions, justification and sources used in the model is provided in Table 56.

Table 56: Base Case Model assumptions

#	Intervention(s)	Assumption and rationale	Source(s)and justification(S)	Management of uncertainty
Treatment benefit				
1	Onasemnogene abeparvovec	Onasemnogene abeparvovec will have a lifelong duration of effect, because the missing/dysfunctional *SMN1* gene is replaced and normal gene biology is restored. Motor function milestones achieved at the end of follow-up in START are sustained until death	KOL model conceptualisation UK clinical advisory board (17) (Section 12.2.5) US ICER (32) Section 12.2	Use of modelled scenario analyses where patients lose milestones to reflect a pessimistic waning of treatment effect
2	Onasemnogene abeparvovec	Children who were observed walking unassisted (B state) during START before 2 years of age are transitioned to the A state (within broad range of normal development) at 5 years of age. Walking independently by 2 years of age is reflective of normal development, as per the WHO reported windows of motor milestone achievement in healthy children	UK clinical advisory board (17) (Section 12.2.5) WHO Motor Development Study (123)	Use of an additional scenario analysis to give A state patients the same costs as B state patients
3	Nusinersen	Duration of effect continues while patients continue treatment with nusinersen; motor function milestones achieved in SHINE (Day 578) are sustained until death, whilst patients remain on treatment	SHINE (31) US ICER (32) Section 12.2	As a proportion of patients in ENDEAR had a 4-point worsening in CHOP-INTEND whilst on nusinersen, this is considered a conservative assumption and therefore not probed further
4	Onasemnogene abeparvovec and nusinersen	The model uses UK HCRU costs and utilities for untreated SMA type 2 and SMA type 3 patients as proxy for pharmacotherapy-treated SMA type 1 patients: • C state (sits unassisted) is assumed to have HCRU costs and utilities of untreated SMA type 2 patients	KOL model conceptualisation UK clinical advisory board (17) (Section 12.2.5) US ICER, C and B states (32)	Use of modelled scenario analyses where different sources for utilities are used Use of additional scenario analyses where different sources for HCRU costs are used

#	Intervention(s)	Assumption and rationale	Source(s)and justification(S)	Management of uncertainty
		• B state (walks unassisted) is assumed to have HCRU costs of untreated SMA type 3 patients and utilities of the general population (base case) • A state (within normal range of development) is assumed to have HCRU costs and utilities of the general population	Sections 10.1.9, 12.2.5, and 12.3.1	
5	Onasemnogene abeparvovec and nusinersen	Milestones achieved are considered as having occurred at the end of the age band to avoid overestimating benefits	KOL expert opinion – model conceptualisation Section 12.2	-
6	All interventions	All base case pairwise analyses use naïve, unanchored comparisons. There are no head-to-head trials comparing onasemnogene abeparvovec to comparators, and sample sizes are limited to conduct robust matched, adjusted indirect comparisons or simulated treatment comparisons. Thus, the model makes no adjustment for differences in patient characteristics between the studies	Unanchored ITC (Section 9.8.1)	Use of modelled scenario analyses to assess a pessimistic treatment benefit for onasemnogene abeparvovec versus comparators by removing those who can walk unassisted from the onasemnogene abeparvovec arm
Loss of treatment effect				
7	Onasemnogene abeparvovec	Onasemnogene abeparvovec patients do not regress in the base case, as per the observed data from START. The waning of treatment effect (i.e. regression from higher functioning health states to worse functioning health states) is probed via a pessimistic modelled scenario analyses: After 25 years patients lose milestones/regress through health states, assuming a pessimistic 90% annual probability of regression	Assumption Section 12.2	-
8	Nusinersen	Regression from higher functioning health states to worse functioning health states is only applicable for patients who discontinue nusinersen. Nusinersen is a chronic therapy with a CSF half-life of around four to six months; therefore, treatment	Nusinersen SmPC (21) Section 12.2	-

#	Intervention(s)	Assumption and rationale	Source(s)and justification(S)	Management of uncertainty
		effect is no longer maintained after cessation of therapy. It is assumed the annual probability of regression through the health states is 90%	KOL opinion – model conceptualisation	
Survival				
9	Onasemnogene abeparvovec	None of the patients in the onasemnogene abeparvovec arm (D state) are assumed to die in the short-term model (up to 30 months old) as per the observed data in START. It should be noted that patients in the onasemnogene abeparvovec arm who transition to the C state (sits unassisted) and the B state (walks unassisted) in the short-term model are subject to a small mortality risk based on their respective survival curves. Given the availability of interim data from ongoing Phase III trials, it is acknowledged that in real world clinical practice a proportion of patients on onasemnogene abeparvovec in the D state may die in the short-term model	START Section 12.2	Use of additional scenario analyses to model an 95% OS and 95% EFS at cycle 2 in the D state to reflect outcomes ongoing Phase III trials
10	Onasemnogene abeparvovec and nusinersen	Survival is improved in correlation with motor milestone achievement, and life expectancy can be estimated using proxies. Pharmacotherapy-treated SMA type 1 patients who are in the: • C state (sits unassisted) are assumed to have a life expectancy like that of untreated SMA type 2 patients • B state (walks unassisted) are assumed to have a life expectancy like that of untreated SMA type 3 patients, which is equivalent to the general population • A state (within broad range of normal development) are assumed to have a life expectancy of the general population	KOL opinion – model conceptualisation UK clinical advisory board (17) (Section 12.2.5) US ICER, C and B states (32) Section 12.2	Use of modelled scenarios to probe more optimistic survival in C state, whereby general population survival is assumed

<table>
<tr><th>#</th><th>Intervention(s)</th><th>Assumption and rationale</th><th>Source(s)and justification(S)</th><th>Management of uncertainty</th></tr>
<tr><td>11</td><td>Onasemnogene abeparvovec and nusinersen</td><td>After the observed trial periods, patients who remain in the D state (not sitting) are assumed to follow natural history survival and permanent ventilation-free survival (EFS) curves, in the absence of long-term evidence of continued survival benefit for non-sitting pharmacotherapy-treated SMA type 1 patients</td><td>Assumption
Section 12.2</td><td>Three different sources for natural history in the D state are provided</td></tr>
<tr><td colspan="5">HCRU costs</td></tr>
<tr><td>12</td><td>Onasemnogene abeparvovec</td><td>It is assumed the HCRU costs required for the one-time IV administration of onasemnogene abeparvovec (including pre-infusion baseline tests, AAV9 antibody testing [to be funded by AveXis], pre-, peri- and post-infusion monitoring) are captured in the existing NHS reference codes of PR01 and AA25. This assumption is based on UK clinical expert advice that the one-time IV infusion with onasemnogene abeparvovec will require one pre-infusion visit at a secondary/tertiary neuromuscular centre followed by a two-night, three-day elective stay at a highly specialised infusion centre</td><td>UK clinical advisory board (17) (Section 12.2.5)
Resource identification
(Section 12.3.3)</td><td>Use of additional scenario analyses to assess significantly higher (10-fold) administration costs. AveXis is also working with UK neuromuscular centres to further define the service delivery required for one-time IV administration of onasemnogene abeparvovec</td></tr>
<tr><td>13</td><td>All interventions</td><td>For the purposes of estimating health state HCRU costs, it is assumed patients receive ventilatory support under the following different healthcare settings:
<table>
<tr><th>Ventilation group</th><th>Paediatric intensive care</th><th>High dependency</th><th>Home-based</th></tr>
<tr><td>Patients on NIV <16 hours per day</td><td>5%</td><td>5%</td><td>90%</td></tr>
<tr><td>Patients on NIV >16 hours per day</td><td>15%</td><td>15%</td><td>70%</td></tr>
<tr><td>Tracheostomy patients</td><td>10%</td><td>30%</td><td>60%</td></tr>
</table></td><td>UK clinical advisory board (17) (Section 12.2.5)
Sections 12.2 and 12.3.3</td><td>Use of additional scenario analysis using alternative sources for HCRU costs</td></tr>
</table>

#	Intervention(s)	Assumption and rationale	Source(s)and justification(S)	Management of uncertainty
Discontinuation				
14	Nusinersen	To reflect the MAA stopping rule, patients discontinue nusinersen in the E state (permanent assisted ventilation) or due to an annual risk of withdrawal (3%). The annual risk of withdrawal accounts for discontinuation due to reasons of patient/caregiver preferences [e.g. decision to avoid further hospital attendance], inability to administer nusinersen by intrathecal administration because of spinal fusion surgery or a worsening in motor function. The rate of annual risk of withdrawal (3%) is from ENDEAR (proportion achieving a 4-point worsening in CHOP-INTEND) and reported withdrawal rates (n=3/95 withdrew treatment) from the nusinersen UK/Ireland EAP.	Nusinersen MAA (19) Nusinersen SmPC (21) Nusinersen UK/Ireland EAP (144) Section 12.2	Discontinuation rates and rules are tested using several additional scenario analyses
Utilities				
15	Onasemnogene abeparvovec and nusinersen	Improved clinical outcomes for pharmacotherapy-treated patients versus patients on BSC translates into greater HRQoL. Although the interim milestones (e.g. head control, rolling, crawling and standing with/without assistance) and non-motor milestone features that may be achieved with pharmacotherapy (e.g. improvements in talking and non-verbal communication, fine motor control and learning etc.) are not modelled as explicit health states, an on-treatment utility benefit is assumed in the treatment arms to account for achieving benefits of treatment, but as additional scenario analyses only. A range of on-treatment utilities increments are modelled: • D state: 0.05 to 0.15 (US ICER used 0.1) • C state: 0.025 to 0.075 (US ICER used 0.05)	US ICER (32) Section 10.1.9	Included as additional scenario analyses only

#	Intervention(s)	Assumption and rationale	Source(s)and justification(S)	Management of uncertainty
16	Onasemnogene abeparvovec and nusinersen	Disutilities associated with adverse events or administration of treatments (e.g. lumbar puncture required for nusinersen) were not included in the model. Given the nature of SMA, it is difficult to separate utilities due to treatment from the complications associated with SMA, which are already accounted for in the health state utility values. As such, separate disutilities for adverse events or administration procedures are not included in the model	US ICER (32) Section 10.1.9	

Abbreviations: AAV9, adeno-associated virus; BSC, best supportive care; CHOP-INTEND, Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders; CSF, cerebrospinal fluid; EAP, early access plan; ERG, Evidence Review Group; HCRU, healthcare resource utilisation; HSUV, health state utility value; US ICER, US Institute for Clinical and Economic Review; ITC, indirect treatment comparison; IV, intravenous; KOL, key opinion leaders; MAA, managed access agreement NIV, non-invasive ventilation; OS, overall survival; QoL, quality of life; SMA, spinal muscular atrophy; SmPC, summary of product characteristics; SMN, spinal moto neurone; UK, United Kingdom; US, United States; WHO, World Health Organization.

12.1.6 Define what the model's health states are intended to capture.

Whilst the health states primarily capture the major motor function milestones achieved by patients, they are also intended to capture the likely associated complications and features of SMA (Table 57). These additional features were included in the vignettes used as part of the UK *de novo* utilities study (Section 10.1.9.2).

Table 57: Functional status across health states

State	Motor features	Additional features
A	Within a broad range of normal development	• Within a broad range of normal development
B	Walks unassisted	• No breathing difficulties • Number and severity of chest infections similar to a typically developing child of the same age • Does not require a feeding tube – few difficulties swallowing, is able to eat and, for instance, swallow water • Talking ability similar to that of a typically developing child of the same age
C	Sits unassisted	• May have breathing problems and sometimes require NIV • Development of chest infections more frequently than a typically developing child of the same age • Some difficulties with eating and swallowing but able to swallow thin liquids and take some food by mouth • Risk of choking • Temporary placement of a gastric tube may be required • Requires help moving • Can talk, but ability to speak will deteriorate over time
D	Not sitting	• Experiences breathing problems and requires regular NIV for a number of hours every night or during the day • Development of chest infections more frequently than a typically developing child of the same age • Difficulties feeding and swallowing • High risk of choking • Only able to swallow thick fluids • Fed by a feeding tube (gastrostomy) surgically placed directly into the stomach • Requires moving regularly to prevent sores • Unable to talk, but can make sounds and cry
E	Permanent assisted ventilation	• Require 24-hour non-invasive ventilation • May require a tracheostomy if NIV is not working well • Require gastrostomy to be surgically placed directly into the stomach due to difficulty feeding and swallowing

State	Motor features	Additional features
		• High risk of choking • Require moving regularly to prevent sores • Develop chest infections more often than healthy children of the same age • Unable to talk, but can make sounds and cry

Abbreviations: NIV, non-invasive ventilation.

12.1.7 Describe any key features of the model not previously reported. A suggested format is presented below in table D4.

Table 58: Key features of model not previously reported

Factor	Chosen values	Justification	Reference
Time horizon of model	Lifetime horizon.	SMA type 1 is a progressive, lifelong, life-limiting disease and patients will continue to need management and/or treatment for the whole of their lives. NICE guidance states that model time horizons should be long enough to capture all benefits of the treatment.	NICE guide to the methods of technology appraisal 2013 (170)
Discount of 3.5% for costs	3.5%	In line with NICE guidance.	NICE guide to the methods of technology appraisal 2013 (170)
Perspective (NHS/PSS)	NHS and PSS in England	In line with NICE guidance.	NICE guide to the methods of technology appraisal 2013 (170)
Cycle length	6-month cycles for first 3 years, 12-month cycles for remainder of model	A 6-monthly model cycle was chosen in the first three years, to allow changes in childhood development and milestone achievement to be adequately captured.	KOL opinion – model conceptualisation

Abbreviations: KOL, key opinion leader; NHS, National Health Service; PSS, personal and social services; SMA, spinal muscular atrophy.

12.2 *Clinical parameters and variables*

12.2.1 Describe how the data from the clinical evidence were used in the cost-effectiveness analysis.

12.2.1.1 Motor function milestone achievement

Onasemnogene abeparvovec

In the short-term model (up to 30 months of age) proportions of patients achieving motor function milestones are taken directly from observed individual patient data in START (Table 59). No extrapolation of motor milestones in the long-term model is assumed. Motor function milestones achieved at the end of follow-up in START are sustained until death.

Children who were observed walking unassisted (B state) during START before 2 years of age are transitioned to the A state (within a broad range of normal development) at 5 years of age. Walking independently by 2 years of age is reflective of normal development, as per

the WHO reported windows of motor milestone achievement in healthy children (118). It should be noted that in the base case analysis, the only difference between the B state (walks unassisted) and A state (within broad range of normal development) is the associated health state HCRU costs – i.e. all other clinical outcomes (utilities and survival) are the same.

Limiting motor milestone achievement (i.e. forward transitions to higher functioning health states) to the first 6 model cycles after treatment with onasemnogene abeparvovec can be considered conservative, as continued improvement in motor function has been observed by clinical investigators in LT-001 (long-term follow-up of START), after 24 months post-treatment (see Section 9.6.2). Thus, there is the potential that patients may gain motor milestones in the future.

Table 59: Proportions of patients achieving motor milestones in START (Cohort 2)

Cycle	Visit (mo.)	Approx. age at end of cycle (mo.)†	Not sitting		Sitting‡ but not walking		Walking	
			n	%	n	%	n	%
1	3	6	12	100%	0	0.00%	0	0.00%
2	9	12	12	100%	0	0.00%	0	0.00%
3	15	18	9	75.00%	3	25.00%	0	0.00%
4	21	24	6	50.00%	5	41.67%	1	8.33%
5	27	30	2	16.67%	8	66.67%	2	16.67%
6	33	36	1	8.33%	9	75.00%	2	16.67%

Abbreviations: mo., month.
† Based on a mean age of treatment of 3.4 months.
‡ Sitting unassisted for ≥5 seconds is in accordance with the criteria of item 22 on the Bayley-III assessment tool gross motor subtest.

Best supportive care

No patients in the BSC arm are assumed to achieve any motor function milestones (e.g. sits unassisted or walks unassisted) at any time points in accordance with the observed data from natural history studies including:

- NeuroNext, Kolb et al. 2017 (27)
- PNCR, Finkel et al. 2014a (12)
- PNCR, De Sanctis et al. 2016 (50)
- NeuroNext and PNCR databases (67) described in Section 9.4.3.1, and
- Sham-control arm in ENDEAR (22)

Nusinersen

The data on proportions of nusinersen patients achieving motor function milestones at different time points were based on observed data from SHINE (long-term follow up of ENDEAR). Castro et al. 2018 (as reported in NICE nusinersen committee papers (31))

reported the proportion of patients achieving sitting at different time points, which are presented in Table 60.

With different numbers of patients at risk at each time point, and as the published data on proportion sitting independently is presented as percentages, multiple steps were followed to estimate the proportions of nusinersen patients sitting at the different time points:

- The numbers of patients sitting at each time point were estimated and were rounded to the nearest integer (value 'A')
- The number of patients at risk (value 'B') were approximated from ventilation-free survival estimates from the digitized KM curve at each time point (as reported in NICE nusinersen committee papers (31))
- The integer values representing the number of patients sitting (value 'A') were divided by the number of patients at risk (value 'B') at each time point to estimate the proportions of patients sitting (value 'C')

The proportions of patients sitting (value 'C') were then used to calculate proportions in each motor function milestone health state at each time point (Table 61). An underlying assumption is that patients who continue nusinersen treatment do not lose milestones gained. Therefore, the proportion of patients achieving sitting unassisted at Day 578 from SHINE is used from cycle 4 onwards, as the proportion achieving this milestone decreased between Day 578 and Day 689 according to data reported in Castro et al. 2018.

Table 60: Proportions of patients achieving motor milestones on nusinersen

Input		Baseline	Day 64	Day 183	Day 302	Day 394	Day 578	Day 689
SHINE data								
Patients with available data, n		81	70	65	51	48	31	17
% Achieved independent sitting†		0%	1%	5%	10%	15%	29%	24%
Calculations								
A	**Independent sitting, n**	0	1	3	5	7	9	4
B	**Alive and ventilation-free patients, n**	81	71	57	45	45	39	39
C	**% of alive and ventilation free sitting independently**	0.00%	1.41%	5.26%	11.11%	15.56%	23.08%	10.26%

† Time spent unassisted not reported. In ENDEAR, independent sitting included HINE-2 score categories: stable sit and pivots (rotates).
Source: Castro et al. 2018 (as reported in NICE nusinersen committee papers (31)). Sources of 'A','B' and 'C' described above in text.

Table 61: Calculated proportions of patients achieving motor milestones on nusinersen

Cycle	Visit (Day)	Approx. age at end of cycle (mo.)‡	Not sitting	Sitting but not walking	Walking
			%	%	%
1	1	6	100.00%	0.00%	0.00%
2	183	12	94.74%	5.26%	0.00%
3	394	18	84.44%	15.56%	0.00%
4	548†	24	76.92%	23.08%	0.00%
5	730	30	76.92%	23.08%§	0.00%
6	913	36	76.92%	23.08%§	0.00%

† Use data reported from SHINE at day 578.
‡ Based on a mean age at first dose of 5.4 months.
§ An underlying assumption is that patients who continue nusinersen treatment do not lose milestones gained. Therefore, the proportion of patients achieving sitting unassisted at Day 578 from SHINE is used from cycle 4 onwards.

Transition probabilities

Transition probabilities between health states were based on the proportion of patients estimated to be sitting unassisted or walking unassisted. The probability of transitioning to a higher functional health state (D state to C state or C state to B state) was calculated using the number of patients who newly achieved motor milestones before the start of each cycle as the numerator and the number of patients in the outgoing state in the previous cycle as the denominator (Table 62).

The model accounts for milestones gained during a cycle in the next full cycle, i.e. calculations are "offset" so that patients are transitioned in the following cycle. This is a conservative approach when assigning motor milestones to cycles. For example, if a patient achieved a motor milestone at age 19 months, that patient only appears as having achieved the milestone for the cycle beginning age 24 months. This is to avoid over-estimating milestone achievement.

Table 62: Transition probabilities for pharmacotherapy treatment arms for alive and event-free patients

Cycle	Age at end of cycle (mo.)	Onasemnogene abeparvovec			Nusinersen		
		D to C	C to B	B to A	D to C	C to B	B to A
1	6	0.00%	0.00%	0.00%	0.00%	0.00%	0.00%
2	12	0.00%	0.00%	0.00%	0.00%	0.00%	0.00%
3	18	25.00%	0.00%	0.00%	5.26%	0.00%	0.00%
4	24	33.33%	33.33%	0.00%	10.86%	0.00%	0.00%
5	30	66.67%	20.00%	0.00%	8.91%	0.00%	0.00%
6	36	50.00%	0.00%	0.00%	0.00%	0.00%	0.00%
7	48	0.00%	0.00%	0.00%	0.00%	0.00%	0.00%
8	60	0.00%	0.00%	0.00%	0.00%	0.00%	0.00%
9	72	0.00%	0.00%	100.00%†	0.00%	0.00%	0.00%

† Children who were observed walking unassisted (B state) during START before 2 years of age who are transitioned to the A state (within broad range of normal development) at 5 years of age.

12.2.1.2 Motor function milestone loss

Onasemnogene abeparvovec

Onasemnogene abeparvovec patients do not regress (i.e. lose milestones) in the base case, as per the observed data from START. To date, there has been no loss of previously attained milestones as part of LT-001 (long-term follow-up of START) or in interim analysis from ongoing Phase III trials for onasemnogene abeparvovec. The waning/limited duration of treatment effect (i.e. regression from higher to lower functioning health states) is probed in a very pessimistic modelled scenario analysis: after 25 years patients lose milestones/regress through health states, assuming a 90% annual probability of regression. CMAP and MUNE values from untreated (i.e. who have not received pharmacotherapy) SMA type 1 patients are <10% of normal values (9). Therefore, a crude and pessimistic assumption was made that if >90% of motor neuron cells are lost (as inferred by CMAP/MUNE data) in untreated SMA type 1 patients, this would approximate to 90% probability of milestones being lost in a year.

Best supportive care

Transitions associated with loss of milestones (C state to D state and B state to C state) are not included for the BSC arm in the model, as SMA type 1 patients receiving BSC never attain motor milestones in the first place.

Nusinersen

Duration of effect continues while patients remain on treatment with nusinersen and motor function milestones achieved in SHINE (Day 578) are sustained until death. Patients only regress (i.e. lose milestones) if they discontinue nusinersen. Nusinersen is a chronic therapy with a cerebrospinal fluid (CSF) half-life of around four to six months; therefore, treatment effect is no longer maintained after cessation of therapy. It is assumed the annual probability of regression through the health states is 90% for patients that discontinue nusinersen. As

described above, this (90%) regression rate is based on CMAP and MUNE values from untreated (i.e. who have not received pharmacotherapy) SMA type 1 patients, which are <10% of normal values (9).

To reflect the nusinersen MAA stopping rule (19), all patients discontinue nusinersen in the E state (permanent assisted ventilation) or due to an annual risk of withdrawal (3%) in the D state and C state. The annual risk of withdrawal accounts for discontinuation due to reasons of patient/caregiver preferences [e.g. decision to avoid further hospital attendance], inability to administer nusinersen by intrathecal administration because of spinal fusion surgery or a worsening in motor function. The rate of annual risk of discontinuation in D state and C state is modelled as 3%. This rate is from taken from data reported in ENDEAR (21) (i.e. 3% of the cohort were reported as achieving a 4-point worsening in CHOP-INTEND) and reported withdrawal rates (n=3/95 withdrew treatment) from the nusinersen UK/Ireland EAP (144).

12.2.1.3 Survival

Survival in each health state is based on observed data and extrapolated survival curves from clinical trials and natural history studies. The sources for survival data for each health state and by treatment arm are described in Table 63 for the base case. Detailed methods used for fitting parametric survival curves to the observed data to extrapolate survival beyond trial and study periods are described in Section 12.2.2.1.

Onasemnogene abeparvovec

In the short-term model for patients in the onasemnogene abeparvovec arm, the observed 24 months post-dose (modelled as up to 30 months of age) data from START were used directly. None of the patients in the onasemnogene abeparvovec arm are assumed to die in the short-term model (up to 30 months old) in the D state as per the observed data in START. It should be noted that patients in the onasemnogene abeparvovec arm who transition to the C state (sits unassisted) and the B state (walks unassisted) in the short-term model are subject to a small mortality risk based on their respective survival curves. In the long-term model, the parametric natural history curves from the BSC survival data were appended to the clinical trial data beyond the trial period for the onasemnogene abeparvovec arm in the D state – details are described in Section 12.2.2.1.

Given the availability of interim data from ongoing Phase III trials, it is acknowledged that in real world clinical practice, a proportion of patients on onasemnogene abeparvovec, in the D state (not sitting), may die and hence this is explored in the short-term model. Therefore, an additional scenario analysis is included to model 95% overall survival and 95% event-free survival at cycle 2 in the D state for onasemnogene abeparvovec to reflect data from ongoing Phase III trials. Overall survival remains extremely high; of the 77 patients dosed with onasemnogene abeparvovec via a single IV infusion in the clinical trial programme (START, STR1VE-EU, STR1VE-US, and SPR1NT) and for whom data were reported in the latest data cut (8 March 2019), 75 (97.4%) are alive. Of the two deaths reported in ongoing trials, both occurred within 5 months of dosing (one at 1.8 months post dose [6.9 months old at death] and one at 4.9 months post dose [7 months old at death]), hence it was considered appropriate to model 95% overall survival and 95% event-free survival at cycle 2 in the D state for this explorative additional scenario analysis.

Nusinersen

In the short-term model for patients in the nusinersen arm, the observed 34 months post initial dose (modelled as up to 36 months of age) data from SHINE were used directly. In the long-term model, the parametric natural history curves from the BSC survival data were appended to the clinical trial data beyond the trial period for the nusinersen arm in the D state – details are described in Section 12.2.2.1.

Best supportive care

As START was a single-arm trial, an external natural history control data set is required to model the BSC arm. The comparison made to BSC in the model is an unanchored, naïve comparison and therefore, as no adjustment has been made for differences (known or unknown) in trial populations or differences in study effects, caution is required in any interpretation of results. It should be noted, however, that the eligibility criteria for START and SHINE (extension of ENDEAR) were very similar with respect to the genetic profile of the SMA type 1 patients enrolled (age at symptom onset <6 months, 2 x *SMN2* copy number) and respiratory function (oxygen saturation levels ≥95 or 96% in START and SHINE, respectively) and that despite the small sample sizes in all clinical trials used, the analysis performed was the best feasible with the data available at the time.

Four studies reporting the natural history of SMA type 1 patients – including overall survival and event (permanent ventilation)-free survival outcomes – were identified as part of the SLR (see Section 9.3.1):

- NeuroNext study, as reported in Kolb et al. 2017 (27) and the AveXis external control database (67)
- PNCR study, as reported Finkel et al. 2014a (12) and the AveXis external control database (67)
- Sham-control arm of the ENDEAR (22)
- Single site, longitudinal study, as reported by Finkel et al. 2014b (59)

For the model base case, the NeuroNext (n=16 with *SMN2* copy x 2) natural history cohort was chosen to inform overall survival and event-free survival for BSC in the D state (non-sitting) as:

- The study closely resembled the entry criteria for START with respect to age and baseline function; for example, the NeuroNext cohort had similar baseline ventilatory and nutritional support requirements as the START cohort
- NeuroNext was an external control data set used as part of the EMA regulatory filing for onasemnogene abeparvovec, and hence detailed clinical effectiveness data versus START are described in Section 9.6.1.1
- Individual patient-level data were available for NeuroNext as part of the external database made available from NeuroNext to AveXis, permitting development of Kaplan-Meier (KM) curves for the observed period and for onward parametric curve fitting, without reliance on the digitisation of figures

- The genetic profile of NeuroNext (n=16) and START were equivalent: all patients had bi-allelic deletions of *SMN1* exon 7, *SMN2* copy x 2 and confirmation of exclusion of the *SMN2* modifier mutation c.859G>C
- The generalisability of NeuroNext to the UK SMA type 1 population treated with BSC was confirmed as the UK Clinical Advisory Board (May 2019) (17)

However, the NeuroNext study had a narrower definition for permanent ventilation (defined as time to permanent invasive ventilatory [intubation] only) when compared with START (27). As such, the narrower endpoint of the NeuroNext study does not capture patients who transition to permanent non-invasive ventilation and may underestimate the number of patients transitioning to the E state. Therefore, two alternative sources for informing overall survival and event-free survival of BSC in the D state – data from PNCR database (De Sanctis et al. 2016 (50)) and the sham-control arm of ENDEAR (Finkel et al. 2017 (22)) – are provided as modelled scenario analyses.

Details about the natural history studies used to inform the base case and modelled scenario analyses are further described in Table 63. The study reported by Finkel et al. 2014b (59) identified in the SLR was not included as a scenario analysis due to is limitations in design (single site in the US) and small sample size (n=7). An alternative source for natural history data in the model were taken from the De Sanctis et al. 2016 publication (50) (identified during full text screening as part of the SLR) – as opposed to the Finkel et al. 2014a (12) cohort or the AveXis PNCR external control data set (67) – as they provide data for a larger sample size (n=26), are more recent (patients enrolled between 2010 and 2014) thus, a better reflection of current standard of care with a higher reported use of ventilatory support and is a multi-country study including a European perspective (includes US and Italy centres). As the De Sanctis et al. 2016 study did not limit inclusion based on *SMN2* copy number, this study is reflective of the real world, mixed genetic profile of SMA type 1 patients, with respect to *SMN2* copy number. It is reported that the majority of patients with SMA type 1 have 2 copies of *SMN2* (73.4%), with the remaining minority having 1 or 3 copies (52).

Table 63: Sources of survival data – base case

Transition	Onasemnogene abeparvovec	Nusinersen	BSC
D to death	**Short-term model, observed data** Ages 0–30 months: START trial (2, 25) **Long-term model, extrapolated data** Ages 30+ months: projected survival using parametric curves fitted to natural history data used for BSC (NeuroNext†)	**Short-term model, observed data** Ages 0–36 months: SHINE trial (31) **Long-term model, extrapolated data** Ages 36+ months: projected survival using parametric curves fitted to natural history data used for BSC (NeuroNext†)	**Short-term model, observed data** Ages 0–24 months: NeuroNext† **Long-term model, extrapolated data** Ages 24+ months: projected survival using fitted parametric curve to observed data from NeuroNext†
D to E	**Short-term model, observed data** Ages 0–30 months: START trial (2, 25) **Long-term model, extrapolated data** Ages 30+ months: projected permanent ventilation-free survival using parametric curves fitted to natural history data used for BSC (NeuroNext†)	**Short-term model, observed data** Ages 0–36 months: SHINE trial (31) **Long-term model, extrapolated data** Ages 36+ months: projected permanent ventilation-free survival using parametric curves fitted to natural history data used for BSC (NeuroNext†)	**Short-term model, observed data** Ages 0–24 months: NeuroNext† **Long-term model, extrapolated data** Ages 24+ months: projected permanent ventilation-free survival using fitted parametric curve to observed data from NeuroNext†
E to death	**Short-term and long-term model:** E state patients requiring PAV are assumed to have long-term survival consistent with an observational study of SMA type 1 patients with tracheostomy or NIV (defined as continuous NRA, including non-invasive ventilation and mechanically assisted cough is the study) published by Gregoretti et al. 2013 (171). The parametric function fitted to the observed data is used for the entire model time horizon, even during the observed period of the observational trial (Section 12.2.2.1)		
C to death	**Short-term and long-term model:** The survival for SMA type 1 patients that can sit unassisted is modelled from the long-term survival of the 52-year prospective and retrospective study of SMA type 2 patients, as reported by Zerres et al. 1997 (172). The parametric function fitted to the observed data is used for the entire model time horizon, even during the observed period of the study		N/A – patients on BSC never reach C state

Transition	Onasemnogene abeparvovec	Nusinersen	BSC
B/A to death	The survival for SMA type 1 patients that can walk unassisted is modelled based on general population survival from the 2014–2016 UK National Life tables (173)		N/A – patients on BSC never reach A/B state

Abbreviations: BSC, best supportive care; N/A, not applicable; NIV, non-invasive ventilation; NRA, non-invasive respiratory muscle aid; PAV, permanent assisted ventilation; SMA, spinal muscular atrophy.

† NeuroNext cohort as reported in AveXis external control database (n=16 patients with *SMN2* copy x 2) is selected as the data source for BSC in the base case (67)

Table 64: Sources of survival data for BSC – D state, base case and scenario analysis

Characteristic	Base case	Scenario analysis	
	NeuroNext† (67) AveXis external control database	**ENDEAR Sham-control Finkel et al. 2017 (22)**	**PNCR De Sanctis et al. 2016 (50)**
Size, n	16	41	26
Definition of permanent assisted ventilation	Intubation only	Tracheostomy or ventilatory support for ≥16 hours per day for >21 continuous days in the absence of an acute reversible event	Tracheostomy or NIV (time on non-invasive ventilatory support not described)
Genetic profile	Homozygous deletion of exon 7 in the *SMN1* gene Two copies of the *SMN2* gene Exclusion of the *SMN2* gene modifier mutation c.859G>C	Homozygous deletion or mutation in the *SMN1* gene Two copies of the *SMN2* gene	Homozygous deletion of exon 7 in the *SMN1* gene *SMN2* copy number not reported
Region(s)	US	US and Germany	US and Italy
Enrolment years	2012 to 2014	2014 to 2015	2010 to 2014
Length of follow-up	24 months	13 months (394 days)	24 months
Key results at study end			
Dead, n (%)	8 (50.0)	16 (39.0)	12 (46.2)

Characteristic	Base case	Scenario analysis	
	NeuroNext† (67) AveXis external control database	ENDEAR Sham-control Finkel et al. 2017 (22)	PNCR De Sanctis et al. 2016 (50)
Dead or PAV, n (%)	10 (62.5)	28 (68.3)	24 (92.3)
Alive and PAV, n (%)	2 (12.5)	12 (29.3)	12 (46.2)
Alive and ventilation-free, n (%)	6 (37.5)	13 (31.7)	2 (7.7)

Abbreviations: BSC, best supportive care; NIV, non-invasive ventilation; PAV, permanent assisted ventilation; SMN, survival motor neurone; US, United States.

† NeuroNext cohort as reported in AveXis external control database (n=16 patients with *SMN2* copy x 2).

12.2.1.4 Utilities

Full details and justification for the patient health state utility values used in the base case and scenario analyses are described in Section 10.1.9. For completion, base case values are shown again below in Table 65.

Table 65: Summary of patient utility values used in the base case

State	Description	Utility value	Standard Error	Reference
E state	Permanent assisted ventilation	0.190	0.0095	Thompson et al 2017 (149)
D state	Not sitting	0.190	0.0095	
C state	Sits unassisted	0.600	0.0300	Tappenden et al 2018 (151)
B state	Walks unassisted	General population		Ara and Brazier 2010 (152)
A state	Broad range of normal development			

12.2.2 Are costs and clinical outcomes extrapolated beyond the study follow-up period(s)? If so, what are the assumptions that underpin this extrapolation and how are they justified?

12.2.2.1 Clinical outcomes extrapolation – survival

For all survival data, parametric survival curves were fitted to the empirical data to extrapolate survival and calculate transition probabilities using published methods (174). All reconstructions of individual patient data and fitting of parametric curves were conducted using the R software package ‘flexsurv’ procedure (details of R code used can be found in the 'Survival_R_Code' tab of the executable model) using published methods (175, 176). Details of the methods used to develop transition probabilities for survival for the probabilistic sensitivity analysis (PSA) are provided in Appendix 8.

Selection of models for survival modelling was informed by NICE decision support unit (DSU) 14 (177). Goodness-of-fit was assessed by the following methods:

- Statistically via Akaike information criterion (AIC) and Bayesian information criterion (BIC)
- Visual inspection

Parametric curves fitted to the survival data included exponential, log-normal, log-logistic, Weibull, generalized gamma, and Gompertz curves; the parametric models with the lowest AIC and BIC were used. All curves were accelerated failure time curves. Following guidance in NICE DSU 14 (177), the same types of parametric models were used for onasemnogene abeparvovec and nusinersen within a health state, i.e. generalised Gamma distributions were used for D state EFS in both the nusinersen and onasemnogene abeparvovec arms. To avoid long curve tails leading to clinically implausible survival, curves were terminated

based on observed life expectancy or input from clinical expert opinion. The specific parametric models used in the base case model are shown in Table 66.

Table 66: Summary of survival curves used for the trial periods and beyond (base case)

Survival curve	Model used for trial period	Model used beyond trial period
State E – all arms	Gompertz	Gompertz
State D – BSC OS	Kaplan-Meier (Empirical)	Generalised Gamma
State D – BSC EFS	Kaplan-Meier (Empirical)	Generalised Gamma
State D – Nusinersen OS	Kaplan-Meier (Empirical)	Generalised Gamma
State D – Nusinersen EFS	Kaplan-Meier (Empirical)	Generalised Gamma
State D – Onasemnogene abeparvovec OS	Kaplan-Meier (Empirical)	Generalised Gamma
State D – Onasemnogene abeparvovec EFS	Kaplan-Meier (Empirical)	Generalised Gamma
State C – Nusinersen OS	Generalised Gamma	Generalised Gamma
State C – Onasemnogene abeparvovec OS	Generalised Gamma	Generalised Gamma
State B – Nusinersen OS	National Life Tables	National Life Tables (173)
State B – Onasemnogene abeparvovec OS	National Life Tables	National Life Tables (173)
State A – Nusinersen OS	National Life Tables	National Life Tables (173)
State A – Onasemnogene abeparvovec OS	National Life Tables	National Life Tables (173)

Abbreviations: BSC, best supportive care; EFS, event-free survival; OS, overall survival.

E state (permanent assisted ventilation) – All arms

For the model, E state patients requiring permanent assisted ventilation are assumed to have long-term survival consistent with an observational study of SMA type 1 patients in Italy with tracheostomy or NIV (defined as continuous non-invasive respiratory muscle aid [NRA], including non-invasive ventilation and mechanically assisted cough is the study) published by Gregoretti et al. 2013 (171).

Because there are no data suggesting that patients who receive disease-modifying treatment experience improved survival after experiencing respiratory insufficiency, it was assumed that all patients in the E state would experience the same survival function with no adjustment by treatment arm.

In Gregoretti et al. 2013 (171), patients with tracheostomy and NIV were analysed as separate treatment arms, so pooling of the data was required. For pooling, the IPD for the tracheostomy and NIV arms of the study were each reconstructed using published methods (175, 176) and the dataset from each arm was merged based on the time points. The published study results did not include number at risk so these were estimated using the method described in Tierney et al. 2007 (176).

The parametric function fitted to the observed data is used for the entire model time horizon, even during the observed period of the observational trial (192 months). This approach is to avoid over-fitting the model to the study population observed in Gregoretti et al. 2013 (171) and to ensure that transition probabilities remained relatively constant over time.

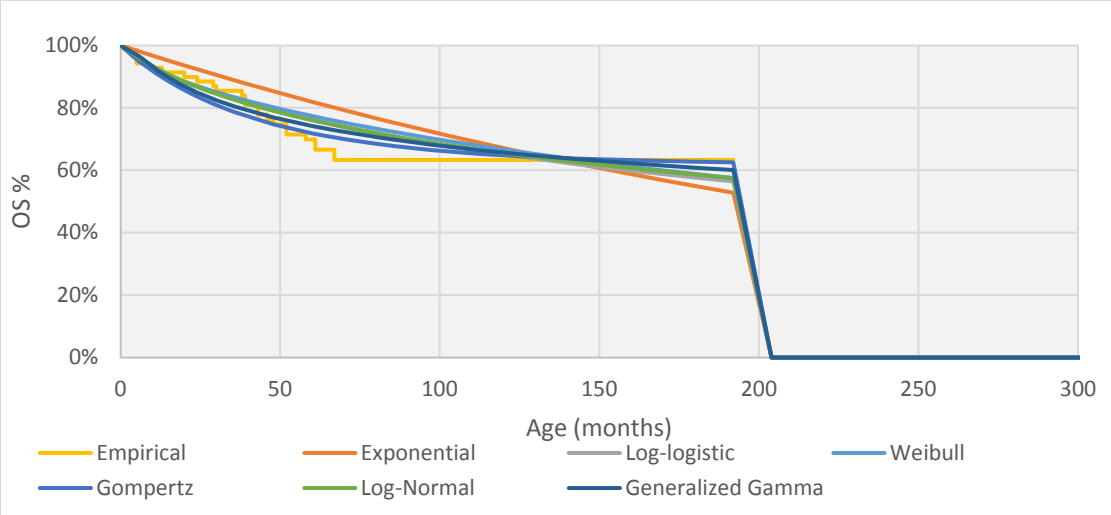
The mathematically best fitting curve was the Gompertz curve, however this curve plateaued and was deemed to be clinically implausible. To maintain clinically plausible results, the fitted curve is truncated at 16 years; using this limit, the fitted curve models the probability of death is 1 by 17 years. The parametric models are visualised below in Figure 33. AIC and BIC values for survival curves assessed in the E state are shown below in Table 67.

Table 67: Assessment of curve fits for the E state

Parametric model	AIC	BIC
Exponential	323.89	326.15
Weibull	319.89	324.42
Log-Normal	315.84	320.37
Log-Logistic	317.84	322.36
G.Gamma	315.39	322.18
Gompertz	309.57	314.09

Abbreviations: AIC, Akaike information criterion; BIC, Bayesian information criterion.

Figure 33: E state overall survival (all treatment arms)



D state (non-sitting) – BSC

In the base case, overall survival and event-free survival for BSC in the D state was based on the NeuroNext natural history trial (27, 67), using 24-month follow-up data for 16 patients with 2 copies of the *SMN2* gene, as per the data described in Section 9.4.3.1.

The Kaplan-Meier (KM) data were used directly for the observed 24 months study period. To extrapolate survival beyond the follow-up period, parametric survival curves were fitted to the generated KM curve of the empirical data. The generalised gamma curve (best fitting curve) was used for the D to Death transition. To avoid implausibly long survival predicted by long parametric curve tails, the model interface for the D state includes a user input survival

threshold, measured as “when overall survival reaches X percent, set survival to zero”. If the parametric models predicted a remaining population survival of less than or equal to 25%[h] in a given cycle, the overall survival was set to zero for that cycle and all subsequent cycles. This default value of 25% has the effect of limiting survival in the BSC arm so that no patient survives beyond their 4th birthday. Once the survival function was calculated, transition probabilities were calculated using the method set out in Briggs et al. 2006 (178):

$$Tp(tu) = 1 - S(t) / S(t-u)^{i}$$

AIC and BIC values for survival curves assessed in the D state for BSC are shown below in Table 68. The parametric models are visualised below in Figure 34.

Table 68: Assessment of curve fits for D state OS: BSC

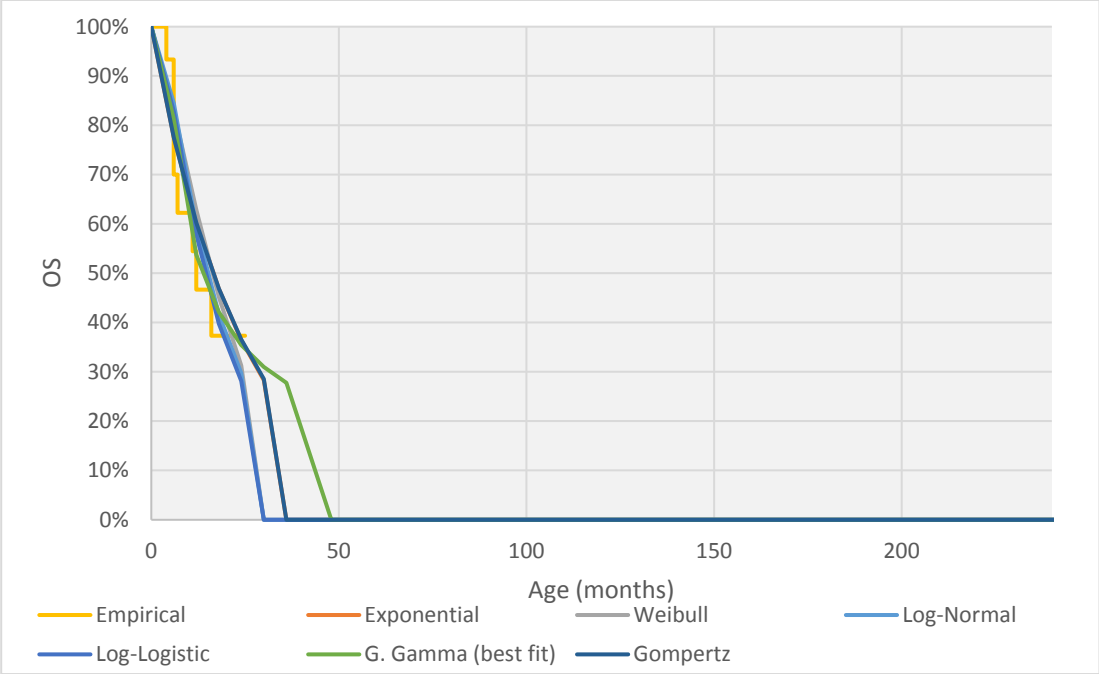
Parametric model	NeuroNext	
	AIC	BIC
Exponential	68.68	69.45
Weibull	69.83	71.38
Log-Normal	67.29	68.83
Log-Logistic	68.08	69.62
G.Gamma	65.00	67.32
Gompertz	70.68	72.23

Abbreviations: AIC, Akaike information criterion; BIC, Bayesian information criterion.

[h] A percent threshold was used instead of a specific age because the NeuroNext curve is also used in extrapolating D state survival for nusinersen and onasemnogene abeparvovec arms beyond their respective observed trial periods. The percent threshold ensures consistency across all arms even when survival curves are adjusted by age to reflect the observed trial survival for treatment arms; i.e. OS always cuts off at 25% regardless of the age of the modelled cohort.

[i] Where S(t) is survival at time t, and u is the length of the cycle.

Figure 34: D state overall survival for BSC (NeuroNext)



To calculate the probability that a patient will transition from D state (non-sitting) to E state (permanent assisted ventilation), an EFS KM curve was generated using the time to the event "Permanent Endotracheal Intubation" (27, 67). The generalised gamma curve (best fitting curve) was used for the D state to E state (permanent assisted ventilation) or D state to Death transition; the associated transition probability was calculated using the Briggs method applied to the EFS function. The probability of transitioning to the E state (permanent assisted ventilation) alone was calculated as follows:

TP (PAV) = TP (Death or PAV) – TP (Death)

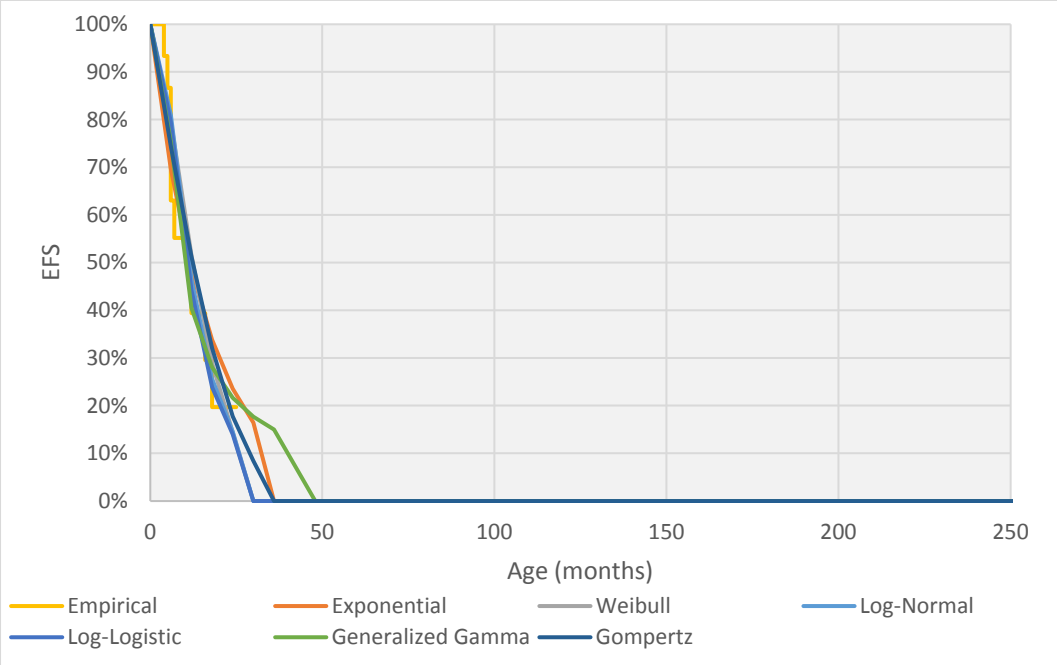
AIC and BIC values for EFS curves assessed in the D state for BSC are shown below in Table 69. The parametric models are visualised below in Figure 35.

Table 69: Assessment of curve fits for the D state EFS: BSC

Parametric model	NeuroNext	
	AIC	BIC
Exponential	78.19	78.96
Weibull	77.56	79.11
Log-Normal	74.63	76.18
Log-Logistic	75.33	76.87
G.Gamma	72.93	75.25
Gompertz	79.56	81.10

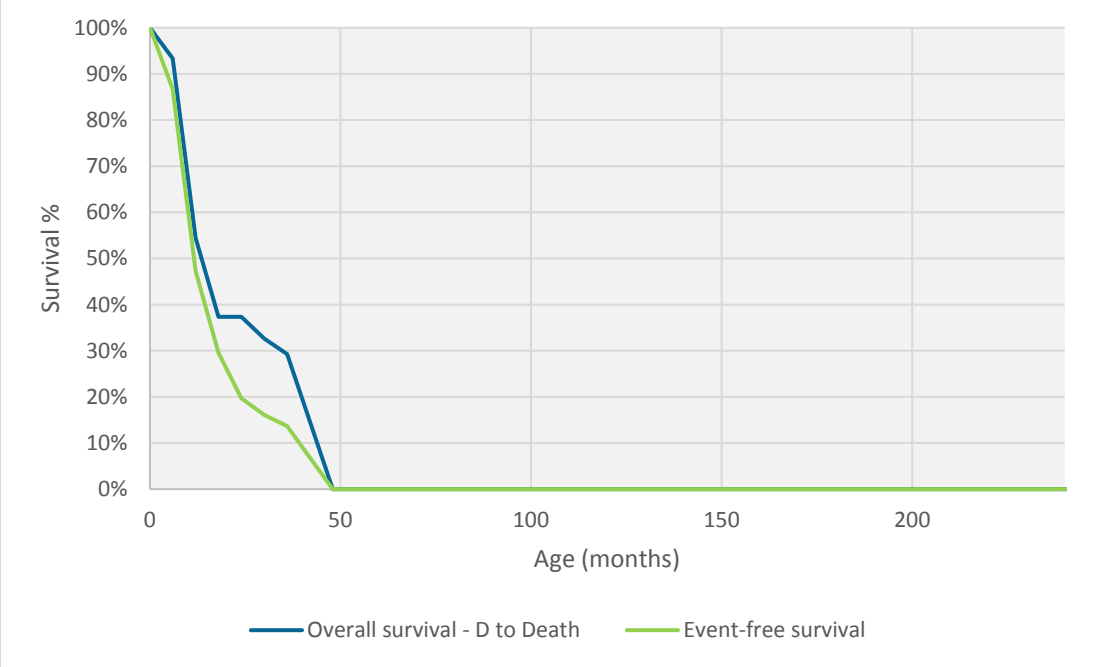
Abbreviations: AIC, Akaike information criterion; BIC, Bayesian information criterion.

Figure 35: State D EFS for BSC (NeuroNext)



The final overall survival and event-free survival functions for BSC in the D state are shown Figure 36.

Figure 36: State D, best fit overall survival and event-free survival curves for BSC (NeuroNext)



D state (non-sitting) – treatment arms

For patients in the onasemnogene abeparvovec and the nusinersen arms, the empirical KM data were used directly for the observed 24 months post-dose (modelled as up to 30 months of age) and 34 months post initial dose (modelled as up to 36 months of age) data from the START and SHINE trials, respectively. Beyond the observed trial periods, extrapolations were generated based on the parametric models used for the BSC arm (i.e. NeuroNext in the base case); i.e. after the observed trial periods patients who remain in the D state (non-sitting) are assumed to follow the natural history curve, in the absence of long-term evidence of continued survival benefit for non-sitting pharmacotherapy-treated SMA type 1 patients. The parametric natural history curves from the BSC survival data were appended to the clinical trial data beyond the trial period. This process was performed separately for both the overall survival and event-free survival.

The overall survival and event-free survival curves for onasemnogene abeparvovec are shown below in Figure 37, Figure 38 and Figure 39. The overall survival and event-free survival curves for nusinersen are shown in Figure 40, Figure 41 and Figure 42. No AIC and BIC data are available for these curves directly as they are composites of the empirical KM data (from observed trial periods) and parametric model extrapolations based on the BSC data.

C state (sits unassisted) – treatment arms

As a result of the underpinning assumption of the model that survival is improved in correlation with motor milestone achievement, and life expectancy can be estimated using proxies, SMA type 1 patients treated with onasemnogene abeparvovec or nusinersen are modelled to experience survival consistent with the natural history of untreated SMA type 2 patients for those in the C state (sits unassisted). Both treatment arms are assumed to experience the same survival benefit. The survival for SMA type 1 patients that can sit unassisted is modelled from the long-term survival of the 52-year prospective and retrospective genetic study of SMA type 2 patients, as reported by Zerres et al. 1997 (172). The individual patient data were reconstructed using published methods (175, 176). Survival was projected with parametric estimation using the generalised gamma curve (best fit). Goodness-of-fit is shown in terms of the AIC and BIC in Table 70 and shown visually in Figure 43. The parametric function fitted to the observed data is used for the entire model time horizon, even during the observed period of the study. This approach is to avoid over-fitting the model to the study population observed and to ensure that transition probabilities remained relatively constant over time.

Table 70: Assessment of curve fits for health state C

Parametric model	AIC	BIC
Exponential	1151.27	1154.66
Weibull	1093.97	1100.76
Log-Normal	1103.72	1110.50
Log-Logistic	1131.50	1138.28
G.Gamma	1087.90	1098.08
Gompertz	1263.74	1270.53

Abbreviations: AIC, Akaike information criterion; BIC, Bayesian information criterion.

Figure 37: State D overall survival for onasemnogene abeparvovec (KM followed by parametric models based on NeuroNext in the base case)

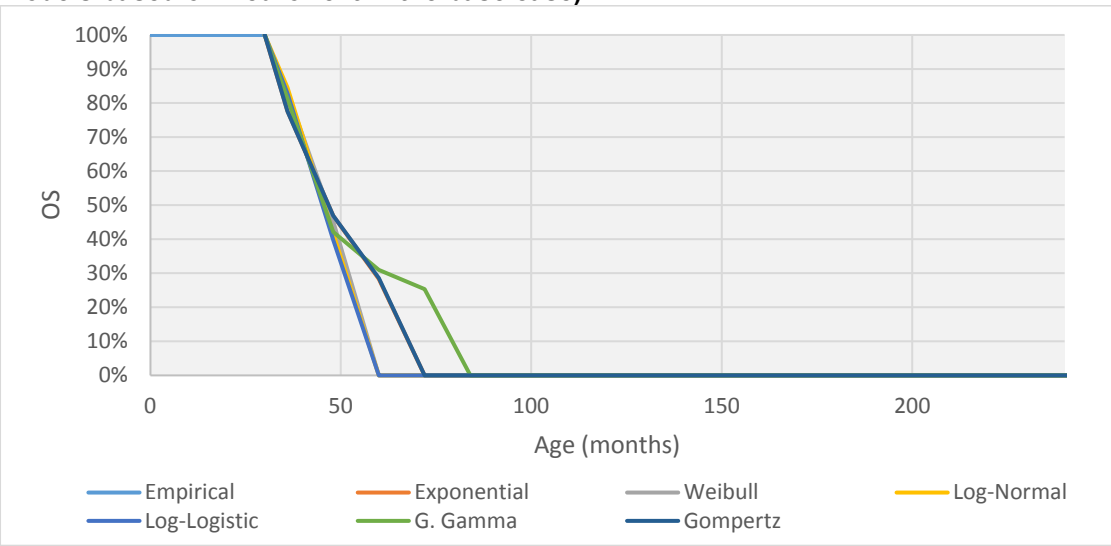


Figure 38: State D EFS for onasemnogene abeparvovec (KM followed by parametric models based on NeuroNext in the base case)

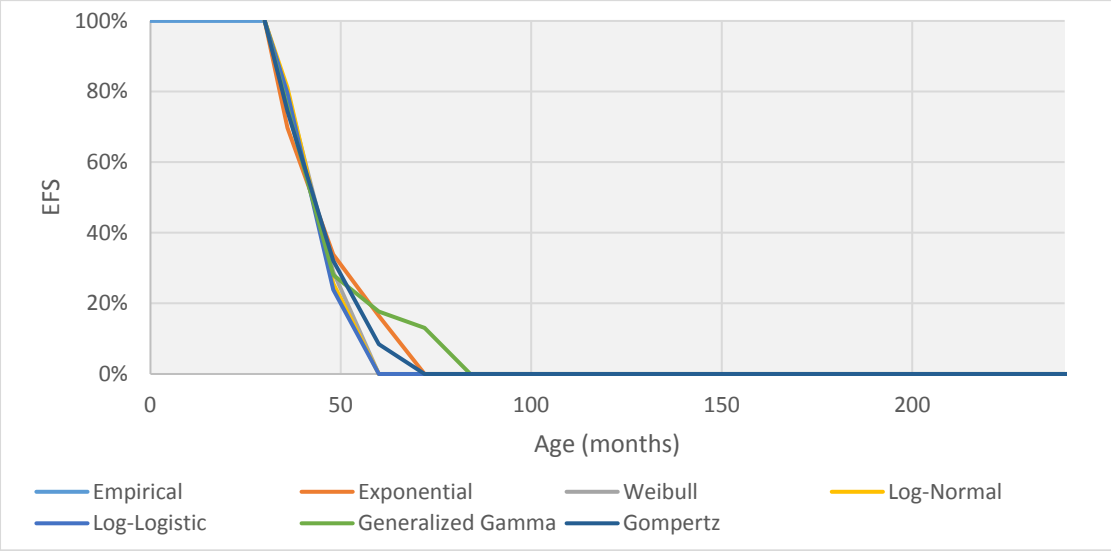


Figure 39: State D, best fit overall survival and event-free survival curves for onasemnogene abeparvovec

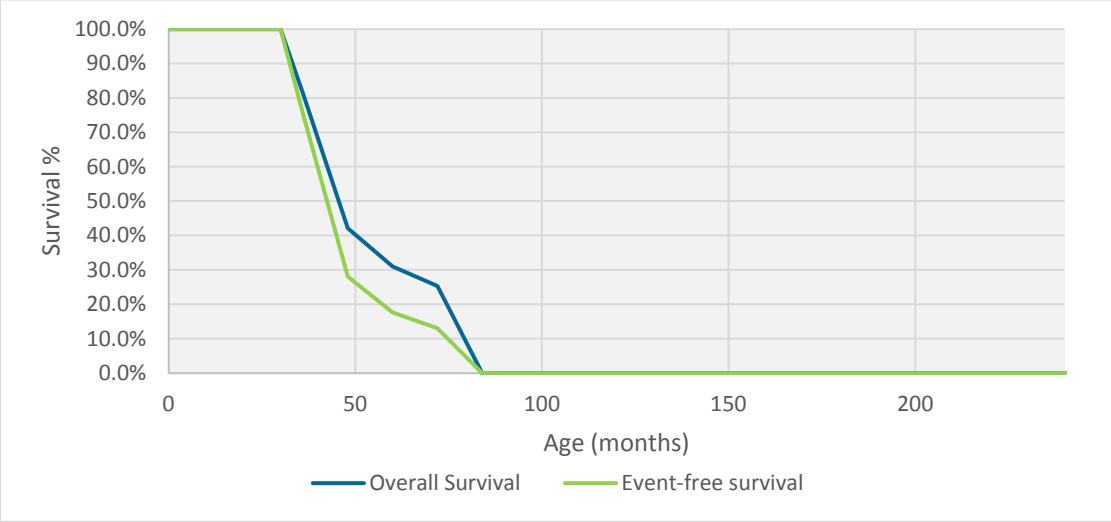


Figure 40: State D overall survival for nusinersen (KM followed by parametric models based on NeuroNext)

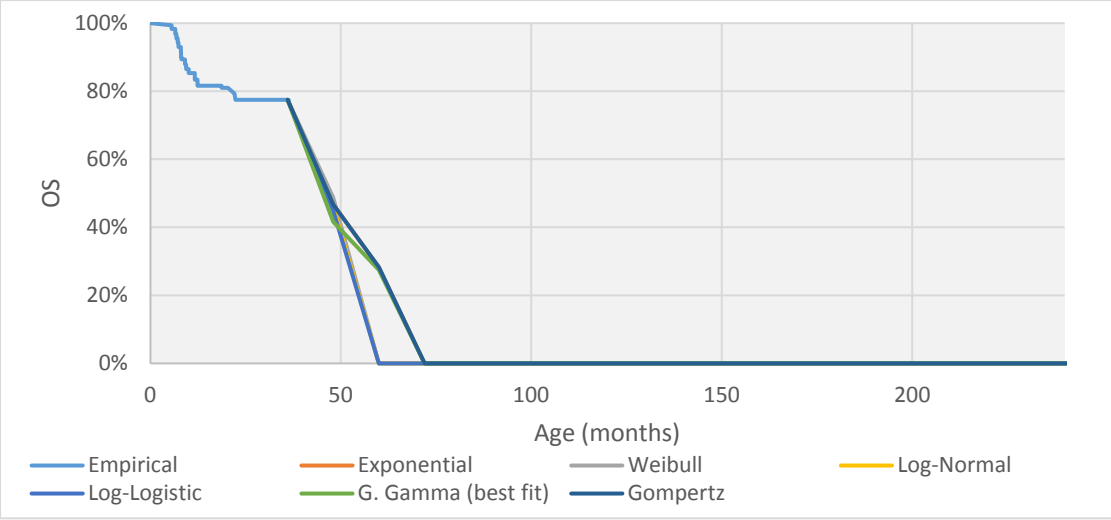


Figure 41: State D EFS for nusinersen (KM followed by parametric models based on NeuroNext)

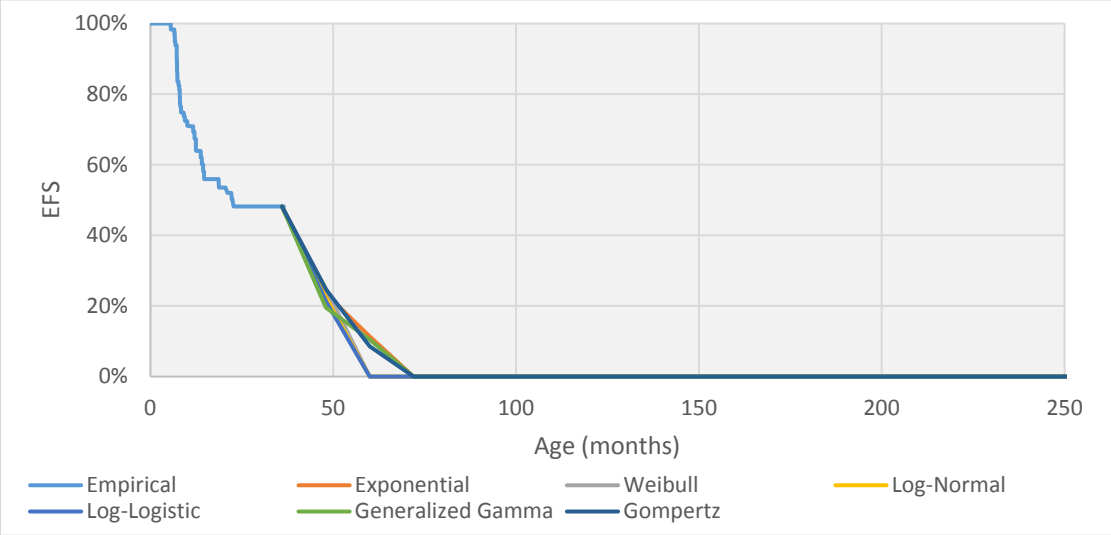


Figure 42: State D, best fit overall survival and event-free survival curves for nusinersen

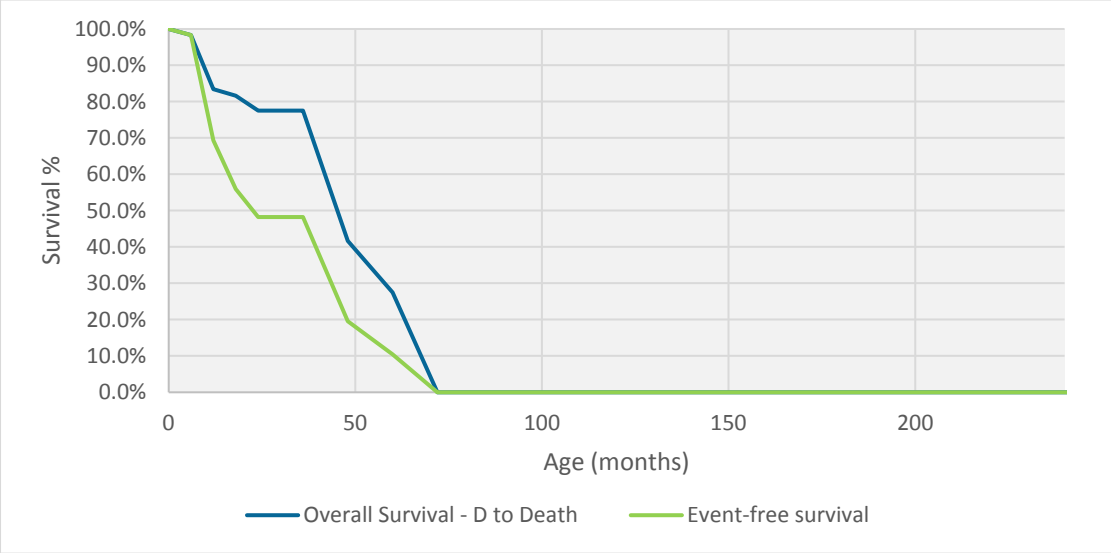
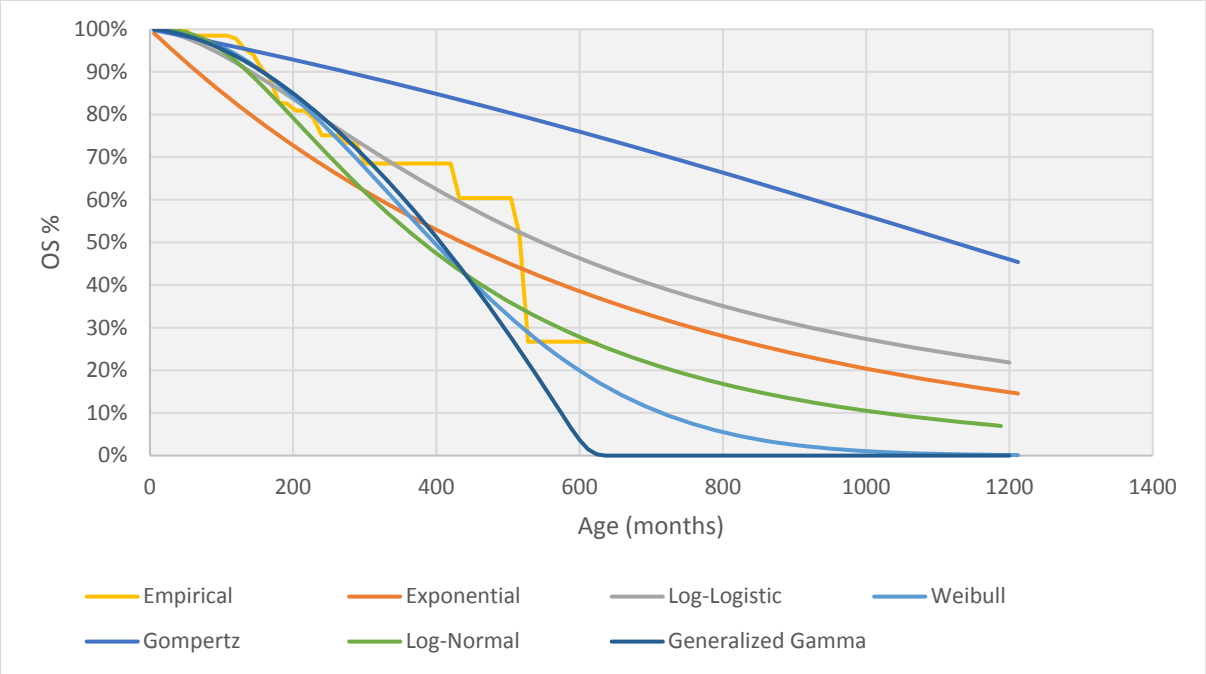


Figure 43: State C overall survival for nusinersen and onasemnogene abeparvovec

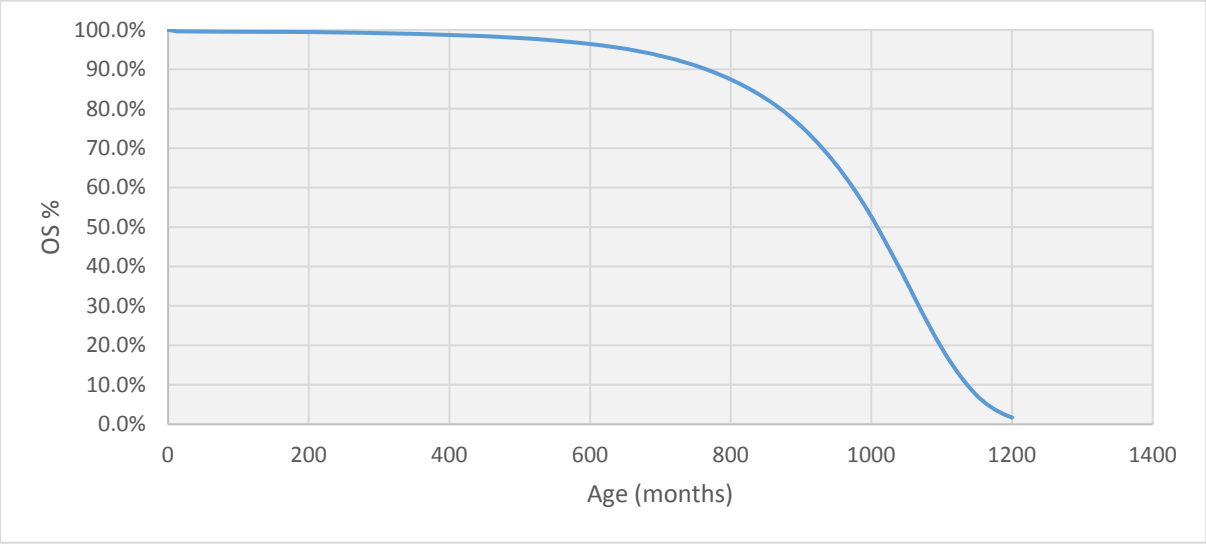


B state (walks unassisted) and A state (within broad range of normal) – treatment arms

Patients who could walk unassisted were assumed to have survival consistent with the natural history of SMA type 3 patients, which is reported to not significantly differ from the survival of the general population (172).

Thus, for both the B state (walks unassisted) and A state (within broad range of normal development) SMA type 1 patients treated with onasemnogene abeparvovec or nusinersen are modelled to experience survival consistent that of the general population. To estimate survival in these health states, the 2014–2016 UK life tables were used to determine the probability of death in each cycle (173). The survival curve for this health state is shown below in Figure 44.

Figure 44: B state and A state overall survival for treatment arms



12.2.2.2 Cost extrapolations

All health state costs are constant; the same annual costs for a given health state in cycle 1 persist for the life time horizon of the model.

12.2.3 Were intermediate outcome measures linked to final outcomes (for example, was a change in a surrogate outcome linked to a final clinical outcome)? If so, how was this relationship estimated, what sources of evidence were used and what other evidence is there to support it?

As described in Section 12.2.1, the clinical outcomes (motor milestone achievement, mortality and the need for permanent ventilation) observed in trials were used directly in the short-term model for both the treatment arms and the BSC arm. For the long-term model, a key assumption is that motor milestone achievement (i.e. the ability to sit unassisted or walk unassisted) in pharmacotherapy-treated SMA type 1 patients is linked to a better overall survival beyond trial follow-up periods; overall survival in the C state (sits unassisted), B state (walks unassisted) and A state (within broad range of normal population) are drawn from proxy populations. This relationship between improvements in motor function and a long-term survival benefit in pharmacotherapy-treated SMA type 1 patients was considered suitable as part of the recently published US ICER model (32). In addition, use of proxy populations to model overall survival in the C state, B state and A state was deemed reasonable as part of a recent UK clinical advisory board (see Section 12.2.5.2).

12.2.4 Were adverse events included in the cost- effectiveness analysis? If appropriate, provide a rationale for the calculation of the risk of each adverse event.

Given the nature of SMA, it is difficult to separate AEs due to treatment from complications associated with SMA itself, which are already accounted for in the health state costs and health state utility values. As such, the costs and disutilities of AEs were not included in the model.

12.2.5 Provide details of the process used when the sponsor's clinical advisers assessed the applicability of available or estimated clinical model parameter and inputs used in the analysis.

12.2.5.1 Model conceptualisation

To obtain external expert opinion on the appropriateness of the cost-effectiveness model structure, AveXis consulted ten international experts including clinical experts (paediatric neurologists and pulmonologists with experience in treating SMA), external academic health economists and an expert physician associated with an SMA patient advocacy group.

The objective of the model conceptualisation expert engagement was to design the most appropriate model framework for SMA type 1; opinions were collated via group telephone or group email exchange. The key conceptualisation questions posed to the experts included:

- The model structure:
    - The use of two health states that reflect the natural history of SMA type 1 – D state (not sitting) and E state (permanent assisted ventilation) – and three higher functioning health states for patients in the pharmacotherapy-treated arms: C state (sits unassisted), B state (walks unassisted), and A state (within a broad range of normal development)
    - The use of natural history SMA type 2 and SMA type 3 populations as proxy (for mortality and HCRU costs) for pharmacotherapy-treated SMA type 1 infants, who can sit unassisted and walk unassisted, respectively
- Rules associated with transition probabilities:
    - Only patients in the D state (not sitting) could transition to the E state (permanent assisted ventilation)
    - Patients in all other functional health states can only regress to death

12.2.5.2 UK clinical advisory board

Objectives

The objectives of the UK clinical advisory board were to:

- Discuss the key areas of uncertainty related to the clinical effectiveness of onasemnogene abeparvovec
- Explore any heterogeneity of health outcomes and benefits within SMA type 1
- Validate key assumptions underpinning the draft cost-effectiveness model
- Discuss the key areas of uncertainty related to the draft cost- effectiveness model

Criteria for selecting experts

For inclusion in the UK clinical advisory board, clinical experts were required to have expertise in treating SMA in the UK using BSC. In addition, some delegates also had experience of:

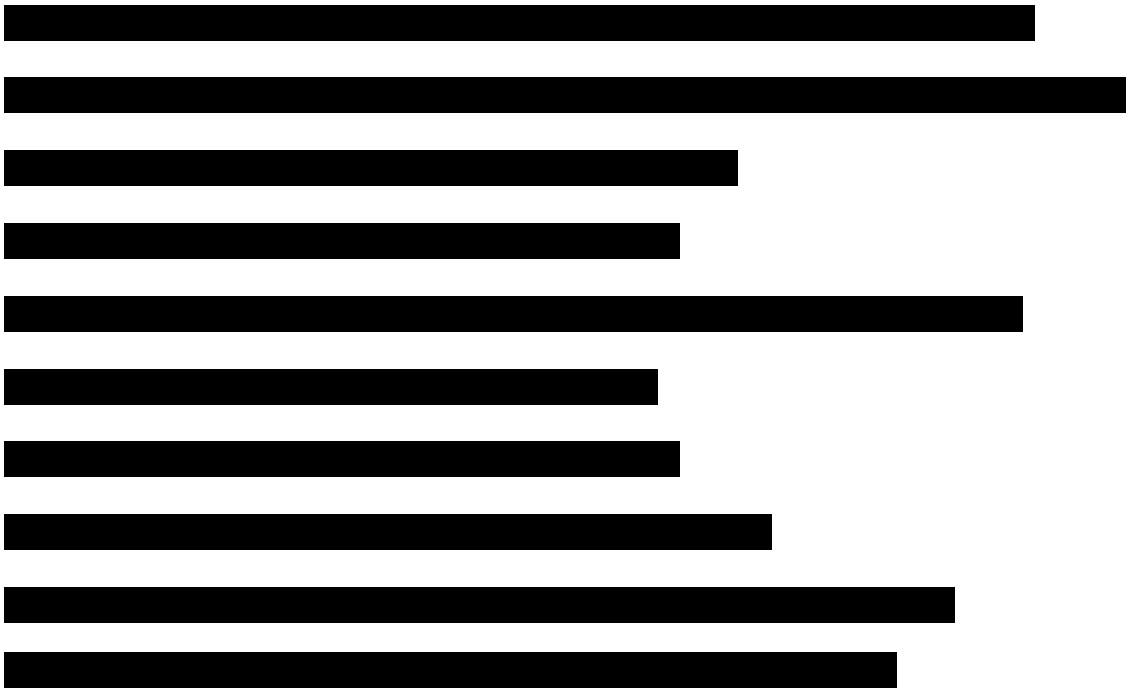
- Referring and/or treating patients with nusinersen via the nusinersen UK EAP
- Referring and/or treating infants with onasemnogene abeparvovec via UK clinical trials centres involved in ongoing clinical trials
- Experience of using gene therapies to treat neuromuscular disorders

In total nine clinical experts and three representatives from patient organisations were invited; all attended except two clinical experts who declined due to clinical commitments.

Experts

The healthcare professionals known to AveXis to have specialist clinical experience of SMA in the UK were contacted and were asked for their availability to participate in an advisory

board. Seven clinical experts and three representatives from patient organisations were able to take part in the advisory board:



Remuneration and conflict of interest

Each participant received an honorarium at Fair Market Value funded by AveXis to cover the time required to prepare for the advisory board (pre-reading) and time to attend at the advisory board. All participants signed a ‘no conflicting work’ statement.

Methods

Before the advisory board pre-reading materials were circulated to each participant, which included clinical trial data from the Phase I clinical trial for onasemnogene abeparvovec (START) and key clinical trial publications on comparators (BSC and nusinersen).

During the advisory board, context slides were presented (179) and questions discussed by the group. Discussion points and group consensuses were recorded in report format (17).

Questions

Full details of all questions asked are provided in a data on file reference (179). Key questions and consensus results are presented in Table 71.

Table 71: Key questions and consensus results UK clinical advisory board (May 2019)

Question	Consensus
Natural history of SMA type 1	
AveXis plans to submit an effectiveness assessment of onasemnogene abeparvovec in SMA type 1 as one group. Is this reasonable, or do subtypes (1A, 1B, 1C) need to be considered?	In clinical practice, infants with SMA type 1 are considered as a single population in terms of treatment decision making. SMA type 1 can be classified as infants with symptom onset at ≤6 months of age
Does the estimate (30–39 new cases of SMA type 1 per year in the England) align to your clinical experience/knowledge of the SMA type 1 population in England?	The initial reaction to the estimate of 30–39 incident SMA type 1 patients / year in England was that this number might be low, but on reflection of the numbers shared in the room from local centres and learnings from the EAP, this number is realistic. These estimates are supported by real world evidence from the nusinersen EAP which reports that in its last year of operation, 32 babies were diagnosed with SMA type 1 and treated with nusinersen in England (personal communication; [redacted], Paediatric Neurologist).
Generalisability of US natural history cohorts to the SMA type 1 population in England	
Are the US natural history cohorts (NeuroNext and PNCR) generalisable to the SMA type 1 population in England?	Yes, broadly the US natural history cohorts (NeuroNext and PNCR) are generalisable to the English SMA type 1 population
	The group noted that motor milestone achievements are not influenced by NIV; NIV only has an impact on life expectancy in SMA type 1 patients
Clinical effectiveness of onasemnogene abeparvovec versus best supportive care	
How representative is the CL-101 (START), Cohort 2 of the SMA type 1 population in England?	It is likely that Cohort 2 in START will be generalisable to 'future' SMA type 1 patients in England, as clinical practice is moving towards earlier symptom recognition and earlier diagnosis due to the increasing awareness of SMA. Remarks were raised about the generalisability of Cohort 2 from START to the England SMA type 1 population, specifically: • Patient 8: It is unlikely a patient would be treated this late (7.9 months) with onasemnogene abeparvovec in clinical practice in England • Patient 6 and 10: In current clinical practice, the diagnosis of symptomatic SMA type 1 patients with a CHOP-INTEND scores of >45 at baseline is unlikely

Question	Consensus
Clinical effectiveness of onasemnogene abeparvovec versus nusinersen	
	Some caution was raised relating to the comparison between onasemnogene abeparvovec and nusinersen based on currently available data. Certain participants stated that their instinct is that onasemnogene abeparvovec is the better of the two treatments with respect to clinical outcomes; however, robust evidence to support this perception is lacking at present
	If considering route and method of administration, then onasemnogene abeparvovec has a clear advantage relative to nusinersen
	The speed of response (as inferred by CHOP-INTEND) relative to natural history is an advantage for onasemnogene abeparvovec/potential limitation for nusinersen
Draft NICE model: economic inputs and assumptions	
Onasemnogene abeparvovec restores normal biology and is assumed to have a lifetime effect for the model base case. What is your view of this assumption?	The model base case assumption is correct that onasemnogene abeparvovec addresses the primary biological problem in SMA type 1 i.e. lack of a functional *SMN1* gene
If a pessimistic scenario was to be modelled, what proportion of patients after being treated with onasemnogene abeparvovec would you model to lose milestones each year after 24 months?	It is very difficult to predict how onasemnogene abeparvovec treated patients may regress in the absence of long-term data; the base case should be adhered to in which milestones achieved with onasemnogene abeparvovec are maintained in the lifetime, and hence are not lost
Children who were observed walking unassisted during clinical trials before age 2 are transitioned to 'within a broad range of normal range of development' (A state) at 5 years of age. What is your view of this assumption?	Children diagnosed and treated early in their disease course with onasemnogene abeparvovec could go on to meet the 'normal' description i.e. they could attend school, participate in family life, etc
Based on your clinical experience, what is the maximum age an SMA patient has been kept on permanent ventilation until? Is 22 years, as reported by Bach et al publication, a plausible maximum age?	It is rare for patients with SMA type 1 who receive permanent ventilation to reach the age reported by Bach. However, a clinical expert reported two cases of permanent ventilated SMA type 1 patients in England who are in their 20's, thus the estimate from Bach is appropriate as an absolute maximum
SMA type 1 children who achieve motor milestones (sitting unassisted and beyond – i.e. health states C, B and A) will not follow the deteriorating trajectory of SMA type 1 natural history.	The use of proxy SMA subtypes is not ideal; but it was recognised to be the best possible approach in the absence of long-term data for onasemnogene abeparvovec-treated patients

Question	Consensus
In the absence of clinical trial data, other SMA types and the general population are used as proxies/surrogates: • Sitting (C state) = survival of untreated SMA type 2 • Walking (B state) = survival of untreated SMA type 3 • Normal (A state) = survival of general population What is your view on this approach to using proxies for survival?	
Are any of the negative health state valuations plausible?	It is plausible for the D and E health states to be associated with negative health state utility values (i.e. considered worse than death)
	It is implausible for the C state to be associated with a negative health state utility value
	The concept of an average QoL score for each health state in the model is nonsensical as SMA is a heterogeneous disease that impacts very young infants and the impact on the patient, caregiver and family is very individual/environment-specific
What is your view on the health state utility values used by US ICER?	Of the health state utility values options shown, the US ICER values were the most plausible but there should be a differentiation between the values for E and D states (i.e. the E state value should be lower than the D state value)
SMA type 1 children who achieve motor milestones (sitting and beyond – i.e. health states C, B and A) will not follow the deteriorating trajectory of SMA type 1 natural history. In the absence of clinical trial data, other SMA types and the general population are used as proxies/surrogates for HCRU costs: • Non-sitting (D state) = costs of an SMA type 1 • Sitting (C state) = costs of an SMA type 2 • Walking (B state) = costs of an SMA type 3 • Normal range (A state) = zero SMA-related costs; patients are expected to be in the 'normal' range of development What is your view on this approach to using proxies for healthcare resource utilisation costs?	The use of proxies for healthcare resource utilisation costs is reasonable

<table>
<tr><th>Question</th><th>Consensus</th></tr>
<tr><td rowspan="2">What proportion of each ventilation group are treated across the four healthcare settings, based on best supportive care of SMA patients in England?</td><td>
<table>
<tr><th>Ventilation group</th><th>Paediatric intensive care</th><th>High dependency</th><th>Children's ward</th><th>Home-based</th><th>Total check</th></tr>
<tr><td>Patients on NIV >16 hours per day</td><td>15%</td><td>15%</td><td>0</td><td>70%</td><td>100%</td></tr>
<tr><td>Patients on NIV <16 hours per day</td><td>5%</td><td>5%</td><td>0</td><td>90%</td><td>100%</td></tr>
<tr><td>Tracheostomy patients</td><td>10%</td><td>30%</td><td>0</td><td>60%</td><td>100%</td></tr>
</table>
</td></tr>
<tr><td>Most infants with SMA type 1 who receive ventilatory support (permanent or non-permanent) would be home-based in England</td></tr>
<tr><td colspan="2">Service redesign for SMA type 1 in England</td></tr>
<tr><td>Positioning of onasemnogene abeparvovec relative to nusinersen</td><td>There is no biological justification to continue or start treatment with nusinersen following administration of onasemnogene abeparvovec</td></tr>
<tr><td>What might the clinical care pathway including onasemnogene abeparvovec look like?</td><td>The one-time IV infusion with onasemnogene abeparvovec will typically require one pre-infusion visit at a secondary/tertiary neuromuscular centre followed by a two-night, three-day elective stay at a highly specialised infusion centre. It was noted by patient representatives that travelling with ill children is a huge burden which should be avoided/minimised as much as possible as part of service redesign</td></tr>
</table>

Abbreviations: CHOP-INTEND, Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders; EAP, early access programme; NICE, National Institute of Health and Care Excellence; NIV, non-invasive ventilation; PNCR, Pediatric Neuromuscular Clinical Research; SMA, spinal muscular atrophy; SMN, survival motor neurone; UK, United Kingdom; US ICER; United States Institute for Clinical and Economic Review.

Data aggregation

No formal data aggregation took place. After each discussion/question, a summary of the advice shared was summarised verbally to the group to reach a consensus statement in response to each topic.

12.2.6 Summarise all the variables included in the cost-effectiveness analysis. Provide cross-references to other parts of the submission. A suggested format is provided in table D5 below.

A summary of the input variables for the model are shown in Table 72.

Table 72: Summary of model input variables

Variable	Base case value	Range, SE or 95% CI (distribution)	Source	Section(s)
Discounting				
Discount rate (costs)	3.5%	N/A for PSA 0% – 5% used in additional scenario analyses	NICE guide to the methods of technology appraisal 2013 (170)	12.1.7 12.4.3.2
Discount rate (outcomes)	3.5%	N/A for PSA 0% – 5% used in additional scenario analyses		
Costs				
Annual SMA care costs				
E state: drug costs	£636	SE: £127.20 (Gamma)	UK HCRU study (18); NHS Schedule of Reference Costs 2017–2018 (180); Appendix 7	12.3.1
E state: medical tests	£225	SE: £45.00 (Gamma)		
E state: medical visits	£2,690	SE: £538.00 (Gamma)		
E state: hospitalisations	£211,235	SE: £42,247.00 (Gamma)		
E state: GP & emergency	£293	SE: £58.60 (Gamma)		
E state: health materials	£2,903	SE: £580.60 (Gamma)		
E state: social services	£46,738	SE: £9,347.60 (Gamma)		
D state: drug costs	£919	SE: £183.80 (Gamma)		
D state: medical tests	£325	SE: £65.00 (Gamma)		
D state: medical visits	£3,890	SE: £778.00 (Gamma)		
D state: hospitalisations	£66,988	SE: £13,397.60 (Gamma)		
D state: GP & emergency	£423	SE: £84.60 (Gamma)		

Variable	Base case value	Range, SE or 95% CI (distribution)	Source	Section(s)
D state: health materials	£3,936	SE: £787.20 (Gamma)		
D state: social services	£27,896	SE: £5,579.20 (Gamma)		
C state: drug costs	£743	SE: £148.60 (Gamma)		
C state: medical tests	£311	SE: £62.20 (Gamma)		
C state: medical visits	£2,247	SE: £449.40 (Gamma)		
C state: hospitalisations	£37,420	SE: £7,484.00 (Gamma)		
C state: GP & emergency	£176	SE: £35.20 (Gamma)		
C state: health materials	£2,046	SE: £409.20 (Gamma)		
C state: social services	£18,598	SE: £3,719.60 (Gamma)		
B state: drug costs	£939	SE: £187.80 (Gamma)		
B state: medical tests	£277	SE: £55.40 (Gamma)		
B state: medical visits	£1,899	SE: £379.80 (Gamma)		
B state: hospitalisations	£468	SE: £93.60 (Gamma)		
B state: GP & emergency	£71	SE: £14.20 (Gamma)		
B state: health materials	£591	SE: £118.20 (Gamma)		
B state: social services	£2,952	SE: £590.40 (Gamma)		
A state: drug costs;	£0	N/A	Assumption, UK advisory board (17)	12.2.5.2
A state: medical tests	£0	N/A		
A state: medical visits	£0	N/A		
A state: hospitalisations	£0	N/A		
A state: GP & emergency	£0	N/A		

Variable	Base case value	Range, SE or 95% CI (distribution)	Source	Section(s)
A state: health materials	£0	N/A		
A state: social services	£0	N/A		
Nusinersen costs				
Technology acquisition cost, per vial	£75,000	Fixed in PSA SE: 20% (£15,000) in DSA Discounts from the list price are included as scenario analyses	UK list price, BNF (181)	12.3.6
Inpatient lumbar puncture				
Aged ≤5 years	£1,502	SE: £300.40 (Gamma)	NHS Schedule of Reference Costs 2017–2018 (180) (Codes: EL - HC72C; EL - HC72B; EL - HC72A)†	12.3.6
Aged 6–18 years	£1,474	SE: £294.80 (Gamma)		
Aged ≥19 years	£843	SE: £168.60 (Gamma)		
Outpatient lumbar puncture				
Aged ≤5 years	£417	SE: £83.40 (Gamma)	NHS Schedule of Reference Costs 2017–2018 (180) (Codes: OPROC - HC72C, service code 421; (OPROC - HC72B, service code 421; OPROC - HC72A, service code 400)†	12.3.6
Aged 6–18 years	£435	SE: £87.00 (Gamma)		
Aged ≥19 years	£294	SE: £58.80 (Gamma)		
Day case lumbar puncture				
Aged ≤5 years	£1,389	SE: £277.80 (Gamma)	NHS Schedule of Reference Costs 2017–2018 (180) (Codes: DC - HC72C; DC - HC72B; DC - HC72A)†	12.3.6
Aged 6–18 years	£1,014	SE: £202.80 (Gamma)		
Aged ≥19 years	£503	SE: £100.60 (Gamma)		
% of patients having an elective inpatient procedure (all age groups)	40%	Sampled from a Dirichlet distribution using a 4:3:3 ratio	Assumption, NICE nusinersen STA (31)	12.3.6

Variable	Base case value	Range, SE or 95% CI (distribution)	Source	Section(s)
% of patients having an outpatient procedure (all age groups)	30%			
% of patients having a day case procedure (all age groups)	30%			
Nusinersen discontinuation				
Proportion of arm discontinuing nusinersen in E state	100%	Fixed in PSA and DSA	Nusinersen MAA (19)	12.2.1.2
Proportion of arm discontinuing nusinersen in C and D states	3%	SE: 0.6% (Beta)	Nusinersen MAA (19), nusinersen SmPC (21) and nusinersen UK/Ireland EAP (144)	12.2.1.2
Rate of milestone loss for patients that discontinue nusinersen in C and D states	90%	SE: 0.18 (Beta)	Assumption	12.2.1.2
Onasemnogene abeparvovec costs				
Onasemnogene abeparvovec drug acquisition cost	£1,674,500	Fixed in PSA SE: 20% (£334,900) in DSA	Indicative price/AveXis planning assumption only (US price of $2,125,000 at 0.788 exchange rate [11 June 2019])	12.3.5
Onasemnogene abeparvovec administration cost	£2,425	SE: £485.00 (Gamma)	NHS Schedule of Reference Costs 2017–2018 (180) Weighted average of codes relating paediatric nervous system disorders and cerebral degenerations or miscellaneous disorders of nervous system (EL- PR01A-E and EL - AA25C-G)	12.3.6
Quality of life adjustments				
Utility: E state	0.190	SE: 5% (0.0095) (Gamma) in PSA	Thompson et al. 2017 (149) US ICER (32)	10.1.9
Utility: D state	0.190	SE: 5% (0.0095) (Gamma) in PSA		

Variable	Base case value	Range, SE or 95% CI (distribution)	Source	Section(s)
Utility: C state	0.600	SE: 5% (0.0300) (Gamma) in PSA		
Utility: B and A states: age 0–24 years	0.954	SE: 5% (0.0477) (Beta) in PSA	Ara and Brazier 2010 (152)	10.1.9
Utility: B and A states: age 25–34 years	0.925	SE: 5% (0.0462) (Beta) in PSA		
Utility: B and A states: age 35–44 years	0.899	SE: 5% (0.0450) (Beta) in PSA		
Utility: B and A states: age 45–54 years	0.867	SE: 5% (0.0434) (Beta) in PSA		
Utility: B and A states: age 55–-64 years	0.829	SE: 5% (0.0414) (Beta) in PSA		
Utility: B and A states: age 65–74 years	0.783	SE: 5% (0.0392) (Beta) in PSA		
Utility: B and A states A: age ≥75 years	0.685	SE: 5% (0.0342) (Beta) in PSA		
Survival limits				
Survival limit (years) for E state	16	SE: 20% (Gamma)	Assumption	12.2.2.1
Survival limit (proportion of remaining population) for D state	25%	SE: 5% (Beta)	Assumption	12.2.2.1
Onasemnogene abeparvovec: rates of milestone loss (scenario analysis only)				
Rate of milestone loss (pessimistic scenarios only) for A , B, C and D states	90%	N/A – scenario analysis only	Assumption	12.2.1.2
Survival curve parameters – shown for base case, best fitting curves only				
E state OS: Gompertz distribution: shape	-0.0194	Cholesky decomposition	Parametric curve fitted to observed data in Gregoretti et al. 2013 (171)	12.2.2.1
E state OS: Gompertz distribution: rate	0.0093			
D state OS: generalised gamma: mu	1.7148	Cholesky decomposition	Parametric curve fitted to observed data in NeuroNext (67)	12.2.2.1
D state OS: generalised gamma: sigma	0.4624			
D state OS: generalised gamma: q	-3.5961			
D state EFS: generalised gamma: mu	1.7054	Cholesky decomposition		12.2.2.1

Variable	Base case value	Range, SE or 95% CI (distribution)	Source	Section(s)
D state EFS: generalised gamma: sigma	0.3847		Parametric curve fitted to observed data in NeuroNext (67)	
D state EFS: generalised gamma: q	-2.8686			
C state: generalised gamma: mu	6.35646	Cholesky decomposition	Parametric curve fitted to observed data in Zerres et al. 1997 (172)	12.2.2.1
C state: generalised gamma: sigma	0.11002			
C state: generalised gamma: q	5.35602			
B state and A state: survival curve	See model sheet: B_A_Survival	N/A	Office for National Statistics 2018 (173)	12.2.2.1

Abbreviations: BNF, British National Formulary; CI, confidence interval; EFS, event-free survival (permanent ventilation-free survival); N/A, not applicable; OS, overall survival; US ICER, United States Institute of Clinical and Economic review.
† Code costs rounded to nearest pound.

12.3 *Resource identification, measurement and valuation*

NHS costs

12.3.1 Describe how the clinical management of the condition is currently costed in the NHS in terms of reference costs and the payment by results (PbR) tariff.

A UK HCRU study using in-depth telephone interviews with UK clinical experts (n=16) was conducted (February 2019 – April 2019) to ensure the model accurately captured the current UK clinical pathway of care for SMA patients. As HCRU costs for SMA type 2 and SMA type 3 are being used as proxy for pharmacotherapy-treated SMA type 1 patients who can sit unassisted (C state) and walk unassisted (B state) milestones, respectively, the current management of SMA in multiple types (SMA type 1, type 2 and type 3) was sought via the UK HCRU study. Full details of the study are provided in the UK HCRU study report (18), but in summary:

Clinical experts

The n=16 clinical experts included [redacted]

Methods

Each clinical expert took part in an individual, in-depth telephone interview, which was semi-directive to explore SMA clinical management overall, specific HCRU was quantified using a prepared data summary sheet (Excel). Weighted means of proportions of patients using specific resources, frequency and where relevant, duration, of each type of resource used were calculated. The total patients seen in the past 12 months was calculated as the aggregate number of SMA patients seen by the clinical experts reporting on this resource over the last 12 months, and the number of patients using this resource was calculated using the prevalence of this resource use reported by each clinical expert for their own patients. The prevalence per resource use was calculated using the total number of patients seen by all clinical experts interviewed, per SMA type, as a denominator [redacted] The mean prevalence was based on responses from clinical experts who were considered the most likely to use or prescribe a type of resource – described as ‘Scenario 3’ in UK HCRU report (18). Thus, in some instances a modification in the denominator for the calculation of mean prevalence according to the number of patients seen by only the relevant clinical experts was required.

Unit costs sources

Multiple sources for unit costs were used to calculate costs associated with the HCRU identified:

- For consultations, inpatient hospitalisations and A&E visits the main source of unit costs was the NHS National Schedule of Reference Costs, Year 2017–18 (180) and the Personal Social Services Research Unit (PSSRU) Costs of Health and Social Care 2018 report (182)
- For resources related to pharmacological therapy, Prescription Cost Analysis (PCA) England data, 2018 were used (183). When different formulations were available for a medication, a weighted average of different formulations deemed suitable for the target population was used, with weights equal to the total number of units distributed in 2017–18.
    - Technology costs and administration costs for nusinersen – although reported by as a HCRU for some SMA type 1 patients in the UK HCRU study – are handled separately in the model as part of the comparator costs (see Section 12.3.6) and hence, are not included as part of the health state HCRU costs.
- For resources related to laboratory tests, respiratory tests/evaluations, orthopaedic devices, surgeries and respiratory devices sources included:
    - NHS National Schedule of Reference Costs, Year 2017–18 (180)
    - NHS England Orthotic services, Local tariffs for direct access (184)
    - NICE Motor neurone disease: assessment and management guideline [NG42] (185)
    - Several published articles and NHS buyer's guides/information leaflets

Full details of the unit costs applied per healthcare resource, including the specific reference codes and sources used, are provided in the supplementary Excel reference appendices to the UK HCRU report (18). A summary of costs for SMA is shown in Table 73.

Table 73: Summary of costs for SMA from the UK HCRU study

	Mean resource use per quarter	Mean resource use per year
D state (SMA type 1)		
Consultations	[redacted]	[redacted]
Data hospitals	[redacted]	[redacted]
Pharmacological therapy†	[redacted]	[redacted]
Tests (I), devices (I), surgeries	[redacted]	[redacted]
Tests (II), devices (II), nutrition	[redacted]	[redacted]
Total	[redacted]	[redacted]

C state (SMA type 2 as proxy)		
Consultations	[redacted]	[redacted]
Data hospitals	[redacted]	[redacted]
Pharmacological therapy	[redacted]	[redacted]
Tests (I), devices (I), surgeries	[redacted]	[redacted]
Tests (II), devices (II), nutrition	[redacted]	[redacted]
Total	[redacted]	[redacted]
B state (SMA type 3 as proxy)		
Consultations	[redacted]	[redacted]
Data hospitals	[redacted]	[redacted]
Pharmacological therapy	[redacted]	[redacted]
Tests (I), devices (I), surgeries	[redacted]	[redacted]
Tests (II), devices (II), nutrition	[redacted]	[redacted]
Total	[redacted]	[redacted]

Abbreviations: HCRU, healthcare resource utilisation; SMA, spinal muscular atrophy.
† Nusinersen drug costs and administration costs are removed, as these are handled separately in the model as part of the comparator costs (see Section 12.3.6) and hence, are not included as part of the health state HCRU costs.

A limitation of the UK HCRU study is that the clinical expert sample did not include palliative care or intensive care/high dependency specialists, and only included one expert (health visitor) with expertise of the community and social care setting. As such, HCRU associated with such specialisms may not be fully captured. Therefore, the costs calculated in the HCRU study were adjusted using resource costs reported by Noyes et al. 2006 (186). The Noyes study provides detailed costs associated with ventilator-dependent children in the UK under different healthcare settings including home-based, high-dependency units and intensive care units. The proportion of patients receiving care in a home-based, high-dependency and intensive care setting was sourced from UK clinical experts and described in Table 74.

Table 74: Healthcare settings of UK SMA patients by ventilatory status

Ventilation group	Intensive care	High dependency	Home-based
Patients on NIV <16 hours per day	5%	5%	90%
Patients on NIV >16 hours per day	15%	15%	70%
Tracheostomy patients	10%	30%	60%

Abbreviations: NIV, non-invasive ventilation; SMA, spinal muscular atrophy; UK, United Kingdom.
Source: UK advisory board (May 2019) (17).

The proportion of patients requiring NIV <16 hours per day for each health state is estimated based on the prevalence of using non-invasive ventilatory aids (BiPAP NIPPY, Breas) as reported in the UK HCRU study:

- D state (SMA type 1): 16% non-ventilated; 84% NIV <16 hours/day

- C state (SMA type 2): 44% non-ventilated; 66% NIV <16 hours/day
- B state (SMA type 3): 80% non-ventilated; 20% NIV <16 hours/day

Costs for the E state (permanent assisted ventilation) were derived from the Noyes et al. 2006 study (186), and a permanently assisted ventilation cohort was not captured in the UK HCRU study. Patients in the E state are either on permanent invasive ventilation (i.e. tracheostomy) or receiving NIV >16 hours / day. The proportions in these two categories were derived from an SMA type 1 cohort in Germany (Pechman et al. 2018 (187)); this source was chosen as it provided ventilation status stratified by *SMN2* copy number and reported the duration of spent in NIV per day. Data from the ≤2 *SMN2* copies group (n=38) provided the closest match to our cost- effectiveness modelled SMA type 1 population. Of the patients receiving permanent assisted ventilation (n=15/38):

- n=5/15 (33.3%) received NIV >16 hours/day
- n=10/15 (66.6%) had a tracheostomy

Full details how the E state, D state, C state and B state HCRU costs were adjusted or calculated using costs reported by Noyes et al. 2006 (186) and the aforementioned proportions for healthcare settings and ventilatory status are provided in Appendix 7. The resulting health sate costs used in the base case are described in Table 75.

Table 75: Annual SMA-care related costs used in the cost- effectiveness base case

Cost category	**SMA type 1**		**SMA type 2 as proxy**	**SMA type 3 as proxy**	**SMA-related costs**
Health state	**E**	**D**	**C**	**B**	**A**
Drugs	£636	£919	£743	£939	£0
Medical tests	£225	£325	£311	£277	£0
Medical visits	£2,690	£3,890	£2,247	£1,899	£0
Hospitalisations	£211,235	£66,988	£37,420	£468	£0
GP and Emergency	£293	£423	£176	£71	£0
Health material	£2,903	£3,936	£2,046	£591	£0
Social services	£46,738	£27,896	£18,598	£2,952	£0
Total	**£264,720**	**£104,377**	**£61,541**	**£7,197**	**£0**

Abbreviations: GP, general practitioner; SMA, spinal muscular atrophy; UK, United Kingdom.

Resource identification, measurement and valuation studies

12.3.2 Provide a systematic search of relevant resource data for the NHS in England. Include a search strategy and inclusion criteria, and consider published and unpublished studies.

As described in Section 11.1, a systematic literature review was undertaken to identify cost and resource use associated with SMA type 1. However, the cost and resource use values

used in the model were identified as per the methods described in Section 12.3.1 and Appendix 7.

12.3.3 Provide details of the process used when clinical advisers assessed the applicability of the resources used in the model.

As per section 12.3.1, the *de novo* UK HCRU study included aggregated data from n=16 clinical experts to estimate HCRU costs associated with the management of SMA. Details of the recruitment and inclusion criteria used to select the clinical experts are provided in the UK HCRU study report (18).

At a recent UK clinical advisory board – see Section 12.5.2 for details – experts provided the consensus that the use of proxies for HCRU costs is reasonable (e.g. SMA type 2 HCRU costs can be used to estimate the HCRU associated with a SMA type 1 baby who can sit unassisted). It was also during this advisory board, consensus was provided on the healthcare settings (intensive care, high dependency or home-based) in which SMA patients receive care, based on their ventilatory status (NIV <16 hours/day, NIV>16 hours/day and tracheostomy).

Technology and comparators' costs

12.3.4 Provide the list price for the technology.

Not applicable. At the time of submission, AveXis is registered with the Department of Health and Social Care (DHSC) for the voluntary pricing scheme (2019 PPRS) but a final list price application for onasemnogene abeparvovec is pending.

12.3.5 If the list price is not used in the de novo cost- effectiveness model, provide the alternative price and a justification.

As no list price was available at the time of submission, an indicative price based on the US public price (USD: 2,125,000) is calculated. A Bank of England exchange rate of 0.788 GBP to the USD (11 June 2019 rate) is applied, to provide an indicative price of £1,674,500. This price (£1,674,500) is an AveXis planning assumption only; as the DHSC final list price application for onasemnogene abeparvovec is pending. AveXis will confirm the NHS List Price during the appraisal process in order not to delay decision-making at NICE.

12.3.6 Summarise the annual costs associated with the technology and the comparator technology (if applicable) applied in the cost effectiveness model. A suggested format is provided in tables D6 and D7. Table D7 should only be completed when the most relevant UK comparator for the cost analysis refers to another technology. Please consider all significant costs associated with treatment that may be of interest to commissioners.

The estimated, indicative total cost associated with the technology per patient for onasemnogene abeparvovec is £1,676,925 (Table 76).

Table 76: Costs per treatment/patient associated with the technology (onasemnogene abeparvovec) in the cost-effectiveness model

Items	Value	Source
Price of the technology per treatment/patient	£1,674,500	AveXis planning assumption only: an indicative price based on the US public price (USD: 2,125,000) is calculated. A Bank of England exchange rate of 0.788 GBP to the USD (11 June 2019 rate) is applied, to provide an indicative price of £1,674,500.
Treatment administration cost	£2,425	NHS Schedule of Reference Costs, 2017–2018 (180) Weighted average of codes relating paediatric nervous system disorders and cerebral degenerations or miscellaneous disorders of nervous system (EL- PR01A-E and EL - AA25C-G)
Total cost per treatment/patient	**£1,676,925**	Calculation

Abbreviations: NHS, National Health Service; US, United States.

The total cost associated with the technology per patient for nusinersen is £456,858 (first year) and £228,429 in subsequent years whilst the patient is still receiving the drug (Table 77).

Table 77: Costs per treatment/patient associated with the comparator technology (nusinersen) in the cost-effectiveness model

Items	Value	Source
Price of the technology per treatment/patient	£450,000 (year 1) £225,000 (year 2 onwards)	£75,000 per dose (UK list price, BNF (181). Four loading doses in the first 6 months; two doses in subsequent 6 months; 3 doses per year from year two onwards
Treatment administration cost	£6,856 (year 1) £3,428 (year 2 onwards)	Weighted average for inpatient (40%), outpatient (30%) and day case (30%) lumbar puncture as report in the nusinersen company NICE STA evidence (31). NHS reference costs 2017/18 (EL - HC72C) [inpatient], (OPROC - HC72C, service code 421) [outpatient], (DC - HC72C) [day case]. Weighted average cost per administration equals £1,143. Note that this cost is for patients of 5 years and younger. Weighted average costs decrease for patients aged from 6 to 18 years to £1,024 and for 19 years or older to £576. Total administration costs would therefore decrease for age groups beyond year 6.
Total cost per treatment/patient	**£456,858** **(year 1)** **£228,429** **(year 2 onwards)**	Total costs per treatment/patient cost will decrease for age groups beyond year 6 (as outlined above).

Abbreviations: BNF, British National Formulary; ID, identification; NICE, National Institute of Health and Care Excellence.

Annual SMA care (i.e. HCRU) costs are not included in the total calculated costs for the technologies but are included in the model as health state costs.

Note that the costs for onasemnogene abeparvovec are incurred in the first year only, as it is a one-off treatment. All costs for BSC are included in health state costs and have zero 'technology' costs.

Health-state costs

12.3.7 If the cost- effectiveness model presents health states, the costs related to each health state should be presented in table D8. The health states should refer to the states in section 12.1.6. Provide a rationale for the choice of values used in the cost- effectiveness model.

Table 78 shows the cost categories that are applied to each of the health states in the model. Section 12.2.6 and section 12.3.1 shows the unit cost data used in the model, and, for those costs which are cycle dependent, shows how the values were derived. Total costs by health state are shown in Section 12.5.9.

Table 78: List of health states and associated costs in the cost-effectiveness model

Cost categories	Health State				
	E Permanent assisted ventilation	**D Not sitting**	**C Sits unassisted**	**B Walks unassisted**	**A Within broad range of development**
Technology	Onasemnogene abeparvovec: all patients receive gene therapy at baseline Nusinersen: all patients receive drug unless discontinued; patients who move to E state do not receive drug				
Technology administration	Onasemnogene abeparvovec: all patients incur administration costs at baseline. As the technology is a one-time, single IV administration, no ongoing administration costs are incurred Nusinersen: all patients incur drug administration costs per dose, which is for lifetime unless the patient discontinues or dies. Patients who move to the E state do not receive nusinersen and do not incur administration costs				
SMA treatment costs	E state costs in each cycle times probability patient is in the cycle	D state costs in each cycle times probability patient is in the cycle	C state costs in each cycle times probability patient is in the cycle	B state costs in each cycle times probability patient is in the cycle	None

Adverse-event costs

12.3.8 Complete table D9 with details of the costs associated with each adverse event included in the cost- effectiveness model. Include all adverse events and complication costs, both during and after longer-term use of the technology.

For nusinersen, as no serious AEs were reported in either arm of ENDEAR and no AEs were considered by trial investigators to be related to treatment in ENDEAR (31), AEs were excluded from consideration in the model. Adverse events associated with lumbar puncture

(e.g. headache and back pain) were observed but the incidence and severity of these were consistent with events expected to occur with lumbar puncture. In addition, these events could not be assessed because of the limited communication abilities in the infant population treated with nusinersen.

All patients in onasemnogene abeparvovec clinical studies were treated with prophylactic oral prednisolone, except for the first patient enrolled into START, who developed elevated transaminases >20 x the upper limit of normal, which appeared to respond to prednisolone. However, since the cost of prednisolone is minor, no AEs are included in the cost-effectiveness model in terms of cost or health impacts.

Miscellaneous costs

12.3.9 Describe any additional costs and cost savings that have not been covered anywhere else (for example, PSS costs, and patient and carer costs). If none, please state.

In the opinion of AveXis, the model captures all of the major costs and cost savings that arise with the introduction of onasemnogene abeparvovec in England as part of the base case. Note that the potential impact on family and patient income/out of pockets expenses from the introduction of the technology is addressed as explorative scenarios in the answers to questions 14.1, 14.3, and 14.4.

12.3.10 Are there any other opportunities for resource savings or redirection of resources that it has not been possible to quantify?

No other opportunities for NHS/PSS resource savings outside of those explored in answers to questions 14.1, 14.3, and 14.4. have been identified.

12.4 *Approach to sensitivity analysis*

Section 12.4 requires the sponsor to carry out sensitivity analyses to explore uncertainty around the structural assumptions and parameters used in the analysis. All inputs used in the analysis will be estimated with a degree of imprecision. For technologies whose final price/acquisition cost has not been confirmed, sensitivity analysis should be conducted over a plausible range of prices.

Analysis of a representative range of plausible scenarios should be presented and each alternative analysis should present separate results.

12.4.1 Has the uncertainty around structural assumptions been investigated? State the types of sensitivity analysis that have been carried out in the cost- effectiveness analysis.

Yes. Structural assumptions were explored in the scenario analyses described in Section 12.4.3 to determine the impact on the results of varying these assumptions.

12.4.2 Was a deterministic and/or probabilistic sensitivity analysis undertaken? If not, why not? How were variables varied and what was the rationale for this? If relevant, the distributions and their sources should be clearly stated.

Yes. Deterministic, probabilistic, and scenario-based sensitivity analyses were undertaken. The variables used, together with the range of the variation (upper and lower values) and the method used, are summarised in Section 12.4.3.

12.4.3 Complete table D10.1, D10.2 and/or D10.3 as appropriate to summarise the variables used in the sensitivity analysis.

12.4.3.1 Values used in the one-way sensitivity analysis

The values used in the one-way sensitivity analysis are shown below in Table 79: all variables were adjusted by +/- 20% or within natural limits.

Table 79: Variables used in one-way deterministic sensitivity analysis

Category	Variable	Base case	Low value	High value
Annual SMA-care health state costs	E state: drug costs	£636	£509	£763
	E state: medical tests	£225	£180	£270
	E state: medical visits	£2,690	£2,152	£3,228
	E state: hospitalisations	£211,235	£168,988	£253,482
	E state: GP & emergency	£293	£234	£352
	E state: health materials	£2,903	£2,322	£3,484
	E state: social services	£46,738	£37,390	£56,086
	D state: drug costs	£919	£735	£1,103
	D state: medical tests	£325	£260	£390
	D state: medical visits	£3,890	£3,112	£4,668
	D state: hospitalisations	£66,988	£53,590	£80,386
	D state: GP & emergency	£423	£338	£508
	D state: health materials	£3,936	£3,149	£4,723
	D state: social services	£27,896	£22,317	£33,475
	C state: drug costs	£743	£594	£892
	C state: medical tests	£311	£249	£373
	C state: medical visits	£2,247	£1,798	£2,696
	C state: hospitalisations	£37,420	£29,936	£44,904
	C state: GP & emergency	£176	£141	£211
	C state: health materials	£2,046	£1,637	£2,455

Category	Variable	Base case	Low value	High value
	C state: social services	£18,598	£14,878	£22,318
	B state: drug costs	£939	£751	£1,127
	B state: medical tests	£277	£222	£332
	B state: medical visits	£1,899	£1,519	£2,279
	B state: hospitalisations	£468	£374	£562
	B state: GP & emergency	£71	£57	£85
	B state: health materials	£591	£473	£709
	B state: social services	£2,952	£2,362	£3,542
Nusinersen costs and administration costs	Technology acquisition cost, per vial	£75,000	£60,000	£90,000
	Inpatient lumbar puncture: Aged ≤5 years	£1,502	£1,202	£1,802
	Inpatient lumbar puncture: Aged 6–18 years	£1,474	£1,179	£1,769
	Inpatient lumbar puncture: Aged ≥19 years	£843	£674	£1,012
	Outpatient lumbar puncture: Aged ≤5 years	£417	£334	£500
	Outpatient lumbar puncture: Aged 6–18 years	£435	£348	£522
	Outpatient lumbar puncture: Aged ≥19 years	£294	£235	£353
	Day case lumbar puncture: Aged ≤5 years	£1,389	£1,111	£1,667
	Day case lumbar puncture: Aged 6–18 years	£1,014	£811	£1,217
	Day case lumbar puncture: Aged ≥19 years	£503	£402	£604
Nusinersen discontinuation rate and rate of milestone loss	Proportion of arm discontinuing nusinersen in C state	3.0%	2.4%	3.6%
	Proportion of arm discontinuing nusinersen in D state	3.0%	2.4%	3.6%
	Rate of milestone loss for patients that discontinue nusinersen: state C	90.0%	72.0%	100.0%

Category	Variable	Base case	Low value	High value
	Rate of milestone loss for patients that discontinue nusinersen: state D	90.0%	72.0%	100.0%
Onasemnogene abeparvovec costs	Onasemnogene abeparvovec drug acquisition cost: indicative price only; AveXis planning assumption	£1,674,500	£1,339,600	£2,009,400
	Onasemnogene abeparvovec administration cost	£2,425	£1,940	£2,910
Quality of Life adjustments	Utility: E state	0.190	0.152	0.228
	Utility: D state	0.190	0.152	0.228
	Utility: state C	0.600	0.480	0.720
	Utility: B and A state: age 0–24 years	0.954	0.763	1.000
	Utility: B and A state: age 25–34 years	0.925	0.740	1.000
	Utility: B and A state: age 35–44 years	0.899	0.720	1.000
	Utility: B and A state: age 45–54 years	0.867	0.694	1.000
	Utility: B and A state: age 55-–64 years	0.829	0.663	0.994
	Utility: B and A state: age 65–74 years	0.783	0.626	0.940
	Utility: B and A state: age ≥75 years	0.685	0.548	0.822
Survival limits	Survival limit (years) for E state	16.0	12.8	19.2
	Survival limit (proportion of remaining population) for D state	25.0%	20.0%	30.0%

Abbreviations: GP, general practitioner; SMA, spinal muscular atrophy.

12.4.3.2 Values used in other sensitivity analyses

We examined the impact on the onasemnogene abeparvovec versus BSC and onasemnogene abeparvovec versus nusinersen ICERs via numerous variations to the underlying data and assumptions, including:

Discount rates:

- Costs and effects at 0%;
- Costs and effects at 5%;
- Costs at 0%, effects at 5%;
- Costs at 5%, effects at 0%;
- Costs and effects at 1.5%.

Cost assumptions:

- Replacing the base case health state costs with the 'Real World Evidence (RWE)' costs presented at the nusinersen NICE third appraisal committee meeting (ACM3) (144). Values used were:
    - 'SMA type 1' costs of £148,214 for the E state and D state
    - 'SMA type 2' costs of £68,322 used as a proxy for the C state
    - 'SMA type 3' costs of £21,765 used as a proxy for the B state
- Replacing the baseline HCRU costs for A state patients (£0) with the base case costs for B state patients (£7,197);
- SMA type 3 costs from the RWE presented at nusinersen ACM3 applied to the B state, other health state costs remain as base case
- SMA type 3 costs from RWE presented at nusinersen ACM3 applied to the A state and B state patients, other health state costs remain as base case
- Pessimistic scenario that the costs of onasemnogene abeparvovec administration are 10X greater than the base case of £2,425 (i.e. £24,250);
- Replacing the nusinersen list price of £75,000 per dose with a [redacted] price reduction [redacted]
- Replacing the nusinersen list price per dose with a value of [redacted] per dose.

Utility values:

- The recent US ICER evaluation of SMA therapies (32) assumed additional 'on-treatment' utility benefits in the treatment arms for achieving interim milestones such as head control, rolling, standing, crawling, etc. This was implemented in the US ICER base case model as a utility of 0.29 for the "not sitting" health state (i.e. an additional utility of 0.1 compared with BSC) and a utility of 0.65 for the "sitting" health

state (i.e. an additional utility of 0.05 compared with BSC). These US ICER on-treatment utility values of 0.1 and 0.05 are applied to the D state and C state, respectively in the treatment arms (onasemnogene abeparvovec and nusinersen) with all other utilities unchanged from base case assumptions

    - Analysis as above but with lower "on-treatment" utilities than used by US ICER. A value of 0.05 was added to the D state (not sitting) and a value of 0.025 was added to the C state (sits unassisted) in the onasemnogene abeparvovec and nusinersen arms;

    - Analysis as above but with higher "on treatment" utilities than used by US ICER. A value of 0.15 was added to the D state (not sitting) and a value of 0.075 was added to the C state (sits unassisted) in the onasemnogene abeparvovec and nusinersen arms;

- The base case values for the C, D and E states were substituted with the utility values derived from the mapping of the PedsQL score in the CHERISH nusinersen study to EQ-5D-Y as described in Section 10.1.9.2: values for these states were 0.878 (B state), 0.764 (C state), 0.756 (D state) and 0.730 (E state);

- The base case values for the C, D and E states were substituted with the utility values derived from the Lloyd et al 2017 Clinician-proxy Case Vignette study as described in Section 10.1.9.2: values for these states were 0.710 (B state), -0.04 (C state), -0.12 (D state) and -0.33 (E state);

- The base case values for the B, C, D and E states were substituted with the utility values derived from the exploratory AveXis UK utilities elicitation study using the TTO results from the 'parent vignettes' as described in as described in Section 10.1.9.2: values for these states were 0.7898 (B state), 0.2628 (C state), -0.2367 (D state) and -0.2634 (E state);

- The impact on the ICERs is explored by removing all utility weightings from all health states (i.e. results are 'cost per life year gained');

- The C state utility value (0.6) is substituted for the B state utility value (age-adjusted, general population utility).

Nusinersen stopping rules:

- Removal of the base case assumption that all nusinersen patients in the E state who have moved directly from the D state would stop receiving nusinersen; i.e. continue with nusinersen for E state patients

- Maintenance of the base case assumption that all nusinersen patients in the E state would stop receiving nusinersen but:

    - Decreased the annual rate of nusinersen discontinuation in the C and D states from 3% (base case) to 0%;

    - Increased the annual rate of nusinersen discontinuation in the C and D states from 3% (base case) to 10%;

Alternative natural history sources

- The NeuroNext natural history cohort (67), which is used to inform overall survival and event-free survival in the D state in the base case is replaced with:
    - Data from Finkel et al. 2017 (ENDEAR sham control) (22);
    - Data from De Sanctis et al. 2016 (PNCR, US and Italy study) (50).

Exploratory scenarios

Several exploratory analyses of scenarios are conducted – some optimistic and some pessimistic – within the model as follows:

- Improved survival for patients in the C state (sit unassisted):
    - Patients who achieve the C state (sits unassisted) have a life expectancy the same as the general population: applied to onasemnogene abeparvovec arm only
    - Patients who achieve the C state (sits unassisted) have a life expectancy the same as the general population: applied to onasemnogene abeparvovec arm and nusinersen arm
- A pessimistic limited duration of treatment effect for onasemnogene abeparvovec is assumed:
    - At 25 years, patients in the onasemnogene abeparvovec arm begin to lose the benefits of treatment and regress from higher functioning health states to worse functioning health states, assuming a pessimistic 90% annual probability of regression and move backwards through the health states – further described in Section 12.2.1.2
- Calculation of milestone attainment in the onasemnogene abeparvovec arm after removal of the patients that walked unassisted (n=2) and removal of the patient who did not achieve the 'sits unassisted' milestone (n=1) from START, Cohort 2.
    - How the clinical outcomes observed in the Phase I/IIa START trial will be replicated in UK clinical practice is associated with uncertainty given the continuing evolvement of clinical practice (see Section 12.2.5.2). To test the effect of changing the population on the results of the economic model an analysis was performed which excluded the patients in START with the highest baseline CHOP-INTEND scores (>45), corresponding to the two patients who walked unassisted in START. These patients were considered to be less reflective of those typically treated in current practice in the UK, where patients are likely to have a CHOP-INTEND score of <45 at the time of diagnosis (17). In addition, the patient treated at the age of 7.9 months in START (corresponding to the patient who did not achieve the sitting unassisted milestone in START) was also excluded from this scenario on the basis that treating a patient of this age is not reflective of current clinical practice in England (17). Therefore, two scenarios were conducted:

        - Onasemnogene abeparvovec milestones and associated transition probabilities are based on 9 patients from START, Cohort 2 (removal of the non-sitter [n=1] and walkers [n=2]). All START, Cohort 2 patients (n=12) are used in the base case.
        - Onasemnogene abeparvovec milestones and associated transition probabilities are based on 10 patients from START, Cohort 2 (removal the walkers [n=2]). All START, Cohort 2 patients (n=12) are used in the base case.

- Including caregiver disutility scores
    - This explorative scenario applies a disutility for caregivers that varies by the health state of the patient, drawing data from a proxy, but related, disease – spina bifida – see Section 10.1.9.2 for details. A study by Tilford et al. 2005 (156) compared QWB scale data from the primary caregivers of children aged 0–17 years (n=98) with spina bifida versus a control sample of parents of non-disabled/unaffected children (n=49). Spina bifida children were categorised into three disability levels according to the location of the child's lesion: 1) sacral, 2) lower lumbar and 3) thoracic. When comparing caregivers of spina bifida patients to the control caregiver sample, the 'spill over' disutility of spina bifida caregivers are reported as: -0.03, -0.03 and -0.08 for the sacral, lower lumbar and thoracic lesion groups, respectively. Values were calculated using the method described by Wittenberg et al. 2013 (59). These caregiver disutilities are incorporated into the exploratory scenario analysis as follows: -0.08 for caregivers of a child in the E state (permanent assisted ventilation) or D state (not sitting) and -0.03 for a child in the C state (sits unassisted).

- Adjusting the overall survival and event-free survival observed in the START trial
    - Based on interim data from ongoing Phase III trials, it is acknowledged that in real world clinical practice a proportion of patients on onasemnogene abeparvovec in the D state (not sitting) may die in the short-term model. Therefore, an additional scenario analysis is included to model 95% overall survival and 95% event-free survival at cycle 2 in the D state for onasemnogene abeparvovec to reflect data from ongoing Phase III trials: Overall survival remains extremely high; of the 77 patients dosed with onasemnogene abeparvovec via a single IV infusion in the clinical trial programme (START, STR1VE-EU, STR1VE-US, and SPR1NT) and for whom data were reported in the latest data cut (8 March 2019), 75 (97.4%) are alive – see Section 12.2.1.3 for details.

12.4.3.3 Values used in the multi-way sensitivity analyses

Multi-way sensitivity analysis

For the multi-way sensitivity analysis, the three variables with the largest impact on the results (excluding the cost of onasemnogene abeparvovec and the cost of nusinersen) were taken/combined from the one way sensitivity results for onasemnogene abeparvovec versus

BSC and for onasemnogene abeparvovec versus nusinersen (Table 80 and Table 81). From the onasemnogene abeparvovec versus BSC analysis these are: i) the cost of hospitalisations for E state patients, ii) the cost of hospitalisations for C state patients and, iii) the patient utility value of the C state. For the onasemnogene abeparvovec versus nusinersen analysis these are: i) the cost of hospitalisations for E state patients, ii) the cost of hospitalisations for C state patients and, iii) the survival limit placed on PAV in the E state. The two multi-way analyses, therefore used the following sets of values for the two comparisons. For each variable we varied the value by +/- 20%.

Table 80: Variables used in multi-way scenario-based sensitivity analysis (onasemnogene abeparvovec versus BSC)

Variable	*Cost of hospitalisations for E state*	*Cost of hospitalisations for C state*	*Patient utility value for C state*
Base case value	£211,235	£37,420	0.6
Base case * 0.8	£168,988	£29,936	0.48
Base case * 1.2	£253,482	£44,904	0.72

Table 81: Variables used in multi-way scenario-based sensitivity analysis (onasemnogene abeparvovec versus nusinersen)

Variable	*Cost of hospitalisations for E state*	*Cost of hospitalisations for C state*	**Survival limit on the E state (years)**
Base case value	£211,235	£37,420	16.0
Base case * 0.8	£168,988	£29,936	12.8
Base case * 1.2	£253,482	£44,904	19.2

Probabilistic Sensitivity Analysis

Variables included in the Probabilistic Sensitivity Analysis (PSA) are shown below in Table 82. For full details of how the best fitting survival curve parameters, and associated transition probabilities, are incorporated into the PSA please consult Appendix 8**.**

Table 82: Values used in the probabilistic sensitivity analysis

Category	Variable	Base case	Distribution
Annual SMA-care health state costs	E state: drug costs	£636	Gamma distribution with a standard error of 20%
	E state: medical tests	£225	
	E state: medical visits	£2,690	
	E state: hospitalisations	£211,235	
	E state: GP & emergency	£293	
	E state: health materials	£2,903	
	E state: social services	£46,738	
	D state: drug costs	£919	
	D state: medical tests	£325	
	D state: medical visits	£3,890	
	D state: hospitalisations	£66,988	
	D state: GP & emergency	£423	
	D state: health materials	£3,936	
	D state: social services	£27,896	
	C state: drug costs	£743	
	C state: medical tests	£311	
	C state: medical visits	£2,247	
	C state: hospitalisations	£37,420	
	C state: GP & emergency	£176	
	C state: health materials	£2,046	

Category	Variable	Base case	Distribution
	C state: social services	£18,598	
	B state: drug costs	£939	
	B state: medical tests	£277	
	B state: medical visits	£1,899	
	B state: hospitalisations	£468	
	B state: GP & emergency	£71	
	B state: health materials	£591	
	B state: social services	£2,952	
Nusinersen costs, administration costs and location	Technology acquisition cost, per vial	£75,000	Value fixed in PSA
	Inpatient lumbar puncture: Aged ≤5 years	£1,502	Gamma distribution with SE of 20%
	Inpatient lumbar puncture: Aged 6–18 years	£1,474	
	Inpatient lumbar puncture: Aged ≥19 years	£843	
	Outpatient lumbar puncture: Aged ≤5 years	£417	
	Outpatient lumbar puncture: Aged 6–18 years	£435	
	Outpatient lumbar puncture: Aged ≥19 years	£294	
	Day case lumbar puncture: Aged ≤5 years	£1,389	
	Day case lumbar puncture: Aged 6–18 years	£1,014	
	Day case lumbar puncture: Aged ≥19 years	£503	
	% of patients having an elective inpatient procedure (all age groups)	40%	Dirichlet – gamma distribution
	% of patients having an outpatient procedure (all age groups)	30%	
	% of patients having a day case procedure (all age groups)	30%	

Category	Variable	Base case	Distribution
Discontinuation rate and milestone loss: nusinersen arm	Rate of milestone loss for patients that discontinue nusinersen: C state	90.00%	Beta distribution with SE of 20%
	Rate of milestone loss for patients that discontinue nusinersen: D state	90.00%	
	Proportion of arm discontinuing nusinersen in C state	3.00%	
	Proportion of arm discontinuing nusinersen in D state	3.00%	
	Proportion of arm discontinuing nusinersen in E state	100%	Fixed in PSA
Onasemnogene abeparvovec costs	Onasemnogene abeparvovec drug acquisition cost: indicative price only; AveXis planning assumption	£1,674,500	Fixed in PSA
	Onasemnogene abeparvovec administration cost	£2,425	Gamma distribution with SE of 20%
Quality of Life adjustments	Utility: E state	0.190	Gamma distribution with SE of 5%
	Utility: D state	0.190	
	Utility: C state	0.600	
	Utility: B and A state: age 0–24 years	0.954	Beta distribution with SE of 5%
	Utility: B and A state: age 25–34 years	0.925	
	Utility: B and A state: age 35–44 years	0.899	
	Utility: B and A state: age 45–54 years	0.867	
	Utility: B and A state: age 55–-64 years	0.829	
	Utility: B and A state: age 65–74 years	0.783	
	Utility: B and A state: age ≥75 years	0.685	
Survival limits	Survival limit (years) for E state	16	Gamma distribution with SE of 20%
	Survival limit (proportion of remaining population) for D state	25%	Beta distribution with SE of 20%
	E state OS: Gompertz distribution: shape	-0.0194	

Category	Variable	Base case	Distribution
Survival curve parameters	E state OS: Gompertz distribution: rate	0.0093	Cholesky decomposition. For full details of how the best fitting survival curve parameters, and associated transition probabilities, are incorporated into the PSA please consult Appendix 8.
	D state OS: generalised gamma: mu	1.7148	
	D state OS: generalised gamma: sigma	0.4624	
	D state OS: generalised gamma: q	-3.5961	
	D state EFS: generalised gamma: mu	1.7054	
	D state EFS: generalised gamma: sigma	0.3847	
	D state EFS: generalised gamma: q	-2.8686	
	State C: generalised gamma: mu	6.35646	

Abbreviations: EFS, event-free survival; GP, general practitioner; OS, overall survival.

12.4.4 If any parameters or variables listed above were omitted from the sensitivity analysis, provide the rationale.

Not applicable. All relevant parameters were included in the 1-way sensitivity analysis, multi-way sensitivity analysis, scenario sensitivity analysis, or probabilistic sensitivity analysis as described in Section 12.4.3.

12.5 *Results of economic analysis*

Section 12.5 requires the sponsor to report the economic analysis results. These should include the following:

- costs, quality-adjusted life years (QALYs) and incremental cost per QALY
- the link between clinical- and cost-effectiveness results
- disaggregated results such as life years gained (LYG), costs associated with treatment, costs associated with adverse events, and costs associated with follow-up/subsequent treatment
- results of the sensitivity analysis.

Base-case analysis

12.5.1 When presenting the results of the base case incremental cost effectiveness analysis in the table below, list the interventions and comparator(s) from least to most expensive. Present incremental cost-effectiveness ratios (ICERs) compared with baseline (usually standard care) and then incremental analysis ranking technologies in terms of dominance and extended dominance. If the company has formally agreed a patient access scheme with the Department of Health, present the results of the base-case incremental cost-effectiveness analysis with the patient access scheme. A suggested format is available in table D11.

In the base-case, the ICER for onasemnogene abeparvovec versus BSC is £177,061 per QALY gained and the ICER for nusinersen versus BSC is £1,354,762 per QALY gained. Total and incremental per patient costs, total and incremental life years gained and total and incremental QALYs gained are presented in Table 83. The ICER for onasemnogene abeparvovec versus nusinersen is £35,788 per QALY gained. Costs and effects (QALYs and life years) are discounted at 3.5%.

Table 83: Base case results

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£) (versus BSC)	Incremental LYG (versus BSC)	Incremental QALYs (versus BSC)	ICER (£/QALY) (versus BSC)
BSC	707,836	3.44	0.65	N/A	N/A	N/A	N/A
Nusinersen	2,270,315	6.97	1.81	1,562,479	3.53	1.16	1,354,762
Onasemnogene abeparvovec	2,614,400	18.27	11.42	1,906,564	14.83	10.77	177,061

Abbreviations: BSC, best supportive care; ICER, incremental cost-effectiveness ratio; LYG, life years gained; N/A, not applicable; QALYs, quality-adjusted life years.

12.5.2 For the outcomes highlighted in the decision problem, please provide the corresponding outcomes from the model and compare them with clinically important outcomes such as those reported in clinical trials. Discuss reasons for any differences between modelled and observed results (for example, adjustment for cross-over). Please use the following table format for each comparator with relevant outcomes included.

Not applicable. The economic model uses onasemnogene abeparvovec and nusinersen trial results until the end of their observation periods. After this period the model uses extrapolated results.

12.5.3 Please provide (if appropriate) the proportion of the cohort in the health state over time (Markov trace) for each state, supplying one for each comparator.

Table 84 shows the probability of a patient being in one of the surviving health states or death over time.

Table 84: Probability of a patient being in surviving health states or death over the lifetime of the model by intervention arm

Patients who received onasemnogene abeparvovec						
Year after procedure	**Dead**	**E State (PAV)**	**D State**	**C State**	**B State**	**A State**
1	0.00%	0.00%	100.00%	0.00%	0.00%	0.00%
5	7.98%	2.03%	1.47%	71.89%	16.63%	0.00%
10	12.76%	1.94%	0.00%	68.68%	0.00%	16.62%
25	32.08%	0.00%	0.00%	51.36%	0.00%	16.56%
50	81.22%	0.00%	0.00%	2.67%	0.00%	16.10%
75	87.38%	0.00%	0.00%	0.00%	0.00%	12.63%
100	99.71%	0.00%	0.00%	0.00%	0.00%	0.29%
Patients who received BSC						
Year after procedure	**Dead**	**E State (PAV)**	**D State**	**C State**	**B State**	**A State**
1	43.08%	9.64%	47.27%	0.00%	0.00%	0.00%
5	79.79%	20.21%	0.00%	0.00%	0.00%	0.00%
10	81.77%	18.23%	0.00%	0.00%	0.00%	0.00%
25	100.00%	0.00%	0.00%	0.00%	0.00%	0.00%
50	100.00%	0.00%	0.00%	0.00%	0.00%	0.00%
75	100.00%	0.00%	0.00%	0.00%	0.00%	0.00%
100	100.00%	0.00%	0.00%	0.00%	0.00%	0.00%

Patients who received nusinersen†						
Year after procedure	**Dead**	**E State (PAV)**	**D State**	**C State**	**B State**	**A State**
1	16.60%	15.39%	68.01%	0.00%	0.00%	0.00%
5	46.93%	37.05%	6.81%	9.21%	0.00%	0.00%
10	58.80%	33.42%	0.23%	7.55%	0.00%	0.00%
25	96.31%	0.00%	0.11%	3.58%	0.00%	0.00%
50	99.91%	0.00%	0.00%	0.08%	0.00%	0.00%
75	100.00%	0.00%	0.00%	0.00%	0.00%	0.00%
100	100.00%	0.00%	0.00%	0.00%	0.00%	0.00%

Abbreviations: BSC, best supportive care; PAV, permanent assisted ventilation.
† Technical note for ERG: for nusinersen the percentages in each group are a combination of the percentage in the main health state plus the corresponding discontinued health state e.g. for state C year 5 this equals 8.90 (main C state) plus 0.31 (discontinued C state).

12.5.4 Please provide details of how the model assumes QALYs accrued over time. For example, Markov traces can be used to demonstrate QALYs accrued in each health state over time.

Table 85 shows QALYs accrued over time for a patient treated with onasemnogene abeparvovec, nusinersen or BSC. Note that this is based on the probability of the patient being in each of the health states in each time period. QALYs are discounted at 3.5%.

Table 85: QALYs accrued over time for a patient based on the probability of being in each health state in each time period (discounted at 3.5%)

Patients who received onasemnogene abeparvovec						
Year after procedure	**Total**	**E State (PAV)**	**D State**	**C State**	**B State**	**A State**
1	0.23	0.00	0.23	0.00	0.00	0.00
5	2.14	0.01	0.37	1.31	0.45	0.00
10	4.35	0.02	0.37	2.91	0.45	0.60
25	8.66	0.04	0.37	5.90	0.45	1.90
50	11.00	0.04	0.37	7.20	0.45	2.94
75	11.36	0.04	0.37	7.20	0.45	3.30
100	11.42	0.04	0.37	7.20	0.45	3.36
Patients who received BSC						
Year after procedure	**Total**	**E State (PAV)**	**D State**	**C State**	**B State**	**A State**
1	0.19	0.02	0.17	0.00	0.00	0.00
5	0.39	0.15	0.24	0.00	0.00	0.00
10	0.53	0.29	0.24	0.00	0.00	0.00
25	0.65	0.41	0.24	0.00	0.00	0.00
50	0.65	0.41	0.24	0.00	0.00	0.00
75	0.65	0.41	0.24	0.00	0.00	0.00
100	0.65	0.41	0.24	0.00	0.00	0.00

Patients who received nusinersen†						
Year after procedure	**Total**	**E State (PAV)**	**D State**	**C State**	**B State**	**A State**
1	0.21	0.01	0.20	0.00	0.00	0.00
5	0.79	0.24	0.37	0.18	0.00	0.00
10	1.24	0.50	0.37	0.37	0.00	0.00
25	1.73	0.73	0.37	0.63	0.00	0.00
50	1.81	0.73	0.37	0.71	0.00	0.00
75	1.81	0.73	0.37	0.71	0.00	0.00
100	1.81	0.73	0.37	0.71	0.00	0.00

Abbreviations: BSC, best supportive care; PAV, permanent assisted ventilation.
† Technical note for ERG: for nusinersen the percentages in each group are a combination of the QALYs in the main health state plus the corresponding discontinued health state e.g. for state C at 10 years this equals 0.35 (main C state) plus 0.01 (discontinued C state).

12.5.5 Please indicate the life years (LY) and QALYs accrued for each clinical outcome listed for each comparator. For outcomes that are a combination of other states, please present disaggregated results. For example:

The disaggregation of accrued LYs and QALYs is presented in Table 86. Note that results are discounted at 3.5% and with half cycle correction.

Table 86: Model outputs by clinical outcomes (discounted at 3.5%)

Patients who received onasemnogene abeparvovec		
Outcome	**Life years**	**QALYs**
E State (PAV)	0.19	0.03
D state	1.94	0.37
C State	12.00	7.20
B State	0.47	0.45
A State	3.66	3.36
TOTAL	18.27	11.42
Patients who received BSC		
Outcome	**Life years**	**QALYs**
E State (PAV)	2.18	0.41
D state	1.26	0.24
C State	0	0
B State	0	0
A State	0	0
TOTAL	3.44	0.65

Patients who received nusinersen		
Outcome	**Life years**	**QALYs**
E State (PAV)	3.83	0.73
D state	1.96	0.37
C State	1.18	0.71
B State	0	0
A State	0	0
TOTAL	6.97	1.81

Abbreviations: BSC, best supportive care; LYG, life years gained; PAV, permanent assisted ventilation; QALYs, quality-adjusted life years.

12.5.6 Please provide details of the disaggregated incremental QALYs by health state. Suggested formats are presented below.

The disaggregation of incremental QALYs by health state are presented in Table 87 and Table 88. Onasemnogene abeparvovec provides large incremental QALY gains: 10.76 QALYs when compared with BSC and 9.61 QALYs when compared with nusinersen. Over 90% of the QALY gains for onasemnogene abeparvovec compared with BSC are due to gains in the C and A states whilst just under 90% of the QALY gains for onasemnogene abeparvovec compared with nusinersen are due to gains in the C and A states.

Table 87: Summary of QALY gain differences by health state (onasemnogene abeparvovec versus BSC) – discounted

Outcome	QALYs onasemnogene abeparvovec	QALYs BSC	Increment	Absolute increment	% absolute increment
E State (PAV)	0.03	0.41	-0.38	0.38	3.30
D state	0.37	0.24	0.13	0.13	1.13
C State	7.20	0.00	7.20	7.20	62.50
B State	0.45	0.00	0.45	0.45	3.91
A State	3.36	0.00	3.36	3.36	29.17
TOTAL	11.42	0.65	10.76	11.52	100

Abbreviations: BSC, best supportive care; PAV, permanent assisted ventilation; QALYs, quality-adjusted life years.

Table 88: Summary of QALY gain differences by health state (onasemnogene abeparvovec versus nusinersen) – discounted

Outcome	QALYs onasemnogene abeparvovec	QALYs nusinersen	Increment	Absolute increment	% absolute increment
E State (PAV)	0.03	0.73	-0.70	0.70	6.38
D state	0.37	0.37	0.000	0.000	0.00
C State	7.20	0.71	6.49	6.49	59.11
B State	0.45	0.00	0.45	0.45	4.10
A State	3.36	0.00	3.36	3.36	30.60
TOTAL	11.42	1.81	9.61	10.98	100

Abbreviations: BSC, best supportive care; PAV, permanent assisted ventilation; QALYs, quality-adjusted life years.

12.5.7 Please provide undiscounted incremental QALYs for the intervention compared with each comparator

Table 89 shows the undiscounted incremental QALYs for the intervention compared with each comparator.

Table 89: Undiscounted QALYs gained from onasemnogene abeparvovec and comparators and incremental QALYs gained from onasemnogene abeparvovec over comparators

Intervention	QALYs from intervention	Incremental QALYs (onasemnogene abeparvovec over comparator)
Onasemnogene abeparvovec	25.05	N/A
Nusinersen	2.52	22.53
BSC	0.80	24.25

Abbreviations: BSC, best supportive care; N/A, not applicable; QALYs, quality-adjusted life years.

12.5.8 Provide details of the costs for the technology and its comparator by category of cost. A suggested format is presented in table D12.

Table 90 shows the costs of onasemnogene abeparvovec and BSC by category of costs. Of the total increase in costs, over 84% are for the technology cost of onasemnogene abeparvovec with 15% for increased SMA treatment/care costs for patients due to increased survival.

Table 91 shows the costs of onasemnogene abeparvovec and nusinersen by category of costs. Of the total absolute incremental increase in costs, over 68% are for the technology cost of onasemnogene abeparvovec. Mean SMA treatment/care costs are 23% lower with onasemnogene abeparvovec than nusinersen (£994,183 versus £1,291,349, respectively).

Table 90: Costs of onasemnogene abeparvovec and comparator by category of cost (onasemnogene abeparvovec versus BSC) (discounted at 3.5%)*

Item	Cost onasemnogene abeparvovec	Cost BSC	Increment	Absolute increment	% absolute increment
Technology cost	£1,617,874	£0	£1,617,874	£1,617,874	84.86
Mean total SMA treatment cost (all care costs)	£994,183	£707,836	£286,346	£286,346	15.02
Administration cost of the technology	£2,343	£0	£2,343	£2,343	0.12
Total	£2,614,400	£707,836	£1,906,564	£1,906,564	100%

Abbreviations: BSC, best supportive care; SMA, spinal muscular atrophy. *Values are reported as per the economic model, discrepancies are due to rounding.

Table 91: Costs of onasemnogene abeparvovec and comparator by category of cost (onasemnogene abeparvovec versus nusinersen) (discounted at 3.5%)

Item	Cost onasemnogene abeparvovec	Cost nusinersen	Increment	Absolute increment	% absolute increment
Technology cost	£1,617,874	£964,907	£652,967	£658,728	68.08
Mean total SMA treatment cost (all care costs)	£994,183	£1,291,349	-£297,166	£297,166	30.71
Administration cost of the technology	£2,343	£14,059	-£11,716	£11,716	1.21
Total	£2,614,400	£2,270,315	£344,085	£967,610	100%

Abbreviations: SMA, spinal muscular atrophy.

12.5.9 If appropriate, provide details of the costs for the technology and its comparator by health state. A suggested format is presented in table D13.

Table 92 and Table 93 show the total costs for onasemnogene abeparvovec by health state versus BSC and versus nusinersen respectively. Note that costs include the costs of the technology (onasemnogene abeparvovec), comparator (nusinersen) and SMA care costs incurred whilst in the health state.

Note also that since onasemnogene abeparvovec is a one-time, single IV treatment we have allocated the discounted cost of onasemnogene abeparvovec and administration between the health states by the proportion of the total (discounted) life years gained by health state. For example, since the 'D' state for onasemnogene abeparvovec produces 1.94 of the total (discounted) 18.27 life years gained we have allocated 10.62% (1.94/18.27) of the total onasemnogene abeparvovec and administration costs to the 'D' state.

Table 92: Total costs of onasemnogene abeparvovec and BSC by health state (discounted at 3.5%)

Health state	Cost onasemnogene abeparvovec	Cost BSC	Increment	Absolute increment	% absolute increment
E state (PAV)	£65,903	£576,220	-£510,317	£510,317	17.43
D state	£375,119	£131,616	£243,503	£243,503	8.32
C state	£1,803,512	£0	£1,803,512	£1,803,512	61.61
B state	£45,113	£0	£45,113	£45,113	1.54
A state	£324,753	£0	£324,753	£324,753	11.09
Total	£2,614,400	£707,836	£1,906,564	£2,927,198	100%*

Abbreviations: BSC, best supportive care; PAV, permanent assisted ventilation.
*Values are reported as per the economic model, discrepancies are due to rounding.

Table 93: Total costs of onasemnogene abeparvovec and nusinersen by health state (discounted at 3.5%)

Health state	Cost onasemnogene abeparvovec	Cost nusinersen	Increment	Absolute increment	% absolute increment
E state (PAV)	£65,903	£1,014,029	-£948,126	£948,126	28.39
D state	£375,119	£924,557	-£549,438	£549,438	16.45
C state	£1,803,512	£331,728	£1,471,784	£1,471,784	44.08
B state	£45,113	£0	£45,113	£45,113	1.35
A state	£324,753	£0	£324,753	£324,753	9.73
Total	£2,614,400	£2,270,315	£344,085	£3,339,214	100%

Abbreviations: PAV, permanent assisted ventilation.

12.5.10 If appropriate, provide details of the costs for the technology and its comparator by adverse event. A suggested format is provided in table D14.

Adverse events are not included in the model: see Section 12.3.8.

Sensitivity analysis results

12.5.11 Present results of deterministic one-way sensitivity analysis of the variables described in table D10.1.

Figure 45 shows the impact on the ICER from the one-way sensitivity analysis for onasemnogene abeparvovec versus BSC: results in table format are shown in Table 94. All variables were varied by +/- 20% or natural limits if these were within the +/- 20% range.

These results are discussed in Section 12.5.14.

Figure 45: Tornado diagram of impact of the one-way sensitivity analysis (+/- 20% or natural limit) on the ICER (onasemnogene abeparvovec versus BSC) – top 20 results only

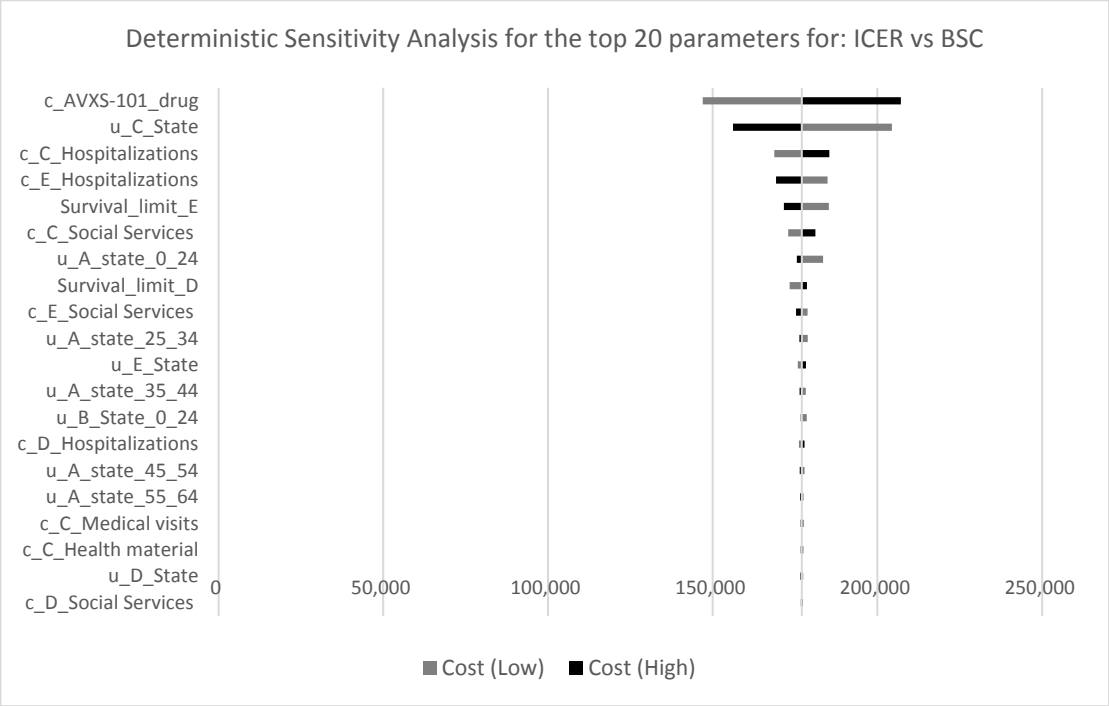


Table 94: Impact of the one-way sensitivity analysis (+/- 20% or natural limit) on the ICER (onasemnogene abeparvovec versus BSC) – top 20 results only

Parameter Description		Low	High	ICER (Low)	ICER (High)	Range	Low % Change	High % Change
1	c_AVXS-101_drug	1,339,600.00	2,009,400.00	147,011	207,111	60,100	17%	17%
2	u_C_State	0.48	0.72	204,406	156,169	48,237	15%	12%
3	c_C_Hospitalizations	29,936.00	44,904.00	168,718	185,404	16,687	5%	5%
4	c_E_Hospitalizations	168,988.00	253,482.00	184,874	169,248	15,627	4%	4%
5	Survival_limit_E	12.80	19.20	185,256	171,605	13,650	5%	3%
6	c_C_Social Services	14,878.40	22,317.60	172,914	181,208	8,293	2%	2%
7	u_A_state_0_24	0.76	1.00	183,521	175,557	7,964	4%	1%
8	Survival_limit_D	0.20	0.30	173,392	178,620	5,228	2%	1%
9	c_E_Social Services	37,390.40	56,085.60	178,790	175,332	3,458	1%	1%
10	u_A_state_25_34	0.74	1.00	178,847	176,346	2,501	1%	0%
11	u_E_State	0.15	0.23	175,825	178,314	2,489	1%	1%
12	u_A_state_35_44	0.72	1.00	178,278	176,388	1,890	1%	0%
13	u_B_State_0_24	0.76	1.00	178,559	176,700	1,859	1%	0%
14	c_D_Hospitalizations	53,590.40	80,385.60	176,210	177,912	1,701	0%	0%
15	u_A_state_45_54	0.69	1.00	177,876	176,443	1,433	0%	0%
16	u_A_state_55_64	0.66	0.99	177,589	176,536	1,052	0%	0%
17	c_C_Medical visits	1,797.60	2,696.40	176,560	177,562	1,002	0%	0%
18	c_C_Health material	1,636.80	2,455.20	176,605	177,517	912	0%	0%
19	u_D_State	0.15	0.23	177,489	176,635	854	0%	0%
20	c_D_Social Services	22,316.80	33,475.20	176,707	177,415	709	0%	0%

Abbreviations: ICER, incremental cost effectiveness ratio.

Figure 46 below shows the impact on the ICER from the one-way sensitivity analysis for onasemnogene abeparvovec versus nusinersen: results in table format are shown in Table 95. All variables were varied by +/- 20% or natural limits if these were within the +/- 20% range.

These results are discussed in Section 12.5.14.

Figure 46: Tornado diagram of impact of the one-way sensitivity analysis (+/- 20% or natural limit) on the ICER (onasemnogene abeparvovec versus nusinersen) – top 20 results only

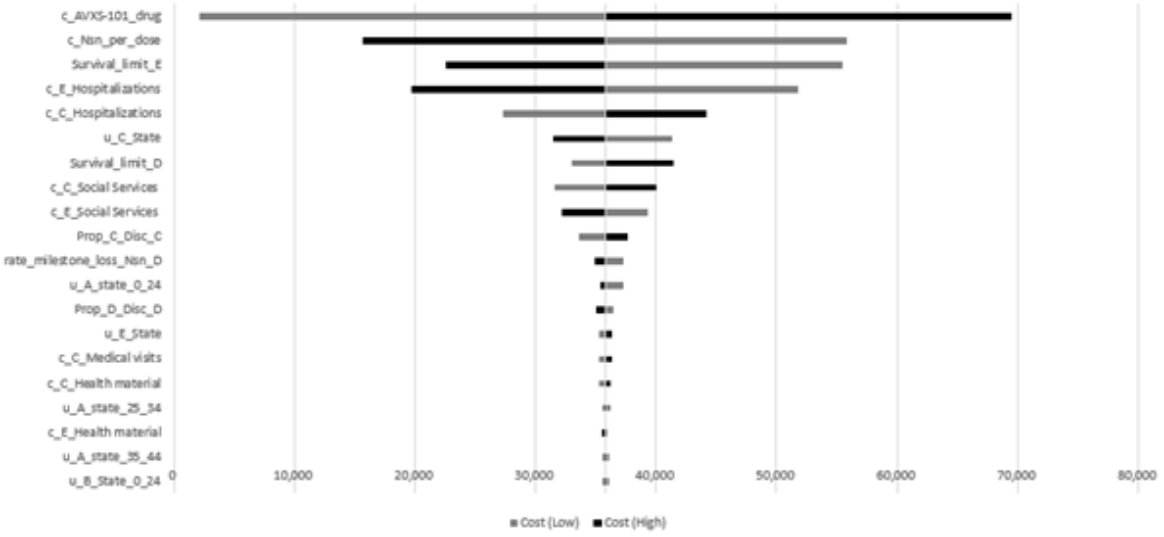


Table 95: Impact of the one-way sensitivity analysis (+/- 20% or natural limit) on the ICER (onasemnogene abeparvovec versus nusinersen) – top 20 results only

Parameter Description		Low	High	Cost (Low)	Cost (High)	Range	Low % Change	High % Change
1	c_AVXS-101_drug	1,339,600.00	2,009,400.00	2,133	69,443	67,310	94%	94%
2	c_Nsn_per_dose	60,000.00	90,000.00	55,860	15,716	40,144	56%	56%
3	Survival_limit_E	12.80	19.20	55,429	22,541	32,888	55%	37%
4	c_E_Hospitalizations	168,988.00	253,482.00	51,806	19,770	32,036	45%	45%
5	c_C_Hospitalizations	29,936.00	44,904.00	27,359	44,217	16,857	24%	24%
6	u_C_State	0.48	0.72	41,381	31,527	9,853	16%	12%
7	Survival_limit_D	0.20	0.30	32,988	41,398	8,410	8%	16%
8	c_C_Social Services	14,878.40	22,317.60	31,599	39,977	8,378	12%	12%
9	c_E_Social Services	37,390.40	56,085.60	39,332	32,244	7,088	10%	10%
10	Prop_C_Disc_C	0.02	0.04	33,624	37,699	4,075	6%	5%
11	rate_milestone_loss_Nsn_D	0.72	1.00	37,285	34,928	2,358	4%	2%
12	u_A_state_0_24	0.76	1.00	37,257	35,448	1,809	4%	1%
13	Prop_D_Disc_D	0.02	0.04	36,518	35,088	1,430	2%	2%
14	u_E_State	0.15	0.23	35,280	36,311	1,031	1%	1%
15	c_C_Medical visits	1,797.60	2,696.40	35,282	36,294	1,012	1%	1%
16	c_C_Health material	1,636.80	2,455.20	35,327	36,249	922	1%	1%
17	u_A_state_25_34	0.74	1.00	36,193	35,626	567	1%	0%
18	c_E_Health material	2,322.40	3,483.60	36,008	35,568	440	1%	1%
19	u_A_state_35_44	0.72	1.00	36,064	35,636	428	1%	0%
20	u_B_State_0_24	0.76	1.00	36,128	35,706	421	1%	0%

Abbreviations: ICER, incremental cost effectiveness ratio.

Table 96 presents further sensitivity analyses. Results show the impact of changing various assumptions on discount rates, cost assumptions, utility values, nusinersen stopping rules, alternative natural history sources and exploratory scenarios.

These sensitivity analyses and scenarios are described in more detail in Section 12.4.3.2 and the results are discussed in Section 12.5.14.

Table 96: Further sensitivity analysis results and scenarios: impact on ICER for onasemnogene abeparvovec versus. BSC and onasemnogene abeparvovec versus nusinersen*

	Onasemnogene abeparvovec	BSC	Nusinersen	ICERs
Base case results	Costs: £2,614,400 QALYs: 11.42	Costs:£707,836 QALYs: 0.65	Costs: £2,270,315 QALYs: 1.81	ON-A vs BSC: £177,061 ON-A vs. Nus: £35,788
DISCOUNT RATES				
Costs and effects at 0%	Costs: £3,313,258 QALYs: 25.05	Costs: £902,516 QALYs: 0.80	Costs: £2,867,523 QALYs: 2.52	ON-A vs BSC: £99,423 ON-A vs. Nus: £19,788
Costs and effects at 5%	Costs: £2,439,873 QALYs: 8.99	Costs: £644,590 QALYs: 0.61	Costs: £2,089,092 QALYs: 1.61	ON-A vs BSC: £214,158 ON-A vs. Nus: £47,514
Costs at 0%, effects at 5%	Costs: £3,313,258 QALYs: 8.99	Costs: £902,516 QALYs: 0.61	Costs: £2,867,523 QALYs: 1.61	ON-A vs BSC: £287,575 ON-A vs. Nus: £60,375
Costs at 5%, effects at 0%	Costs: £2,439,873 QALYs: 25.05	Costs: £644,590 QALYs: 0.80	Costs: £2,089,092 QALYs: 2.52	ON-A vs BSC: £74,040 ON-A vs. Nus: £15,572
Costs and effects at 1.5%	Costs: £2,945,007 QALYs: 17.02	Costs: £809,684 QALYs: 0.73	Costs: £2,574,275 QALYs: 2.16	ON-A vs BSC: £131,083 ON-A vs. Nus: £24,949
COST ASSUMPTIONS				
Use of RWE costs (scenario with SMA type 1 costs doubled) presented at the nusinersen NICE ACM3	Costs: £2,766,367 QALYs: 11.42	Costs: £509,513 QALYs: 0.65	Costs: £1,918,080 QALYs: 1.81	ON-A vs BSC: £209,592 ON-A vs. Nus: £88,230
Base case costs for B state patients also applied to A state patients	Costs: £2,640,767 QALYs: 11.42	Costs: £707,836 QALYs: 0.65	Costs: £2,270,315 QALYs: 1.81	ON-A vs BSC: £179,510 ON-A vs. Nus: £38,530
SMA type 3 costs from the RWE presented at nusinersen ACM3 applied to the B state, other health state costs remain as base case	Costs: £2,621,301 QALYs: 11.42	Costs: £707,836 QALYs: 0.65	Costs: £2,270,315 QALYs: 1.81	ON-A vs BSC: £177,702 ON-A vs. Nus: £36,506
SMA type 3 costs from RWE presented at nusinersen ACM3 applied to the A state and B state patients, other health state costs remain as base case	Costs: £2,701,040 QALYs: 11.42	Costs: £707,836 QALYs: 0.65	Costs: £2,270,315 QALYs: 1.81	ON-A vs BSC: £185,107 ON-A vs. Nus: £44,799

	Onasemnogene abeparvovec	BSC	Nusinersen	ICERs
Cost of onasemnogene abeparvovec administration 10x higher than base case	Costs: £2,635,487 QALYs: 11.42	Costs: £707,836 QALYs: 0.65	Costs: £2,270,315 QALYs: 1.81	ON-A vs BSC: £179,019 ON-A vs. Nus: £37,981
Nusinersen at [redacted] of list price [redacted]	Costs: £2,614,400 QALYs: 11.42	Costs: £707,836 QALYs: 0.65	Costs: £1,787,861 QALYs: 1.81	ON-A vs BSC: £177,061 ON-A vs. Nus: £85,968
Nusinersen at [redacted] per dose	Costs: £2,614,400 QALYs: 11.42	Costs: £707,836 QALYs: 0.65	Costs: £1,305,408 QALYs: 1.81	ON-A vs BSC: £177,061 ON-A vs. Nus: £136,147
UTILITY VALUES				
On-treatment utility as per US ICER (0.1 for D state; 0.05 for C state)	Costs: £2,614,400 QALYs: 12.22	Costs: £707,836 QALYs: 0.65	Costs: £2,270,315 QALYs: 2.06	ON-A vs BSC: £164,892 ON-A vs. Nus: £33,886
On-treatment utility using lower values than US ICER (0.05 for D state; 0.025 for C state)	Costs: £2,614,400 QALYs: 11.82	Costs: £707,836 QALYs: 0.65	Costs: £2,270,315 QALYs: 1.93	ON-A vs BSC: £170,763 ON-A vs. Nus: £34,812
On-treatment utility using higher values than US ICER (0.15 for D state; 0.075 for C state)	Costs: £2,614,400 QALYs: 12.61	Costs: £707,836 QALYs: 0.65	Costs: £2,270,315 QALYs: 2.19	ON-A vs BSC: £159,412 ON-A vs. Nus: £33,009
Using CHERISH values	Costs: £2,614,400 QALYs: 14.55	Costs: £707,836 QALYs: 2.54	Costs: £2,270,315 QALYs: 5.18	ON-A vs BSC: £158,717 ON-A vs. Nus: £36,701
Using Lloyd vignette study	Costs: £2,614,400 QALYs: 2.92	Costs: £707,836 QALYs: -0.87	Costs: £2,270,315 QALYs: -1.55	ON-A vs BSC: £502,601 ON-A vs. Nus: £76,968
Using exploratory AveXis UK utilities elicitation study using the TTO results from the 'parent' vignettes for states B to E	Costs: £2,614,400 QALYs: [redacted]	Costs: £707,836 QALYs: -0.87	Costs: £2,270,315 QALYs: [redacted]	ON-A vs BSC: £262,843 ON-A vs. Nus: £45,595
No utility weights (cost per life year gained)	Costs: £2,614,400 Life years: 18.27	Costs: £707,836 Life years: 3.44	Costs: £2,270,315 Life years: 6.97	ON-A vs BSC: £128,529 ON-A vs. Nus: £30,446
The C state utility value (0.6) is substituted for the B state utility value (age-adjusted, general population utility)	Costs: £2,614,400 Life years: 11.25	Costs: £707,836 Life years: 0.65	Costs: £2,270,315 Life years: 1.81	ON-A vs BSC: £179,859 ON-A vs. Nus: £36,423
NUSINERSEN STOPPING RULES				
Continue with nusinersen for E state patients	Costs: £2,614,400 QALYs: 11.42	Costs: £707,836 QALYs: 0.65	Costs: £2,971,567 QALYs: 1.81	ON-A vs BSC: £177,061 ON-A vs. Nus: -£37,149

	Onasemnogene abeparvovec	BSC	Nusinersen	ICERs
E state patients stopped as per base case but annual rate of nusinersen discontinuation in the C and D states decreased from 3% (base case) to 0%;	Costs: £2,614,400 QALYs: 11.42	Costs: £707,836 QALYs: 0.65	Costs: £2,395,917 QALYs: 2.15	ON-A vs BSC: £177,061 ON-A vs. Nus: £23,567
E state patients stopped as per base case but annual rate of nusinersen discontinuation in the C and D states increased from 3% (base case) to 10%;	Costs: £2,614,400 QALYs: 11.42	Costs: £707,836 QALYs: 0.65	Costs: £2,227,605 QALYs: 1.55	ON-A vs BSC: £177,061 ON-A vs. Nus: £39,179
ALTERNATIVE NATURAL HISTORY SOURCE				
Use of Finkel et al. 2017a (ENDEAR sham control)	Costs: £2,586,021 QALYs: 11.58	Costs: £931,032 QALYs: 0.85	Costs: £2,154,735 QALYs: 1.72	ON-A vs BSC: £154,235 ON-A vs. Nus: £43,750
Use of De Sanctis et al. 2016 (PNCR, US and Italy study)	Costs: £2,663,863 QALYs: 11.61	Costs: £1,604,377 QALYs: 1.31	Costs: £2,446,943 QALYs: 1.97	ON-A vs BSC: £100,499 ON-A vs. Nus: £16,922
EXPLORATORY SCENARIOS				
Patients in the C state (sits unassisted) have a life expectancy the same as the general population: applied to onasemnogene abeparvovec arm only	Costs: £2,999,317 QALYs: 15.18	Costs: £707,836 QALYs: 0.65	Costs: £2,270,315 QALYs: 1.81	ON-A vs BSC: £157,729 ON-A vs. Nus: £54,506
Patients in the C state (sits unassisted) have a life expectancy the same as the general population: applied to onasemnogene abeparvovec arm and nusinersen arm	Costs: £2,999,317 QALYs: 15.18	Costs: £707,836 QALYs: 0.65	Costs: £2,350,285 QALYs: 1.98	ON-A vs BSC: £157,729 ON-A vs. Nus: £49,153
Limited duration of effect for onasemnogene abeparvovec: begins at 25 years	Costs: £2,524,827 QALYs: 9.01	Costs: £707,836 QALYs: 0.65	Costs: £2,270,315 QALYs: 1.81	ON-A vs BSC: £217,504 ON-A vs. Nus: £35,346
Onasemnogene abeparvovec milestones and associated transition probabilities are based on 9 patients from START, Cohort 2 (removal of the non-sitter [n=1] and walkers [n=2]).	Costs: £2,812,729 QALYs: 9.89	Costs: £707,836 QALYs: 0.65	Costs: £2,270,315 QALYs: 1.81	ON-A vs BSC: £227,878 ON-A vs. Nus: £67,100
Onasemnogene abeparvovec milestones and associated transition probabilities are based on 10 patients from START, Cohort 2 (removal the walkers [n=2]).	Costs: £2,775,239 QALYs: 9.00	Costs: £707,836 QALYs: 0.65	Costs: £2,270,315 QALYs: 1.81	ON-A vs BSC: £247,706 ON-A vs. Nus: £70,198
Caregiver disutility scores included	Costs: £2,614,400 QALYs: 10.89	Costs: £707,836 QALYs: 0.38	Costs: £2,270,315 QALYs: 1.31	ON-A vs BSC: £181,364 ON-A vs. Nus: £35,906

	Onasemnogene abeparvovec	BSC	Nusinersen	ICERs
Survival adjustment: 95% OS and 95% EFS at cycle 2 in the D state for onasemnogene abeparvovec	Costs: £2,568,517 QALYs: 10.86	Costs: £707,836 QALYs: 0.65	Costs: £2,270,315 QALYs: 1.81	ON-A vs BSC: £182,352 ON-A vs. Nus: £32,949

Abbreviations: ACM3, third appraisal committee meeting; BSC, best supportive care; EFS, event-free survival; ICER, incremental cost effectiveness ratio; Nus, nusinersen; ON-A, onasemnogene abeparvovec; OS, overall survival; PNCR, Pediatric Neuromuscular Clinical Research; QALY, quality-adjusted life-year; RWE, real-world evidence; UK, United Kingdom; US, United States; vs. versus. *Values are reported per the economic model, discrepancies are due to rounding.

12.5.12 Present results of deterministic multi-way scenario sensitivity analysis described in table D10.2.

Table 97 and Table 98 below present the results of a three-way sensitivity analysis.

From the one-way sensitivity results for onasemnogene abeparvovec versus BSC we took the three variables with the largest impact on the results (excluding the cost of onasemnogene abeparvovec). These are: i) the cost of hospitalisations for E state patients, ii) the cost of hospitalisations for C state patients and, iii) the C state patient utility value. The tables show the results of varying these parameters in combination by the same percentage change as used in the one-way analysis.

From the one-way sensitivity results for onasemnogene abeparvovec versus nusinersen the three variables with the largest impact on the results were further investigated (excluding the cost of onasemnogene abeparvovec and the cost of nusinersen). These are: i) the cost of hospitalisations for E state patients, ii) the cost of hospitalisations for C state patients and, iii) the survival limit placed on PAV in the E state. The tables show the results of varying these parameters in combination by the same percentage change as used in the one-way analysis.

These analyses are described in more detail in Section 12.4.3 and the results are discussed in Section 12.5.14.

Table 97: Multi-way analysis of three variables for onasemnogene abeparvovec versus BSC: ICER results

	Hospitalisations in E state cost = base case	Hospitalisations in E state cost = base case * 0.8	Hospitalisations in E state cost = base case * 1.2
Hospitalisations in C state cost = base case	U1; £177,061 U2; £204,406 U3; £156,169	U1; £184,874 U2; £213,426 U3; £163,060	U1; £169,248 U2; £195,386 U3; £149,278
Hospitalisations in C state cost = base case * 0.8	U1; £168,718 U2; £194,774 U3; £148,810	U1; £176,531 U2; £203,794 U3; £155,702	U1; £160,904 U2; £185,754 U3; £141,919
Hospitalisations in C state cost = base case * 1.2	U1; £185,404 U2; £214,038 U3; £163,528	U1; £193,217 U2; £223,058 U3; £170,419	U1; £177,591 U2; £205,018 U3; £156,636

Abbreviations: BSC, best supportive care; ICER, incremental cost effectiveness ratio.
Note: U1 = base case utility value; U2 = base case utility value * 0.8; U3 = base case utility value * 1.2.

Table 98: Multi-way analysis of three variables for onasemnogene abeparvovec versus nusinersen: ICER results

	Hospitalisations in E state cost = base case	Hospitalisations in E state cost = base case * 0.8	Hospitalisations in E state cost = base case * 1.2
Hospitalisations in C state cost = base case	S1; £35,788 S2; £55,429 S3; £22,541	S1; £51,806 S2; £67,998 S3; £40,885	S1; £19,770 S2; £42,860 S3; £4,197
Hospitalisations in C state cost = base case * 0.8	S1; £27,359 S2; £47,122 S3; £14,030	S1; £43,377 S2; £59,691 S3; £32,374	S1; £11,342 S2; £34,553 S3; -£4,314
Hospitalisations in C state cost = base case * 1.2	S1; £44,217 S2; £63,735 S3; £31,052	S1; £60,235 S2; £76,304 S3; £49,396	S1; £28,199 S2; £51,167 S3; £12,708

Abbreviations: ICER, incremental cost effectiveness ratio.
Note: S1 = base case survival limit in 'E' state; S2 = base case survival limit in 'E' state * 0.8; S3 = base case survival limit in 'E' state * 1.2

12.5.13 Present results of the probabilistic sensitivity analysis described in table D10.3.

Figure 47 below shows the results from 1,000 simulations comparing the incremental cost effectiveness of onasemnogene abeparvovec over BSC.

Figure 48 below shows the results from 1,000 simulations comparing the incremental cost effectiveness of onasemnogene abeparvovec over nusinersen.

Figure 49 shows the Cost Effectiveness Acceptability Curve from 1,000 simulations comparing onasemnogene abeparvovec, nusinersen and BSC.

Figure 47: Incremental cost effectiveness results – 1,000 simulations of onasemnogene abeparvovec versus BSC

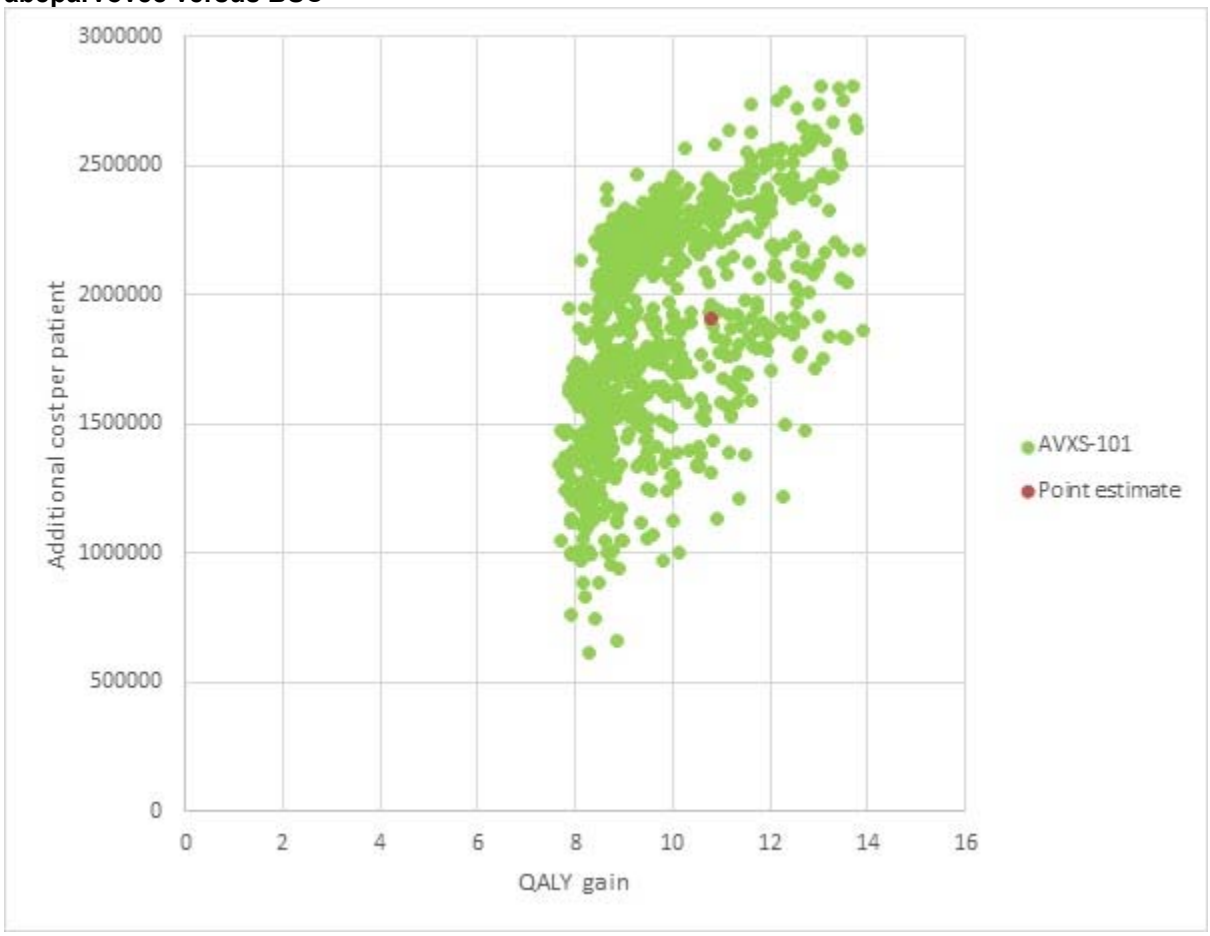


Figure 48: Incremental cost effectiveness results – 1,000 simulations of onasemnogene abeparvovec versus nusinersen

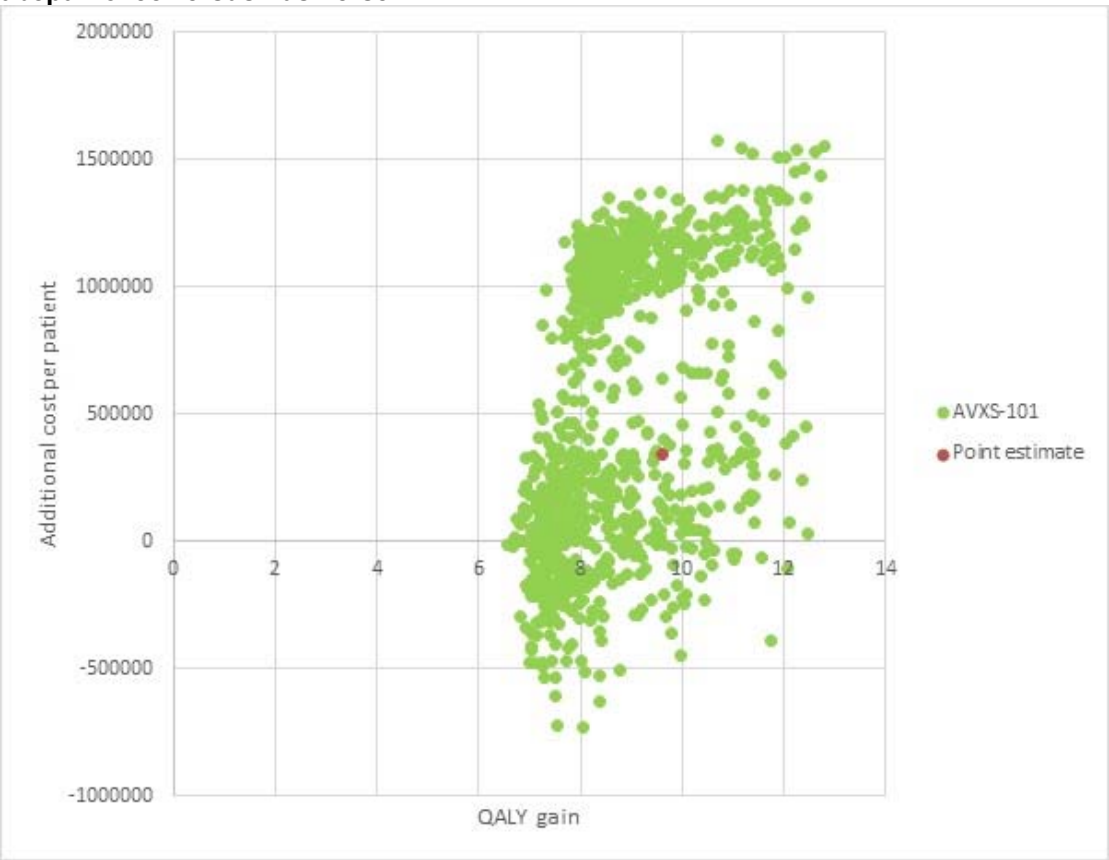


Figure 49: Cost effectiveness acceptability curve –onasemnogene abeparvovec, nusinersen and BSC

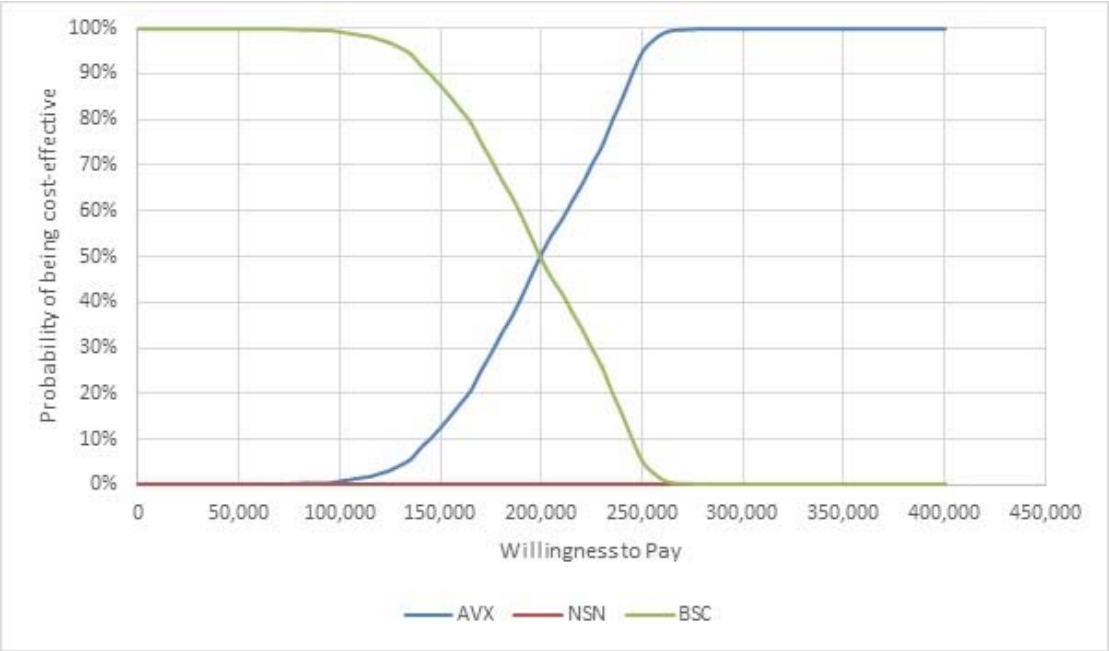


Table 99 below shows the maximum and minimum results for the three interventions for costs, life years and QALYs.

Finally, Table 100 shows the ICER results, onasemnogene abeparvovec versus BSC and onasemnogene abeparvovec versus nusinersen from the simulations.

These results are discussed in answer to question 12.5.14.

Table 99: Results from 1,000 simulations of onasemnogene abeparvovec, BSC and nusinersen

	Max costs	Min costs	Max LYs	Min LYs	Max QALYs	Min QALYs
BSC	£1,818,871	£111,543	5.49	1.23	1.44	0.07
Nusinersen	£3,308,423	£1,148,878	8.87	2.80	2.64	0.73
Onasemnogene abeparvovec	£3,119,030	£2,147,708	22.77	14.04	14.68	8.24

Abbreviations: BSC, best supportive care; LY, life-ears; QALY, quality-adjusted life-years.

Table 100: ICER results from 1,000 simulations of onasemnogene abeparvovec, BSC and nusinersen

ICER ranges	Max ICER	Min ICER	Mean costs/mean QALYs	Median	95% plausible interval - low	95% plausible interval - high
Onasemnogene abeparvovec versus nusinersen	157,917	-95,925	63,888	64,211	-44,818	142,287
Onasemnogene abeparvovec versus BSC	278,448	74,877	196,703	199,384	121,624	255,478
Nusinersen versus BSC	2,017,567	1,004,370	1,441,156	1,455,088	1,180,219	1,777,912

Abbreviations: BSC, best supportive care; ICER, incremental cost effectiveness ratio; QALY, quality-adjusted life-years.

12.5.14 What were the main findings of each of the sensitivity analyses?

One-way sensitivity analysis

All variables were varied by +/- 20% or natural limits if these were within the +/- 20% range.

The only variables that impacted on the ICER by 5% or greater in either direction were: i) the cost of onasemnogene abeparvovec (high ICER of £207,111; low ICER of £147,011); ii) the patient utility value attached to the C state (high ICER of £204,406; low ICER of £156,169) and; iii) the cost of hospitalisations for C state patients (high ICER of £185,404; low ICER of £168,718).

We conducted further one-way analyses of the results. Only results that change the ICER by relatively large amounts or require further explanation are discussed. Full results are shown in Section 12.5.11.

- **Discount rates:** Discounting costs and effects at 0% decreases the ICER by almost 44% whilst discounting costs at 5% but applying no discounting to effects decreases the ICER by over 58%. Discounting effects at 5% but not discounting costs increases the ICER by over 62%. Discounting both costs and effects at 1.5% decreases the ICER by almost 26% to £131,083

- **Cost assumptions:** Of the cost assumptions tested in the model, four had minor effects on the ICER (baseline costs for B state patients also applied to A state patients; SMA type 3 costs from RWE presented at nusinersen ACM3 (144) used for B state patients; SMA type 3 costs from RWE presented at nusinersen ACM3 (144) used for A state and B state patients and cost of onasemnogene abeparvovec administration 10x higher than baseline). The ICER increased by 17% (from £177,061 to £209,592) when the base case health state costs were replaced with the RWE costs (scenario with SMA type 1 costs doubled) presented at the nusinersen ACM3

- **Utility values:** The use of the utilities mapped from PedsQL in CHERISH (149) and the use of applying no utility weights (i.e. cost per LYG) both lead to the ICER falling from £177,061 to £158,717 and to £128,529, respectively. When the Lloyd et al. 2017 clinician-proxy vignette study (147) is used, the ICER increases to £502,601: note that the number of QALYs gained from BSC in this scenario is -0.87. The use of the exploratory AveXis UK utilities elicitation study (154) increases the ICER by 48% to £262,843: note that the number of QALYs gained from BSC in this case is -0.87. Applying the weights use by US ICER for ‘on-treatment’ utility improved (decreased) the ICER by approximately 7% to £164,892

- **Alternative natural history source:** Both of the alternative natural history sources improve (decrease) the ICER: by 15% when Finkel et al. 2017 (ENDEAR Sham control arm) (22) is used and by 43% when De Sanctis et al. 2016 (PNCR, US and Italy study) (50) is used.

Multi-way sensitivity analysis

The multi-way sensitivity analysis compared the three variables (excluding the cost of onasemnogene abeparvovec) that had the largest impact on the ICER as shown by the one-way analysis. These were the patient utility value attached to the C state (0.6 in the base case) the cost of hospitalisations in the C state (£37,420 in the base case) and the cost of hospitalisations in the E state (£211,235 in the base case). Values were varied by +/- 20%.

The results ranged from a low of £141,919 (20% increase in E state hospitalisation costs, 20% reduction in C state hospitalisation costs and 20% increase in the C state utility value) to a high of £223,058 (20% reduction in E state hospitalisation costs, 20% increase in C state hospitalisation costs and 20% reduction in C state utility value). These are a fall of 19.8% and an increase of 26%, when compared with the base case ICER, respectively.

Further sensitivity analysis and exploratory scenarios

For the pessimistic scenario analysis that assumed a limited duration of effect for onasemnogene abeparvovec beginning at 25 years the ICER rises to £217,504.

In the optimistic scenario that assumes there is improved survival for any patient that can sit unassisted (C state) in the onasemnogene abeparvovec arm, the ICER falls by 11% to £157,729.

The ICER rises slightly (by £5,291 to £182,352) using the assumption that overall survival and event-free survival drops to 95% (rather than 100% in the base case) at cycle 2 for onasemnogene abeparvovec treated patients.

Including caregiver disutility scores impacts on the ICER only slightly, increasing by 2.4% to £181,364.

Finally, the two scenarios where we removed either a) 3 patients (non-sitters [n=1] and walkers [n=2]) and b) 2 patients (walkers only [n=2]) from the START Cohort 2 results when calculating milestone attainment transition probabilities in the onasemnogene abeparvovec arm the ICER increased by 33.2% (to £227,878) and by 39.9% (to £247,706), respectively.

Probabilistic sensitivity analysis

The minimum and maximum number of QALYs produced for BSC from the 1,000 simulations were 0.07 and 1.44; the minimum and maximum total costs were £111,543 and £1,818,871.

The minimum and maximum number of QALYs produced for onasemnogene abeparvovec from the 1,000 simulations were 8.24 and 14.68; the minimum and maximum total costs were £2,147,708 and £3,119,030.

The minimum and maximum ICERs produced from the simulations were £74,877 and £278,448 with a 95% credible range of between £121,624 and £255,478.

The mean and median ICERs produced from the simulations were £196,703 and £199,384, respectively. This simulation mean is 11% higher than the deterministic result of £177,061. Analysis of the results showed that this may be in part due to the number of life years gained from the onasemnogene abeparvovec simulations where 79.4% of the runs produced total

life years less than the onasemnogene abeparvovec deterministic value of 37.4 (undiscounted) life years (range 29.4 to 53.6). A total of 69.3% of the ICERs produced from the PSA simulations were above the deterministic ICER.

12.5.14.1 Onasemnogene abeparvovec versus nusinersen

One-way sensitivity analysis

All variables were varied by +/- 20% or natural limits if these were within the +/- 20% range.

All of the results in the one-way sensitivity analysis resulted in ICERs that were below £70,000 per QALY gained. Ten variables impacted on the ICER by 5% or greater in either direction. In descending order these were: i) the cost of onasemnogene abeparvovec (high ICER of £69,443; low ICER of £2,133); ii) the cost of nusinersen per dose (high ICER of £55,860; low ICER of £15,716); iii) the survival limit for patients in the E state (high ICER of £55,429; low ICER of £22,541); iv) the cost of hospitalisation for patients in the E state (high ICER of £51,806; low ICER of £19,770); v) the cost of hospitalisation for patients in the C state (high ICER of £44,217; low ICER of £27,359); vi) the patient utility value attached to the C state (high ICER of £41,381; low ICER of £31,527); vii) the survival limit for patients in the D state (high ICER of £41,398; low ICER of £32,988); viii) the cost of social services for patients in the C state (high ICER of £39,977; low ICER of £31,599); ix) the cost of social services for patients in the E state (high ICER of £39,332; low ICER of £32,244) and; x) the proportion of C state patients on nusinersen who discontinue each year (high ICER of £37,699; low ICER of £33,624).

We conducted further one-way analyses of the results. Only results that change the ICER by relatively large amounts or require further explanation are discussed. Full results are shown in Section 12.5.11.

- **Discount rates:** Discounting costs and effects at 0% decreases the ICER by almost 44% whilst discounting costs at 5% but applying no discounting to effects decreases the ICER by over 56%. Discounting effects at 5% but not discounting costs increases the ICER by over 68%. Discounting both costs and effects at 1.5% decreases the ICER by over 30% to £24,949

- **Cost assumptions:** In none of the five cost assumptions tested in the model (excluding changing the price per dose of nusinersen) did the ICER for onasemnogene abeparvovec versus nusinersen go above £90,000. Of these five cost assumptions four had a minor effect on the ICER (baseline costs for B state patients also applied to A state patients, SMA type 3 costs from RWE presented at nusinersen ACM3 (144) used for B state patients, SMA type 3 costs from RWE presented at nusinersen ACM3 (144) used for A state and B state patients and cost of onasemnogene abeparvovec administration 10x higher than baseline). The ICER increased by 147% (from £35,788 to £88,230) when the base case health state costs were replaced with the RWE costs (scenario with SMA type 1 costs doubled) presented at the nusinersen ACM3. Reducing the price of nusinersen by [redacted] increased the ICER by 140% to £85,968 whilst lowering the price of nusinersen to [redacted] produced an ICER of £136,147

- **Utility values:** The use of the alternative sources for patient utility values all result in the ICER for onasemnogene abeparvovec versus nusinersen being below £80,000. The use of the utilities mapped from PedsQL in CHERISH (149) and the use of applying no utility weights (i.e. cost per LYG) both lead to minimal changes in the ICER (increasing by less than 3% when CHERISH is used and decreasing by 15% when no utility weights are applied). When the Lloyd et al. 2017 (147) clinician-proxy vignette study is used the ICER increases to £76,968 from the base case of £35,788: note that the number of QALYs gained from nusinersen in this case is -1.55 (i.e. overall negative QALYs) whilst the number of QALYs gained from onasemnogene abeparvovec remains positive at 2.92. The use of the exploratory AveXis UK utilities elicitation study (154) increases the ICER by 27% to £45,595: note that the number of QALYs gained from nusinersen in this case is [redacted] (i.e. overall negative QALYs) whilst the number of QALYs gained from onasemnogene abeparvovec remains positive at [redacted]. Applying the weights use by US ICER for 'on-treatment' utility improved (decreased) the ICER by 5% to £33,886.

- **Nusinersen stopping rules**: When the stopping rule of 'discontinue if patients move to E state (PAV)' is removed, onasemnogene abeparvovec becomes dominant with an ICER of -£37,149. When the stopping rule is employed in the E state but an assumption that yearly discontinuations with nusinersen is 0% (rather than the 3% in the base case analysis) the ICER decreases from £35,788 to £23,567 (nusinersen costs increase proportionally more than the increase in nusinersen QALYs gained). When the stopping rule is employed in the E state but an assumption that yearly discontinuations with nusinersen is 10% (rather than the 3% in the base case analysis) the ICER increases from to £39,179 (nusinersen costs fall proportionally more than the fall in nusinersen QALYs).

- **Alternative natural history source:** Use of the Finkel et al. 2017 (ENDEAR Sham control arm) (22) alternative natural history source increases the ICER by 22%; use of the De Sanctis et al. 2016 (PNCR, US and Italy study) (50) alternative natural history source decreases the ICER by over 53%.

Multi-way sensitivity analysis

The multi-way sensitivity analysis compared the three variables (excluding the costs of onasemnogene abeparvovec and nusinersen) that had the largest impact on the ICER as shown by the one-way analysis. These were the survival limit in the E state (16 years in the base case) the cost of hospitalisations in the C state (£37,420 in the base case) and the cost of hospitalisations in the E state (£211,235 in the base case). Values were varied by +/- 20%.

The results ranged from a low of -£4,314 (20% increase in E state hospitalisation costs, 20% reduction in C state hospitalisation costs and the survival limit in the E state increased by 20%) to a high of £76,304 (20% reduction in E state hospitalisation costs, 20% increase in C sate hospitalisation costs and the survival limit in the E state decreased by 20%). These correspond to a fall, compared with the base case ICER, of 112% and an increase, compared with the base case ICER, of 113% respectively.

Further sensitivity analysis and exploratory scenarios

In none of the ten scenarios tested in the model was the ICER for onasemnogene abeparvovec versus nusinersen above £71,000.

For the pessimistic scenario analysis that assumed a limited duration of effect for onasemnogene abeparvovec beginning at 25 years the ICER falls to £35,346.

The optimistic scenario that assumes there is improved survival for patients that can sit unassisted (C state) in the onasemnogene abeparvovec arm only, produces an ICER of £54,506 (increased costs and increased QALYs). Assuming any patient (onasemnogene abeparvovec or nusinersen) that can sit unassisted (C state) has improved survival, increases the ICER to £49,153.

The ICER falls to £32,949 using the assumption that overall survival and event-free survival drops to 95% (rather than 100% in the base case) at cycle 2 for onasemnogene abeparvovec treated patients.

Including caregiver disutility scores has minimal effect on the ICER (from £35,788 to £35,906).

Finally, the two scenarios where we removed either a) 3 patients (non-sitters [n=1] and walkers [n=2]) and b) 2 patients (walkers only [n=2]) from the START Cohort 2 results when calculating milestone attainment transition probabilities in the onasemnogene abeparvovec arm the ICER increased by 87% (to £67,100) and by 96% (to £70,198) respectively.

Probabilistic sensitivity analysis

The minimum and maximum number of QALYs produced for nusinersen from the 1,000 simulations were 0.73 and 2.64; the minimum and maximum total costs were £1,148,878 and £3,308,423.

The minimum and maximum number of QALYs produced for onasemnogene abeparvovec from the 1,000 simulations were 8.24 and 14.68; the minimum and maximum total costs were £2,147,708 and £3,119,030.

The minimum and maximum ICERs produced from the simulations were -£95,925 and £157,917 with a 95% credible range of between -£44,818 and £142,287.

The mean and median ICERs produced from the simulations were £63,888 and £64,211, respectively. This simulation mean is 79% higher than the deterministic result of £35,788. Analysis of the results showed that this may be in part due to the number of life years gained from the onasemnogene abeparvovec simulations where 79.4% of the runs produced total life years less than the onasemnogene abeparvovec deterministic value of 37.4 (undiscounted) life years (range 29.4 to 53.6). A total of 56.8% of the ICERs produced from the simulations were above the deterministic ICER: however, almost 20% of the simulation runs showed onasemnogene abeparvovec to be dominant over nusinersen.

12.5.15 What are the key drivers of the cost results?

Table 101 shows the percentage of total lifetime costs for each cost category for each of the three interventions. A 3.5% discount rate has been used.

Table 101: Percentage of total costs by cost category

Cost Category	Intervention		
	Onasemnogene abeparvovec	BSC	Nusinersen
Product cost	61.89%	0.00%	42.50%
Product admin cost	0.09%	0.00%	0.62%
Care costs			
Drugs	0.43%	0.36%	0.23%
Medical tests	0.17%	0.13%	0.08%
Medical visits	1.37%	1.52%	0.91%
Hospitalisations	23.67%	76.89%	43.37%
GP & emergency	0.12%	0.17%	0.10%
Health materials	1.26%	1.59%	0.94%
Social services	11.00%	19.34%	11.26%
Total	100.00%	100.00%	100.00%

Abbreviations: BSC, best supportive care; GP, general practitioner.

The cost of onasemnogene abeparvovec is the major cost component of total onasemnogene abeparvovec costs followed by the cost of hospitalisations and then the cost of social services support.

For BSC the major cost is the cost of hospitalisations followed by the cost of social services support.

For nusinersen, the cost of hospitalisations is slightly more than the drug cost of nusinersen.

Miscellaneous results

12.5.16 Describe any additional results that have not been specifically requested in this template. If none, please state.

None.

12.6 *Subgroup analysis*

For many technologies, the capacity to benefit from treatment will differ for patients with differing characteristics. Sponsors are required to complete section 12.6 in accordance with the subgroups identified in the scope and for any additional subgroups considered relevant.

Types of subgroups that are not considered relevant are those based solely on the following factors.

Individual utilities for health states and patient preference.

Subgroups based solely on differential treatment costs for individuals according to their social characteristics.

Subgroups specified in relation to the costs of providing treatment in different geographical locations within the UK (for example, if the costs of facilities available for providing the technology vary according to location).

12.6.1 Specify whether analysis of subgroups was undertaken and how these subgroups were identified. Cross-reference the response to the decision problem in table A1.

No subgroup analysis was undertaken.

12.6.2 Define the characteristics of patients in the subgroup(s).

Not applicable.

12.6.3 Describe how the subgroups were included in the cost-effectiveness analysis.

Not applicable.

12.6.4 What were the results of the subgroup analysis/analyses, if conducted? The results should be presented in a table similar to that in section 12.5.6 (base-case analysis). Please also present the undiscounted incremental QALYs consistent with section 12.5.7

Not applicable.

12.6.5 Were any subgroups not included in the submission? If so, which ones, and why were they not considered?

Not applicable.

12.7 *Validation*

12.7.1 Describe the methods used to validate and cross-validate (for example with external evidence sources) and quality-assure the model. Provide references to the results produced and cross-reference to evidence identified in the clinical and resources sections.

Face validation of the appropriateness of the conceptual model (modelling technique, structure, health states, key sources for model input data, and model outcomes) was judged by clinical experts via clinical expert engagement during model conceptualisation and via a UK advisory board – see Section 12.2.5. The validity of the computerised models was assessed through derivation of Markov traces and by comparing modelled mortality and disease progression probabilities with the populated data. Extreme value and unit testing comprised setting model transition probabilities to 0 and 1, respectively and turning off specific costs and utility components as well as mortality.

12.8 *Interpretation of economic evidence*

12.8.1 Are the results from this cost-effectiveness analysis consistent with the published economic literature? If not, why do the results from this evaluation differ, and why should the results in the submission be given more credence than those in the published literature?

In our SLR of prior economic models, we found no models comparing onasemnogene abeparvovec to other treatment options in patients with SMA, however, we note that cost-effectiveness analyses of onasemnogene abeparvovec in SMA type 1 patients with a US perspective (32, 188) have subsequently been published after the date of our SLR search (11 March 2019); including:

- Final evidence report by US ICER (32), assessing onasemnogene abeparvovec versus BSC
- Publication by Malone et al. 2019 (188), assessing onasemnogene abeparvovec versus nusinersen

As both these assessments are conducted with a US-perspective, drawing upon the estimated incremental costs incurred is not considered completely relevant when making comparisons to our *de novo* cost-effectiveness analysis, due to the very different cost structures between the US and the UK. Both these published US assessments share very similar model frameworks when compared our *de novo* model: 1) they employ a short-term model concordant with clinical study data followed by a long-term extrapolation model; 2) they adopt a relatively simple model structure, using only four (US ICER (32)) or five (Malone et al. 2019 (188)) functional health states ranging from ‘permanent ventilation’ to either ‘walking’ (US ICER (32)) or within broad range of normal development (Malone et al. 2019 (188)). When comparing the total QALYs reported in the US assessments to our *de novo* model, estimates are broadly aligned see Table 102.

Table 102: QALYs reported by estimated SMA incident cases by region

Intervention	Discounted QALYs			Undiscounted QALYs		
	NICE HST model	US ICER	Malone et al. 2019	NICE HST model	US ICER	Malone et al. 2019
Onasemnogene abeparvovec	11.42	12.23	15.65	25.05	NR	29.86
Nusinersen	1.81	3.24	5.29	2.52	NR	7.21
BSC	0.65	0.46	NR	0.80	NR	NR

Abbreviations: BSC, best supportive care; HST, highly specialised technology; NICE, National Institute of Health and Care Excellence; QALY, quality-adjusted life-year; US ICER, United States Institute of Clinical and Economic Review.
Sources: NICE HST mode; executable file; US ICER (32); Malone et al. 2019 (188).

However, such comparisons are caveated by there being several key differences between these published assessments and our own, for example:

- Malone et al. 2019 (188) – uses different sources of data for: utilities (mapped from CHERISH); motor milestones for nusinersen arm (from ENDEAR only [not SHINE]); motor milestone for treatment arms in long-term model (employs extrapolation based on CHOP-INTEND); general population mortality in B state and A state (US data set); nusinersen stopping rules (no discontinuation applied for nusinersen)

- US ICER (32) – uses different sources of data for: BSC overall survival and event-free survival (ENDEAR sham control arm); long-term overall survival for treatment arms in non-sitting state (used death from non-invasive respiratory muscle aid survival curve only as reported in Gregoretti et al. 2013 (171) and non-sitting treatment arm patients could not explicitly transition to E state); utilities (applies on on-treatment utility in the base case); mortality in the permanent assisted ventilation state (used death from non-invasive respiratory muscle aid survival curve only as reported in Gregoretti et al. 2013 (171)); motor milestones for nusinersen arm (used SHINE but adopts optimistic assumption that the proportion of patients sitting among those alive who are not followed up is the same as the observed proportion of patients sitting among who attended the follow up visits); general population mortality in walking state (US data set); nusinersen stopping rule (patients on nusinersen who did not achieve motor function milestones at 24 months discontinued the treatment).

The *de novo* cost-effectiveness model for onasemnogene abeparvovec presented here, is deemed more applicable to the decision problem, as it has been parametrised and validated using an England-healthcare perspective, using more up to date and relevant clinical data sources, when compared to the aforementioned US assessments.

Whilst cost-effectiveness analyses assessing nusinersen versus BSC in the treatment of SMA type 1 (often referred to ‘infantile-onset’ model) were identified in the literature from several perspectives, including Sweden (164), Scotland (165), England (31) and Canadian (166), all adopted a complex 10-state Markov model, following patients from baseline to alternative health states: worsen, stabilise, improve (response based states), and death. From the ‘stable’ or ‘improved’ states patients could also transition to milestone based functioning states: ‘sits without support’, ‘stands without assistance’, ‘walks with assistance’,

'stands/walks unaided'. According to feedback from HTA bodies, this model structure was considered overly complex, prevented a thorough understanding of its functioning and added to uncertainty in estimates of cost effectiveness. As a much simpler model structure (five health states, with no reliance on extrapolation of milestones from the short-term model to the long-term model) has been developed for the *de novo* model for onasemnogene abeparvovec in this submission, a detailed comparison to the approach and outcomes (QALYs/costs) described in the published nusinersen 'infantile-onset' model is not considered appropriate.

12.8.2 Is the cost- effectiveness analysis relevant to all groups of patients and specialised services in England that could potentially use the technology as identified in the scope?

Yes; AveXis considers the cost-effectiveness analysis relevant to all groups of patients and specialised services in England that could potentially use onasemnogene abeparvovec. However, it is recognised that the cost-effectiveness analysis does not formally include data in pre-symptomatic patients with a genetic phenotype predictive of SMA type 1. Only very early, interim data from the ongoing pre-symptomatic trial (SPR1NT) were available at the time of this submission, precluding its incorporation into a cost-effectiveness analysis. Additional interim data from SPR1NT will become available in approximately September 2019 and January 2020. Whilst, the cost-effectiveness model only derives efficacy data from START, this trial showed that the substantial benefits in survival, motor function, and developmental milestone achievements relative to natural history cohorts were particularly striking for several patients treated at younger ages (less than 3 months of age, Section 9.6.1.1). Hence, this observation supports the one-time use of onasemnogene abeparvovec as early as possible, including pre-symptomatic patients, with the aim of intervening ahead of extensive neurodegeneration. In additon, due to the eligibility criteria of trials – in combination with the natural SMA type 1 epidemiology (i.e. large majority of SMA type 1 patients have two copies of the *SMN2* gene) – a formal assessment in infants with symptomatic SMA type 1 with an *SMN2* copy number other than two copies cannot be presented.

12.8.3 What are the main strengths and weaknesses of the analysis? How might these affect the interpretation of the results?

A limitation of the model is that all base case pairwise analyses use naïve, unanchored comparisons. There are no head-to-head trials comparing onasemnogene abeparvovec to comparators (BSC or nusinersen), and sample sizes are limited to conduct robust matched, adjusted indirect comparisons or simulated treatment comparisons. Thus, the model makes no adjustment for differences in patient characteristics between the studies used for each treatment arm:

- With respect to the unanchored, naïve comparison to BSC, efforts have been made to source natural history data for overall survival and event-free survival in a SMA type 1 population that resembles START as close as possible, as described in section 12.2.1.3. For example, the natural history study chosen in the base case (NeuroNext) closely resembled the entry criteria for START with respect to age and baseline function and the

genetic profile of NeuroNext and START cohorts were equivalent: all patients had bi-allelic deletions of SMN1 exon 7, *SMN2* copy x 2 and confirmation of exclusion of the *SMN2* modifier mutation c.859G>C. Due to the narrow definition for permanent ventilation in NeuroNext versus START, it is recognised the NeuroNext study may underestimate the number of patients transitioning to permanent ventilation (E state) relative to current clinical practice in England that also employs NIV for ventilatory support. Therefore, alternative natural history sources are provided as scenarios. For example, the De Sanctis et al. 2016 (50) natural history study may be a better reflection of current standard of care with a higher reported proportion of patients alive and using permanent ventilatory support (tracheostomy or NIV) at study end, when compared with NeuroNext.

- With respect to the unanchored, naïve comparison to nusinersen, whilst the analysis performed was the best feasible with the data available, it is recognised all results should be interpreted with the following methodological limitations in mind; there was a lack of controlling for potential confounding factors; no adjustment for prognostic variables and effect modifiers between trials; differences in patient characteristics and study outcomes between clinical trial populations, and small sample sizes (particularly for onasemnogene abeparvovec) in the clinical trials used. It is noted that patients in START had a lower mean age at treatment administration (103.4 days) versus ENDEAR/SHINE (164.3 days), and also fewer required ventilatory support at baseline (17%) versus ENDEAE/SHINE (26%); such differences may favour onasemnogene abeparvovec in that these baseline characteristics could indicate START had a slightly younger and less severe cohort compared to ENDEAR/SHINE. However, to probe this area of uncertainty, sensitivity analyses are provided that assume a smaller treatment benefit versus nusinersen. It should be noted, however, that onasemnogene abeparvovec is cost-effective even in the sensitivity analysis where milestone achievement and associated transition probabilities are based on patients from START, Cohort 2 with the two patients who walk unassisted removed: in this pessimistic sensitivity analysis the ICER for onasemnogene abeparvovec versus nusinersen remains <£100K willingness to pay threshold (£70,198).

Another limitation is that the sample sizes of the clinical studies used to inform the cost-effectiveness model (particualrly for the onasemnogene abeparvovec and BSC arms) are small, which is typical of trials in populations with ultra-rare paediatric diseases. We address the uncertainty associated with small sample size for the onasemnogene abeparvovec arm, by providing the interim data from our ongoing trials, which provide clinical effectiveness data in an additional 62 patients (i.e. 77 patients treated in total) as of the latest data cut available (8 March 2019): the rapid and unprecedented overall survival and motor milestone achievements observed in START have been broadly replicated in early results from ongoing Phase III clinical studies. We address the uncertainty associated with small sample size for the natural history arm, again by providing two alternative natural history sources as scenarios.

Another feature of all treatment arms in the cost-effectiveness model is that the follow-up time is relatively short (24 months to 34 months), when compared with the lifetime time horizon of the model. As a result, observed data are only available for the first 6 model cycles for the pharmacotherapy arms, after which long-term extrapolation of overall survival

and event-free survival are required. However, NICE reference case and well-established methods have been adopted to ensure parametric curve fitting, best fit selection and incorporation into the PSA has been completed. We address the uncertainty in duration of effect of onasemnogene abeparvovec by providing clinical data from LT-001, with the results indicating that a single IV infusion of onasemnogene abeparvovec has continued to provide prolonged and durable efficacy after 2.8 to 4.4 years of follow-up post-dose in Cohort 2 and that no patients have lost motor milestones since the completion of START. In addition, a pessimistic exploratory sensitivity analysis is provided that examines a hypothetical waning of treating effect for onasemnogene abeparvovec.

The modelling approach used (Markov state-transition) was deemed the most adequate to reflect the natural history of SMA type 1, with the data available. The model also accounts for the chronic nature of the condition by taking a lifetime perspective, and accomodates a spectrum of motor function health states. The primary strength of this economic analysis is that the model framework was conceptualised with clinical experts, drawing on frameworks developed for nusinersen and models for similar rare genetic disorders. This enabled the model to capture the patient experience in a reasonable number of health states.

However, a limitation is that the model suggests that patients within the modeled cohort align with each mutually exclusive health state due to the underlying Markov model framework. Patients were also only able to transition into the health state directly above or below in each cycle and could not skip health states when transitioning (i.e. patients in the D health state could not transition to the B or A health state in 1 cycle). In addtion, although the model accounts for the major components of the disease, it is recognised that the entire impact of SMA type 1 may not be fully accounted for, as a result of having to ‘distil’ a chronic, progressive and devasting disease into only a small number of health states. Developing a model to include the entire potential range in patients’ progression and responses to treatment, with limited supporting data would likely lead to an overly complex and highly uncertain analysis, therefore, a pragmatic model using a cohort approach has been developed. It is difficult to model the full benefits of a transformative one-time treatment and, due to the scarcity of evidence, the cost and economic implications for SMA type 1 may not have been fully captured. Indeed, there are potential budget savings outside of the NICE reference case perspective that treatment with onasemnogene abeparvovec could achieve, including educational budgets, local government budgets, and welfare budgets.

A further limitation of the data informing the cost-effectiveness model was that utility measurements were based upon populations external to the clinical trials, and reliant on assumptions that proxy populations could be used. Whilst it is well accepted that SMA has a substantial effect on the HRQoL of parents, caregivers and families, robust UK utility data for the SMA population and their caregivers are lacking. In addition, methods for performing economic evaluations including caregiver burden are still under development, and currently there are no formally accepted mechanisms of including caregiver disutilities due to bereavement and loss of a child. The uncertainty associated with health state utilities has been addressed by the provision of number of sensitivity analyses, including using different sources of utility data, assessing caregiver disutility and applying an on-treatment utility benefit.

12.8.4 What further analyses could be undertaken to enhance the robustness/completeness of the results?

As described above, many of the limitations associated with the cost-effectiveness model related to the underpinning clinical data. Therefore, as more longer-term data become available for onasemnogene abeparvovec, and comparator arms, cost-effectiveness analyses may be supplemented with longer-term clinical outcomes.

13 Cost to the NHS and Personal Social Services

The purpose of Section 13 is to allow the evaluation of the affordability of the technology.

13.1 *How many patients are eligible for treatment in England? Present results for the full marketing authorisation and for any subgroups considered. Also present results for the subsequent 5 years.*

In clinical practice, onasemnogene abeparvovec is expected to be used only in newly diagnosed infants with SMA type 1, which will in practice limit the eligible population to incident patients only.

The following approach was taken to estimate the incident SMA type 1 population of England: SMA (all types) has an annual incidence of approximately 9.4:100,000 live births, as reported by Lally et al 2017 (4); this incidence rate is applied to the most recent live births data for England (reported as 646,794 live births in 2017 (6)), to estimate that there are 61 incident cases of SMA (all types) per year in England; applying that SMA type 1 accounts for 58% of all cases of SMA (5), this results in 35 incident cases of SMA type 1 per year in England. It is assumed this will be the case each year, for the next 5 years.

Real world evidence from the nusinersen UK early access programme (EAP) reported that in its last 12 months of operation, 32 babies were diagnosed with SMA type 1 and treated with nusinersen in England (personal communication; [redacted], Paediatric Neurologist). These 32 patients are considered to represent a “steady-state” of incident patients presenting for pharmacotherapy. Therefore, it is assumed that 3 of the expected 35 incident patients did not present for pharmacotherapy during this period and that this proportion, 9%, would not present for pharmacotherapy in any modelled treatment scenario. Potential reasons for this may include factors such as the poor condition of the baby or the beliefs/preferences of the family. Therefore, it is estimated that each year there are 32 incident cases of SMA type 1 per year in England who present for pharmacotherapy. The remaining criteria applied to assess eligibility depend on AAV9 antibody screening and treatment choice/availability, as shown in Figure 50.

Figure 50: Patient eligibility for pharmacotherapy

SMA type 1 incident cases (n=35, 100%)			
Present for pharmacotherapy (n=32, 91%)			Do not present for pharmacotherapy (n=3, 9%)
Eligible for onasemnogene abeparvovec or nusinersen (86%)		Not eligible for onasemnogene abeparvovec due to anti-AAV9 antibody titre (14%)	
% treatment choice for onasemnogene abeparvovec	% treatment choice for nusinersen, if available, or BSC if not	100% treated with nusinersen, if available, or BSC if not	100% BSC

Abbreviations: AAV9, adeno-associated virus 9; BSC, best supportive care; SMA, spinal muscular atrophy.

Anti-AAV9 antibody screening

Some patients eligible for pharmacotherapy will not be eligible for onasemnogene abeparvovec due to a high anti-AAV9 antibody titre (an anti-AAV9 antibody titre of above 1 in 50 is an exclusion criterion used in the onasemnogene abeparvovec clinical trials). In the ongoing STR1VE-EU clinical trial, being conducted in Europe, the proportion of SMA type 1 incident cases ineligible for onasemnogene abeparvovec due to a high anti-AAV9 titre was 4 of 29 cases (14%) screened (Table 28). STR1VE-EU screening data are the most generalisable to the English incident population given that new born screening is not currently routinely available in the UK. Therefore, we assume of the patients who present for pharmacotherapy, 14% are not eligible for treatment with onasemnogene abeparvovec.

Treatment choice/availability

The budget impact model compares the 'current situation' to 'onasemnogene abeparvovec becomes available' under two scenarios:

Scenario 1: Nusinersen is not available

a) 'Current situation' = BSC is the only treatment option for SMA type 1 patients

b) 'Onasemnogene abeparvovec becomes available' = Onasemnogene abeparvovec is introduced, and is the only pharmacotherapy treatment option available

Scenario 2: Nusinersen is available

a) 'Current situation' = BSC and nusinersen are treatment options for SMA type 1 patients

b) 'Onasemnogene abeparvovec becomes available' = Onasemnogene abeparvovec is introduced as an alternative active treatment to nusinersen alongside BSC

13.2 *Describe the expected uptake of the technology and the changes in its demand over the next five years.*

Expected market shares for onasemnogene abeparvovec in 'Scenario 1: nusinersen in not available' and 'Scenario 2: nusinersen is available' scenario are described below.

Scenario 1: Nusinersen is not available

a) 'Current situation' (Table 103): 100% of cases would receive BSC

b) 'Onasemnogene abeparvovec becomes available' (Table 104): As described in Section 13.1, 14% of incident patients would be unsuitable for onasemnogene abeparvovec due to high anti-AAV9 antibody titres. Therefore, this 14% has been excluded from the patients who present for pharmacotherapy (i.e. 14% of the 91% presenting for pharmacotherapy [i.e. 12.74%] as discussed in Section 13.1). Based on the above, we have estimated that 78.26% of the patients would receive onasemnogene abeparvovec. For BSC, we have estimated that in addition to the 9% (who do not present for pharmacotherapy as discussed in Section 13.1), the 12.74% of the patients who would be unsuitable to receive onasemnogene abeparvovec (as discussed above) would also receive BSC. Therefore, it is estimated that in total 21.74% of the patients would receive BSC.

Table 103: Assumption of the distribution of SMA type 1 cases by treatment in the 'current situation' – nusinersen is not available

Intervention	Year 1	Year 2	Year 3	Year 4	Year 5
Onasemnogene abeparvovec	0%	0%	0%	0%	0%
Nusinersen	0%	0%	0%	0%	0%
BSC	100%	100%	100%	100%	100%

Abbreviations: BSC, best supportive care; SMA, spinal muscular atrophy.

Table 104: Assumption of the distribution of SMA type 1 cases by treatment in the 'onasemnogene abeparvovec becomes available' – nusinersen is not available

Intervention	Year 1	Year 2	Year 3	Year 4	Year 5
Onasemnogene abeparvovec	78.26%	78.26%	78.26%	78.26%	78.26%
Nusinersen	0%	0%	0%	0%	0%
BSC	21.74%	21.74%	21.74%	21.74%	21.74%

Abbreviations: BSC, best supportive care; SMA, spinal muscular atrophy

Scenario 2: Nusinersen is available

a) 'Current situation' (Table 105): We have used the real-world experience of the nusinersen UK EAP as described in Section 13.1, with only 9% of incident babies not receiving treatment with nusinersen (attributed to BSC) and hence 91% of cases receiving nusinersen.

b) 'Onasemnogene abeparvovec becomes available' (Table 106): To estimate the expected uptake of onasemnogene abeparvovec we have used data from market research conducted for AveXis in the UK between 20 March 2019 and 5 April 2019 that interviewed 5 neurologists. The estimated treatment share of SMA type 1 patients under the age of 7 months that would be treated with onasemnogene

abeparvovec was 66%. However, 14% of the 66% has been assumed to be unsuitable for onasemnogene abeparvovec due to high anti-AAV9 antibody titres (as described in Section 13.1), which has resulted in an estimated expected uptake rate of 56.76% in year 1. From year 2 onwards, it is assumed that observed positive clinical outcomes and increasing familiarity with gene therapies will lead to an increase in the expected market share for onasemnogene abeparvovec in subsequent years to a level of 68%, 75%, 78% and 78% in the next 4 years (that is, no calculations are used to derive the percentage of patients on onasemnogene abeparvovec from year 2 onwards, as they are based on market uptake assumptions). As discussed in Section 13.1, BSC was assumed to be received by 9% of the patients (i.e. those who do not present for pharmacotherapy). Based on the above estimates and assumptions, the patients, who would not be treated with either BSC or onasemnogene abeparvovec, would receive nusinersen. Therefore, the uptake of nusinersen has been estimated to decrease from 34.24% in year 1 to 13% in year 5 (Table 106).

Table 105: Assumption of the distribution of SMA type 1 cases by treatment in the 'current situation' – nusinersen is available

Intervention	Year 1	Year 2	Year 3	Year 4	Year 5
Onasemnogene abeparvovec	0%	0%	0%	0%	0%
Nusinersen	91%	91%	91%	91%	91%
BSC	9%	9%	9%	9%	9%

Abbreviations: BSC, best supportive care; SMA, spinal muscular atrophy.

Table 106: Assumption of the distribution of SMA type 1 cases by treatment in the 'onasemnogene abeparvovec becomes available' situation – nusinersen is available

Intervention	Year 1	Year 2	Year 3	Year 4	Year 5
Onasemnogene abeparvovec	56.76%	68%	75%	78%	78%
Nusinersen	34.24%	23%	16%	13%	13%
BSC	9%	9%	9%	9%	9%

Abbreviations: BSC, best supportive care; SMA, spinal muscular atrophy.

13.3 *In addition to technology costs, please describe other significant costs associated with treatment that may be of interest to NHS England (for example, additional procedures etc).*

None expected; however, AveXis is committed to working with neuromuscular centres, including potential infusion centres and regional specialist centres, to scope and design a service delivery that includes onasemnogene abeparvovec.

Infants will require a test for the AAV9 antibody prior to treatment with onasemnogene abeparvovec. However, AAV9 antibody testing will be funded and coordinated by AveXis at a central European lab (Viroclinics, The Netherlands).

13.4 *Describe any estimates of resource savings associated with the use of the technology.*

Because of the large increases in the quantity and quality of life that onasemnogene abeparvovec produces compared with BSC, the opportunities for absolute resource savings are limited. Patients who would otherwise have died still require some treatment related support. Section 12.5.8 shows that (discounted) mean total treatment costs (i.e. all SMA care costs) would be expected to rise from £707,836 for BSC patients to £994,183 for onasemnogene abeparvovec treated patients.

Onasemnogene abeparvovec is expected to reduce total (discounted) life time care costs by £297,166 compared with nusinersen. Although more life years are produced with onasemnogene abeparvovec than with nusinersen, and some SMA-related care is required for these patients (the majority of which are in the C state), these costs are more than offset by the reductions in the probabilities that patients will be in the more expensive to treat D state and E state. For example, Section 12.5.3 shows that the probability of a nusinersen treated patient being in the E state at 5 years after treatment is 37.05% whilst the probability for an onasemnogene abeparvovec treated patient being in the E state at five years is only 2.03%.

In addition, treatment administration costs for onasemnogene abeparvovec are predicted to be lower than those of nusinersen (£2,343 versus £14,059).

13.5 *Are there any other opportunities for resource savings or redirection of resources that it has not been possible to quantify?*

No opportunities for resource savings or redirection of resources are applicable for NHS/PSS/government funded programmes, apart from possible disability payments and education costs (see question 14.2). If possible, changes to caregiver time/resources are considered to be applicable, see Section 14.4.

13.6 *Describe any costs or savings associated with the technology that are incurred outside of the NHS and PSS.*

Patient travel costs are incurred for each nusinersen administration six times in the first year and three times per year thereafter: onasemnogene abeparvovec travel costs are for the single visit only. However, these costs will be small compared with other costs that are included in the model.

Possible costs for lost patient income are discussed in answer to question 14.1. Possible costs for lost caregiver income are discussed in answer to question 14.4.

13.7 *What is the estimated budget impact for the NHS and PSS over the first year of uptake of the technology, and over the next 5 years?*

The budget impact model is constructed as a module within the cost-effectiveness model. The numbers of patients who would be eligible for treatment within each year of a 5-year

period and the current treatment options that onasemnogene abeparvovec would replace for each year are selected. All cost data for the analysis are drawn from the cost-effectiveness model. Discounting is not applied within the budget impact model. The model calculates the total cost of treatment for patients treated through Years 1 to 5 inclusive by reference to the model underlying the cost-effectiveness analysis. If a patient were to join in Year 2, then the model would begin calculation, again, from Year 1, but the Year 1 data for this patient are added to the Year 2 data for the first patient. Similarly, the Year 2 data for the second year patient are added to the Year 3 data for the patient who joined in Year 1.

We show i) the budget impact of onasemnogene abeparvovec replacing a single BSC patient or a single nusinersen treated patient over a 5 year period and ii) the budget impact using the estimated incident population treated with onasemnogene abeparvovec when this technology becomes available in the two aforementioned scenarios: Scenario 1: nusinersen is not available; Scenario 2: nusinersen is available

13.7.1 Budget impact of onasemnogene abeparvovec replacing either a single BSC patient or a single nusinersen patient

Table 107 and Table 108 show the annual cost per year for up to 5 years of 1 patient treated with onasemnogene abeparvovec rather than BSC. The total budget impact (sum of years 1 to 5 of ‘total budget impact’ row in Table 108) is £1,685,218.

Table 109 and Table 110 show the annual cost per year for up to 5 years of 1 patient treated with onasemnogene abeparvovec rather than nusinersen. The total budget impact (sum of years 1 to 5 of ‘total budget impact’ row in Table 110) is £764,581.

Table 107: Five year budget impact of treating 1 patient with onasemnogene abeparvovec ('onasemnogene abeparvovec becomes available') rather than BSC ('current situation')

Annual cost outcomes	Year 1	Year 2	Year 3	Year 4	Year 5
BSC only available					
Drug acquisition costs	0	0	0	0	0
Drug administration costs	0	0	0	0	0
Total drug costs	0	0	0	0	0
SMA medical costs	91,488	70,223	73,813	55,647	53,500
Total SMA care costs	91,488	70,223	73,813	55,647	53,500
Total costs	**91,488**	**70,223**	**73,813**	**55,647**	**53,500**
Onasemnogene abeparvovec becomes available'					
Onasemnogene abeparvovec: drug acquisition costs	1,674,500	0	0	0	0
Onasemnogene abeparvovec: drug administration costs	2,425	0	0	0	0
Onasemnogene abeparvovec: total drug costs	1,676,925	0	0	0	0
Nusinersen: drug acquisition costs	0	0	0	0	0
Nusinersen: drug administration costs	0	0	0	0	0
Nusinersen: total drug costs	0	0	0	0	0
Total drug costs	1,676,925	0	0	0	0
SMA medical costs	104,377	86,041	57,288	52,984	52,274
Total SMA care costs	104,377	86,041	57,288	52,984	52,274
Total costs	**1,781,302**	**86,041**	**57,288**	**52,984**	**52,274**

Abbreviations: BSC, best supportive care; SMA, spinal muscular atrophy.

Table 108: Five year budget impact of treating 1 patient with onasemnogene abeparvovec rather than BSC – net position

Budget impact	Year 1	Year 2	Year 3	Year 4	Year 5
Pharmacy budget impact	1,676,925	0	0	0	0
SMA care budget impact	12,889	15,817	–16,525	–2,663	–1,225
Total budget impact	**1,689,814**	**15,817**	**–16,525**	**–2,663**	**–1,225**

Abbreviations: BSC, best supportive care; ; SMA, spinal muscular atrophy.

Table 109: Five year budget impact of treating 1 patient with onasemnogene abeparvovec ('onasemnogene abeparvovec becomes available') rather than nusinersen ('current situation')

Annual cost outcomes	Year 1	Year 2	Year 3	Year 4	Year 5
Nusinersen only available					
Nusinersen: drug acquisition costs	383,766	105,626	92,258	47,849	33,988
Nusinersen: drug administration costs	5,847	1,609	1,406	729	518
Total drug costs	389,613	107,235	93,663	48,578	34,506
SMA medical costs	107,163	129,418	128,232	115,948	110,951
Total SMA care costs	107,163	129,418	128,232	115,948	110,951
Total costs	**496,776**	**236,653**	**221,895**	**164,526**	**145,457**
Onasemnogene abeparvovec becomes available					
Onasemnogene abeparvovec: drug acquisition costs	1,674,500	0	0	0	0
Onasemnogene abeparvovec: drug administration costs	2,425	0	0	0	0
Onasemnogene abeparvovec: total drug costs	1,676,925	0	0	0	0
Nusinersen: drug acquisition costs	0	0	0	0	0
Nusinersen: drug administration costs	0	0	0	0	0
Nusinersen: total drug costs	0	0	0	0	0
Total drug costs	1,676,925	0	0	0	0
SMA medical costs	104,377	86,041	57,288	52,984	52,274
Total SMA care costs	104,377	86,041	57,288	52,984	52,274
Total costs	**1,781,302**	**86,041**	**57,288**	**52,984**	**52,274**

Abbreviations: SMA, spinal muscular atrophy.

Table 110: Five year budget impact of treating 1 patient with onasemnogene abeparvovec rather than nusinersen – net position

Budget impact	Year 1	Year 2	Year 3	Year 4	Year 5
Pharmacy budget impact	1,287,312	–107,235	–93,663	–48,578	–38,506
SMA care budget impact	–2,786	–43,377	–70,944	–62,964	–58,677
Total budget impact	**1,284,526**	**–150,613**	**–164,607**	**–111,542**	**–93,183**

13.7.2 Budget impact of onasemnogene abeparvovec on the estimated incident population of onasemnogene abeparvovec being introduced where nusinersen is a) not available and, b) available

Scenario 1: Nusinersen is not available

Rationale and calculations underlying the expected market shares under this scenario are described in detail Section 13.2, but are shown again below for completeness in Table 111 and Table 112.

Table 111: Assumption of the distribution of SMA type 1 cases by treatment in the 'current situation' – nusinersen is not available

Intervention	Year 1	Year 2	Year 3	Year 4	Year 5
Onasemnogene abeparvovec	0%	0%	0%	0%	0%
Nusinersen	0%	0%	0%	0%	0%
BSC	100%	100%	100%	100%	100%

Abbreviations: BSC, best supportive care; SMA, spinal muscular atrophy.

Table 112: Assumption of the distribution of SMA type 1 cases by treatment in the 'onasemnogene abeparvovec becomes available' situation – nusinersen is not available

Intervention	Year 1	Year 2	Year 3	Year 4	Year 5
Onasemnogene abeparvovec	78.26%	78.26%	78.26%	78.26%	78.26%
Nusinersen	0%	0%	0%	0%	0%
BSC	21.74%	21.74%	21.74%	21.74%	21.74%

Abbreviations: BSC, best supportive care; SMA, spinal muscular atrophy.

Table 113 and Table 114 show the annual cost per year for up to 5 years, assuming 35 incident SMA type 1 cases per year for each of the five years. The total budget impact (sum of years 1 to 5 in 'total budget impact' row in Table 114) is £231,624,876.

Table 113: Five year budget impact of 35 incident cases per year for each of the five years treated with onasemnogene abeparvovec (or BSC) ('onasemnogene abeparvovec becomes available') rather than BSC ('BSC only available')

Annual cost outcomes	Year 1	Year 2	Year 3	Year 4	Year 5
BSC only available					
Nusinersen: drug acquisition costs	0	0	0	0	0
Nusinersen: drug administration costs	0	0	0	0	0
Total drug costs	0	0	0	0	0
SMA medical costs	3,202,084	5,659,900	8,243,340	10,190,988	12,063,476
Total SMA care costs	3,202,084	5,659,900	8,243,340	10,190,988	12,063,476
Total costs	**3,202,084**	**5,659,900**	**8,243,340**	**10,190,988**	**12,063,476**
Onasemnogene abeparvovec becomes available					
Onasemnogene abeparvovec: drug acquisition costs	45,866,230	45,866,230	45,866,230	45,866,230	45,866,230
Onasemnogene abeparvovec: drug administration costs	66,423	66,423	66,423	66,423	66,423
Onasemnogene abeparvovec: total drug costs	45,932,653	45,932,653	45,932,653	45,932,653	45,932,653
Nusinersen: drug acquisition costs	0	0	0	0	0
Nusinersen: drug administration costs	0	0	0	0	0
Nusinersen: total drug costs	0	0	0	0	0
Total drug costs	45,932,653	45,932,653	45,932,653	45,932,653	45,932,653
SMA medical costs	3,555,123	6,446,188	8,576,999	10,451,696	12,291,394
Total SMA care costs	3,555,123	6,446,188	8,576,999	10,451,696	12,291,394
Total costs	**49,487,776**	**52,378,841**	**54,509,652**	**56,384,349**	**58,224,047**

Abbreviations: BSC, best supportive care; SMA, spinal muscular atrophy.

Table 114: Five year budget impact of treating of 35 incident cases per year for each of the five years treated with onasemnogene abeparvovec (or BSC) rather than BSC - net position

Budget impact	Year 1	Year 2	Year 3	Year 4	Year 5
Pharmacy budget impact	45,932,653	45,932,653	45,932,653	45,932,653	45,932,653
SMA care budget impact	353,039	786,288	333,659	260,708	227,917
Total budget impact	**46,285,692**	**46,718,941**	**46,266,312**	**46,193,361**	**46,160,570**

Abbreviations: BSC, best supportive care; SMA, spinal muscular atrophy.
Note: All values are taken from the economic model and are subject to rounding. Any discrepancies between results presented in the table and text are due to rounding.

Scenario 2: Nusinersen is available

Rationale and calculations underlying the expected market shares under this scenario are described in detail Section 13.2, but are shown again below for completion in Table 115 and Table 116.

Table 115: Assumption of the distribution of SMA type 1 cases by treatment in the 'current situation' – nusinersen is available

Intervention	Year 1	Year 2	Year 3	Year 4	Year 5
Onasemnogene abeparvovec	0%	0%	0%	0%	0%
Nusinersen	91%	91%	91%	91%	91%
BSC	9%	9%	9%	9%	9%

Abbreviations: BSC, best supportive care; SMA, spinal muscular atrophy.

Table 116: Assumption of the distribution of SMA type 1 cases by treatment in the 'onasemnogene abeparvovec becomes available' – nusinersen is available

Intervention	Year 1	Year 2	Year 3	Year 4	Year 5
Onasemnogene abeparvovec	56.76%	68%	75%	78%	78%
Nusinersen	34.24%	23%	16%	13%	13%
BSC	9%	9%	9%	9%	9%

Abbreviations: BSC, best supportive care; SMA, spinal muscular atrophy.

Table 117 and Table 118 show the annual cost per year for up to 5 years of 35 SMA type 1 incident cases per year for each of the five years under these assumptions. The total budget impact (sum of years 1 to 5 in 'total budget impact' row in Table 118) is £127,072,377.

Table 117: Five year budget impact of 35 incident cases per year for each of the five years treated with onasemnogene abeparvovec, nusinersen, or BSC ('onasemnogene abeparvovec becomes available') rather than BSC or nusinersen ('BSC/nusinersen only available')

Annual cost outcomes	Year 1	Year 2	Year 3	Year 4	Year 5
BSC/nusinersen only available					
Nusinersen: drug acquisition costs	12,222,956	15,587,144	18,525,551	20,049,555	21,132,073
Nusinersen: drug administration costs	186,213	237,465	282,231	305,448	321,940
Total drug costs	12,409,168	15,824,609	18,807,782	20,355,004	21,454,013
SMA medical costs	3,701,333	8,044,500	12,361,193	16,229,415	19,931,733
Total SMA care costs	3,701,333	8,044,500	12,361,193	16,229,415	19,931,733
Total costs	**16,110,502**	**23,869,108**	**31,168,974**	**36,584,419**	**41,385,746**
Onasemnogene abeparvovec becomes available					
Onasemnogene abeparvovec: drug acquisition costs	33,265,617	39,853,100	43,955,625	45,713,850	45,713,850
Onasemnogene abeparvovec: drug administration costs	48,175	57,715	63,656	66,203	66,203
Onasemnogene abeparvovec: total drug costs	33,313,792	39,910,815	44,019,281	45,780,053	45,780,053
Nusinersen: drug acquisition costs	4,599,055	4,355,140	4,104,997	3,653,744	3,535,878
Nusinersen: drug administration costs	70,065	66,349	62,538	55,664	53,868
Nusinersen: total drug costs	4,669,120	4,421,490	4,167,535	3,709,408	3,589,746
Total drug costs	37,982,912	44,332,305	48,186,816	49,489,460	49,369,798
SMA medical costs	3,645,984	7,116,453	9,846,299	12,075,387	14,154,713
Total SMA care costs	3,645,984	7,116,453	9,846,299	12,075,387	14,145,713
Total costs	**41,628,896**	**51,448,757**	**58,033,115**	**61,564,847**	**63,515,511**

Abbreviations: BSC, best supportive care; SMA, spinal muscular atrophy.

Table 118: Five year budget impact of treating of 35 incident cases per year for each of the five years treated with onasemnogene abeparvovec (or BSC) rather than BSC – net position

Budget impact	Year 1	Year 2	Year 3	Year 4	Year 5
Pharmacy budget impact	25,573,744	28,507,696	29,379,034	29,134,457	27,915,785
SMA care budget impact	-55,349	-928,047	-2,514,893	-4,154,028	-5,786,021
Total budget impact	**25,518,395**	**27,579,649**	**26,864,141**	**24,980,428**	**22,129,764**

Abbreviations: BSC, best supportive care; SMA, spinal muscular atrophy.
Note: All values are taken from the economic model and are subject to rounding. Any discrepancies between results presented in the table and text are due to rounding.

13.8 *Describe the main limitations within the budget impact analysis (for example quality of data inputs and sources and analysis etc).*

Section 12.8.3 provides details of the limitations of the cost-effectiveness analysis. The limitations relating to the availability of the underlying data and any structural assumptions also apply to the budget impact analysis. In addition, small variations in the total number of patients treated per year may have a significant effect on the total budget impact. Finally, assumptions by AveXis on the number of patients who may be treated with onasemnogene abeparvovec in each of the first 5 years are planning assumptions and the true degree of the use of the technology relative to continued use of BSC and, if available, the discounted price to the NHS of nusinersen is unknown.

Section E – Impact of the technology beyond direct health benefits

The purpose of Section 14 is to establish the impact of the technology beyond direct health benefits, that is, on costs and benefits outside of the NHS and PSS, and on the potential for research. Sponsors should refer to section 5.5.11 – 5.5.13 of the Guide to Methods for Technology Appraisal 2013 for more information.

It is also aimed at describing factors that are relevant to the provision of the (highly) specialised service by NHS England. Such factors might include issues relating to specialised service organisation and provision, resource allocation and equity, societal or ethical issues, plus any impact on patients or carers.

14 Impact of the technology beyond direct health benefits

14.1 *Describe whether a substantial proportion of the costs (savings) or benefits are incurred outside of the NHS and personal social services, or are associated with significant benefits other than health.*

Both onasemnogene abeparvovec and nusinersen may have benefits beyond the outcomes assessed in trials. For example, if pharmacotherapy improves or retains children's mobility, children may attend school, reach educational achievement and participate in the workforce in the future. Greater independence for the child may also allow caregivers to return to work. An effective treatment also may reduce anxiety and stress among caregivers and wider communities, reduce other resources used (e.g. educational system), and promote more interaction between children with SMA and others in the community. Furthermore, even small improvements in motor abilities can allow patients greater ability for self-care and independence.

Patient educational achievement and workforce participation

Patients treated with onasemnogene abeparvovec or nusinersen could participate in the workforce in the future. Therefore, the possible educational achievement of patients and the impact on workforce participation was explored.

A comprehensive study of the educational achievement of patients with SMA was conducted by the Lewin Group for the Muscular Dystrophy Association in 2012 (189) to obtain US estimates.

Table 119 shows the highest level of education for SMA patients (which was attributed to the C state and B state) and the general US population (which was attributed to the A state). Of note, is that the SMA population from the Lewin Group study reported a higher percentage of SMA patients having a post-graduate degree than the general US population (19% vs. 11.4%).

Table 119: Potential educational achievement for patients who may live to working age

	Not available/ no attainment	Some high school	High School Graduate	Some college/ Associate Degree	College Degree	Post-graduate degree
C state†	4%	6%	13%	28%	30%	19%
B state†	4%	6%	13%	28%	30%	19%
A state	3.7%	7.3%	28.9%	28.6%	20.0%	11.4%

† Values from source have been rounded
Source: United States, Census Bureau: Educational Attainment in the United States, 2017 (190); Lewin Group for the Muscular Dystrophy Association in 2012 (189).

Information on UK median annual earnings (191), unemployment rates (192) and the percentage of people with disabilities that are employed by educational achievement level (193) was collated (Table 120).

Table 120: UK - General population income based on educational achievement

Educational achievement	Median annual earnings	Unemployment rate	People with disabilities - employed
Some high school	£17,868	5.6%	17.0%
High school graduate	£23,628	3.1%	45.6%
Some College/Associate Degree	£29,469	3.1%	45.6%
College Graduate	£34,909	2.3%	71.7%
Post-Graduate Degree	£40,527	2.3%	71.7%

For the A state patients the average expected income per patient per year by educational achievement was calculated as: percentage expected educational achievement from Lewin Group study * median annual UK income by educational achievement * the expected employment rate. The average income per patient from the sum of these weighted values was then calculated.

For C state patients, the same approach was used and the employment rate was that of people with disabilities. For patients in B state, the unemployment rate was assumed to be between the rate for the general population and for people with disabilities (note: set at 50% - user variable).

The resulting average income per patient (£19,141 for C state patients, £25,057 for B state patients and £28,427 for A state patients) was then input to the model between the ages of 25 and 68.

The consequences of introducing these lifetime potential earnings on total costs was that the total per patient costs for nusinersen fell by £2,300 (from £2,270,315 to £2,268,015) whilst the total per patient costs for onasemnogene abeparvovec treated patients fell by £81,465 (from £2,614,400 to £2,532,935).

The impact on the ICER's of introducing these lifetime patient income benefits is that the ICER for onasemnogene abeparvovec versus BSC falls from £177,061 to £169,495, whilst the ICER for onasemnogene abeparvovec versus nusinersen falls from £35,788 to £27,554.

14.2 *List the costs (or cost savings) to government bodies other than the NHS.*

Patients treated with onasemnogene abeparvovec who would have otherwise died if treated with nusinersen or BSC may be entitled to disability payments. Similarly, since some of these patients may be unemployed, unemployment benefits may be required. Finally, some patients may have special education requirements during childhood and adolescence.

14.3 *List the costs borne by patients that are not reimbursed by the NHS.*

Parents/caregivers may incur additional paid professional care costs over that provided by the NHS. In addition, modifications to housing and vehicles may not be provided by the NHS or related services. Survey B from the SMA UK Patient and Caregiver survey (March 2019) (76) found the mean annual out of pocket (OOP) costs incurred for health materials and travel and accommodation (associated appointment costs and hospital stays) per SMA person were on average £8,025 per year.

We applied these costs to all E, D and C state patients in the model. The ICER for onasemnogene abeparvovec versus BSC increased from £177,061 to £185,033 whilst the ICER for onasemnogene abeparvovec versus nusinersen increased from £35,788 to £41,768. These increases are due to the extra life years gained from onasemnogene abeparvovec over BSC and nusinersen

14.4 *Provide estimates of time spent by family members of providing care. Describe and justify the valuation methods used.*

Information on the level of care required for patients with SMA by health state over time was collated from clinical experts (Table 121). These values derived from clinical experts are broadly in line with the average number of unpaid caregiving hours / week available from the SMA UK Patient and Caregiver survey (March 2019) (76): Walks unassisted (66 hours/week [9 hours/day]; Sits unassisted (100 hours/week [14 hours/day]); Not sitting (117 hours/week [17 hours/day]).

Table 121: Level of care required, by health state and age band

Cycle	Age band	SMA-specific care required (hours/day)				
		E	D	C	B	A
1–4	0<24 months	16–24	16–24	16–24	16–24	SMA-specific care not needed
5–8	24<60 months	16–24	16–24	16–24	16–24	SMA-specific care not needed
9–21	5–17 years	16–24	16–24	8–15	8–15	SMA-specific care not needed
22+	18+ years.	16–24	16–24	1–8	SMA-specific care not needed	SMA-specific care not needed

Source: Clinical expert advice
Abbreviations: SMA, spinal muscular atrophy.

We then used SMA results from the Lewin Group study for the Muscular Dystrophy Association in 2012 (189) and converted the estimated lost income by level of care required to UK £'s using a Purchasing Power Parity value of 0.69 from the OECD (194) (Table 122).

Table 122: Predicted lost family income (US$ converted to GBP)

Level of care required	Lost income
Lost family income - US$ (2018)	
16–24 hours/day	$21,598
8–15 hours/day	$7,323
1–8 hours/day	$4,170
SMA-specific care not needed	$0
Lost family income - GBP (2018)	
16–24 hours/day	£16,989
8–15 hours/day	£5,760
1–8 hours/day	£3,280
SMA-specific care not needed	£0

Abbreviations: GBP, Great British Pound; US, United States.

The resulting values were applied to the various health states dependent on the age of the patient (Table 123).

Table 123: Lost family income by health state and age band

Cycle	Age at end of cycle	E	D	C	B	A
1–4	0–<24 months	£8,494	£8,494	£8,494	£8,494	0
5–6	24–<36 months	£8,494	£8,494	£8,494	£8,494	0
7–8	36–<60 months	£16,989	£16,989	£16,989	£16,989	0
9–21	5–17 years	£16,989	£16,989	£5,760	£5,760	0
22+	18+ years	£16,989	£16,989	£3,280	£0	0

The consequences of introducing these lifetime potential earnings on total costs are that the total per patient costs for nusinersen increase by £107,815 (from £2,270,315 to £2,378,131) whilst the total per patient costs for onasemnogene abeparvovec treated patients increases by £126,249 (from £2,614,400 to £2,740,649).

The impact on the ICER's of introducing these lifetime productivity estimates is that the ICER for onasemnogene abeparvovec versus BSC increases from £177,061 to £183,362 whilst the ICER for onasemnogene abeparvovec versus nusinersen increases from £35,788 to £37,705.

When these results for lost family income are combined with the results from including potential income gains as discussed in Section 14.1, the baseline ICER (no inclusion for lost family income nor potential income gains) for onasemnogene abeparvovec versus BSC decreases from £177,061 to £175,796 whilst the ICER for onasemnogene abeparvovec versus nusinersen decreases from £35,788 to £29,471.

We also used the results from the SMA UK Patient and Caregiver survey (March 2019) (76) to examine the impact on total costs. The survey found that the average annual cost for loss of productivity per unpaid caregiver at £14,350 based on reducing their hours by 25 hours per week. Using these costs in the model increased the total costs for BSC patients by £49,331 per year, by £99,718 for nusinersen treated patients and by £202,608 for onasemnogene abeparvovec treated patients. We note, however, that the £14,350 figure is an average for all SMA patients and that these results probably underestimate the time inputs for non-sitting patients and overestimate the time inputs for walking patients.

It should be noted that these caregiver estimates are based only on a single carer. The SMA UK Patient and Caregiver survey (March 2019) (76) indicates that a wide range of carers provide support to patients with SMA ranging from immediate family friends and neighbours.

14.5 *Describe the impact of the technology on strengthening the evidence base on the clinical effectiveness of the treatment or disease area. If any research initiatives relating to the treatment or disease area are planned or ongoing, please provide details.*

Onasemnogene abeparvovec has demonstrated efficacy and safety in infants with SMA type 1 in the clinical trial programme to date (Section 9.6). In addition, the impact (both proven and potential) has been recognised by clinical experts in the UK (Section 12.2.5.2). In START, observations of substantial benefits in survival, motor function, and developmental milestone achievements relative to natural history cohorts were reported (67), which were particularly striking for several patients treated at younger ages (Section 9.6.1.1). This supports the administration of gene replacement therapy as early as possible to prevent extensive neurodegeneration. In addition, results of the cognitive assessment of infants treated with the therapeutic dose of onasemnogene abeparvovec suggest that these children have cognitive skills similar to typically developing children, contradicting the theory that infants with SMA type 1 tend to be cognitively delayed (130, 195).

The efficacy and safety of onasemnogene abeparvovec is being investigated in ongoing trials in larger patient cohorts and broader geographical locations (STR1VE-EU and US) than those assessed in START, as well as pre-symptomatic patients and patients with different *SMN2* copy numbers in SPR1NT. The long-term efficacy and safety of onasemnogene abeparvovec will also be monitored in LT-001. To provide further long-term data AveXis also plan to introduce a patient registry (RESTORE) – see Section 14.7.

14.6 *Describe the anticipated impact of the technology on innovation in the UK.*

As described in Section 8.5, onasemnogene abeparvovec represents a step change in the clinical management of SMA type 1 in the UK on the basis of its ability to change the natural course of the disease. Further, as the first one-time gene replacement therapy for SMA type 1, onasemnogene offers a transformative approach to therapy, eliminating the need for the chronic treatment burden associated with nusinersen. The introduction of onasemnogene abeparvovec provides a signal to the UK Life Sciences industry that pursuing research of single administration through to clinical practice is possible.

It is anticipated that the use of onasemnogene abeparvovec will lead to greater understanding of the epidemiology, pathology, and management of SMA type 1 and potential opportunities to optimise treatment. Improved understanding of SMA type 1 and the phenotype of infants following administration of onasemnogene abeparvovec may also provide insights into SMA type 2 or 3, enabling improvements in the management of infants with SMA beyond those with SMA type 1. In addition, the introduction of new-born screening for SMA in the UK as a result of the availability of a novel treatment could lead to identification of infants with SMA pre-symptomatically and the opportunity to improve clinical outcomes as a result of treatment prior to extensive neuronal damage.

14.7 *Describe any plans for the creation of a patient registry (if one does not currently exist) or the collection of clinical effectiveness data to evaluate the benefits of the technology over the next 5 years.*

AveXis is establishing a patient registry (RESTORE) to provide long-term data on the efficacy and safety of onasemnogene abeparvovec. The registry will follow approximately 500 infants with SMA in clinical practice, including 100 patients treated with existing or upcoming approved treatments. Infants in the US, UK, France, Germany, Italy, Spain, and other countries will be included in the registry. Information collated will include patient demographics, genetic status, family and medical history, and details of treatments received. The output from the registry will include long-term effectiveness and safety outcomes in a real-world observational setting, including the pulmonary and nutritional requirements of patients, hospitalisations, AEs, and caregiver burden and QoL. The registry will collate data for patients every 6 months until the 24 month visit and then annually for up to 15 years or until death.

In addition to the RESTORE registry, AveXis is collating long-term data for patients treated with onasemnogene abeparvovec in START in the ongoing observational long-term, single-centre study LT-001 and will also collate long-term data in LT-002. The longitudinal clinical data of infants treated with onasemnogene abeparvovec is also expected to be captured by the existing SMA REACH registry.

14.8 *Describe any plans on how the clinical effectiveness of the technology will be reviewed.*

The clinical effectiveness of onasemnogene abeparvovec will be reviewed annually in the LT-001 and LT-002 long-term follow-up studies. Assessment will include analysis of whether the highest milestone attained in START has been maintained. In the RESTORE patient registry, the pulmonary and nutritional requirements of patients, hospitalisations, AEs, and caregiver burden and QoL will be assessed every 6 months until the 24 month visit and then annually for up to 15 years or until death. Results and data from ongoing trials (STR1VE-US, STR1VE-ES and SPR1NT) will also be analysed once available. In addition, the longitudinal clinical data of infants treated with onasemnogene abeparvovec is also expected to be captured by the existing SMA REACH registry.

14.9 *What level of expertise in the relevant disease area is required to ensure safe and effective use of the technology?*

As described in Section 8.4, patients with SMA type 1 treated with onasemnogene abeparvovec will be managed by an MDT led by a paediatric neurologist at designated specialist neuromuscular centres. As infants will be treated with onasemnogene abeparvovec at specialist infusion centres AveXis expect any training required for the administration of onasemnogene abeparvovec to be minimal. AveXis will provide training for clinicians, pharmacists and other relevant HCPs in the appropriate handling and administration of onasemnogene abeparvovec to ensure that infusion centres are fully

prepared. A peripheral IV infusion is not a complex procedure and is completed within 60 minutes. Hospital infusion centres will follow local biosafety procedures.

14.10 *Would any additional infrastructure be required to ensure the safe and effective use of the technology and equitable access for all eligible patients?*

It is anticipated that the management of patients prior to and following a single IV infusion with onasemnogene abeparvovec will be provided by the network of specialised paediatric neuromuscular services which is already commissioned for the provision and delivery of BSC to infants with SMA type 1. However, as the treatment is to be tailored to individual infants and infused in very few highly specialised centres (3 or 4), a protocol is likely to be required to facilitate the one-time infusion of onasemnogene abeparvovec. AveXis is committed to working with UK neuromuscular centres to scope and design a service delivery that includes onasemnogene abeparvovec. This work includes engaging with clinical experts, expert patient advisory groups and NHS stakeholders (e.g. NHS England and NICE).

An assessment of baseline characteristics will be conducted and patients will require a test for the AAV9 antibody prior to treatment (1). AAV9 antibody testing will be initiated at the patients' local neuromuscular centre to inform the discussion of treatment options between clinicians and families. AAV9 antibody testing could potentially be performed at the same time as *SMN1/SMN2* genetic testing. AAV9 antibody testing will be funded and coordinated by AveXis at a central European lab (Viroclinics, The Netherlands) and results produced within 4 days. The exact requirements of AAV9 antibody testing are subject to the SmPC, which is being finalised at the time of this submission.

Section F - Managed Access Arrangements (please see sections 55-59 of the HST methods guide on MAAs)

15 Managed Access Arrangement

15.1 *Describe the gaps identified in the evidence base, and the level of engagement with clinical and patient groups to develop the MAA*

Although a MAA for onasemnogene abeparvovec is not currently proposed, AveXis is committed to working with NICE and relevant UK stakeholders (clinicians, patient-society groups and commissioners) to assess the suitability of a MAA or alternative arrangements as part of this HST appraisal.

15.2 *Describe the specifics of the MAA proposal, including:*

- ***The duration of the arrangement, with a rationale***
- ***What evidence will be collected to reduce uncertainty***
- ***How this evidence will be collected and analysed***
- ***The clinical criteria to identify patients eligible to participate in the MAA, and criteria for continuing or stopping treatment during the MAA***
- ***Any additional infrastructure requirements to deliver the MAA (e.g. databases or staffing)***
- ***Funding arrangement, including any commercial proposals or financial risk management plans***
- ***The roles and responsibilities of clinical and patient groups during the MAA***
- ***What will happen to patients receiving treatment who are no longer eligible for treatment if a more restricted or negative recommendation is issued after the guidance has been reviewed***

Not applicable.

15.3 *Describe the effect the MAA proposal will have on value for money; if possible, include the results of economic analyses based on the MAA*

Not applicable.

16 References

1. AveXis. Data on File: Draft SmPC onasemnogene abeparvovec. 2019.
2. Mendell JR, Al-Zaidy S, Shell R, et al. Single-Dose Gene-Replacement Therapy for Spinal Muscular Atrophy. N Engl J Med. 2017 Nov 2;377(18):1713-22.
3. Mulcahy PJ, Iremonger K, Karyka E, et al. Gene therapy: a promising approach to treating spinal muscular atrophy. Hum Gene Ther. 2014 Jul;25(7):575-86.
4. Lally C, Jones C, Farwell W, et al. Indirect estimation of the prevalence of spinal muscular atrophy Type I, II, and III in the United States. Orphanet Journal of Rare Diseases. 2017 November 28;12(1):175.
5. Verhaart IEC, Robertson A, Wilson IJ, et al. Prevalence, incidence and carrier frequency of 5q-linked spinal muscular atrophy - a literature review. Orphanet J Rare Dis. 2017 Jul 4;12(1):124.
6. Office for National Statistics. Birth Summary Tables, England and Wales 2017, 18 Jul 2018. Available at: https://www.ons.gov.uk/peoplepopulationandcommunity/birthsdeathsandmarriages/livebirths/bulletins/birthsummarytablesenglandandwales/2017/relateddata. .
7. Kolb SJ, Kissel JT. Spinal muscular atrophy: a timely review. Arch Neurol. 2011 Aug;68(8):979-84.
8. Farrar MA, Vucic S, Johnston HM, et al. Pathophysiological insights derived by natural history and motor function of spinal muscular atrophy. J Pediatr. 2013 Jan;162(1):155-9.
9. Swoboda KJ, Prior TW, Scott CB, et al. Natural history of denervation in SMA: relation to age, SMN2 copy number, and function. Ann Neurol. 2005 May;57(5):704-12.
10. Soler-Botija C, Ferrer I, Gich I, et al. Neuronal death is enhanced and begins during foetal development in type I spinal muscular atrophy spinal cord. Brain. 2002 Jul;125(Pt 7):1624-34.
11. Kolb SJ, Kissel JT. Spinal Muscular Atrophy. Neurol Clin. 2015 Nov;33(4):831-46.
12. Finkel RS, McDermott MP, Kaufmann P, et al. Observational study of spinal muscular atrophy type I and implications for clinical trials. Neurology. 2014a Aug 26;83(9):810-7.
13. Qian Y, McGraw S, Henne J, et al. Understanding the experiences and needs of individuals with Spinal Muscular Atrophy and their parents: a qualitative study. BMC Neurol. 2015 Oct 24;15:217.
14. Alanizi A, A., D'Argenzio, L,D., Hacohan, Y,H., Edel, L,E., Wallis, C,W., Chan, E,C., Abel, F,A., Munot, P,M., Robb, S,R., Craig, F,C., Muntoni, F,M., Manzur, A,M. Spinal Motor Atrophy Type 1: clinical outcome and evolution of care of SMA1 at a single neuromuscular centre in the decade 2007-2017. Abstract presented on the 4th January 2018 at the Developmental medicine and child neurology conference. 2018.
15. Finkel RS, Mercuri E, Meyer OH, et al. Diagnosis and management of spinal muscular atrophy: Part 2: Pulmonary and acute care; medications, supplements and immunizations; other organ systems; and ethics. Neuromuscul Disord. 2018 Mar;28(3):197-207.
16. Mercuri E, Finkel RS, Muntoni F, et al. Diagnosis and management of spinal muscular atrophy: Part 1: Recommendations for diagnosis, rehabilitation, orthopedic and nutritional care. Neuromuscul Disord. 2018a Feb;28(2):103-15.
17. AveXis. Data on file: UK Clinical Advisory Board: Summary Report. 28 May 2019. 2019.
18. AveXis. Date on file: UK Healthcare Resource Use Study Report. 14 June 2019. 2019.
19. National Institute for Health and Care Excellence. Managed Access Agreement - Nusinersen for treating spinal muscular atrophy. Published date: 24 July 2019. 2019.

20. National Institute for Health and Care Excellence. Technology appraisal guidance [TA588] - Nusinersen for treating spinal muscular atrophy. Published date: 24 July 2019. 2019.
21. Electronic Medicines Compendium (eMC), . Spinraza Summary of Product Characteristics. July 2019. Available at: https://www.medicines.org.uk/emc/product/2715/smpc. . 2019.
22. Finkel RS, Mercuri E, Darras BT, et al. Nusinersen versus Sham Control in Infantile-Onset Spinal Muscular Atrophy. N Engl J Med. 2017a Nov 2;377(18):1723-32.
23. La Foresta S, Faraone C, Sframeli M, et al. Intrathecal administration of Nusinersen in type 1 SMA: successful psychological program in a single Italian center. Neurol Sci. 2018 Nov;39(11):1961-4.
24. Al-Zaidy S, Pickard AS, Kotha K, et al. Health outcomes in spinal muscular atrophy type 1 following AVXS-101 gene replacement therapy. Pediatr Pulmonol. 2019 Feb;54(2):179-85.
25. Avexis. Data on file. Clinical Study Report (CSR). START (CL-101). 2018.
26. Kolb SJ, Coffey CS, Yankey JW, et al. Baseline results of the NeuroNEXT spinal muscular atrophy infant biomarker study. Ann Clin Transl Neurol. 2016 Feb;3(2):132-45.
27. Kolb SJ, Coffey CS, Yankey JW, et al. Natural history of infantile-onset spinal muscular atrophy. Ann Neurol. 2017 Dec;82(6):883-91.
28. AveXis. Data on file: Day 120 efficacy data update (31 Dec 2018). 2019.
29. Mendell JR, Shell R., Lehman, K.J., McColly, M., Lowes, L.P., Alfano, L.N., Miller, N.F., Iammarino, M.A., Church, K., Ogrinc, F.G., Ouyang, H., Kernbauer, E., Shah, S., L'Italien, J., Sproule, D.M., Feltner, D.E., Al-Zaidy, S. AVXS-101 Gene-Replacement Therapy in Spinal Muscular Atrophy Type 1: Long-Term Follow-Up From the Phase 1/2a Clinical Trial. Poster presented at AAN 2019. Data on file. 2019.
30. AveXis. Data on file. Indirect treatment Comparison (ITC) of onasemnogene abeparvovec and nusinersen. Technical report. Version 6. July 2019 2019.
31. National Institute for Health and Care Excellence. Single Technology Appraisal. Nusinersen for treating spinal muscular atrophy [ID1069], Appraisal Consultation Document Committee Papers. Published: 14 August 2018. 2018.
32. US Institute for Clinical and Economic Review. Spinraza® and Zolgensma® for Spinal Muscular Atrophy: Effectiveness and Value. Final Evidence Report. April 3, 2019. (Updated May 24, 2019). 2019.
33. National Institute for Health and Care Excellence. Highly Specialised Technologies Evaluation. Onasemnogene abeparvovec for treating spinal muscular atrophy type 1. Final scope. 2019.
34. Thomas CE, Ehrhardt A, Kay MA. Progress and problems with the use of viral vectors for gene therapy. Nat Rev Genet. 2003 May;4(5):346-58.
35. Saraiva J, Nobre RJ, Pereira de Almeida L. Gene therapy for the CNS using AAVs: The impact of systemic delivery by AAV9. J Control Release. 2016 Nov 10;241:94-109.
36. Merkel SF, Andrews AM, Lutton EM, et al. Trafficking of adeno-associated virus vectors across a model of the blood-brain barrier; a comparative study of transcytosis and transduction using primary human brain endothelial cells. J Neurochem. 2017 Jan;140(2):216-30.
37. Bevan AK, Duque S, Foust KD, et al. Systemic gene delivery in large species for targeting spinal cord, brain, and peripheral tissues for pediatric disorders. Mol Ther. 2011 Nov;19(11):1971-80.
38. Foust KD, Nurre E, Montgomery CL, et al. Intravascular AAV9 preferentially targets neonatal neurons and adult astrocytes. Nat Biotechnol. 2009 Jan;27(1):59-65.

39. Naso MF, Tomkowicz B, Perry WL, 3rd, et al. Adeno-Associated Virus (AAV) as a Vector for Gene Therapy. BioDrugs. 2017 Aug;31(4):317-34.
40. Akst J. Targeting DNA. Published in The Scientist. Available at: https://www.the-scientist.com/features/targeting-dna-40937. 2012.
41. AveXis. Data on file. STR1VE-EU (CL-302) Protocol. Version 4.0, 17 May 2019. 2019.
42. AveXis. Data on file. Clinical Overview. onasemnogene abeparvovec [data_cut_08Mar2019]. 2019.
43. AveXis. Data on file: Day 120 efficacy data cut (27 September 2018). 2019.
44. AveXis. Data on file: Day 120 safety update (27 September 2018). 2019.
45. AveXis. Data on file. STR1VE-US (CL-303) Protocol. Version 4.0, 4 Oct 2018. 2018.
46. AveXis. AveXis. Data on file. SPR1NT (CL-304) Protocol. Version 4.0, 30 May 2019. 2019.
47. AveXis. Data on file. LT-001 Protocol. Version 4.0. 5 Oct 2018. 2018.
48. AveXis. Data on file. LT-002 Protocol. Version 3.0, 17 Jun 2019. 2019.
49. AveXis. Data on file. LT-002 Statistical Analysis Plan (SAP). Version 0.3, 15 Jan 2019. 2019.
50. De Sanctis R, Coratti G, Pasternak A, et al. Developmental milestones in type I spinal muscular atrophy. 2016.
51. Wirth B, Brichta L, Schrank B, et al. Mildly affected patients with spinal muscular atrophy are partially protected by an increased SMN2 copy number. Hum Genet. 2006 May;119(4):422-8.
52. Feldkotter M, Schwarzer V, Wirth R, et al. Quantitative analyses of SMN1 and SMN2 based on real-time lightCycler PCR: fast and highly reliable carrier testing and prediction of severity of spinal muscular atrophy. Am J Hum Genet. 2002 Feb;70(2):358-68.
53. Spinal Muscular Atrophy UK. Looking after your baby with spinal muscular atrophy type 1. . Available at https://smauk.org.uk/looking-after-your-baby (accessed March 2019). 2019.
54. Wadman RI, Stam M, Gijzen M, et al. Association of motor milestones, SMN2 copy and outcome in spinal muscular atrophy types 0-4. J Neurol Neurosurg Psychiatry. 2017 Apr;88(4):365-7.
55. Prior TW FE. Spinal muscular atrophy. Last updated: December 22, 2016. In: Pagon RA, Adam MP, Ardinger HH, et al, eds. GeneReviews® [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2017. 2016.
56. Lin CW, Kalb SJ, Yeh WS. Delay in Diagnosis of Spinal Muscular Atrophy: A Systematic Literature Review. Pediatr Neurol. 2015 Oct;53(4):293-300.
57. Hao le T, Duy PQ, Jontes JD, et al. Temporal requirement for SMN in motoneuron development. Hum Mol Genet. 2013 Jul 1;22(13):2612-25.
58. Monani UR, Osborne MA, Lutz CM. Chapter 11 - Temporal Requirements for the Survival Motor Neuron Protein. In: Sumner CJ, Paushkin S, Ko C-P, editors. Spinal Muscular Atrophy: Academic Press; 2017. p. 183-9.
59. Finkel RS, Weiner DJ, Mayer OH, et al. Respiratory muscle function in infants with spinal muscular atrophy type I. Pediatr Pulmonol. 2014b Dec;49(12):1234-42.
60. De Sanctis R, Pane M, Coratti G, et al. Clinical phenotypes and trajectories of disease progression in type 1 spinal muscular atrophy. Neuromuscul Disord. 2018 Jan;28(1):24-8.
61. D'Amico A, Mercuri E, Tiziano FD, et al. Spinal muscular atrophy. Orphanet J Rare Dis. 2011 Nov 2;6:71.
62. Bach JR. Is Noninvasive Ventilation Always the Most Appropriate Manner of Long-term Ventilation for Infants With Spinal Muscular Atrophy Type 1? Yes, Almost Always. CHEST. 2017;151(5):962-5.

63. Oskoui M, Levy G, Garland CJ, et al. The changing natural history of spinal muscular atrophy type 1. Neurology. 2007 Nov 13;69(20):1931-6.
64. Wang CH, Finkel RS, Bertini ES, et al. Consensus statement for standard of care in spinal muscular atrophy. J Child Neurol. 2007 Aug;22(8):1027-49.
65. AveXis. Data on file. UK HES INCIDENCE data - 2013 - 2017. 2019.
66. Specht S, Eglon, G., Turner, M., Straub, V., Bettolo, C,M. Mortality in patients with spinal muscular atrophy over the last 10 years in the Northeast of the UK. Poster presented at the Twelfth UK Neuromuscular Translational Research Conference 4th –5th April 2019. 2019.
67. AveXis. Data on file. PNCR and NeuroNext database report. 2018.
68. Finkel RS. Electrophysiological and motor function scale association in a pre-symptomatic infant with spinal muscular atrophy type I. Neuromuscul Disord. 2013 Feb;23(2):112-5.
69. Govoni A, Gagliardi D, Comi GP, et al. Time Is Motor Neuron: Therapeutic Window and Its Correlation with Pathogenetic Mechanisms in Spinal Muscular Atrophy. Mol Neurobiol. 2018 Aug;55(8):6307-18.
70. Borkowska J, Rudnik-Schoneborn S, Hausmanowa-Petrusewicz I, et al. Early infantile form of spinal muscular atrophy (Werdnig-Hoffmann disease) with prolonged survival. Folia Neuropathol. 2002;40(1):19-26.
71. Ioos C, Leclair-Richard D, Mrad S, et al. Respiratory capacity course in patients with infantile spinal muscular atrophy. Chest. 2004 Sep;126(3):831-7.
72. Bach JR, Baird JS, Plosky D, et al. Spinal muscular atrophy type 1: management and outcomes. Pediatr Pulmonol. 2002 Jul;34(1):16-22.
73. Chung BH, Wong VC, Ip P. Spinal muscular atrophy: survival pattern and functional status. Pediatrics. 2004 Nov;114(5):e548-53.
74. Lopez-Bastida J, Pena-Longobardo LM, Aranda-Reneo I, et al. Social/economic costs and health-related quality of life in patients with spinal muscular atrophy (SMA) in Spain. Orphanet J Rare Dis. 2017 Aug 18;12(1):141.
75. Iannaccone ST, Hynan LS, Morton A, et al. The PedsQL in pediatric patients with Spinal Muscular Atrophy: feasibility, reliability, and validity of the Pediatric Quality of Life Inventory Generic Core Scales and Neuromuscular Module. Neuromuscul Disord. 2009 Dec;19(12):805-12.
76. National Institute for Health and Care Excellence. SMA UK Patient and Caregiver Survey – Summary of results – 5 March 2019. 2019.
77. Klug C, Schreiber-Katz O, Thiele S, et al. Disease burden of spinal muscular atrophy in Germany. Orphanet J Rare Dis. 2016 May 4;11(1):58.
78. Bach JR, Vega J, Majors J, et al. Spinal muscular atrophy type 1 quality of life. Am J Phys Med Rehabil. 2003 Feb;82(2):137-42.
79. Higgs EJ, McClaren BJ, Sahhar MA, et al. 'A short time but a lovely little short time': Bereaved parents' experiences of having a child with spinal muscular atrophy type 1. Journal of Paediatrics and Child Health. 2016;52(1):40-6.
80. NHS England. Urgent Clinical Commissioning Policy Statement: Nusinersen for genetically confirmed Spinal Muscular Atrophy (SMA) type 1 for eligible patients under the Expanded Access Programme (EAP). Available at https://www.england.nhs.uk/wp-content/uploads/2018/12/Nusinersen-for-genetically-confirmed-spinal-muscular-atrophy-Type-1-for-eligible-patients-under-the-expanded-a.pdf (accessed March 2019). 2018.
81. Colella P, Ronzitti G, Mingozzi F. Emerging Issues in AAV-Mediated In Vivo Gene Therapy. Mol Ther Methods Clin Dev. 2018 Mar 16;8:87-104.
82. Calcedo R, Morizono H, Wang L, et al. Adeno-associated virus antibody profiles in newborns, children, and adolescents. Clin Vaccine Immunol. 2011 Sep;18(9):1586-8.

83. Mimuro J, Mizukami H, Shima M, et al. The prevalence of neutralizing antibodies against adeno-associated virus capsids is reduced in young Japanese individuals. J Med Virol. 2014 Nov;86(11):1990-7.
84. Day JW, Finkel, R.S., Mercuri, E., Swoboda, K.J., Kernbauer, E., Ogrinc, F.G., Menier, M., Sproule, D.M., Feltner, D.E., Mendell, J.R. Adeno-Associated Virus Serotype 9 Antibodies in Patients With Spinal Muscular Atrophy Screened for Treatment With Onasemnogene Abeparvovec. The 2019 Annual SMA Conference, Anaheim, CA, June 27–30, 2019. (Data on file). 2019a.
85. AveXis. Data on file. Systematic literature review of clinical and economic evidence for interventions for spinal muscular atrophy. Technical Report. Version 6. 20 May 2019. . 2019.
86. Scottish Intercollegiate Guidelines Network. SIGN Search filters. https://www.sign.ac.uk/search-filters.html. 2019.
87. Canadian Agency for Drugs and Technologies in Health. CADTH resources. https://www.cadth.ca/resources. 2019.
88. US National Institutes of Health Clinical Trial Registry. http://www.clinicaltrials.gov. .
89. EU Clinical Trials Registry. https://www.clinicaltrialsregister.eu/. .
90. Moher D, Liberati A, Tetzlaff J, et al. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. J Clin Epidemiol. 2009 Oct;62(10):1006-12.
91. Higgins JP, Altman DG, Gotzsche PC, et al. The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. Bmj. 2011 Oct 18;343:d5928.
92. Wells G, Shea B, O'Connell J. The Newcastle-Ottawa Scale (NOS) for Assessing The Quality of Nonrandomised Studies in Meta-analyses. 2013 [updated 2013; cited 2016 October 1]; Available from: http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp.; 2013.
93. University of York Centre for Reviews and Dissemination. Quality Assessment. Systematic Reviews. Available at: https://www.york.ac.uk/media/crd/Systematic_Reviews.pdf. 2009.
94. Drummond MF, Jefferson TO. Guidelines for authors and peer reviewers of economic submissions to the BMJ. The BMJ Economic Evaluation Working Party. Bmj. 1996 Aug 3;313(7052):275-83.
95. Bertini E, Dessaud E, Mercuri E, et al. Safety and efficacy of olesoxime in patients with type 2 or non-ambulatory type 3 spinal muscular atrophy: a randomised, double-blind, placebo-controlled phase 2 trial. Lancet Neurol. 2017 Jul;16(7):513-22.
96. Chen TH, Chang JG, Yang YH, et al. Randomized, double-blind, placebo-controlled trial of hydroxyurea in spinal muscular atrophy. Neurology. 2010 Dec 14;75(24):2190-7.
97. Mercuri E, Darras BT, Chiriboga CA, et al. Nusinersen versus Sham Control in Later-Onset Spinal Muscular Atrophy. N Engl J Med. 2018b Feb 15;378(7):625-35.
98. Chiriboga CA, Swoboda KJ, Darras BT, et al. Results from a phase 1 study of nusinersen (ISIS-SMN(Rx)) in children with spinal muscular atrophy. Neurology. 2016 Mar 8;86(10):890-7.
99. Finkel RS, Chiriboga CA, Vajsar J, et al. Treatment of infantile-onset spinal muscular atrophy with nusinersen: a phase 2, open-label, dose-escalation study. Lancet. 2016 Dec 17;388(10063):3017-26.
100. Shieh PB, Acsadi G, Mueller-Felber W, et al. Safety and Efficacy of Nusinersen in Infants/Children with Spinal Muscular Atrophy (SMA): Part 1 of the Phase 2 EMBRACE Study (P2.324). Available at: https://n.neurology.org/content/90/15_Supplement/P2.324. Neurology. 2018;90(15 Supplement):P2.324.

101. Frongia A, De Benito, D., Alarcon-Cornejo, M., Carrera-Garcia, L., Borras, A., Padros, N. . Salbutamol treatment in Type 2 SMA patients: 18 months assessment. . Journal of Neuromuscular Diseases. 2018.
102. Chiriboga C, A., Mercuri, E., Fischer, D., Kraus, D., Yeung, W,H., Kletzl, H., Gerber, M., Cleary, Y., Gorni, K., Khwaja, O. JEWELFISH: Risdiplam (RG7916) increases SMN protein in non-naïve patients with SMA. Poster presented at the 23rd International Annual Congress of the World Muscle Society, Mendoza, Argentina, October 2–6, 2018. Available at: https://medically.roche.com/content/dam/pdmahub/non-restricted/neurology/wms-2018/WMS_2018_JEWELFISH_risdiplam_poster_Chiriboga.pdf. 2018.
103. Kirschner J, Schorling D, Hauschke D, et al. Somatropin treatment of spinal muscular atrophy: a placebo-controlled, double-blind crossover pilot study. Neuromuscul Disord. 2014 Feb;24(2):134-42.
104. Kissel JT, Scott CB, Reyna SP, et al. SMA CARNIVAL TRIAL PART II: a prospective, single-armed trial of L-carnitine and valproic acid in ambulatory children with spinal muscular atrophy. PLoS One. 2011;6(7):e21296.
105. Krosschell KJ, Kissel JT, Townsend EL, et al. Clinical trial of L-Carnitine and valproic acid in spinal muscular atrophy type I. Muscle Nerve. 2018 Feb;57(2):193-9.
106. Deconinck N, Born, A., Baranello, G., Bertini, E., Goemans, N., Pingili, R. . Branaplam in Type 1 Spinal Muscular Atrophy: Respiratory support and feeding. . Journal of Neuromuscular Diseases. 2018.
107. De Vivo D, Bertini, E., Hwu, W., et al. . Nusinersen in Infants Who Initiative Treatment in a Presymptomatic Stage of Spinal Muscular Atrophy (SMA): Interim Efficacy and Safety Results from the Phase 2 NURTURE Study. Muscular Dystrophy Association (MDA) Clinical Conference. 2018.
108. Muntoni F, Buchbjerg J, Bertini E, et al. A Long-Term, Open-Label Follow-Up Study of Olesoxime in Patients with Type 2 or Non-Ambulatory Type 3 Spinal Muscular Atrophy who Participated in a Placebo-Controlled Phase 2 Trial (S46.002). Neurology. 2018;90(15 Supplement):S46.002.
109. Russman BS, Iannaccone ST, Samaha FJ. A phase 1 trial of riluzole in spinal muscular atrophy. Arch Neurol. 2003 Nov;60(11):1601-3.
110. Finkel R, Castro, D., Farrar, M.A., Tulinius, M., Krosschell, K.J., Saito, K., Zhang, Y., Bhan, I., Farwell, W., Reyna, S.P. Longer-term assessment of nusinersen safety/efficacy in infantile-onset spinal muscular atrophy: interim analysis of SHINE. . Journal of Neuromuscular Diseases. 2018.
111. Swoboda KJ, Scott CB, Crawford TO, et al. SMA CARNI-VAL trial part I: double-blind, randomized, placebo-controlled trial of L-carnitine and valproic acid in spinal muscular atrophy. PLoS One. 2010 Aug 19;5(8):e12140.
112. Swoboda KJ, Scott CB, Reyna SP, et al. Phase II open label study of valproic acid in spinal muscular atrophy. PLoS One. 2009;4(5):e5268.
113. Finkel R, Kuntz N, Mercuri E, et al. Efficacy and safety of nusinersen in infants with spinal muscular atrophy (SMA): Final results from the phase 3 ENDEAR study. European Journal of Paediatric Neurology. 2017b;21:e14-e5.
114. Servais L, Farrar M, Finkel R, et al. Nusinersen demonstrates greater efficacy in infants with shorter disease duration: End of study results from the ENDEAR study in infants with spinal muscular atrophy (SMA). Neuromuscular Disorders. 2017;27:S211.
115. McNeil E, Finkel, R., Darras, B., Kirschner, J., Farrar, M., Ryan, M., Zhong, Z., Gheuns, S., Farwell, W. Nusinersen improves motor function in infants with and without permanent ventilation: results from the ENDEAR Study in Infantile-Onset Spinal Muscular Atrophy (SMA). Annals of neurology. 2017;82:S264-S265.
116. Yan L, Kuntz, N., Farwell, W., Zhong, Z.J., Sun, P., Gheuens, S., Schneider, E., Finkel. R. Nusinersen in infants with spinal muscular atrophy(SMA): design/interim

results of the ENDEAR study. No to hattatsu [brain and development] (Official Journal of The Japanese Society of Child Neurology). 2017;49.
117. Farrar MA, Park SB, Vucic S, et al. Emerging therapies and challenges in spinal muscular atrophy. Ann Neurol. 2017 Mar;81(3):355-68.
118. World Health Organization. WHO Motor Development Study: windows of achievement for six gross motor development milestones. Acta Paediatr Suppl. 2006a Apr;450:86-95.
119. Bayley N. Bayley scales of infant and toddler development: Bayley-III: Harcourt Assessment, Psych. Corporation. 2006.
120. Wijnhoven TM, de Onis M, Onyango AW, et al. Assessment of gross motor development in the WHO Multicentre Growth Reference Study. Food Nutr Bull. 2004 Mar;25(1 Suppl):S37-45.
121. Glanzman AM, McDermott MP, Montes J, et al. Validation of the Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders (CHOP INTEND). Pediatr Phys Ther. 2011 Winter;23(4):322-6.
122. Glanzman AM, Mazzone E, Main M, et al. The Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders (CHOP INTEND): test development and reliability. Neuromuscul Disord. 2010 Mar;20(3):155-61.
123. World Health Organization. WHO Multicentre Growth Reference Study Group: WHO Child Growth Standards based on length/height, weight and age. Acta Paediatr Suppl. 2006b Apr;450:76-85.
124. Mercuri E, Baranello, G., Day, J.W., Bruno, C., Corti, S., Chiriboga, C.A., Crawford, T.O., Darras, B.T., Finkel, R.S., Connolly, A.M., Iannaccone, S.T., Kuntz, N.L., Masson, R., Peña, L.D.M., Schultz, M., Shieh, P.B., Smith, E.C., Feltner, D.E., Ouyang, H., Lavrov, A., Kernbauer, E., Williamson, S., L'Italien, J., Sproule, D.M., Mendell, J.R., Muntoni, F. Onasemnogene Abeparvovec Gene-Replacement Therapy for Spinal Muscular Atrophy Type 1: Clinical Update (STR1VE and STR1VE-EU). Presentation at EAN 2019. (Data on file). 2019.
125. Strauss KA, Swoboda, K.J., Farrar, M.A., McMillan, H.J., Parsons, J., Krueger, J.M., Iannaccone, S.T., Chiriboga, C.A., Kwon, J.A.,M Saito, K., Scoto, M.,. Schult, M., Kernbauer, E., Farrow, M., Ogrinc, F.G., Kavanagh, S., Feltner, D.E., McGill, B.E., L'Italien, J., Sproule, D.M., Muntoni, F. Onasemnogene Abeparvovec-xioi in Presymptomatic Spinal Muscular Atrophy: SPR1NT Study Update as of March 8, 2019 . Presentation at CureSMA 2019. (Data on file). 2019a.
126. de Onis M, Garza, C., Victora, C.G., Bhan, M.K., Norum, K.R. The WHO multicentre growth reference study (MGRS): Rationale, planning, and implementation. Food and Nutrition Bulletin. 2004;25(1 supplement 1).
127. Prior TW, Krainer AR, Hua Y, et al. A positive modifier of spinal muscular atrophy in the SMN2 gene. Am J Hum Genet. 2009 Sep;85(3):408-13.
128. Alfano L LL, Al-Zaidy S, et al. . AVXS-101 phase 1 gene replacement therapy clinical trial in SMA type 1: patients treated early with the proposed therapeutic dose were able to sit unassisted at a younger age. Oral presentation at: the 70th Annual American Academy of Neurology (AAN) Meeting; April 21-27, 2018; Los Angeles, CA.
129. Bromberg MB, Swoboda KJ. Motor unit number estimation in infants and children with spinal muscular atrophy. Muscle Nerve. 2002 Mar;25(3):445-7.
130. Lowes LPA, L.N.; Miller, N.f.; Iammarino, M.; Dugan, M.; Berry, K.; Al-Zaidy, S.; Mendell J.R. Gene replacement therapy study for spinal muscular atrophy type 1: patients demonstrate cognitive, fine motor and language abilities within the normal range [poster]. Presented at the International Scientific Congress on Spinal Muscular Atrophy; January 25-27, 2018b; Krakow, Poland. 2018.
131. Day JW, Chiriboga, C.A., Crawford, T.O., Darras, B.T., Finkel, R.S., Connolly, A.M., Iannaccone, S.T., Kuntz, N.L., Peña, L.D.M., Schultz, M., Shieh, P.B., Smith, E.C.,

Shell1, R., Feltner, D.E., Ogrinc, F.G., Ouyang, H., Macek, T.A., Kernbauer, E., Muehring, L.M., L'Italien, J., Sproule, D.M., Kaspar, B.K., Mendell, J.R. AVXS-101 Gene-Replacement Therapy (GRT) for Spinal Muscular Atrophy Type 1 (SMA1): Pivotal Phase 3 Study (STR1VE) Update. Poster presentation (data on file). AAN. 2019b.
132. Hoy SM. Onasemnogene Abeparvovec: First Global Approval. Drugs. 2019 Jul 3.
133. Strauss KA, Swoboda, K.J., Farrar, M.A., McMillan, H.J., Parsons, J., Krueger, J.M., Iannaccone, S.T., Chiriboga, C.A., Kwon, J.M., Saito, K., Scoto, M., Schultz, M., Kernbauer, E., Farrow, M., Ogrinc, F.G., Kavanagh, S., Feltner, D.E., McGill, B.E., Spector, S.A., L'Italien, J., Sproule, D.M., Muntoni, F. AVXS-101 Gene-Replacement Therapy in Presymptomatic Spinal Muscular Atrophy: SPR1NT Study Update. Poster presentation (data on file). 2019 AAN. 2019b.
134. Chatwin M, Bush A, Simonds AK. Outcome of goal-directed non-invasive ventilation and mechanical insufflation/exsufflation in spinal muscular atrophy type I. Arch Dis Child. 2011 May;96(5):426-32.
135. Shieh P, Chen, E., Punekar, RS., Tan, H. . Treatment patterns and cost of care among patients with spinal muscular atrophy. CureSMA Annual Meeting; 2017; Orlando, FL. 2017.
136. Main M, Kairon H, Mercuri E, et al. The Hammersmith functional motor scale for children with spinal muscular atrophy: a scale to test ability and monitor progress in children with limited ambulation. European journal of paediatric neurology : EJPN : official journal of the European Paediatric Neurology Society. 2003 2003;7(4):155-9.
137. Sproule DM, Hasnain R, Koenigsberger D, et al. Age at Disease Onset Predicts Likelihood and Rapidity of Growth Failure Among Infants and Young Children With Spinal Muscular Atrophy Types 1 and 2. Journal of Child Neurology. 2012;27(7):845-51.
138. Foust KD, Wang X, McGovern VL, et al. Rescue of the spinal muscular atrophy phenotype in a mouse model by early postnatal delivery of SMN. Nat Biotechnol. 2010 Mar;28(3):271-4.
139. Meyer K, Ferraiuolo L, Schmelzer L, et al. Improving single injection CSF delivery of AAV9-mediated gene therapy for SMA: a dose-response study in mice and nonhuman primates. Mol Ther. 2015 Mar;23(3):477-87.
140. Ip S, Paulus JK, Balk EM, et al. AHRQ Methods for Effective Health Care. Role of Single Group Studies in Agency for Healthcare Research and Quality Comparative Effectiveness Reviews. Rockville (MD): Agency for Healthcare Research and Quality (US); 2013.
141. AveXis. Data on file. Biodistribution of onasemnogene abeparvovec (AVXS-101) DNA, mRNA, and SMN protein in human tissue. Presented at MDA Clinical and Scientific Conference, April 13-17. 2019.
142. AveXis. Data on file. EMA Day 120 responses. 2019.
143. Jansen JP, Trikalinos T, Cappelleri JC, et al. Indirect treatment comparison/network meta-analysis study questionnaire to assess relevance and credibility to inform health care decision making: an ISPOR-AMCP-NPC Good Practice Task Force report. Value Health. 2014 Mar;17(2):157-73.
144. National Institute for Health and Care Excellence. Nusinersen for treating spinal muscular atrophy [GID-TA10281]. 3rd appraisal committee meeting public gallery slides. 6 March 2019. 2019.
145. Arnold WD, Kassar D, Kissel JT. Spinal muscular atrophy: diagnosis and management in a new therapeutic era. Muscle Nerve. 2015 Feb;51(2):157-67.
146. Kirschner JS, KJ. Mercuri, E. Darras, B. Chirirboga, C. Nusinersen experience in individuals with spinal muscular atrophy type 3. J Neuromuscul Dis. 2018.

147. Lloyd AJGK, Thompson, R., Vaidya, S., Teynor, M. . Estimation of the health-related quality of life benefits of treatment for spinal muscular atrophy (SMA). ISPOR 20th Annual European Congress; 2017; Glasgow, Scotland.
148. Strauss KA, Carson VJ, Brigatti KW, et al. Preliminary Safety and Tolerability of a Novel Subcutaneous Intrathecal Catheter System for Repeated Outpatient Dosing of Nusinersen to Children and Adults With Spinal Muscular Atrophy. J Pediatr Orthop. 2018 Nov/Dec;38(10):e610-e7.
149. Thompson R, Vaidya S, Teynor M. The Utility of Different Approachs to Developing Health Utilities Data in Childhood Rare Diseases; A Case Study in Spinal Muscular Atrophy (SMA). Value in Health. 2017;20(9):A725-A6.
150. Zuluaga S, Knight C, Thompson R, et al. Adequately Reflecting The Clinical Benefits In Rare Disease Economic Modeling Using Sma Type I As A Casestudy. Value in Health. 2017;20(9):A722.
151. Tappenden P HJ, Kaltenthaler E, Hock E, Rawdin A, Mukuria C, Clowes M, Simonds A, Childs A. . Nusinersen for treating spinal muscular atrophy: A Single Technology Appraisal. School of Health and Related Research (ScHARR). . 2018.
152. Ara R, Brazier JE. Populating an economic model with health state utility values: moving toward better practice. Value Health. 2010 Aug;13(5):509-18.
153. Khan KA, Petrou S, Rivero-Arias O, et al. Mapping EQ-5D utility scores from the PedsQL generic core scales. Pharmacoeconomics. 2014 Jul;32(7):693-706.
154. AveXis. Data on file. UK Health State Utilities Elicitation for Spinal Muscular Atrophy - Report. 01 August 2019. 2019. 2019.
155. Torrance GW, Feeny D, Furlong W. Visual analog scales: do they have a role in the measurement of preferences for health states? Med Decis Making. 2001 Jul-Aug;21(4):329-34.
156. Tilford JM, Grosse SD, Robbins JM, et al. Health state preference scores of children with spina bifida and their caregivers. Qual Life Res. 2005 May;14(4):1087-98.
157. Wittenberg E, Prosser LA. Disutility of illness for caregivers and families: a systematic review of the literature. Pharmacoeconomics. 2013 Jun;31(6):489-500.
158. Lee M, Jr., França UL, Graham RJ, et al. Pre-Nusinersen Hospitalization Costs of Children With Spinal Muscular Atrophy. Pediatric Neurology. 2019;92:3-5.
159. Dabbous O, Seda J, Sproule DM. Economic Burden of Infant-Onset (Type 1) Spinal Muscular Atrophy: A Retrospective Claims Database Analysis. Value in Health. 2018;21:S251.
160. Goble J, Dai D, Boulos F, et al. The Economic Burden of Spinal Muscular Atrophy Patients in a Commercially-Insured Population in the United States (P1.6-054). Neurology. 2019;92(15 Supplement):P1.6-054.
161. Hall E, Wells W, Teynore M, et al. Healthcare resource utilization and costs of spinal muscular atrophy care in the U.S. Medicaid population. Journal of Managed Care & Specialty Pharmacy. 2017;23(10):50-1.
162. Armstrong EP, Malone DC, Yeh WS, et al. The economic burden of spinal muscular atrophy. J Med Econ. 2016 Aug;19(8):822-6.
163. Koch SJ, Arego DE, Bowser B. Outpatient rehabilitation for chronic neuromuscular diseases. Am J Phys Med. 1986 Oct;65(5):245-57.
164. Zuluaga-Sanchez S, Teynor M, Knight C, et al. Cost Effectiveness of Nusinersen in the Treatment of Patients with Infantile-Onset and Later-Onset Spinal Muscular Atrophy in Sweden. Pharmacoeconomics. 2019 Feb 4.
165. SMC. Nusinersen 12mg solution for injection (Spinraza®) [SMC No. 1318/18]. 2018.
166. Canadian Agency for Drugs and Technologies. CADTH Canadian Drug Expert Committee Recommendation: Nusinersen (Spinraza - Biogen Canada Inc.): Indication: Treatment of 5q Spinal Muscular Atrophy. Ottawa (ON): Canadian Agency for Drugs and Technologies in Health; 2017.

167. National Centre for Pharmacoeconomics. Cost-effectiveness of nusinersern (Spinraza) for the treatment of 5q spinal muscular atrophy (SMA). 2017.
168. Swedish Dental and Pharmaceutical Benefits Agency [Tandvårds- och läkemedelsförmånsverket T. Spinraza (nusinersen). 2017.
169. Agency for the Quality and Accreditation in Health Care and Social Welfare [Agencija za kvalitetu I akreditaciju u zdravstvu I socijalnoy skrbi]. Nusinersen (Spinraza) in the treatment of patients with spinal muscular atrophy (SMA) [Nusinersen (Spinraza) u liječenju bolesnika sa spinalnom mišićnom atrofijom (SMA)]. 2017.
170. National Institute for Health Care Excellence. Guide to the methods of technology appraisal. 2013.
171. Gregoretti C, Ottonello G, Chiarini Testa MB, et al. Survival of patients with spinal muscular atrophy type 1. Pediatrics. 2013 May;131(5):e1509-14.
172. Zerres K, Rudnik-Schoneborn S, Forrest E, et al. A collaborative study on the natural history of childhood and juvenile onset proximal spinal muscular atrophy (type II and III SMA): 569 patients. J Neurol Sci. 1997 Feb 27;146(1):67-72.
173. Office for national statistics. National Life Tables. United Kingdom. Based on data from the years 2014-2016. Published September 2018. Available at: https://www.ons.gov.uk/file?uri=/peoplepopulationandcommunity/birthsdeathsandmarriages/lifeexpectancies/datasets/nationallifetablesunitedkingdomreferencetables/current/nltuk1517reg.xls
174. Diaby V, Adunlin G, Montero AJ. Survival modeling for the estimation of transition probabilities in model-based economic evaluations in the absence of individual patient data: a tutorial. Pharmacoeconomics. 2014 Feb;32(2):101-8.
175. Hoyle MW, Henley W. Improved curve fits to summary survival data: application to economic evaluation of health technologies. BMC Med Res Methodol. 2011 Oct 10;11:139.
176. Tierney JF, Stewart LA, Ghersi D, et al. Practical methods for incorporating summary time-to-event data into meta-analysis. Trials. 2007 Jun 7;8:16.
177. National Institute for Health and Care Excellence Decision Support Unit (NICE DSU). TSD 14: Survival analysis for economic evaluations alongside clinical trials – extrapolation with patient-level data. Accessed 17th June 2019. Available at: http://nicedsu.org.uk/technical-support-documents/survival-analysis-tsd/.
178. Briggs AH, Claxton K, Sculpher MJ. Decision modelling for health economic evaluation. Oxford: Oxford University Press; 2006.
179. AveXis. Data on file: UK Clinical Advisory Board: Slide deck. 28 May 2019. 2019.
180. Department of Health and Social Care (NHS Improvement). NHS National Schedule of reference costs 2017 to 2018. Updated Dec 2018.
181. British National Formulary. Spinraza 12mg/5ml solution for injection vials (Biogen Idec Ltd). Available at: https://bnf.nice.org.uk/medicinal-forms/nusinersen.html.
182. Curtis LAaB, Amanda. Unit Costs of Health and Social Care 2018. Project report. University of Kent https://doi.org/10.22024/UniKent/01.02.70995. 2018.
183. NHS Digital. Prescription Cost Analysis, England. 18 March 2018. https://data.gov.uk/dataset/3eecf351-fca5-4f00-87b8-6a2282fa0d13/prescription-cost-analysis-england.
184. NHS England. NHS Commissioning: Orthotic services; Local tariffs for direct access. Available at:, https://www.england.nhs.uk/wp-content/uploads/2015/11/orthcs-rep-attach-5.pdf.
185. National Institute for Health and Care Excellence. NICE, Motor neurone disease: assessment and management, 24 Feb 2016. Available at: https://www.nice.org.uk/guidance/ng42/resources/motor-neurone-disease-assessment-and-management-pdf-1837449470149. 2016.

186. Noyes J, Godfrey C, Beecham J. Resource use and service costs for ventilator-dependent children and young people in the UK. Health & Social Care in the Community. 2006;14(6):508-22.
187. Pechmann A, Langer T, Schorling D, et al. Evaluation of Children with SMA Type 1 Under Treatment with Nusinersen within the Expanded Access Program in Germany. J Neuromuscul Dis. 2018;5(2):135-43.
188. Malone DC, Dean R, Arjunji R, et al. Cost-effectiveness analysis of using onasemnogene abeparvocec (AVXS-101) in spinal muscular atrophy type 1 patients. Journal of Market Access & Health Policy. 2019 2019/01/01;7(1):1601484.
189. The Lewin Group. Cost of Amyotrophic Lateral Sclerosis, Muscular Dystrophy, and Spinal Muscular Atrophy in the United States. . 2012.
190. United States CB. Educational Attainment in the United States, 2017. Available at: https://www.census.gov/data/tables/2017/demo/education-attainment/cps-detailed-tables.html.
191. Organisation for Economic Co-operation and Development. Education and earnings available at: https://stats.oecd.org/Index.aspx?DataSetCode=EAG_EARNINGS applied to Annual income for A level graduate from https://www.statista.com/statistics/281936/average-salary-by-education-level-in-the-united-kingdom-uk.
192. Organisation for Economic Co-operation and Development. Unemployment rates by education level. Available at: https://data.oecd.org/unemp/unemployment-rates-by-education-level.htm. .
193. Powell. People with disabilities in employment. House of Commons Library Briefing paper, Number 7540, 8 January 2018. 2018.
194. Organisation for Economic Co-operation and Development. Purchasing power aprities. Available at https://data.oecd.org/conversion/purchasing-power-parities-ppp.htm. .
195. Polido GJ, Barbosa AF, Morimoto CH, et al. Matching pairs difficulty in children with spinal muscular atrophy type I. Neuromuscul Disord. 2017 May;27(5):419-27.

Note, full text PDF copies of the following references are not included in the reference pack:

- Bayley N. Bayley scales of infant and toddler development: Bayley-III: Harcourt Assessment, Psych. Corporation. 2006.
- Briggs AH, Claxton K, Sculpher MJ. Decision modelling for health economic evaluation. Oxford: Oxford University Press; 2006.

17 Appendices

Appendices associated with this submission are provided as a standalone document.

18 Related procedures for evidence submission

18.1 *Cost- effectiveness models*

An electronic executable version of the cost-effectiveness model should be submitted to NICE with the full submission.

NICE accepts executable models using standard software – that is, Excel, TreeAge Pro, R or WinBUGs. If you plan to submit a model in a non-standard package, NICE should be informed in advance. NICE, in association with the ERG, will investigate whether the requested software is acceptable, and establish if you need to provide NICE and the ERG with temporary licences for the non-standard software for the duration of the assessment. NICE reserves the right to reject cost models in non-standard software. A fully executable electronic copy of the model must be submitted to NICE with full access to the programming code. Care should be taken to ensure that the submitted versions of the model programme and the written content of the evidence submission match.

NICE may distribute the executable version of the cost model to a consultee if they request it. If a request is received, NICE will release the model as long as it does not contain information that was designated confidential by the model owner, or the confidential material can be redacted by the model owner without producing severe limitations on the functionality of the model. The consultee will be advised that the model is protected by intellectual property rights and can be used only for the purposes of commenting on the model's reliability and informing comments on the medical technology consultation document.

Sponsors must ensure that all relevant material pertinent to the decision problem has been disclosed to NICE at the time of submission. NICE may request additional information not submitted in the original submission of evidence. Any other information will be accepted at NICE's discretion.

When making a full submission, sponsors should check that:

- an electronic copy of the submission has been given to NICE with all confidential information highlighted and underlined
- a copy of the instructions for use, regulatory documentation and quality systems certificate have been submitted
- an executable electronic copy of the cost model has been submitted
- the checklist of confidential information provided by NICE has been completed and submitted.
- A PDF version of all studies (or other appropriate format for unpublished data, for example, a structured abstract) included in the submission have been submitted

18.2 *Disclosure of information*

To ensure that the assessment process is as transparent as possible, NICE considers it highly desirable that evidence pivotal to the Highly Specialised Technology Evaluation Committee's decisions should be publicly available at the point of issuing the consultation document and final guidance.

Under exceptional circumstances, unpublished evidence is accepted under agreement of confidentiality. Such evidence includes 'commercial in confidence' information and data that are awaiting publication ('academic in confidence').

When data are 'commercial in confidence' or 'academic in confidence', it is the sponsor's responsibility to highlight such data clearly, and to provide reasons why they are confidential and the timescale within which they will remain confidential. The checklist of confidential information should be completed: if it is not provided, NICE will assume that there is no confidential information in the submission. It is the responsibility of the manufacturer or sponsor to ensure that the confidential information checklist is kept up to date.

It is the responsibility of the sponsor to ensure that any confidential information in their evidence submission is clearly underlined and highlighted correctly. NICE is assured that information marked 'academic in confidence' can be presented and discussed during the public part of the Highly Specialised Technology Evaluation Committee meeting. NICE is confident that such public presentation does not affect the subsequent publication of the information, which is the prerequisite allowing for the marking of information as 'academic in confidence'.

Please therefore underline all confidential information, and highlight information that is submitted under 'commercial in confidence' in blue and information submitted under 'academic in confidence' in yellow.

NICE will ask sponsors to reconsider restrictions on the release of data if there appears to be no obvious reason for the restrictions, or if such restrictions would make it difficult or impossible for NICE to show the evidential basis for its guidance. Information that has been put into the public domain, anywhere in the world, cannot be marked as confidential.

Confidential information submitted will be made available for review by the ERG and the Highly Specialised Technology Evaluation Committee. NICE will at all times seek to protect the confidentiality of the information submitted, but nothing will restrict the disclosure of information by NICE that is required by law (including in particular, but without limitation, the Freedom of Information Act 2000).

The Freedom of Information Act 2000, which came into force on 1 January 2005, enables any person to obtain information from public authorities such as NICE. The Act obliges NICE to respond to requests about the recorded information it holds, and it gives people a right of access to that information. This obligation extends to submissions made to NICE. Information that is designated as 'commercial in confidence' may be exempt under the Act. On receipt of a request for information, the NICE secretariat will make every effort to contact the designated company representative to confirm the status of any information previously deemed 'commercial in confidence' before making any decision on disclosure.

18.3 *Equality*

NICE is committed to promoting equality and eliminating unlawful discrimination, including paying particular attention to groups protected by equalities legislation. The scoping process is designed to identify groups who are relevant to the evaluation of the technology, and to reflect the diversity of the population. NICE consults on whether there are any issues

relevant to equalities within the scope of the evaluation, or if there is information that could be included in the evidence presented to the Highly Specialised Technology Evaluation Committee to enable them to take account of equalities issues when developing guidance.

Evidence submitters are asked to consider whether the chosen decision problem could be impacted by NICE's responsibility in this respect, including when considering subgroups and access to recommendations that use a clinical or biological criterion.

For further information, please see the NICE website (www.nice.org.uk/aboutnice/howwework/NICEEqualityScheme.jsp).

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Highly Specialised Technologies Evaluation Programme

INTERIM

ZOLGENSMA® (onasemnogene abeparvovec) for treating spinal muscular atrophy type 1 [ID1473]

Specification for company submission of evidence

Supplementary Appendix

1 May 2020

Key:
'Commercial in confidence' in turquoise
'Academic in confidence' in yellow
'Depersonalised data' in pink

Sections and data that have been updated since the company submission submitted in October 2019 are provided in the '**List of amendments implemented'** on page 8 of this Supplementary Appendix. These amendments accommodate:

•Additional clinical data for onasemnogene abeparvovec available from the 31 December 2019 data cut, including completed results for the Phase III trial STR1VE-US

•Updates to the economic model to accommodate the 'ERG-preferred base case' described in the interim ERG report (received January 2020)

Contents

List of tables and figures

Abbreviations

AAV9	Adeno-associated virus subtype 9
ACM	Appraisal committee meeting
AE	Adverse event
AIC	Akaike information criterion
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
BIC	Bayesian information criterion
BIM	Budget impact model
BiPAP	Bi-level positive airway pressure
BSC	Best supportive care
CHMP	Committee for Medicinal Products for Human Use
CHOP-INTEND	Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders
CI	Confidence interval
CMAP	Compound motor action potential
CPAP	Continuous positive airway pressure
CSF	Cerebrospinal fluid
CSR	Clinical study report
DILI	Drug-induced liver injury
DSU	Decision support unit
EAP	Early access programme
ECG	Electrocardiogram
EFS	Event-free survival
EMA	European Medicines Agency
EQ-5D	EuroQol-5 Dimensions
ERG	Evidence review group
EU	Europe
FAS	Full analysis set
FDA	Food and Drug Administration
GBP	Great British Pound
GGT	Gamma-glutamyl transferase
GMS	Gross motor skills
GOSH	Great Ormond Street Hospital
GP	General Practitioner
HCRU	Health care resource utilisation

HFMSE	Hammersmith Functional Motor Scale - Expanded
HIV	Human immunodeficiency virus
HRQoL	Health-related quality of life
HST	Highly specialised technology
ICER	Incremental cost effectiveness ratio
IMP	Investigational medicinal product
IT	Intrathecal
ITC	indirect treatment comparison
ITT	Intention to treat
IV	Intravenous
KM	Kaplan-Meier
KOL	Key opinion leader
LYG	Life-years gained
MAA	Managed access agreement
MDT	Multidisciplinary team
mITT	Modified intention to treat
mo.	Month
MUNE	Motor unit number estimation
N/A	Not applicable
NA	Not available
NCH	Nationwide Children's Hospital
ND	Nasoduodenal;
NeuroNext	Network for Excellence in Neuroscience Clinical Trials
NG	Nasogastric
NHS	National Health Service
NHSE	National Health Service England
NICE	National Institute for Health and Care Excellence
NIV	Non-invasive ventilation
NJ	Nasojejunal
NR	Not reported
NRA	Non-invasive respiratory muscle aid
OECD	Organisation for Economic Co-operation and Development
OOP	Out of pocket
OS	Overall survival

PAS	Patient access scheme
PAV	Permanent assisted ventilation
PCA	Prescription Cost Analysis
PCR	Polymerase chain reaction
PedsQL	Pediatric Quality of Life Inventory
PEG	Percutaneous endoscopic gastrostomy
PNCR	Pediatric Neuromuscular Clinical Research database
PSSRU	Personal Social Services Research Unit
QALY	Quality-adjusted life-year
QoL	Quality of life
qPCR	Quantitative polymerase chain reaction
QWB	Quality of Well-Being
RWE	Real World Evidence
SAE	Serious adverse event
SAS	Safety analysis set
SD	Standard deviation
SE	Standard error
SLR	Systematic literature review
SMA	Spinal muscular atrophy
SMN	Survival motor neurone
SmPC	Summary of product characteristics
STA	Single technology appraisal
TEAE	Treatment emergent adverse event
TTO	Time-Trade-Off
UCL	University College London
ULN	Upper limit of normal
UK	United Kingdom
US	United States
US ICER	United States Institute of Clinical and Economic Review
WBC	White blood cell
WHO	World Health Organization
WHO MGRS	World Health Organization Multicentre Growth Reference Trial

List of amendments implemented

The below table lists the sections that have been updated since the company submission submitted in October 2019, to reflect the amendments made in response to the 'Evidence Review Group (ERG)-preferred base case' described in the interim ERG report (received January 2020) and to accommodate updated clinical data for onasemnogene abeparvovec (31 December 2019 data cut).

Clinical data updates:

Section(s)	#	Updates	In response to
6.3.1.1.2	**1**	Results of the fine and gross motor subsets of the Bayley Scale assessment are presented for START	Results of the gross motor subset of the Bayley Scale were not reported in the original company submission
3.1, 6.3.1.3, 6.4.2.4, 6.6	**2**	Efficacy and safety data from the completed STR1VE-US study are presented in this submission	Available updated clinical data since original submission
3.1, 0, 6.4, 6.6	**3**	Interim efficacy and safety data for STR1VE-EU, SPR1NT, and LT001 have been updated with results from the most recent data cut, 31 December 2019	Available updated clinical data since original submission
3.1, 6.5	**4**	Real-world evidence data from the RESTORE registry as of the 31 December 2019 data cut are included in this submission	Available updated clinical data since original submission

Economic model updates:

Section(s)	#	Updates	In response to
8.2.2.1	**1**	**C and B state survival: Overall survival in the short-term model based on empirical data** • The original model used the fitted survival curves for the entire duration of the model from Zerres et al. 1997 and general population mortality tables for the C state ('sits unassisted') and B state ('walks unassisted'), respectively. In this approach, the modelled cohort is subject to a mortality risk in all cycles, which contrasts with the empirical data from START and STR1VE-US in which patients who sit unassisted and walk unassisted have a 100% survival for up to 24 months post-dose (circa 30 months of age) and 18 months of age, respectively. • The revised economic model base case applies 100% survival in the first 5 cycles (up to 30 months of age) for the C and B states, to reflect the empirical survival data available for sitting and walking patients treated with onasemnogene abeparvovec. • These amendments can be observed in the model tab titled 'C_Survival' and 'B_A_Survival'. • When implementing this in the base case, a minor error in the logic was discovered and has since been corrected	'ERG-preferred' base case
8.2.2.1	**2**	**E state survival: Exponential distribution for the extrapolation of the NRA OS KM from Gregoretti et al. 2013** • The original model used the 'pooled cohort' (57.5% receiving tracheostomy and 42.5% receiving NRA [non-invasive ventilation]) from Gregoretti et al. 2013 to model overall survival in the E state ('permanent assisted ventilation'). • The revised economic model base case uses the exponential distribution for the extrapolation of the NRA overall survival KM curve (i.e. curve is based on patients with permanent non-invasive ventilation only) from Gregoretti et al. 2013. Maximum survival is set to 16 years. • It is noted that in the NRA group, Gregoretti et al 2013 states that seven patients (7/31 [22.6%]) went on to receive tracheostomy, but it is not clear whether these patients are included in the survival estimates in the NRA curve. However, these data are used to define the proportion receiving tracheostomy (22.6%) versus non-invasive ventilation (77.4%) for calculating health care resource utilisation costs for the E state. • These amendments can be observed in the model tabs titled 'E_Survival' and 'MedicalCostCalculator'.	'ERG-preferred' base case

Section(s)	#	Updates	In response to
8.2.2.1	**3**	**D state survival: D state OS survival limit of 48 months and use of Weibull distribution, for both the onasemnogene abeparvovec and BSC arms** • The original model used the generalised gamma distribution for the OS and EFS curves for the D state ('not sitting') for natural history data from NeuroNext. The revised economic model base case uses the Weibull distribution for the extrapolation of the OS and EFS KM data, since this fitted distribution naturally declines down to zero at 48 months (four years), which is the maximum survival limit (truncation point) assumed for the D state in the BSC arm. • In the original model the survival limit is set to 48 months and 84 months for the D state, in the BSC and onasemnogene abeparvovec arms, respectively. Feedback from the ERG stated that a survival benefit for onasemnogene abeparvovec in the D state may not be unreasonable due to interim milestones being achieved, such as head control and rolling, compared with BSC. However, as there are limited data to substantiate the survival benefit, the ERG preferred to set the survival limit (truncation point) for the OS curve of the D state for the onasemnogene abeparvovec arm to 48 months, to match the BSC arm. Thus, the revised economic model base case uses a survival limit of 48 months in the D state for both the onasemnogene abeparvovec and BSC arms. • This amendment is implemented in the revised economic model by an added function, which allows the user to amend the survival limit in the D state for each treatment arm individually and independently from one another. • These amendments can be observed in the model tabs titled 'D_Survival_BSC' and 'D_Survival_AVXS'.	'ERG-preferred' base case
7.1.1	**4**	**Utility of zero for the E state** • The original model used a health state utility value of '0.190' for the E state, as per the approach adopted by the independent US ICER group. However, clinical expert advice sourced independently by the ERG, indicated that the E state should have a lower utility value than the D state (which is also 0.190 in the base case). Therefore, the ERG considers application of zero utility in the E state to be most appropriate. The revised economic model base case uses a utility value of zero for the E state • This amendment can be observed in the model tab titled 'Utilities'	'ERG-preferred' base case
7.1.1	**5**	**On treatment utility for the D and C state** • In the original model, on-treatment utility values were included as scenario analyses only	'ERG-preferred' base case

Section(s)	#	Updates	In response to
		• Feedback from the ERG indicated this approach to exclude on-treatment benefits from the base case to be conservative. In addition, the on-treatment utility scenario aligns with the base case assumptions for utility implemented in the US ICER model and the ERG considers the scenario appropriate. • Thus, the revised economic model base case applies on-treatment utility increments of 0.10 and 0.05 for the onasemnogene abeparvovec arm in the D and C states, respectively • These amendments can be observed in the model tab titled 'Utilities'	
8.3.1.1	**6**	**B health state costs applied to the A state** • In the original model, patients who walk independently are transitioned to the A state after 5 years of age, after which they incur zero SMA-related health care costs. The ERG's clinical experts stated that it is not unreasonable to expect that a patient who is able to walk independently would develop normally, however, there is no evidence that patients who have achieved the ability to walk will incur no additional costs compared with a healthy individual of the same age. The ERG's preferred base case is to apply B state costs to the A state (essentially no A state for the model). This approach is adopted in the revised economic model base case. • These amendments can be observed in the model tab titled 'Medical'	'ERG-preferred' base case
8.3.1.1	**7**	**Updated NHS Reference costs and PSSRU costs** • Update of costs originally obtained from the 2017/18 NHS Reference costs to the 2018/19 NHS National Cost Collection data. • Update of costs originally obtained from the 2018 PSSRU costs to 2019 PSSRU costs • These amendments can be observed in the model tabs titled 'Medical', 'MedicalCostCalculator' and 'AVXS-101Costs'	Available updated cost data since original submission
8.2.2.1	**8**	**Implementation of the "three curve" approach for OS and EFS in the D state** • In response to feedback from the ERG a "three curve" approach is adopted for D state transitions: o *D → E state*: Transition probabilities from the D state to the E state are calculated using an aggregated OS and an aggregated EFS curve (i.e. no adjustment made for patients on permanent assisted ventilation) generated from NeuroNext natural history study. o *D → Death*: Transition probabilities from the D state to death are calculated using a disaggregated OS curve (i.e. adjusted to patients not on permanent assisted ventilation). This	ERG feedback in the interim ERG report

Section(s)	#	Updates	In response to
		approach ensures that overall survival in the D state is not artificially increased by the survival of patients receiving permanent assisted ventilation • This "three curve" approach has been applied to all three sources of natural history data for the D state for which individual patient-level data are available: NeuroNext (base case), PNCR (scenario) and De Sanctis et al 2016 (scenario) • These amendments can be observed in the model tabs titled 'D_Survival_BSC' and 'D_Survival_AVXS' • To accommodate this "three-curve" approach, logic to the D to E formulas has been added to avoid negative transition probabilities in some instances	
8.3.3.1	**9**	**Update of cost of onasemnogene abeparvovec** • An updated list price for onasemnogene abeparvovec is applied to the revised economic model • This amendment can be observed in the model tab titled 'AVXS-101Costs'	Available updated cost data since original submission
8.2.1	**10**	**Use of pooled clinical trial data from START and STR1VE-US** • In the original model, clinical outcome data (motor milestones, OS and EFS) were from the Phase I/IIa START trial (Cohort 2, n=12) only • As the Phase III STR1VE-US trial (n=22) completed in December 2019, data from STR1VE-US are pooled with START. In the revised economic model, clinical outcome data for the onasemnogene abeparvovec arm are based on a POOLED dataset from the START and STR1VE-US trials. • These amendments can be observed in the model tabs titled 'D_Survival_AVXS', 'AVXS_Milestones' and 'AVXS_IPD'	Available updated clinical data (completion of the STR1VE-US trial) since the original submission
8.5	**11**	**Updated results** • Update of all base case, sensitivity and scenario analyses results due to above amendments in the modelling approach and inputs • These updates can be observed in the model tabs titled 'Results', 'Results2', 'Results3', 'Results4', 'Results5' and 'BIMModel8'	Amendments listed above

Abbreviations: BSC, best supportive care; EFS, event-free survival; ERG, Evidence Review Group; KM, Kaplan-Meier; NHS, National Health Service; NRA, non-invasive respiratory muscle aid ; OS, overall survival; PNCR, Pediatric Neuromuscular Clinical Research database; PSSRU, Personal Social Services Research Unit; US ICER; United States Institute of Clinical and Economic Review.

Table note: The model amends numbered 2–8 in the table above, inclusive, have also been updated appropriately in the nusinersen arm of the model. However, as nusinersen is no longer a relevant comparator for this appraisal, the amended model tabs related to nusinersen are not highlighted in the table above.

Executive Summary

Key messages

- Onasemnogene abeparvovec was granted a positive Committee for Medicinal Products for Human Use (CHMP) opinion on 26 March 2020 (1, 2). The proposed indication of onasemnogene abeparvovec is for the treatment of:
  - patients with 5q spinal muscular atrophy (SMA) with a bi-allelic mutation in the survival motor neuron (*SMN) 1* 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 three copies of the *SMN2* gene
- Onasemnogene abeparvovec has demonstrated rapid, substantial and sustained benefit across patient relevant endpoints with a manageable safety profile in infants with SMA type 1 and in pre-symptomatic infants with genetically diagnosed SMA and up to three copies of the *SMN2* gene
- Data from the now completed Phase III trial STR1VE-US support the unprecedented efficacy outcomes achieved by infants with SMA type 1 treated with onasemnogene abeparvovec in the Phase I/IIa START study:
  - SMA type 1 patients treated with a one-time intravenous (IV) administration of onasemnogene abeparvovec achieve developmental milestones including motor milestones (e.g. sitting and walking independently) and speech, and have ventilation-free survival rates not previously observed in natural history studies (3-5)
  - In the absence of treatment, those with SMA type 1 never sit unsupported and die or require permanent-assisted ventilation by 2 years of age (3-5)
- Interim data from the Phase III SPR1NT study demonstrate that pre-symptomatic infants with genetically diagnosed SMA and two or three copies of the *SMN2* gene treated with a one-time IV administration of onasemnogene abeparvovec are following the age-appropriate developmental trajectory of healthy peers, supporting the exceptional impact of early treatment
- Onasemnogene abeparvovec has been shown to have a manageable safety profile; in the context of the substantial and urgent unmet medical needs of patients with the most severe forms of SMA, the safety and efficacy data currently available strongly support a positive benefit-risk relationship for a single IV administration of 1.1×10^{14} vg/kg onasemnogene abeparvovec for the treatment of patients with 5q SMA with a bi-allelic mutation in the *SMN1* gene and up to three copies of the *SMN2* gene
- The revised economic model incorporating START and STR1VE-US data and ERG-preferred base case assumptions shows that onasemnogene abeparvovec achieves large incremental quality-adjusted life-year (QALY) gains (9.80 discounted; 20.80 undiscounted) versus best supportive care (BSC). The company has provided a confidential patient access scheme (PAS) with results presented in the PAS evidence template document. Under the provided confidential PAS, onasemnogene abeparvovec is cost-effective versus BSC

- In England, onasemnogene abeparvovec is positioned for the treatment of children with SMA type 1 and pre-symptomatic infants with a genotype predictive of SMA type 1 (i.e. those with up to three copies of the *SMN2* gene)

Clinical data overview

This supplementary appendix provides data for the completed START and STR1VE-US trials and interim data for the ongoing trials STR1VE-EU, SPR1NT and LT-001. No other clinical trials are required for the conditional approval by regulators, and hence this updated data package provides NICE with all relevant clinical data available. The efficacy data presented indicate that a single dose of onasemnogene abeparvovec has substantial clinical efficacy across multiple patient relevant endpoints in infants with SMA, including survival, motor function, developmental motor milestones and ventilatory and nutritional endpoints, in contrast to the observations from natural history studies. Furthermore, early data from SPR1NT indicates that pre-symptomatic infants with genetically diagnosed SMA treated with a single dose of onasemnogene abeparvovec are following the age-appropriate developmental trajectory of healthy peers, demonstrating the exceptional potential benefits of treatment.

START

- START is a Phase I/IIa open-label, dose-escalation clinical trial of IV onasemnogene abeparvovec in infants with SMA type 1 with two copies of *SMN2* (Cohort 1: 6.7×10^{13} vg/kg, n=3; Cohort 2: 2.0×10^{14} vg/kg[1], n=12)
- All (15/15) infants in START were alive and free of permanent ventilation at 24 months post dose (mainly up to 30 months of age); a survival without permanent ventilation rate of only 8% at 20 months of age was reported for infants with SMA type 1 managed with BSC alone in an external natural history study (3)
- Based on independent video confirmation, motor milestones were achieved and maintained over time in START. In contrast, no patients in natural history cohorts achieved any motor milestones (6, 25). No patients (n=15) in START lost motor milestones during the 24-month study period
    - At the end of START, 91.7% of infants in Cohort 2 (n=12) were able to hold their head erect without support for ≥3 seconds and sit alone for ≥5 seconds, 75.0% were able to sit alone for ≥30 seconds, and 16.7% were able to walk unassisted
    - In addition, 91.7% (11/12) of infants in Cohort 2 were able to speak and could swallow effectively enough to feed orally by 24 months post dose. In comparison, infants with SMA type 1 managed with BSC alone are expected to lose the ability to swallow or maintain adequate nutritional intake by 1 year of age
- In START, four patients were reported to have five treatment related adverse events (AE); in all cases, AEs were transient, clinically asymptomatic elevated serum aminotransferase levels and resolved with prednisolone treatment

[1] Direct testing of the actual lot of investigational product used in START by an improved and more fully qualified analytical method (droplet digital PCR) has determined the actual dose received by Cohort 1 to be 3.7×10^{13} vg/kg and the actual dose received by Cohort 2 to be 1.1×10^{14} vg/kg (the same method has been used to establish an equivalent dose for the IMP in all Phase III trials).

LT-001

- LT-001 is the ongoing, long-term extension study of START, assessing the efficacy and safety of onasemnogene abeparvovec for up to 15 years. In total, 13/15 patients from START are enrolled in LT-001 (3 patients from Cohort 1 [low dose] and 10 patients from Cohort 2 [therapeutic dose])
- The unprecedented survival and ventilatory outcomes achieved in START are being maintained in LT-001. At the 31 December 2019 data cut, all patients treated with the therapeutic dose of onasemnogene abeparvovec in START (Cohort 2) were alive and free from permanent ventilation; the median age of patients in Cohort 2 was 4.5 years (range: 4.3–5.6) and the median duration of follow-up was 4.4 years (range: 4.1–5.0)
- No patients treated with the therapeutic dose of onasemnogene abeparvovec in START have lost motor milestones and two patients have gained the additional video-confirmed milestone of standing with assistance during LT-001
- No new treatment related AEs or fatal serious treatment related AEs were reported in LT-001

STR1VE-US

- STR1VE-US is a completed Phase III, open-label, single-arm trial investigating the efficacy of a one-time IV administration of onasemnogene abeparvovec in infants with SMA type 1 with two copies of *SMN2* compared with natural history controls up to 18 months of age. The 18 months of age visit served as the end of study visit, after which eligible patients may enter the long-term follow-up study (LT-002)
- Results from STR1VE-US show a similar trajectory to infants in START; the co-primary endpoints of survival without permanent ventilation at 14 months of age and independent sitting for ≥30 seconds at the 18-month visit were achieved by 90.9% and 59.1% of 22 infants, respectively
- The co-secondary endpoints of being independent of ventilatory support and maintaining the ability to thrive (nutritional composite endpoint) at 18 months of age were achieved by 81.8% and 40.9% of patients, respectively. In addition, 15 (68.1%) infants did not require any non-invasive ventilatory support at any point during the study
- CHOP-INTEND total score showed a rapid improvement and demonstrates the efficacy of onasemnogene abeparvovec on motor function; 21 infants (95.5%) maintained or achieved a score ≥40, 14 (63.6%) maintained or achieved a score ≥50, and five infants (22.7%) achieved a maximum/near maximum score of ≥60. These are notable achievements as infants with SMA type 1 receiving BSC alone rarely achieve and never maintain a CHOP-INTEND score of ≥40 and show a rapid decline in CHOP-INTEND scores over time (4)

STR1VE-EU

- STR1VE-EU is an ongoing, Phase III, open-label, single-arm, single-dose study of onasemnogene abeparvovec which enrolled symptomatic patients with SMA type 1 with two copies of *SMN2*. The 18 months of age visit will serve as the end of study visit, after which eligible patients may enter the long-term follow-up study (LT-002)
- At the time of the data cut, enrolment for STR1VE-EU was complete with a total of 33 patients having received a one-time administration of onasemnogene abeparvovec, all

of whom had two copies of *SMN2*. The median duration of follow-up at last visit was 11.9 months (range: 1.8–15.4), and the median age of patients at last visit was 15.4 months (range: 6.9–18.6)

- The relatively short median duration of follow-up at last visit precludes strong conclusions being drawn about milestone attainment; i.e. additional time is needed to determine the extent of milestone attainment in this trial. [redacted] achieved the ability to sit without support for ≥30 seconds[2] and [redacted] achieved the primary objective of sitting without support for ≥10 seconds up to 18 months of age[3].
- [redacted] in the ITT population[4] were alive and free of permanent ventilation as of their last study visit; [redacted] who had survived without permanent ventilation were ≥14 months of age at the time of the data cut (secondary objective)

SPR1NT

- SPR1NT is an ongoing Phase III, open-label, single-arm, single-dose, multicentre study of IV onasemnogene abeparvovec in pre-symptomatic infants with genetically diagnosed SMA with two or three copies of *SMN2.* After the study follow-up period (18 or 24 months of age), eligible patients may enter the long-term follow-up study (LT-002*)*
  - Cohort 1: infants with two copies of *SMN2* (n=14)
  - Cohort 2: infants with three copies of *SMN2* (n=15)
- Of the 29 infants with either two or three copies of *SMN2*, all were alive and free of permanent ventilation at the 31 December 2019 data cut
- No infants in SPR1NT needed feeding support and none required ventilatory support of any kind, including non-invasive ventilation, invasive ventilation, cough assist, or bi-level positive airway pressure (BiPAP) at the 31 December 2019 data cut
- Motor function and motor milestone achievement in SPR1NT are consistent with normal, age-appropriate development. Although follow-up periods were relatively short at the 31 December 2019 data cut, pre-symptomatic infants treated with onasemnogene abeparvovec appeared to be following the age-appropriate developmental trajectory of healthy peers, demonstrating the exceptional benefits of treatment

Value for money

- The company has addressed the feedback provided by the ERG and adopted all six of the 'ERG-preferred base case' inputs in the revised economic model presented. In addition, the revised economic model incorporates a larger body of clinical data for onasemnogene abeparvovec, as motor milestones and survival data are based on a POOLED dataset from START and the now completed Phase III STR1VE-US trial
- AveXis has submitted a price application to the Department of Health & Social Care and has updated the list price in the economic model accordingly
- In the updated base case analysis (presented in Section 8.5.1), onasemnogene abeparvovec versus best supportive care (BSC) achieves large incremental QALY gains (9.80 discounted; 20.80 undiscounted) with an incremental cost effectiveness ratio (ICER) of £230,568 per QALY gained.

- The company has provided a confidential patient access scheme (PAS) with results presented in the PAS evidence template document. Under the provided confidential PAS, onasemnogene abeparvovec is cost-effective versus BSC

[2] Defined as Bayley Scales Gross Motor subset item #26: Child sits alone without support for ≥30 seconds

[3] WHO MGRS definition as sitting up with back straight and head erect for ≥10 seconds; child does not use arms or hands to balance body or support position (6).

[4] One patient ([redacted]) was dosed at the age of 181 days and was therefore not included in the ITT population.

1 Statement of the decision problem

The decision problem is outlined in Table 1.

Table 1: Statement of the decision problem

	Final scope issued by NICE (7)	Variation from scope in the submission	Rationale for variation from scope
Population	Children with SMA type 1	As per scope, but the population also includes pre-symptomatic infants with a genotype predictive of SMA type 1 (i.e. those with up to three copies of the *SMN2* gene)	Interim results from the ongoing SPR1NT trial in pre-symptomatic infants with SMA demonstrate the potential to achieve normal development when onasemnogene abeparvovec is administered very early during the disease course; these clinical data justify the Committee considering this specific SMA population at the earliest opportunity
Intervention	Onasemnogene abeparvovec	As per scope, but for clarity the intervention is: onasemnogene abeparvovec via single-dose intravenous infusion only	N/A
Comparator(s)	• Best supportive care • Nusinersen (subject to ongoing NICE appraisal)	Only best supportive care will be a comparator. Nusinersen is no longer considered a relevant comparator by NICE.	Decision-making by NICE
Outcomes	The outcome measures to be considered include: • Motor function (including, where applicable, age-appropriate motor milestones such as sitting, standing, walking) • Frequency and duration of hospitalisation. • Speech and communication • Respiratory function	As per scope, but a composite endpoint of permanent ventilation-free survival – often termed as event-free survival (EFS) in the assessment of SMA – is also assessed	EFS (defined as survival free from permanent ventilation) is a primary or secondary efficacy endpoint in the onasemnogene abeparvovec clinical trial programme Due to the lack of robust utilities for caregivers of SMA type 1 patients

	Final scope issued by NICE (7)	Variation from scope in the submission	Rationale for variation from scope
	• Complications of SMA (including, for example, scoliosis and muscle contractures) • Need for non-invasive or invasive ventilation • Mortality • Adverse effects of treatment • Health-related quality of life (for patients and carers) Clinical effectiveness • Overall magnitude of health benefits to patients and, when relevant, carers • Robustness of the current evidence and the contribution the guidance might make to strengthen it • Treatment continuation rules (if relevant)	As per scope, but health-related quality of life of caregivers will be explored in modelling scenario analyses only	
Subgroups to be considered	Within the proposed label, heterogeneity of health benefits within the population will be explored	As per scope, heterogeneity of health benefits within the population is explored qualitatively but no formal quantitative subgroups are presented	N/A
Nature of the condition	• Disease morbidity and patient clinical disability with current standard of care • Impact of the disease on carer's quality of life • Extent and nature of current treatment options	As per scope	N/A

	Final scope issued by NICE (7)	Variation from scope in the submission	Rationale for variation from scope
Cost to the NHS and PSS, and Value for Money	• Cost effectiveness using incremental cost per quality-adjusted life year • Patient access schemes and other commercial agreements • The nature and extent of the resources needed to enable the new technology to be used	As per scope; the company provides a confidential patient access scheme alongside this supplementary appendix, please see the PAS evidence template document	
Impact of the technology beyond direct health benefits, and on the delivery of the specialised service	• Whether there are significant benefits other than health • Whether a substantial proportion of the costs (savings) or benefits are incurred outside of the NHS and personal and social services • The potential for long-term benefits to the NHS of research and innovation • The impact of the technology on the overall delivery of the specialised service • Staffing and infrastructure requirements, including training and planning for expertise	As per scope, however, the assessment of caregiver productivity loss, caregiver/patient out of pocket costs and patient educational achievement/ workforce participation are explored via modelling scenario analyses only	Limited UK-specific data for the SMA type 1 population in relation to costs incurred outside of the NHS and PSS exists, therefore, impacts of the technology beyond direct health benefits are explored by modelling scenario analyses only in Section 14 of the original company submission

	Final scope issued by NICE (7)	Variation from scope in the submission	Rationale for variation from scope
Special considerations, including issues related to equality	• There are no special considerations in equality regarding prescribed characteristics, however, the practicalities of families having to travel for treatment at specialised centres should be considered • Guidance will only be issued in accordance with the marketing authorisation • If evidence allows, and included within the marketing authorisation, consideration may be given to a subgroup of people with pre-symptomatic disease • Guidance will take into account any Managed Access Arrangements	As per scope	N/A

Abbreviations: EFS, event-free survival; N/A, not applicable; NHS, National Health Service; NICE, National Institute for Health and Care Excellence; PSS, personal and social services; SMA, spinal muscular atrophy; *SMN*, survival motor neuron; TBC, to be confirmed.

2 Regulatory information

2.1 *Does the technology have a UK marketing authorisation for the indication detailed in the submission? If so, give the date on which authorisation was received. If not, state the currently regulatory status, with relevant dates (for example, date of application and/or expected approval dates).*

Regulatory approval for onasemnogene abeparvovec is being sought via the European Medicines Agency (EMA) centralised procedure.

A positive Committee for Medicinal Products for Human Use (CHMP) opinion for onasemnogene abeparvovec was received on 26 March 2020 following consideration of the full clinical evidence package up to the 31st December 2019 data cut, as provided to NICE in this submission (1, 2). The proposed indication of onasemnogene abeparvovec is 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

- patients with 5q SMA with a bi-allelic mutation in the *SMN1* gene and up to three copies of the *SMN2* gene.

Conditional marketing authorisation is expected in May/June 2020.

2.2 *If the technology has not been launched, please supply the anticipated date of availability in the UK.*

AveXis is open to agreeing early, interim commercial arrangements with the NHS across the UK to facilitate patient access to onasemnogene abeparvovec as soon as possible following marketing authorisation whilst HTA appraisals are ongoing. AveXis expects to make onasemnogene abeparvovec available through routine arrangements across the UK following conclusion of HTA appraisals by NICE and the SMC and subsequent funding by the NHS. AveXis will be in a position to supply onasemnogene abeparvovec directly following marketing authorisation to help address the high unmet medical need of infants with SMA.

2.3 *Does the technology have regulatory approval outside the UK? If so, please provide details.*

Onasemnogene abeparvovec gained regulatory approval by the US Food and Drug Administration (FDA) in May 2019 and in Japan in March 2020. Regulatory approvals in other jurisdictions (e.g. Switzerland, Australia and Brazil) are ongoing but are incomplete at this time of this submission.

2.4 *If the technology has been launched in the UK provide information on the use in England.*

Onasemnogene abeparvovec has not yet been launched in the UK. Four patients enrolled and received onasemnogene abeparvovec in England as part of the ongoing STR1VE-EU study. One additional patient in STR1VE-EU was screened for inclusion in the UK, received onasemnogene abeparvovec and initial follow-up in Italy, and then returned to the UK. One patient from England is enrolled in the ongoing SPR1NT study. Treatment with onasemnogene abeparvovec was provided at the Great North Children's Hospital at the Royal Victoria Infirmary in Newcastle upon Tyne and at Great Ormond Street Hospital, London.

3 Ongoing studies

3.1 *Provide details of all completed and ongoing studies on the technology from which additional evidence relevant to the decision problem is likely to be available in the next 12 months.*

A comprehensive clinical development programme including Phase I–III clinical trials is being conducted for onasemnogene abeparvovec in patients with SMA. Data from two completed studies (START and STR1VE-US) are presented in full and interim efficacy results as of 31 December 2019 from three ongoing studies (STR1VE-EU, SPR1NT, and LT-001) are provided in this supplementary appendix submission (Table 2). In total, 100 patients received an IV administration of onasemnogene abeparvovec in START, STR1VE-US, STR1VE-EU, and SPR1NT; 97 patients received the therapeutic dose of onasemnogene abeparvovec and three received the low dose.

To provide further long-term data, AveXis is sponsoring a prospective Global SMA Disease Registry (RESTORE, AVXS-101-RG-001) which will follow at least 500 patients with SMA in clinical practice for up to 15 years or until death, including approximately 20% of patients treated with existing or upcoming approved treatments. Cohort clinical characteristics, treatments received, and outcomes from patients with available data from the registry are presented in Section 6.5.

The following studies of onasemnogene abeparvovec are ongoing but only interim results are available at the time of this submission and the data are not presented:

1. **CL-306:** The Phase III clinical trial CL-306 (STR1VE-APAC), is a an open-label, single-arm, single-dose study of IV onasemnogene abeparvovec in patients with SMA type 1 with one or two copies of *SMN2* in three investigative sites located in Japan, South Korea, and Taiwan. Interim data are not currently available for CL-306
2. **LT-002**: A long-term follow-up study of infants treated with onasemnogene abeparvovec in AveXis clinical trials including the IV studies SPR1NT, STR1VE-EU, STR1VE-US, and STRONG. This study commenced in September 2019 and will include approximately 70–100 patients followed for a total of 15 years post-dose when enrolment is complete. To date, seven patients are enrolled in LT-002; currently, all patients enrolled in LT-002 received onasemnogene abeparvovec by intrathecal administration in STRONG

The safety and tolerability of intrathecal administration of onasemnogene abeparvovec is also being investigated in patients with SMA type 2 in AVXS-101-CL-102 (STRONG, clinicaltrials.gov link); however, as onasemnogene abeparvovec was administered via intrathecal administration, this clinical trial is outside the scope of the decision problem addressed in this submission and is therefore not described.

No further studies of onasemnogene abeparvovec are required for the conditional approval by regulators, and hence this updated data package provides NICE with all relevant clinical data available.

Table 2: Summary of clinical studies of onasemnogene abeparvovec included in the submission

Characteristic	START	LT-001	STR1VE-US	STR1VE-EU	SPR1NT
Phase	Phase I/IIa	Long-term extension of START	Phase III	Phase III	Phase III
Status of study	Complete	Ongoing	Complete	Ongoing	Ongoing
Design	Open label, dose-escalation trial	Open label	Open label, single-arm, single-dose trial	Open label, single-arm, single-dose trial	Open label, single-arm, single-dose trial
Population	Symptomatic	Symptomatic	Symptomatic	Symptomatic	Pre-symptomatic
SMA type	Type 1	Type 1	Type 1	Type 1	Genetically diagnosed and pre-symptomatic SMA
SMN2 copy number – permitted in protocol	2 copies	2 copies	1 or 2 copies	1 or 2 copies	2 copies (Cohort 1) or 3 copies (Cohort 2)†
SMN2 copy number – for patients enrolled	2 copies	2 copies	2 copies	2 copies	2 copies (Cohort 1) or 3 copies (Cohort 2)†
Patients with c.859G>c modification in exon 7 of *SMN2* included in efficacy analysis populations	No	No	No‡	No‡	No‡
Intervention(s) and comparators(s)	Intervention: Onasemnogene abeparvovec Cohort 1 received low dose 6.7×10^{13} vg/kg§; Cohort 2 received therapeutic dose 2.0×10^{14} vg/kg§	Study drug was not administered in LT-001; patients were dosed in START	Intervention: Onasemnogene abeparvovec 1.1×10^{14} vg/kg Comparator: Natural history cohort¶	Intervention: Onasemnogene abeparvovec 1.1×10^{14} vg/kg Comparator: Natural history cohort¶	Intervention: Onasemnogene abeparvovec 1.1×10^{14} vg/kg Comparator: Natural history cohort¶

Characteristic	START	LT-001	STR1VE-US	STR1VE-EU	SPR1NT
	Comparator: natural history cohort[¶]				
Primary endpoint	Safety: • AEs • Laboratory evaluations • Drug-induced liver injury • Vital signs • ECGs • Immunologic response Primary efficacy: • Survival[††]	Primary efficacy: • Physical examinations to assess developmental milestones • New milestones demonstrated by patients which were not documented during START must be supported by video evidence	Co-primary efficacy: • Proportion of patients achieving functional independent sitting for ≥30 seconds[‡‡] at the 18 months of age study visit • Survival at 14 months of age[§§]	Primary efficacy: • Proportion of patients achieving the milestone of sitting without support for at least 10 seconds[¶¶] up to 18 months of age	Primary efficacy: • Two copies of *SMN2*: Proportion of patients achieving the ability of functional independent sitting for ≥30 seconds up to 18 months of age Three copies of *SMN2*: Proportion of patients achieving the ability to stand without support for at ≥3 seconds up to 24 months of age
Status of enrolment	Complete	Complete	Complete	Complete	Complete
Patients enrolled as of 31 December 2019	3 (Cohort 1) 12 (Cohort 2)	3 (Cohort 1) 10 (Cohort 2)	22	33	14 (Cohort 1) 15 (Cohort 2)[†]
Follow-up period	24 months post dose	15 years	18 months of age	18 months of age	18 months of age (Cohort 1) 24 months of age (Cohort 2)

Characteristic	START	LT-001	STR1VE-US	STR1VE-EU	SPR1NT
Reference	Mendell et al. 2017 (8) Al-Zaidy et al. 2019 (9) CSR (10)	Al-Zaidy et al. 2019 (9) Protocol (11) Clinical overview (31 December 2019 data cut) (12) 180-Day efficacy update (31 December 2019) (13) 180-Day safety update (31 December 2019) (14)	Protocol (15) Clinical overview (31 December 2019 data cut) (12) CSR (16)	Protocol (17) Clinical overview (31 December 2019 data cut) (12) 180-Day efficacy update (31 December 2019) (13) 180-Day safety update (31 December 2019) (14)	Protocol (18) Clinical overview (31 December 2019 data cut) (12) 180-Day efficacy update (31 December 2019) (13) 180-Day safety update (31 December 2019) (14)

Abbreviations: AE, adverse event; BiPAP, bi-level positive airway pressure; ECG, electrocardiogram; IMP, investigational medicinal product; ITT, intention to treat; SMA, spinal muscular atrophy.

† Pre-symptomatic patients with four copies of *SMN2* were in the original SPR1NT protocol but later removed as per protocol amendment dated 27 September 2018. One patient with four copies of *SMN2* was enrolled and received an IV administration of onasemnogene abeparvovec but was excluded from the ITT efficacy population and is therefore not reported in the interim efficacy results from the 31 December data cut; this patient remains part of the safety population.

‡ Whilst inclusion criteria of the trial permitted those with the modifier mutation, the ITT population excludes those with the *SMN2* gene modifier mutation (c.859G>C) and no infants with the modifier mutation were enrolled.

§ Direct testing of the actual lot of investigational product used in START by an improved and more fully qualified analytical method (droplet digital PCR) has determined the actual dose received by Cohort 1 to be 3.7×10^{13} vg/kg and the actual dose received by Cohort 2 to be 1.1×10^{14} vg/kg (the same method has been used to establish an equivalent dose for the IMP in all Phase III trials).

¶ Well characterised external datasets from SMA natural history studies (PNCR and NeuroNext (5)) are used to provide an external control comparator.

†† Defined as time from birth to either (a) requirement of ≥16-hour respiratory assistance per day (includes BiPAP) continuously for ≥2 weeks in the absence of an acute reversible illness, excluding perioperative ventilation or (b) death. This is described as a co-primary but is treated, statistically, as a secondary endpoint.

‡‡ Defined as Bayley Scales Gross Motor subset item #26: Child sits alone without support for ≥30 seconds.

§§ Defined as avoidance of either (a) death or (b) permanent ventilation, at 14 months of age. Permanent ventilation is defined by tracheostomy or by the requirement of ≥16 hours of respiratory assistance per day (via non-invasive ventilatory support) for ≥14 consecutive days in the absence of an acute reversible illness, excluding perioperative ventilation.

¶¶ WHO definition: child sits up straight with head erect for ≥10 seconds; child does not use hands or arms to balance body or support position.

3.2 *If the technology is, or is planned to be, subject to any other form of assessment in the UK, please give details of the assessment, organisation and expected timescale.*

AveXis will submit an application for onasemnogene abeparvovec to the Scottish Medicines Consortium in 2020.

4 Equality

4.1 *Please let us know if you think that this evaluation:*

- ***could exclude from full consideration any people protected by the equality legislation who fall within the patient population for which [the treatment(s)] is/are/will be licensed;***
- ***could lead to recommendations that have a different impact on people protected by the equality legislation than on the wider population, e.g. by making it more difficult in practice for a specific group to access the technology;***
- ***could lead to recommendations that have any adverse impact on people with a particular disability or disabilities***

There are no special considerations in equality.

4.2 *How will the submission address these issues and any equality issues raised in the scope?*

Not applicable.

5 Disease morbidity

5.1 *Please provide the number of patients in England who will be covered by this particular therapeutic indication in the marketing authorisation each year and provide the source of data.*

SMA (all types) has an annual incidence of approximately 9.4:100,000 live births (19); SMA type 1 accounts for approximately 58% of cases of SMA (19). Due to the high mortality rate of infants with SMA type 1, with few affected children surviving free from permanent ventilation beyond 2 years of age under BSC, the reported prevalence in the literature varies, ranging from 0.04 to 0.28 per 100,000 population (20). A recent National Congenital Anomaly and Rare Disease Registration Service (NCARDRS) data briefing which used HES data reported an SMA type 1 prevalence of 1.9 per million population in England (21).

In English clinical practice, onasemnogene abeparvovec is expected to be used in children with SMA type 1, and in pre-symptomatic infants with a genotype predictive of SMA type 1 (i.e. those with up to three copies of the *SMN2* gene).

Epidemiological data indicate that approximately 59 people are born with SMA (all types) per year in England, using an SMA (all types) incidence of 9.4:100,000 live births applied to the number of live births (625,651) reported in England in 2018 (Table 3) (19). Using the estimate that SMA type 1 accounts for approximately 58% of incident cases of SMA, it is calculated that **34 infants with SMA type 1** would be eligible for treatment with onasemnogene abeparvovec in England each year, assuming a timely genetic diagnosis based on clinical manifestations (20, 22). Whilst, it is recognised that national newborn screening for SMA is not currently established practice in England, early referral for genetic diagnosis is offered in situations where there is a sibling history of SMA. Thus, a minority of these 34 incident cases may be diagnosed pre-symptomatically via early referral due to sibling history of SMA. These estimates can be relied upon in this appraisal as they are supported by real world evidence (RWE) from:

- The nusinersen UK early access programme (EAP) which reports that in its last year of operation, 32 babies were diagnosed with SMA type 1 and treated with nusinersen in England (personal communication; [redacted], Paediatric Neurologist)
- Analysis of England Hospital Episodes Statistics (HES) data indicate that the number of incident SMA type 1 patients (defined as those aged from 0 months to 12 months at point of first coding [ICD-10, G12.0]) in England ranged from 28–32 cases per year between April 2013 – March 2017 (23)

In addition to the incident SMA type 1 population described above, there is also a prevalent SMA type 1 population (including those older than 6 months and/or those who have received another SMA-related therapy). Applying the prevalence rate of SMA type 1 as recently reported by the NCARDRS of 1.9 per million population (21)., equates to approximately 100

prevalent patients with SMA type 1 in England. This prevalent SMA type 1 population size has been validated by England clinicians at a recent clinical advisory board (April 2020).

For both incident and prevalent SMA type 1 populations, further eligibility criteria need to be considered such as antibody AAV9 titre levels, advancement of disease and patient/caregiver treatment choice, as in some cases BSC alone may be chosen even in the presence of available treatments. Please see Section 9 for further details of patient number calculations.

Table 3: Estimated SMA incident cases by region

Region	Live births, n	SMA incident cases		Year†	ONS date‡
		Type 1, n	All types, n		
England	625,651	34	59	2018	01-Aug-19

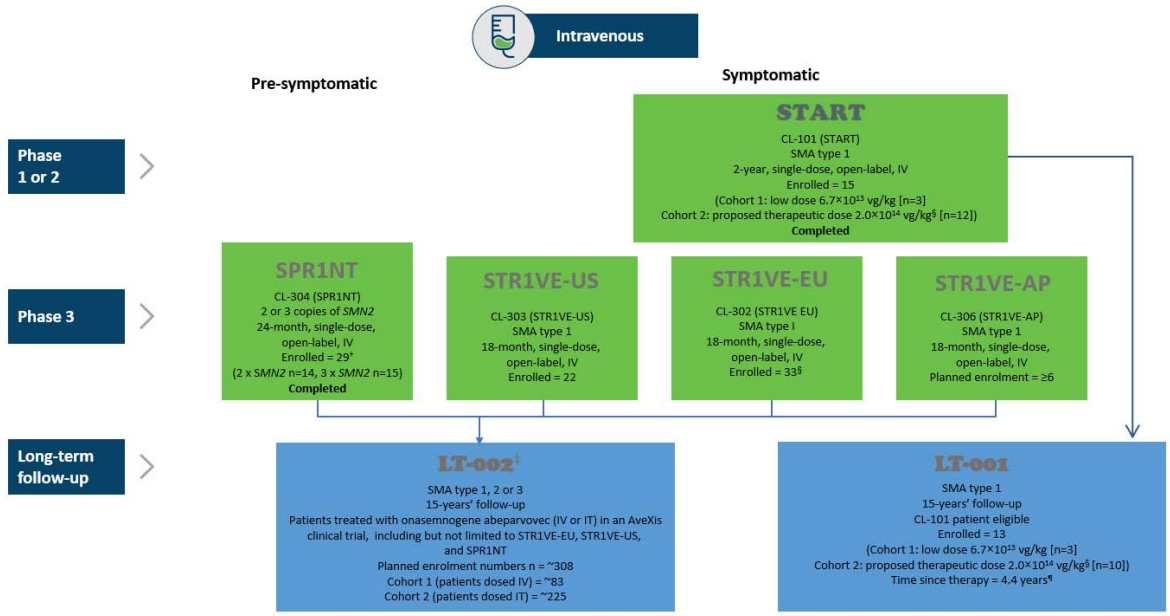
Abbreviations: ONS, Office for National Statistics; SMA, spinal muscular atrophy; UK, United Kingdom.
Assumptions: Incident rate, SMA = 9.4:100,000 live births (19). Rate of SMA, type 1 = 58% (20).
† Year in which live births were recorded. ‡ Date of Office for National Statistics live birth data publication.
Source: Office for National Statistics, 2019 (22).

6 Published and unpublished clinical evidence

6.1 *Summary of methodology of relevant studies*

Two clinical trials are complete and three are ongoing in which infants with symptomatic SMA type 1 (START, STR1VE-US, STR1VE-EU, LT-001, LT-002) or pre-symptomatic SMA (SPR1NT) received a one-time IV administration of onasemnogene abeparvovec (Figure 1). Data from the completed studies (START and STR1VE-US) are presented in full, along with interim data cuts from the ongoing studies. The next efficacy data cut for the ongoing studies LT-001, SPR1NT, and STR1VE-EU, is in [redacted]. A further long-term follow-up study, LT-002, enrolling infants treated with onasemnogene abeparvovec in AveXis clinical trials, commenced in September 2019. To date, no patients treated with IV onasemnogene abeparvovec are enrolled in LT-002 and therefore no results are presented in this submission.

Figure 1: Overview of all completed and ongoing studies in the clinical trial programme for IV onasemnogene abeparvovec



Abbreviations: IV, intravenous; IMP, investigational medicinal product; SMA, spinal muscular atrophy.
† Pre-symptomatic patients with four copies of *SMN2* were in the original SPR1NT protocol but later removed as per protocol amendment dated 27 September 2018. One patient with four copies of *SMN2* was enrolled but excluded from the ITT efficacy population for Cohort 2 (three copies of *SMN2*) and is therefore not reported in the interim efficacy results; this patient remains part of the safety population
‡ LT-002 commenced in September 2019; to date, seven patients are enrolled in LT-002.
§ Direct testing of the actual lot of IMP used in START by an improved and more fully qualified analytical method has determined the actual dose received by Cohort 2 as 1.1 x 10^{14} vg/kg. The same method has been used to establish an equivalent dose for the IMP in all Phase III trials.
¶ The median duration of therapy in LT-001 of patients treated with the therapeutic dose of onasemnogene abeparvovec in START (n=10) as of the 31 December 2019 (range 49.2-61.9 months) (13).

START was a Phase I/IIa study in which safety was the primary outcome and efficacy was a secondary objective. However, as discussed in Section 6.3.1.1 results from START demonstrated unprecedented evidence of efficacy in improving the survival, motor function, and achievement and maintenance of developmental milestones and bulbar function (i.e. swallowing, oral feeding, and speech) of patients with SMA type 1. Given the lethality of SMA, the extremely poor prognosis for patients who do not receive treatment (original company submission Section 2.1.1.3), and the favourable efficacy and safety profile observed in START, it was considered that it would be unethical to include placebo arms in further onasemnogene abeparvovec trials. All interventional studies in the clinical development programme therefore had an open-label design with all patients receiving a one-time infusion of onasemnogene abeparvovec; the START study also included a dose comparison evaluation. To support the open-label design of the onasemnogene abeparvovec studies, well characterised datasets from the SMA natural history studies (the PNCR database and NeuroNext) were identified as appropriate for use as historical controls (3-5).

6.1.1 Study design and methodology for each of the published and unpublished relevant studies. A separate table should be completed for each study.

The methods of the completed and ongoing studies in the onasemnogene abeparvovec clinical trial programme are outlined in Table 4 to Table 9.

Following the outcomes of a non-clinical study concerning dorsal root ganglia mononuclear cell inflammation, the following amendments have been made to study protocols for onasemnogene abeparvovec trials:

- Protocols include additional age appropriate sensory testing, and call for attention to new symptoms of pain, numbness, or paraesthesia's as part of the neurologic exam at baseline and at each visit in all ongoing clinical trial protocols for onasemnogene abeparvovec
- For ongoing and long-term observational trials, the list of events of special interest (AESIs) has been revised by the addition of sensory abnormalities suggestive of ganglionopathy

Table 4: Summary of methodology for START (AVXS-1010-CL-101)

Study name	START: Phase I gene transfer clinical trial for spinal muscular atrophy type 1 delivering AVXS-101
Objective	To assess the safety of onasemnogene abeparvovec
Location	US
Design	Phase I/IIa, open-label, one-time infusion, ascending-dose, single-centre study
Duration of study	Start date: 5 May 2014 Date of completion: 15 December 2017
Patient population	Patients with SMA type 1 possessing 2 copies of *SMN2* without c.859G>c modification in exon 7
Sample size	15 patients
Inclusion criteria	Six months of age† and younger at day of vector infusion with SMA type 1 as defined by the following features: • Bi-allelic *SMN1* gene mutations (deletion or point mutation) with 2 copies of *SMN2* (no more and no fewer) • Patients 6 months of age and younger with disease onset up to 6 months of age • Hypotonia by clinical evaluation with delay in motor skills, poor head control, round shoulder posture, and hypermobility of joints
Exclusion criteria	• Active viral infection (included HIV or serology positive for hepatitis B or C) • Use of invasive ventilatory support (tracheostomy with positive pressure) or pulse oximetry <95% saturation at the screening visit • Non-invasive ventilator support (e.g. BiPAP) for >16 hours/day • Concomitant illness that in the opinion of the Investigator created unnecessary risks for gene transfer • Concomitant use of: drugs for treatment of myopathy or neuropathy, agents used to treat diabetes mellitus, or ongoing immunosuppressive therapy or immunosuppressive therapy within 3 months of starting the study (e.g. corticosteroids, cyclosporine, tacrolimus, methotrexate, cyclophosphamide, IV immunoglobulin, rituximab) • Antibody to anti-AAV9 titres >1:50 • Abnormal laboratory values considered clinically significant (GGT >3 × ULN, bilirubin ≥3.0 mg/dL, creatinine ≥1.8 mg/dL, haemoglobin <8 or >18 g/dL; white blood cells >20,000/mm^3) • Participation in a recent SMA treatment clinical trial or receipt of an investigational or commercial compound, product or therapy administered with the intention to treat SMA (e.g. nusinersen, valproic acid) that in the opinion of the Investigator created unnecessary risks for gene transfer • Patient with signs of aspiration based on a swallowing test and unwilling to use an alternative method to oral feeding • Patients with c.859G>C modification in exon 7, based on predicted mild phenotype

Intervention(s) (n =) and comparator(s) (n =)	Onasemnogene abeparvovec (IV) • Cohort 1 received a low dose 6.7×10^{13} vg/kg (n=3) • Cohort 2 received a therapeutic dose 2.0×10^{14} vg/kg‡ (n=12) Comparator: natural history cohort§
Baseline differences	See full details of baseline characteristics in Section 6.1.3.
Duration of follow-up, participants lost to follow-up information	During the first year of the 2-year safety follow-up period, patients returned for post-dose follow-up visits on Days 7, 14, 21, and 30, followed by monthly visits through Month 12 During the second year, patients with CHOP-INTEND scores ≥62 were assessed with the Bayley Scales and completed visits every 3 months; all other patients completed monthly visits (subsequently changed to quarterly visits)
Statistical tests	Efficacy analyses conducted for START were considered descriptive by agreement with FDA and were performed without a statistical analysis plan The following analysis sets were used for the statistical analyses: SAS, ITT, FAS, EES, mITT, per protocol set, and ability to thrive ITT population Changes from baseline to each study visit were analysed with the use of a mixed-effects model for repeated measurements. The mixed model included the fixed effects of cohort and visit and a covariate of baseline score. Statistical analyses were performed with the use of SAS software, version 9.4. All hypothesis testing was conducted at the 0.05 level of significance except for the endpoint of survival, which was conducted at the 0.025 level of significance. Tests were 1-sided or 2-sided, as appropriate, and were considered descriptive. Categorical measures, such as percent surviving event-free, were summarised using counts and percentages.
Primary outcomes (including scoring methods and timings of assessments)	Safety: AEs, laboratory evaluations, DILI, vital signs, ECGs, physical examinations, and immunologic response Primary efficacy endpoint: Survival, defined as time from birth to either (a) requirement of ≥16-hour respiratory assistance per day (includes BiPAP) continuously for ≥2 weeks in the absence of an acute reversible illness, excluding perioperative ventilation or (b) death Efficacy analyses were conducted at the following time points: • The date at which all patients had completed a study visit after reaching 13.6 months of age • When the last enrolled patient had a study visit after reaching 20 months of age • When all patients completed 24 months of post-dose follow-up
Secondary outcomes (including scoring methods and timings of assessments)	Secondary efficacy endpoints • Change in CHOP-INTEND from baseline score • Demonstration of improvement of motor function and muscle strength as determined by achievement of significant development milestones including but not limited to the ability to sit alone and roll over unassisted

Exploratory efficacy endpoints	• Maintain ability to thrive defined as meeting the following criteria at the each of the three efficacy data time points: o The ability to tolerate thin liquids as demonstrated through a formal swallowing test o Did not receive nutrition through mechanical support (e.g. feeding tube) o Maintained weight (>3rd percentile for age and gender as defined by WHO guidelines) at the time of the primary efficacy data cut-off ▪ A patient was defined as not requiring non-oral nutrition at baseline if the patient 1) did not use non-oral nutrition of any kind and 2) demonstrated intact swallowing at the baseline assessment such that the patient did not receive a recommendation for non-oral nutrition prior to onasemnogene abeparvovec administration • Independence from ventilatory support defined as requiring no daily ventilator support/usage at the 3 efficacy analysis time points, in the absence of acute reversible illness and excluding perioperative ventilation • Achievement of CHOP-INTEND threshold scores of ≥40, ≥50, and ≥60 by the time of the primary efficacy data cut-off and at 24 months post-infusion • Development of significant motor function milestones per gross motor skills checklist • Achievement of functional independent sitting (≥30 seconds) based on video reviews by an external expert • Change from baseline in fine and gross motor components of the Bayley Scales of Infant and Toddler Development • Motor neuron function assessed through CMAP and MUNE • The proportion of patients who used non-oral feeding (gastrostomy with Nissen fundoplication, gastrostomy without Nissen fundoplication, nasogastric, or nasojejunal) • The types of and reasons for invasive ventilatory support required by patients • Hospitalisations during the study

Abbreviations: AAV9, adeno-associated virus serotype 9; AE, adverse event; BiPAP, bi-level positive airway pressure; CHOP-INTEND, Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders; CMAP, compound motor action potential; DILI, drug-induced liver injury; ECG, electrocardiogram; EES, efficacy evaluable set; FAS, full analysis set; GGT, gamma-glutamyl transferase; HIV, human immunodeficiency virus; IMP, investigational medicinal product; ITT, intention-to treat; IV, intravenous; MUNE, motor unit number estimation; mITT, modified ITT; PNCR, Pediatric Neuromuscular Clinical Research database; SAS, safety analysis set; SMA, spinal muscular atrophy; *SMN*, survival motor neuron; ULN, upper limit of normal; WHO, World Health Organization.

† This inclusion criterion was revised to allow enrolment of patients 6 months of age or younger. The first 9 patients were enrolled under previous version(s) of the protocol, which allowed an age range of 9 months or younger.

‡ Direct testing of the actual lot of IMP used in START by an improved and more fully qualified analytical method has determined the actual dose received by Cohort 2 to be 1.1×10^{14} vg/kg. The same method has been used to establish an equivalent dose for the IMP in all Phase III trials.

§ Well characterised external datasets from SMA natural history studies (PNCR and NeuroNext (5)) are used to provide an external control comparator.

Table 5: Summary of methodology for LT-001 (extension of START)

Study name	LT-001: A long-term follow-up safety study of patients in the AVXS-101-CL-101 gene replacement therapy clinical trial for spinal muscular atrophy type 1 delivering AVXS-101
Objective	To collect long-term follow-up safety data of patients with SMA type 1 who were treated with onasemnogene abeparvovec in START
Location	US
Design	Long-term, safety follow-up study
Duration of study	Start date: 15 August 2017 Estimated date of completion: December 2033
Patient population	Patients with SMA type 1 who were treated with onasemnogene abeparvovec in START
Sample size	Planned: up to 15 (enrolled n=13)
Inclusion criteria	• Patient who received onasemnogene abeparvovec in the START gene replacement therapy clinical trial for SMA type 1 • Parent/legal guardian willing and able to complete the informed consent process and comply with study procedures and visit schedule
Exclusion criteria	• Parent/legal guardian unable or unwilling to participate in the long-term follow-up safety study
Intervention(s) (n =) and comparator(s) (n =)	Study drug was not administered in LT-001, patients received a one-time IV administration of onasemnogene in START
Baseline differences	See full details of baseline characteristics in Section 6.1.3.
Duration of follow-up, participants lost to follow-up information	The study will consist of an initial 5-year phase, during which subjects will be seen annually for evaluation of long-term safety, followed by a 10-year observational phase. Upon completion of the initial five years of follow-up visits, patients will be contacted via phone annually for the remaining 10-year follow-up period. During the 10-year observational phase, caregivers and patients will be contacted at least once a year and site staff will review a yearly questionnaire designed to elicit information regarding medical history, adverse events, and other clinical conditions. Additionally, patient record transfers from their local physician and/or neurologist will be requested in conjunction with the annual phone contacts for review by the investigator
Statistical tests	This is a long-term follow-up study with safety as the primary measure. Sample size was not determined through statistical justification

Primary outcomes (including scoring methods and timings of assessments)	<u>Safety assessments:</u> • Medical history and record review • Physical examinations, including height, weight, vital signs, ventilation, nutritional support, and developmental milestone assessments • Clinical laboratory evaluations • Pulmonary assessments • Echocardiograms, holter monitoring, electrocardiograms <u>Efficacy assessments:</u> • Physical examinations to assess developmental milestones o New milestones demonstrated by patients which were not documented during START must be supported by video evidence
Secondary outcomes (including scoring methods and timings of assessments)	N/A

Abbreviations: N/A, not applicable; SMA, spinal muscular atrophy.

Table 6: Summary of methodology for STR1VE-US (AVXS-101-CL-303)

Study name	STR1VE-US: Phase III, open-label, single-arm, single-dose gene replacement therapy clinical trial for patients with spinal muscular atrophy type 1 with one or two *SMN2* copies delivering onasemnogene abeparvovec by intravenous infusion
Objective	To determine the efficacy of onasemnogene abeparvovec
Location	US
Design	Phase III, open-label, single-arm, one-time infusion gene replacement study
Duration of study	Start date: 24 October 2017 Date of completion: 12 December 2019
Patient population	Patients with SMA type 1 with 1 or 2 copies of *SMN2* <6 months of age at the time of gene replacement therapy
Sample size	21 (enrolled n=22)
Inclusion criteria	• Diagnosis of SMA based on gene mutation analysis with bi-allelic *SMN1* mutations (deletion or point mutations) and 1 or 2 copies of *SMN2* (inclusive of the known *SMN2* gene modifier mutation [c.859G>C]) • Patients must be <6 months (<180 days) of age at the time of onasemnogene abeparvovec infusion • Patients must have a swallowing evaluation test performed prior to administration of gene replacement therapy • Up-to-date on childhood vaccinations
Exclusion criteria	• Previous, planned or expected scoliosis repair surgery/procedure during the study assessment period • Pulse oximetry <96% saturation at screening while the patient is awake or asleep without any supplemental oxygen or respiratory support, or for altitudes >1,000 m, oxygen saturation <92% awake or asleep without any supplemental oxygen or respiratory support. Pulse oximetry saturation may decrease to <96% after screening provided that the saturation does not decrease by ≥4 percentage points • Tracheostomy or current use or requirement of non-invasive ventilatory support averaging ≥6 hours daily over the 7 days prior to the screening visit; or ≥6 hours/day on average during the screening period or requiring ventilatory support while awake over the 7 days prior to screening or at any point during the screening period prior to dosing • Patients with signs of aspiration/inability to tolerate non-thickened liquids based on a formal swallowing test performed as part of screening. Patients with a gastrostomy tube who pass the swallowing test will be allowed to enrol in the study • Patients whose weight-for-age is below the third percentile based on WHO Child Growth Standards (24) • Active viral infection (includes HIV or positive serology for hepatitis B or C, or Zika virus) • Serious non-respiratory tract illness requiring systemic treatment and/or hospitalisation within 2 weeks prior to screening

	• Upper or lower respiratory infection requiring medical attention, medical intervention, or increase in supportive care of any manner within 4 weeks prior to screening • Severe non-pulmonary/respiratory tract infection (e.g. pyelonephritis, or meningitis) within 4 weeks before administration of gene replacement therapy or concomitant illness that, in the opinion of the Principal Investigator, creates unnecessary risks for gene replacement therapy • Known allergy or hypersensitivity to prednisolone or other glucocorticosteroids or their excipients • Concomitant use of any of the following: drugs for treatment of myopathy or neuropathy, agents used to treat diabetes mellitus, or ongoing immunosuppressive therapy, plasmapheresis, immunomodulators such as adalimumab, immunosuppressive therapy within 3 months prior to gene replacement therapy (e.g. corticosteroids, cyclosporine, tacrolimus, methotrexate, cyclophosphamide, IV immunoglobulin, rituximab) • Anti-AAV9 antibody titre >1:50. Should a potential patient demonstrate anti-AAV9 antibody titer >1:50, he or she may receive retesting within 30 days of the screening period and will be eligible to participate if the anti-AAV9 antibody titer upon retesting is ≤1:50 o The mothers of enrolled patients were also screened for anti-AAV9 antibodies. Mothers who tested positive for antibodies to AAV9 were be asked to refrain from further feedings with breast milk. If anti-AAV9 antibodies were identified, the patient stopped consuming breast milk from the biological mother. Patients consuming banked breast milk from donor sources that could not be test for anti-AAV9 antibodies were transitioned to formula prior to participation • Clinically significant abnormal laboratory values (GGT, ALT, and AST >3 × ULN, bilirubin ≥3.0 mg/dL, creatinine ≥1.0 mg/dL, Hgb <8 or >18 g/dL, WBC >20,000/cmm) prior to gene replacement therapy • Participation in recent SMA treatment clinical study (with the exception of observational cohort studies or non-interventional studies) or receipt of an investigational or commercial compound, product, or therapy administered with the intention to treat SMA (e.g. nusinersen, valproic acid) at any time prior to screening for this study. Oral β-agonists must be discontinued at least 30 days before gene replacement therapy dosing. Inhaled albuterol specifically prescribed for the purposes of respiratory (bronchodilator) management is acceptable and not a contraindication at any time prior to screening for this study • Expectation of major surgical procedures during the study assessment period (e.g. spinal surgery or tracheostomy) • Gestational age at birth <35 weeks (245 days)
Intervention(s) (n =) and comparator(s) (n =)	Onasemnogene abeparvovec at 1.1 X 10^{14} vg/kg† will be administered as a one-time peripheral IV infusion over approximately 30–60 minutes (enrolled n=22) Comparator: natural history cohort‡
Baseline differences	See full details of baseline characteristics in Section 6.1.3.

Duration of follow-up, participants lost to follow-up information	During the outpatient follow-up period (Day 4 to End of Study at 18 months of age), patients returned at regularly scheduled intervals for efficacy and safety assessments. Missed visits were rescheduled as soon as possible, but within 7 days and still within the required visit window. For the 14 and 18 months of age visits, the patient will return within 0 to 14 days after the date on which the patient reaches 14 and 18 months of age, respectively. The 18 months of age visit will also serve as the End of Study visit. After the End of Study visit, eligible patients may roll over into the long-term follow-up study
Statistical tests	<u>Primary efficacy endpoints:</u> The number and percent of patients whom, through video evidence, exhibit the milestone achievement of sitting without support at any visit up to and including 18 months of age study visit will be summarised for the ITT population. A one-sided Exact Binomial Test will be used to test the null hypothesis of p=0.1% at significance level of 0.025. Furthermore, the corresponding 95% confidence intervals will be estimated by the exact method for binomial proportions. The observed proportion surviving in the current study was compared with the natural history data of the matching cohort using a two-sample Fisher's exact test, along with the corresponding 95% confidence intervals
Primary outcomes (including scoring methods and timings of assessments)	<u>Co-primary outcomes:</u> • Proportion of patients who achieved functional independent sitting for ≥30 seconds at the 18 months of age study visit • Survival, defined as avoidance of either (a) death or (b) permanent ventilation, at 14 months of age. Permanent ventilation is defined by tracheostomy or by the requirement of ≥16 hours of respiratory assistance per day (via non-invasive ventilatory support) for ≥14 consecutive days in the absence of an acute reversible illness, excluding perioperative ventilation
Secondary outcomes (including scoring methods and timings of assessments)	<u>Co-secondary outcomes:</u> • Proportion of patients maintaining the ability to thrive, defined as the ability to tolerate thin liquids (as demonstrated through a formal swallowing test) and to maintain weight (>3rd percentile based on WHO Child Growth Standards (24) for age and gender) without need of gastrostomy or other mechanical or non-oral nutritional support at 18 months of age • Proportion of patients who are independent of ventilatory support, defined as requiring no daily ventilator support/usage at 18 months of age, excluding acute reversible illness and perioperative ventilation, as defined above through assessment of actual usage data captured from the device (Phillips Trilogy)
Exploratory efficacy endpoints	• Achievement of the ability to: o hold head erect without support o roll from back to both sides o sit with support o sit independently (>10 seconds; WHO Motor Developmental Milestones (6)) o crawl

	○ pull to stand ○ stand with assistance ○ stand alone ○ walk with assistance ○ walk alone • Change from baseline in fine and gross motor components of the Bayley Scales of Infant and Toddler Development • Change from baseline in gross motor function as determined by improvement CHOP-INTEND score • Proportion of patients achieving CHOP-INTEND score ≥40 • Proportion of patients achieving CHOP-INTEND score ≥50 • Proportion of patients achieving CHOP-INTEND score ≥58 • Change in peroneal nerve CMAP amplitude • Age at which independent sitting (30 seconds) is first achieved

Abbreviations: AAV9, adeno-associated virus serotype 9; CMAP, compound motor action potential; GGT, gamma glutamyl- transpeptidase; Hgb, haemoglobin; HIV, human immunodeficiency virus; IMP, investigational medicinal product; ITT, intention-to-treat; IV, intravenous; PNCR, Pediatric Neuromuscular Clinical Research database; SMA, spinal muscular atrophy; *SMN*, survival motor neuron; US, United States; WBC, white blood cell; WHO, World Health Organization.

† Equivalent to the dose received by the Cohort 2 in START as determined by direct product testing with improved analytical methods. Direct testing of the actual lot of IMP used in START by an improved and more fully qualified analytical method has determined the actual dose received by Cohort 2 to be 1.1×10^{14} vg/kg. The same method has been used to establish an equivalent dose for the IMP in all Phase III trials.

‡ Well characterised external datasets from SMA natural history studies (PNCR and NeuroNext (5)) are used to provide an external control comparator.

Table 7: Summary of methodology for STR1VE-EU (AVXS-101-CL-302)

Study name	STR1VE-EU: Phase III, open-label, single-arm, single-dose gene replacement therapy clinical trial for patients with spinal muscular atrophy type 1 with one or two *SMN2* copies delivering AVXS-101 by intravenous infusion
Objective	To assess the efficacy of onasemnogene abeparvovec
Location	12−16 European investigative sites located in the following countries: Belgium, France, Germany, Italy, Netherlands, Spain, UK, Sweden
Design	Phase III open-label, single-arm, one-time infusion trial investigating the efficacy and safety of onasemnogene abeparvovec in patients with SMA type 1
Duration of study	Start date: 29 August 2018. Estimated date of completion: Q4 2020
Patient population	Symptomatic SMA type 1 patients genetically defined by no functional *SMN1* as well as 1 or 2 copies of *SMN2* who are ≤6 months of age at time of gene replacement therapy infusion
Sample size	Enrolled n=33
Inclusion criteria	• Patients with SMA type 1 as determined by diagnosis of SMA based on gene mutation analysis with bi-allelic *SMN1* mutations (deletion or point mutations) and one or two copies of *SMN2* (inclusive of the known *SMN2* gene modifier mutation [c.859G>C]) • Aged <6 months (<180 days) at the time of onasemnogene abeparvovec infusion • Patients must have a swallowing evaluation test performed prior to administration of gene replacement therapy • Up-to-date on childhood vaccinations
Exclusion criteria	• Previous, planned or expected scoliosis repair surgery/procedure prior to 18 months of age • Use of invasive ventilatory support (tracheostomy with positive pressure) or pulse oximetry <95% saturation at screening (saturation must not decrease ≥4 percentage points between screening and dosing with confirmatory oximetry reading), patients may be put on non-invasive ventilatory support for <12 hours per day at the discretion of their physician or trial staff) • Use or requirement of non-invasive ventilatory support for ≥12 hours daily in the 2 weeks prior to dosing • Patient with signs of aspiration based on a swallowing test or whose weight-for-age falls below the third percentile based on WHO Child Growth Standards, and unwilling to use an alternative method to oral feeding • Active viral infection (includes HIV or positive serology for hepatitis B or C, or known Zika virus infection) • Serious non-respiratory tract illness requiring systemic treatment and/or hospitalization within 2 weeks prior to screening • Upper or lower respiratory infection requiring medical attention, medical intervention, or increase in supportive care of any manner within 4 weeks prior to screening • Severe non-pulmonary/respiratory tract infection (e.g. pyelonephritis, or meningitis) within 4 weeks before administration of gene replacement therapy or concomitant illness that, in the opinion of the Investigator, creates unnecessary risks for gene replacement

	• Known allergy or hypersensitivity to prednisolone or other glucocorticosteroids or their excipients • Concomitant use of any of the following: drugs for treatment of myopathy or neuropathy, agents used to treat diabetes mellitus, or ongoing immunosuppressive therapy, plasmapheresis, immunomodulators such as adalimumab, or immunosuppressive therapy within 3 months prior to gene replacement therapy • Anti-AAV9 antibody titre >1:50. Should a potential patient demonstrate anti-AAV9 antibody titer >1:50, he or she may receive retesting within 30 days of the screening period and will be eligible to participate if the anti-AAV9 antibody titer upon retesting is ≤1:50 • Clinically significant abnormal laboratory values prior to gene replacement therapy (GGT, ALT, and AST >3x ULN; bilirubin ≥3.0 mg/dL; creatinine ≥1.0 mg/dL; Hgb <8 or >18 g/dL; WBC >20,000/cmm) • Participation in recent SMA treatment clinical trial (with the exception of observational cohort studies or non-interventional studies) or receipt of an investigational or commercial compound, product or therapy administered with the intention to treat SMA (e.g. nusinersen, valproic acid) at any time prior to screening for this trial. Oral beta-agonists must be discontinued ≥30 days prior to dosing • Expectation of major surgical procedures during the trial assessment period (e.g. spinal surgery or tracheostomy) • Patients <35 weeks gestational age at time of birth
Intervention(s) (n =) and comparator(s) (n =)	Intervention: peripheral IV infusion of 1.1 X 10^{14} vg/kg† onasemnogene abeparvovec (enrolled n=33) Comparator: natural history cohort‡
Baseline differences	See full details of baseline characteristics in Section 6.1.3.
Duration of follow-up, participants lost to follow-up information	Patients will return for follow-up visits on Days 7, 14, 21, and 30. Patients will return monthly thereafter, following the Day 30 visit, for 18 months from dose administration.

Statistical tests	Primary efficacy endpoint: The number and percent of patients whom, through video evidence, exhibit the milestone achievement of sitting without support at any visit up to and including 18 months of age study visit will be summarised for the ITT population. A one-sided Exact Binomial Test will be used to test the null hypothesis of p=0.1% at significance level of 0.025. Furthermore, the corresponding 95% confidence intervals will be estimated by the exact method for binomial proportions. Secondary efficacy endpoint: The observed proportion surviving in the current study was compared with the natural history data of the matching cohort using a two-sample Fisher's exact test, along with the corresponding 95% confidence intervals.
Primary outcomes (including scoring methods and timings of assessments)	The primary objective was to demonstrate efficacy by achievement of the developmental milestone of sitting without support for at least 10 seconds up to 18 months of age (as assessed by WHO Motor Development Milestones)
Secondary outcomes (including scoring methods and timings of assessments)	To determine efficacy based on survival at 14 months of age, defined by the avoidance of combined endpoint of either (a) death or (b) permanent ventilation (defined by tracheostomy or by the requirement of ≥16 hours of respiratory assistance per day [via non-invasive ventilatory support] for ≥14 consecutive days in the absence of an acute reversible illness, excluding perioperative ventilation)
Exploratory efficacy endpoints	• Achievement of the ability to: o hold head erect without support o roll over o sit with support (25) o achieve functional independent sitting for at least 30 seconds (25) o crawl as defined by WHO Motor Developmental Milestones (6) o pull to stand o stand with assistance as defined by WHO Motor Developmental Milestones (6) o stand alone as defined by WHO Motor Developmental Milestones (6) o walk with assistance as defined by WHO Motor Developmental Milestones (6) o walk alone as defined by WHO Motor Developmental Milestones (6)

	• Change from baseline in fine and gross motor components of the Bayley Scales of Infant and Toddler Development • Change from baseline in gross motor function as determined by improvement CHOP-INTEND score • Ability to remain independent of ventilator support, defined as requiring no daily ventilator support/usage at 18 months of age • Maintain ability to thrive defined as meeting the following criteria at the each of the 3 efficacy data time points: o The ability to tolerate thin liquids as demonstrated through a formal swallowing test o Did not receive nutrition through mechanical support (e.g. feeding tube) o Maintained weight (>3rd percentile for age and gender as defined by WHO guidelines) at the time of the primary efficacy data cut-off

Abbreviations: AAV9, adeno-associated virus serotype 9; ALT, alanine aminotransferase; AST, aspartate aminotransferase; CHOP-INTEND, Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders ; GGT, gamma-glutamyl transpeptidase; Hgb, haemoglobin; HIV, human immunodeficiency virus; IMP, investigational medicinal product; ITT, intention-to-treat; IV, intravenous; PNCR, Pediatric Neuromuscular Clinical Research database; SMA, spinal muscular atrophy; *SMN*, survival motor neuron; UK, United Kingdom; ULN, upper limit of normal; WBC, white blood cell; WHO, World Health Organization.

† Equivalent to the dose received by the Cohort 2 in START as determined by direct product testing with improved analytical methods. Direct testing of the actual lot of IMP used in START by an improved and more fully qualified analytical method has determined the actual dose received by Cohort 2 to be 1.1×10^{14} vg/kg. The same method has been used to establish an equivalent dose for the IMP in all Phase III trials.

‡ Well characterised external datasets from SMA natural history studies (PNCR and NeuroNext (5)) are used to provide an external control comparator.

Table 8: Summary of methodology for SPR1NT (AVXS-101-CL-304)

Study name	SPR1NT: A global study of a single, one-time dose of AVXS-101 delivered to infants with genetically diagnosed and pre-symptomatic spinal muscular atrophy with multiple copies of *SMN2*
Objective	To evaluate the safety and efficacy of onasemnogene abeparvovec in infants with genetically diagnosed and pre-symptomatic spinal muscular atrophy
Location	Australia, Belgium, Canada, Japan, UK, and the US[†]
Design	Phase III, open-label, single-arm study of a one-time infusion of onasemnogene abeparvovec in patients with spinal muscular atrophy
Duration of study	Start date: 10 April 2018 Estimated date of completion: *SMN2* 2 copies: Q4 2020; *SMN2* 3 copies: Q2 2021
Patient population	Pre-symptomatic patients with bi-allelic deletion of *SMN1* with 2 or 3 copies of *SMN2* and ≤6 weeks of age at the time of gene replacement therapy who meet enrolment criteria
Sample size	Planned: ≥27 (enrolled n=29[‡])
Inclusion criteria	**All patients** • Age ≤6 weeks (≤42 days) at time of dose • Ability to tolerate thin liquids as demonstrated through a formal bedside swallowing test • CMAP ≥2 mV at baseline; centralised review of CMAP data will be conducted • Gestational age of 35 to 42 weeks • Genetic diagnosis as described below, obtained from an acceptable newborn or pre-natal screening test method **Patients with 2 copies of *SMN2*** • Patients with pre-symptomatic SMA type 1 as determined by 2 copies of *SMN2* **Patients with 3 copies of *SMN2*** • Patients with pre-symptomatic SMA type 2 as determined by 3 copies of *SMN2*
Exclusion criteria	• Weight at screening visit <2 kg • Hypoxaemia (oxygen saturation <96% awake or asleep without any supplemental oxygen or respiratory support) at the screening visit or for altitudes >1,000 m, oxygen saturation <92% awake or asleep without any supplemental oxygen or respiratory support at the screening visit • Any clinical signs or symptoms at screening or immediately prior to dosing that are, in the opinion of the Investigator, strongly suggestive of SMA (e.g. tongue fasciculation, hypotonia, areflexia) • Tracheostomy or current prophylactic use or requirement of non-invasive ventilatory support at any time and for any duration prior to screening or during the screening period

	• Patients with signs of aspiration/inability to tolerate non-thickened liquids based on a formal swallowing test performed as part of screening or patients receiving any non-oral feeding method • Clinically significant abnormalities in haematology or clinical chemistry parameters as determined by the investigator or medical monitor • Treatment with an investigational or commercial product, including nusinersen, given for the treatment of SMA. This includes any history of gene replacement therapy, prior antisense oligonucleotide treatment, or cell transplantation. • Patients whose weight-for-age is below the third percentile based on WHO Child Growth Standards (24) • Biological mother with active viral infection as determined by screening laboratory samples (includes HIV or positive serology for hepatitis B or C) • Serious non-respiratory tract illness requiring systemic treatment and/or hospitalisation within 2 weeks prior to screening • Upper or lower respiratory infection requiring medical attention, medical intervention, or increase in supportive care of any manner within 4 weeks prior to dosing • Severe non-pulmonary/respiratory tract infection (e.g. pyelonephritis, or meningitis) within 4 weeks before administration of gene replacement therapy or concomitant illness that, in the opinion of the Investigator or Sponsor medical monitor, creates unnecessary risks for gene replacement therapy • Known allergy or hypersensitivity to prednisolone or other glucocorticosteroids or their excipients • Previous, planned or expected major surgical procedure including scoliosis repair surgery/procedure during the study assessment period • Concomitant use of any of the following: drugs for treatment of myopathy or neuropathy, agents used to treat diabetes mellitus, or ongoing immunosuppressive therapy, plasmapheresis, immunomodulators such as adalimumab, immunosuppressive therapy within 4 weeks prior to gene replacement therapy (e.g. corticosteroids, cyclosporine, tacrolimus, methotrexate, cyclophosphamide, IV immunoglobulin, rituximab) • Anti-AAV9 antibody titre >1:50 • Biological mother refuses anti-AAV9 antibody testing prior to dosing o The mothers of potential participants were screened for anti-AAV9 antibodies. Patient samples for anti-AAV9 screening were collected if biological mother's titer result was positive. If anti-AAV9 antibodies were identified, the investigator discussed with the mother whether to continue or to stop breastfeeding. Patients consuming banked breast milk from donor sources that could not be tested for anti-AAV9 antibodies were transitioned to formula prior to participation. Patients who do not have a biological mother available to screen for antibodies to AAV9 will have blood drawn for screening of anti-AAV9 antibodies.
Intervention(s) (n =) and comparator(s) (n =)	Onasemnogene abeparvovec at 1.1 X 10^{14} vg/kg[§] will be administered as a one-time peripheral IV infusion over approximately 60 minutes (planned n=30, enrolled n=29[‡]) Comparator: natural history cohort[¶]

Baseline differences	See full details of baseline characteristics in Section 6.1.3.
Duration of follow-up, participants lost to follow-up information	During the outpatient follow-up period (Days 3 to End of Study at 18 or 24 months of age, dependent upon respective *SMN2* copy number), patients will return at regularly scheduled intervals for efficacy and safety assessments until the End of Study when the patient reaches 18 months of age (*SMN2* = 2), 24 months of age (*SMN2* = 3)
Statistical tests	Primary efficacy endpoint in patients with 2 copies of *SMN2*: The proportion of patients who exhibit the milestone achievement of sitting without support for at least 30 seconds up to 18 months of age will be summarised for the ITT population. A one-sided Exact Binomial Test will be used to test the null hypothesis of p=0.1% at significance level of 0.025 Primary efficacy endpoint in patients with 3 copies of *SMN2*: The proportion of patients who achieve the ability to stand without support for at least three seconds up to 24 months of age will be compared with the natural history data of the matching cohort using a two sample 2-sided superiority Fisher exact test with a significance level of 0.05
Primary outcomes (including scoring methods and timings of assessments)	Safety: • Incidence of AEs and/or serious AEs • Change from baseline in clinical laboratory parameters Primary efficacy: • **2 copies of *SMN2*:** Proportion of patients achieving the ability of functional independent sitting for at least 30 seconds up to 18 months of age • **3 copies of *SMN2*:** Proportion of patients achieving the ability to stand without support for at least 3 seconds up to 24 months of age
Secondary outcomes (including scoring methods and timings of assessments)	Secondary efficacy: **2 copies of *SMN2*:** • Proportion of patients that have survived and have not required permanent ventilation in the absence of acute illness and perioperatively, assessed at 14 months of age. Permanent ventilation is defined as tracheostomy or the requirement of ≥16 hours of respiratory assistance per day (via non-invasive ventilatory support) for ≥14 consecutive days in the absence of an acute reversible illness, excluding perioperative ventilation • Proportion of patients that have achieved the ability to maintain weight at or above the third percentile without need for non-oral/mechanical feeding support at any visit up to 18 months of age **3 copies of *SMN2*:** • Proportion of patients demonstrating the ability to walk alone defined as the ability to take at least five steps independently displaying coordination and balance at any visit up to 24 months of age

Exploratory efficacy endpoints	**2 copies of *SMN2*:** • Achievement of motor milestones as assessed by WHO Multicentre Growth Reference Study (6) criteria at any visit up to 18 months of age: o Sitting without support o Hands and knees crawling o Standing with assistance o Walking with assistance o Standing alone o Walking alone • Time to respiratory intervention • Requirement for respiratory intervention at 18 months of age • Avoidance of death or the requirement of permanent ventilation in the absence of acute illness or perioperatively as assessed at 18 months of age • Proportion of patients alive and without tracheostomy at 18 months of age • Proportion of patients achieving an improvement over baseline of ≥15 points on Bayley Gross and Fine Motor Subsets (raw score) at any visit up to 18 months of age • Ability to achieve a scaled score on Bayley Gross and Fine Motor Subtests within 1.5 standard deviations of a chronological development reference standard at any visit up to 18 months of age • Achievement of a CHOP-INTEND motor function scale score ≥40 at any visit up to 18 months of age • Achievement of CHOP-INTEND score >50 at any visit up to 18 months of age • Achievement of CHOP-INTEND score ≥58 at any visit up to 18 months of age • Maintenance of achieved milestones at visits up to 18 months of age in the absence of acute illness or perioperatively **3 copies of *SMN2*:** • Achievement of motor milestones as assessed by WHO Multicentre Growth Reference Study (6) criteria at any visit up to 24 months of age: o Standing with assistance o Walking with assistance • Time to respiratory intervention • Proportion of patients requiring respiratory intervention at 24 months of age • Survival, defined as avoidance of death or the requirement of permanent ventilation in the absence of acute illness or perioperatively as assessed at 24 months of age • Improvement over baseline of ≥15 points on Bayley Gross and Fine Motor Subsets (raw score) at any visit up to 24 months of age

	• Achievement of a scaled score on Bayley Gross and Fine Motor Subtests within 1.5 standard deviations of a chronological development reference standard as assessed at any visit up to 24 months of age • Ability to maintain weight at or above the third percentile without need for non-oral/mechanical feeding support at any visit up to 24 months of age • Maintenance of achieved milestones at visits up to 24 months of age in the absence of acute illness or perioperatively

Abbreviations: AAV9, adeno-associated virus serotype 9; AE, adverse event; CMAP, compound muscle action potential; HIV, human immunodeficiency virus; IMP, investigational medicinal product; IV, intravenous; ITT, intention-to-treat; PNCR, Pediatric Neuromuscular Clinical Research database; SMA, spinal muscular atrophy; *SMN*, survival motor neuron; UK, United Kingdom; US, United States; WHO, World Health Organization.

† Number of infants enrolled to each country: Australia = 4; Belgium = 1; Canada = 1; Japan = 3; UK = 1; US = 20.

‡ Pre-symptomatic patients with four copies of *SMN2* were included in the original SPR1NT protocol but later removed as per protocol amendment dated 27 September 2018. One patient with four copies of *SMN2* has been enrolled but excluded from the ITT efficacy population and is therefore not reported in the interim efficacy results; this patient remains part of the safety population.

§ Equivalent to the dose received by the Cohort 2 in START as determined by direct product testing with improved analytical methods. Direct testing of the actual lot of IMP used in START by an improved and more fully qualified analytical method has determined the actual dose received by Cohort 2 to be 1.1×10^{14} vg/kg. The same method has been used to establish an equivalent dose for the IMP in all Phase III trials.

¶ Well characterised external datasets from SMA natural history studies (PNCR and NeuroNext (5)) are used to provide an external control comparator.

Table 9: Summary of methodology for LT-002 (long-term extension study)

Study name	LT-002: A long-term follow-up study of patients in the clinical trials for spinal muscular atrophy receiving AVXS-101
Objective	To collect long-term follow-up safety and efficacy data of patients with SMA type 1, 2, or 3 who were treated with onasemnogene abeparvovec in an onasemnogene abeparvovec clinical trial, including but not limited AVXS-101-CL-302 (Phase III), AVXS-101-CL-303 (Phase III), and AVXS-101-CL-304 (Phase III) In addition, patients treated with onasemnogene abeparvovec (intravenous or intrathecal) in future parent studies may be enrolled
Location	Studies may be conducted in any location worldwide
Design	Long-term, safety and efficacy follow-up study
Duration of study	Start date: 10 February 2020 Estimated date of completion: Q4 2034
Patient population	Patients participating in clinical trials for SMA type 1, 2, or 3 who were treated with onasemnogene abeparvovec
Sample size	Planned: approximately 308 • Cohort 1 (patients dosed IV): approximately 83 • Cohort 2 (patients dosed IT): approximately 225
Inclusion criteria	• Patients with SMA (with 1, 2 or 3 copies of survival motor neuron gene 2) who received onasemnogene abeparvovec gene replacement therapy in an AveXis clinical study • Patient/parent/legal guardian willing and able to complete the informed consent process and comply with study procedures and visit schedule
Exclusion criteria	• Patient/parent/legal guardian unable or unwilling to participate in the long-term follow-up study
Intervention(s) (n =) and comparator(s) (n =)	Study drug was not administered in LT-002
Baseline differences	N/A

Duration of follow-up, participants lost to follow-up information	Monitoring will continue for up to 15 years from the date of onasemnogene abeparvovec dosing. The number of study visits required in LT-002 will depend on the length of participation in the parent study. For example, patients followed 1 year in the parent study will participate in LT-002 for 14 years, patients followed 2 years in the parent study will participate for 13 years, and patients followed for 3 years in the parent study will participate for 12 years. If the HFMSE was performed during the parent study, within 6 months of the baseline visit in LT-002, it does not need to be repeated (parent study HMFSE may serve as the baseline for LT-002). If not done as part of the last visit in the parent study, or if the last HMFSE was conducted >6 months prior to the initial visit in LT-002, the HMFSE evaluation may be performed at the initial visit of LT-002. Patients will then return bi-annually for follow-up study visits for 2 years. Thereafter, in-person annual follow-up visits will be conducted for years 3 to 5. Patients will then be contacted via phone annually for the remainder of the study, until 15 years from the date of onasemnogene abeparvovec dosing
Statistical tests	The primary analysis of evaluating safety and efficacy data will be conducted when the last patient has completed the initial 5-year phase annual safety follow-up study visit or has discontinued study follow-up. Since less data will be collected during the 10-year observational phase which is based on annual telephone contact, analyses on serious adverse events, adverse events of special interest and pulmonary assessment will be implemented at the end of study using data collected during the 10-year observational phase Descriptive statistical methods will be used to summarise the data from this study. Continuous data, such as lab values, will be summarised using count, mean, median, standard deviation, minimum, and maximum. For continuous data specified to be analysed using parametric procedures, non-parametric procedures will be used if the parametric procedure is felt to be inappropriate
Primary outcomes (including scoring methods and timings of assessments)	<u>Safety assessments:</u> • Medical history and record review • Physical examinations, including height, weight, vital signs, ventilatory and nutritional support • Clinical laboratory evaluations • Pulmonary assessments • Cardiac assessments • Observational phase questionnaire <u>Efficacy assessments:</u> • Physical examinations to assess developmental milestones • New milestones demonstrated by patients which were not documented during onasemnogene abeparvovec study must be supported by video evidence • HFMSE to be performed during first 2 years of study in all patients • Pulmonary assessments • Swallowing questionnaire

Secondary outcomes (including scoring methods and timings of assessments)	N/A

Abbreviations: HFMSE, Hammersmith Functional Motor Scale - Expanded; N/A, not applicable; SMA, spinal muscular atrophy.

6.1.1.1 Description of clinical assessments

An overview of the outcome measures used in the onasemnogene abeparvovec clinical trial programme is provided below; tests were selected on the basis of the literature and the natural history of SMA (3, 4).

Survival without permanent ventilation

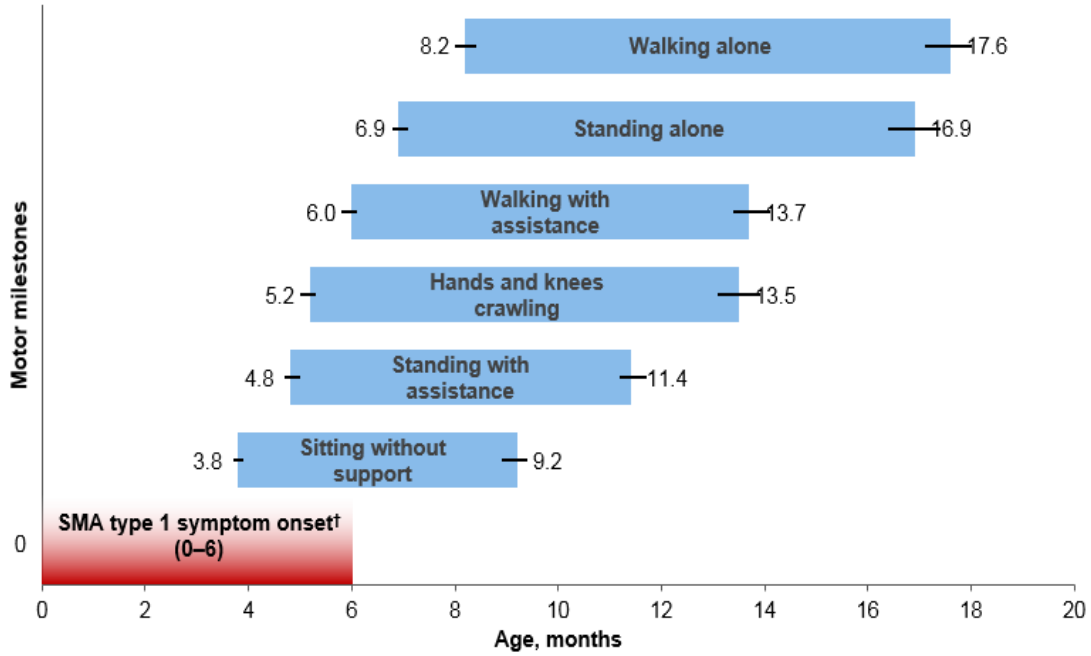
A combined endpoint of survival without permanent ventilation was considered appropriate as, while permanent ventilation can extend the life of infants with SMA, patients with severe disease will never achieve developmental milestones such as sitting, walking, or talking. A single endpoint of mortality would therefore underestimate the benefit of treatment, as permanent ventilation can be considered a surrogate for death given that a child who did not receive such intervention would be unlikely to survive.

The survival of patients with SMA was defined by the avoidance of the combined endpoint of either (a) death or (b) permanent ventilation, defined as tracheostomy or the requirement of ≥16 hours of respiratory assistance per day (via non-invasive ventilatory support) for ≥14 consecutive days in the absence of an acute reversible illness, excluding perioperative ventilation. This was in line with the definition of survival used in the PNCR study (3) and was a more conservative endpoint than that used in the NeuroNext study, in which data reflect tracheostomy-free survival, a less conservative endpoint (a child could receive 24 hours per day of non-invasive support without triggering the combined endpoint, for example) (4). Independence from ventilatory support and instances and reasons for invasive ventilatory support were also monitored during the onasemnogene abeparvovec clinical development programme.

Development of significant motor function milestones based on video reviews by an independent reviewer

Healthy children typically attain the motor milestones presented in Figure 2 by 20 months of age, however, the order of attainment of these milestones and the age at milestone attainment varies even between healthy children.

Figure 2: Age of SMA onset compared with the windows of normal motor-milestone achievement



Abbreviations: CI, confidence interval; SMA, spinal muscular atrophy.
Notes: Red shading represents the age of symptom onset for SMA type 1. Blue bars represent windows of normal motor-milestone achievement. Numerical values indicate the range (1st and 99th percentiles, respectively) of the windows of normal motor-milestone achievement; black lines represent the 95% CI for range (1st and 99th percentiles, respectively) of the windows of normal motor-milestone achievement.
† Although the age range for SMA type 1 symptom onset overlaps with the lower end of some of the windows of normal motor-milestone achievement, the underlying disease pathology is present before SMA type 1 symptom onset. A small proportion of children with SMA type 1 may attain limited milestones, such as head control, however, these milestones are achieved only transiently and are not maintained.
Source: Prior and Finanger 1993 (26); Farrar et al. 2017 (27); WHO Multicentre Growth Reference Study Group (28).

The development of motor function is impaired in infants with SMA type 1, leading to the lack of milestone achievement in SMA natural history studies (3, 29, 30). Therefore, the achievement of significant development milestones by infants in onasemnogene abeparvovec clinical trials was investigated through assessment by a central reviewer. Compiled video recordings of the CHOP-INTEND, Bayley Scales (31), submitted home videos, and physical examinations were sent to an independent reviewer for confirmation of development milestones. Details of the milestones assessed in individual studies are presented in Table 4 to Table 8; a consistent and objective approach was used to assess motor milestone achievements in the onasemnogene abeparvovec clinical programme to enable comparisons between studies. The motor milestones assessed as key efficacy endpoints included:

- Bayley Scales Gross Motor subset item #26 Sits without support for ≥30 seconds – **co-primary endpoint in STR1VE-US and primary endpoint in SPR1NT for infants with two copies of *SMN2***
- Sitting without support is defined by the World Health Organization Multicentre Growth Reference Trial (WHO MGRS) as sitting up with back straight and head erect for ≥10 seconds; child does not use arms or hands to balance body or support position (6) – **primary endpoint in STR1VE-EU**
- Bayley Scales gross motor subtest item #40: Child stands alone for ≥3 seconds after you release his or her hands - **primary endpoint in SPR1NT for infants with three copies of *SMN2***

Definitions of additional motor milestones assessed in the onasemnogene abeparvovec clinical trial programme are presented in Table 10. It should be noted that differences between the Bayley, WHO MGRS, and GMS definitions of motor milestones mean that they are associated with different levels of motor function and therefore different levels of difficulty to accomplish. In START and STR1VE-US, each Bayley Scale developmental milestone assessment was video recorded to enable confirmation of milestone attainment by an independent centralised reviewer. In STR1VE-US the WHO milestone of sitting without support for ≥10 seconds was also video recorded. In STR1VE-EU and SPR1NT, WHO motor developmental milestones and Bayley Scales developmental milestone assessments are video recorded.

Table 10: Definitions of motor milestones assessed in the onasemnogene abeparvovec clinical trial programme

Milestone	Definition
Head control	Bayley Scales Gross Motor subset item #4 Child holds head erect for ≥3 seconds without support
Rolls over	Bayley Scales Gross Motor subset item #20 Child turns from back to both right and left sides
Sits with support	Bayley Scales Gross Motor subset item #19 Child sits with slight support for at least 30 seconds
Sits without support	Bayley Scales Gross Motor Subset item #22 Child sits alone without support for ≥5 seconds
Crawls	Bayley Scales gross motor subtest item #34: Child makes forward progress of at least 5 feet by crawling on hands and knees
	WHO MGRS definition: Child alternately moves forward or backward on hands and knees. The stomach does not touch the supporting surface. There are continuous and consecutive movements, at least 3 in a row
Pulls to stand	Bayley Scales gross motor subtest item #35 Child raises self to standing position using chair or other convenient object for support
Stands with assistance	Bayley Scales gross motor subtest item #33: Child supports his or her own weight for at least 2 seconds, using your hands for balance only
	WHO MGRS definition: Child stands in upright position on both feet, holding onto a stable object (e.g. furniture) with both hands without leaning on it. The body does not touch the stable object, and the legs support most of the body weight. Child thus stands with assistance for ≥10 seconds
Stands alone	WHO MGRS definition: Standing alone. Child stands in upright position on both feet (not on the toes) with the back straight. The legs support 100% of the child's weight. There is no contact with a person or object. Child stands alone for at least 10 seconds
Walks with assistance	GMS checklist definition: walk with support
	Bayley Scales gross motor subtest item #37: Child walks by making coordinated, alternated stepping movements
	WHO MGRS definition: Walking with assistance Child is in upright position with the back straight. Child makes sideways or forward steps by holding onto a stable object (e.g. furniture) with 1 or both hands. One leg moves forward while the other supports part of the body weight. Child takes at least 5 steps in this manner
Walks alone	GMS checklist definition: take independent steps
	Bayley Scales gross motor subtest item #43: Child takes at least 5 steps independently, displaying coordination and balance
	WHO MGRS definition: Walking alone Child takes at least 5 steps independently in upright position with the back straight. One leg moves forward while the other supports most of the body weight. There is no contact with a person or object

The Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders

The CHOP-INTEND is a motor function scale developed and validated for use specifically to monitor motor function status and decline amongst children with SMA type 1, and is administered by a qualified clinical evaluator (25, 32). The CHOP-INTEND scale (range 0 to 64, with higher score indicating better functional status) examines several aspects of motor function, including head control, righting reactions, and trunk movements in supported sitting, supine (lying facing upwards), and prone (lying facing downwards) positions. Anti-gravity movements in assisted rolling, ventral suspension, and supported standing are also measured.

In the START study, if a patient achieved 2 consecutive CHOP-INTEND scores of ≥62, a teleconference was conducted between the principal investigator, the physical therapist, and the sponsor to review the patient status and determine whether or not continued CHOP-INTEND assessments were necessary. If it was decided that no further assessments were necessary, the physical therapist ceased completion of the CHOP-INTEND assessment at subsequent visits; otherwise, CHOP-INTEND assessments continued monthly during Year 1 and quarterly during Year 2 in the START trial. In the STR1VE-EU, STR1VE-US, and SPR1NT studies, patients who achieved three consecutive CHOP-INTEND scores ≥58 did not undergo any additional CHOP-INTEND examinations.

The proportion of patients who achieved CHOP-INTEND thresholds of ≥40, ≥50, and ≥60 (START) or ≥58 (STR1VE-EU, STR1VE-US, and SPR1NT) was assessed in the onasemnogene abeparvovec clinical development programme. The rationale for selecting these thresholds is as follows:

- A score ≥40 is beyond that reported in the literature for maximum transiently achieved function amongst symptomatic patients with SMA type 1 beyond 6 months of age (3)
- Achieving a score ≥50 would suggest the potential to gain milestones such as independent sitting
- A score ≥60 (START) or ≥58 (STR1VE-EU, STR1VE-US, and SPR1NT) marks the effective ceiling using the CHOP-INTEND

Bayley Scales

The Bayley Scales of Infant and Toddler Development (Version 3) are a standardised, norm-referenced infant assessment of developmental functioning across five domains: cognitive, language, motor, social-emotional, and adaptive behaviour (31). The Bayley Scales are administered by a physical therapist. The mean score is 10, with standard deviation of ±3 points; thus, a scaled score of ≤7 on the Bayley Scales would be considered to be low.

An overview of the schedule of Bayley Scales assessments in onasemnogene abeparvovec clinical trials is presented in Table 11.

- **START:** In START, the gross and fine motor subtests (part of the motor domain) were administered if a child reached or exceeded a CHOP-INTEND score of 60/64 at each monthly visit until patients reached 15 months of age or 12 months post-dose,

whichever was later, and then every 3 months except for subjects still being seen monthly for CHOP-INTEND assessments. The language (receptive communication and expressive communication) and cognition domains were administered every three months if a patient reached or exceeded a score of 60/64 on the CHOP-INTEND. The CHOP-INTEND assessment was to be discontinued and only the Bayley Scales was to be administered for patients who achieved two consecutive CHOP-INTEND scores of ≥62

- **STR1VE-US:** In STR1VE-US the gross and fine motor subtests of the motor domain were administered at screening and at each monthly visit whereas the cognitive and language domains of the Bayley Scales were administered at screening, every 6 months starting at Month 6, and at End of Study when the patient reaches 18 months of age (or early termination). For patients for whom English is not their first language, the language subtests and cognitive scale portions of the Bayley Scales were not performed

- **STR1VE-EU**: In STR1VE-EU, the full and gross and fine motor subsets of the motor domain were administered at screening and at each monthly visit. The language and cognition domains of the Bayley Scales are not evaluated in STR1VE-EU

- **SPR1NT**: In SPR1NT, the Bayley Scales gross and fine motor subtests were administered to all patients at screening, Day 30, Day 60 (Month 2), Day 90 (Month 3), every three months starting at 6 months of age, and at End of Study when the patient reached 18 or 24 months of age (or early termination) for Cohort 1 and Cohort 2, respectively. The language and cognition domains of the Bayley Scales are not evaluated in SPR1NT

Table 11: Schedule of Bayley Scale assessments in onasemnogene abeparvovec clinical trials

Study	Study Interval	Baseline	Follow Up					
		Screening	(Outpatient)					
	Visit	1	6	7	8	Monthly	Every 3 months	Every 6 months
	Days in Study	–30 (± 7)	30	60	90			
START†	Gross and fine motor subsets	X	X	X	X	X	X‡	X
	Language and cognition domains	X					X	X
STR1VE-US	Gross and fine motor subsets	X	X	X	X	X	X	X
	Language and cognition domains	X						X
STR1VE-EU	Gross and fine motor subsets	X	X	X	X	X	X	X
	Language and cognition domains	Not assessed						
SPR1NT	Gross and fine motor subsets	X	X	X			X	X
	Language and cognition domains	Not assessed						

† Bayley Scale assessments were administered in START if a child reached or exceeded a CHOP-INTEND score of 60/64.

‡ The gross and fine motor portion of the Bayley Scales were completed monthly during the first year. During the second year of START the gross and fine motor portion of the Bayley Scales were conducted every three months, except for subjects still being seen monthly for CHOP-INTEND assessments.

Maintaining ability to thrive

The ability to thrive was assessed in START, STR1VE-US, STR1VE-EU, and SPR1NT. The ability to thrive is defined as meeting the following:

1. The ability to tolerate thin liquids as demonstrated through a formal swallowing test
2. Not requiring nutrition through mechanical support such as a feeding tube
3. Maintained weight >3rd percentile based on WHO Child Growth Standards (24) for age and gender

Nutritional status and swallowing function

In infants with sever SMA treated with BSC the development of tongue and swallowing weakness increases swallowing and feeding difficulty over time, and leads to weight loss, pulmonary aspiration and the need for mechanical feeding (3, 33, 34).

The number (%) of patients who used non-oral feeding at any time from baseline to the efficacy analysis time points was summarised by cohort and type of feeding tube (gastrostomy with Nissen fundoplication, gastrostomy without Nissen fundoplication, nasogastric, or nasojejunal). Swallowing function, determined through video-fluoroscopic swallowing studies (START) or a standard bedside swallowing test (START, STR1VE-US, STR1VE-EU, SPR1NT), was assessed at baseline and every 6 months during the follow-up period.

Motor neuron function

Compound muscle action potential (CMAP) amplitude is an indicator of motor neuron health and denervation severity. SMA infants have substantially reduced CMAP and motor unit number estimation (MUNE) responses compared with reference data from neonate to 2 years of age (CMAP: 1,800–5,000 mV; MUNE: 100–250). (3, 4). The CMAP size is found using supramaximal stimulation of the motor nerve to a defined muscle or muscle group. It is recorded using surface electrodes, and is representative of the sum of the surface detected motor unit action potentials from muscles innervated by that nerve. The MUNE is a technique that uses electromyography to estimate the number of motor units in a muscle. MUNE uses a general formula of:

$$Number\ of\ motor\ units = \frac{compound\ muscle\ action\ potential\ size}{mean\ surface-detected\ motor\ unit\ action\ potential\ size}$$

Both CMAP and MUNE were recorded from surface electrodes at baseline and every 6 months after onasemnogene abeparvovec infusion in START. CMAP was assessed in STR1VE-US and SPR1NT; neurophysiology assessments were not performed in STR1VE-EU.

6.1.2 Provide details on data from any single study that have been drawn from more than one source (for example a poster and unpublished report) and/or when trials are linked this should be made clear (for example, an open-label extension to randomised controlled trial).

An overview of the clinical development programme for onasemnogene abeparvovec in SMA which consists of one completed Phase I/IIa trial (START), one completed Phase III trial (STR1VE-US), two ongoing Phase III trials (SPR1NT and STR1VE-EU), and two ongoing long-term, follow-up studies (LT-001 and LT-002) is provided in Section 6.1. Data for the START study reported in the submission have been drawn from two publications where possible, Mendell et al. 2017 (8) and Al-Zaidy et al. 2019 (9), and the clinical study report (CSR) where additional detail is necessary (10). At the end of the START study, patients were invited to enrol in the ongoing observational long-term, single-centre study LT-001 to obtain a long-term data set. LT-001 involves evaluation of the efficacy of onasemnogene abeparvovec by a single annual assessment of whether the highest milestone attained in START has been maintained (or improved) up to 15 years of follow up in LT-001. Data for LT-001 have been drawn from Al Zaidy et al. 2019 and multiple interim data cuts presented as safety and efficacy reports (12-14). For STR1VE-US, data have been drawn from the CSR and data presented in the 31 December 2019 clinical overview document (12, 16).

6.1.3 If applicable provide details of and the rationale for, patients that were lost to follow-up or withdrew from the studies.

No patients withdrew from START or were lost to follow-up. Of the 15 patients enrolled in START, 13 patients enrolled in the long-term follow-up study, LT-001. The parents/carers of the two patients from START who were not enrolled in LT-001 were not required to provide a reason for the decision not to enrol. At the time of the latest data cut, one patient discontinued STR1VE-EU due to death (Section 6.4.2.5).

In total, three of the 22 infants enrolled in STR1VE-US were lost to follow-up or withdrew:

- One patient discontinued the study due to death (not considered related to study drug) on Study Day 171 at the age of 7.8 months (Section 6.4.2.4)
- One patient withdrew consent on Study Day 203 at the age of 11.9 months; this patient met the criteria for permanent assisted ventilation (PAV) status on Study Day 176 at the age of 11 months
- One patient was discontinued at the age of 18 months due to an adverse event of respiratory distress (not considered related to study drug). Although this patient did not complete the Month 18 visit, at withdrawal (18 months of age) this patient was alive and not on PAV

6.1.4 Highlight any differences between patient populations and methodology in all included studies.

The key differences between the included studies are as follows:

- Efficacy is a primary objective in the STR1VE-US, STR1VE-EU and SPR1NT studies and a secondary objective in the completed START study
- The STR1VE-US, and STR1VE-EU studies include symptomatic patients with SMA type 1, as did the START study; SPR1NT includes pre-symptomatic SMA patients with two or three copies of *SMN2*
- Infants in START, STR1VE-US, and STR1VE-EU were required to have had a swallowing evaluation test performed prior to administration of gene replacement therapy and be willing to use an alternative method to oral feeding if necessary. In order to be eligible for enrolment in SPR1NT, patients were required to be able to swallow thin liquids
- To be included in START, STR1VE-US, and STR1VE-EU, patients were required to be free from invasive ventilatory support. Patients receiving non-invasive ventilator support (BiPAP) for ≤16 hours per day prior to gene therapy at the discretion of their physician or study staff were eligible for inclusion in START. Patients were considered eligible for inclusion in STR1VE-US and STR1VE-EU provided that they did not require non-invasive ventilatory support averaging ≥6 hours/day over the 7 days prior to the screening visit; or ≥6 hours/day on average during the screening period or requiring ventilatory support while awake over the 7 days prior to screening or at any point during the screening period prior to gene replacement therapy
- START enrolled patients with SMA type 1 with two copies of *SMN2*. The STR1VE studies (US and EU) had a slightly broader inclusion criteria, permitting the inclusion of SMA type 1 patients with 1 or 2 copies of *SMN2*; however, only patients with two copies of *SMN2* were enrolled. The SPR1NT study enrolled patients with two or three copies of *SMN2*[5]; both *SMN2* copy number populations form part of the ITT population in SPR1NT and patients will be followed in discrete cohorts based upon *SMN2* copy number, and analysed separately based upon genotype-specific primary endpoints (sitting independently, standing without support)
- START excluded patients with SMA type 1 who had the *SMN2* [c.859G>C] modification in exon 7 (which increases the amount of full-length mRNA transcripts produced, thus resulting in, and predictive of, a less severe SMA phenotype). The STR1VE (US and EU) and SPR1NT studies allowed enrolment of SMA patients inclusive of this known *SMN2* gene modifier mutation [c.859G>C]; however, patients

[5] Pre-symptomatic patients with four copies of *SMN2* were in the original SPR1NT protocol but later removed as per protocol amendment dated 27 September 2018. One patient with four copies of *SMN2* was enrolled but excluded from the ITT efficacy population and is therefore not reported in the interim efficacy results; this patient remains part of the safety population.

with this *SMN2* gene modifier mutation [c.859G>C] will be excluded from the ITT efficacy analysis, and assessed as part of additional analyses only. As of the 31 December 2019 data cut (13), no infants with the *SMN2* gene modifier mutation [c.859G>C] have been enrolled in the clinical development programme for the IV administration of onasemnogene abeparvovec

- START included two different onasemnogene abeparvovec dosing cohorts; Cohort 1 received a nominal one-time peripheral IV infusion of 6.7 x 10^{13} vg/kg (low dose) and Cohort 2 received a nominal one-time peripheral IV infusion of 2.0 x 10^{14} vg/kg (therapeutic dose), when measured initially by an early development stage quantitative polymerase chain reaction (qPCR) assay. Direct testing of the actual lot of investigational product used in START by an improved and more fully qualified analytical method (droplet digital PCR [ddPCR]) has determined the actual dose received by Cohort 1 to be 3.7 x 10^{13} vg/kg. The retrospectively-estimated dosage range received by Cohort 2 to be 1.1 x 10^{14} vg/kg is approximately 1.1 × 10^{14} to 1.4 × 10^{14} vg/kg. It is important to note that the ddPCR value is a more accurate measurement of the vector genome content than the qPCR value, and does not represent a reduction in the dose administered. The therapeutic IV dose of the onasemnogene abeparvovec manufactured by AveXis and used in the STR1VE-US, STR1VE-EU and SPR1NT studies is determined by the ddPCR assay and is 1.1 X 10^{14} vg/kg

- To address the need for long-term data, patients receiving onasemnogene abeparvovec in START were enrolled in the ongoing observational long-term study LT-001, that includes a single annual assessment of whether the highest milestone attained in START has been maintained up to 15 years of follow up. To date (31 December 2019 data cut (13)), the median time since one-time onasemnogene abeparvovec administration in patients treated with the therapeutic dose in START (Cohort 2) was 52.5 months (4.4 years); with longest duration of therapy recorded at 61.9 months (5.2 years) since dosing in START. Additional long-term data for patients treated with onasemnogene abeparvovec will be provided by LT-002, a study of infants treated with onasemnogene abeparvovec (IV or IT) in AveXis clinical trials (including, but not limited to SPR1NT, STR1VE-EU and STR1VE-US) followed for a total of 15 years post-dose. To date, seven patients are enrolled in LT-002

- To provide further long-term data AveXis is sponsoring a Global SMA Disease Registry (RESTORE, AVXS-101-RG-001). The registry will follow at least 500 patients with SMA in clinical practice in the US, UK, France, Germany, Italy, Spain, and other countries, including approximately 20% of patients treated with existing or upcoming approved treatments. The demographics, genetic status, family and medical history of patients will be collated as will details of treatments received. The output from the registry will include long-term effectiveness and safety outcomes in a real-world observational setting, including the pulmonary and nutritional requirements of patients, hospitalisations, AEs, and caregiver burden and QoL. The registry will collate data for patients every 6 months until the 24-month visit and then annually for up to 15 years or until death, whichever is sooner. As of 31 January 2020, [redacted] patients were enrolled into the RESTORE registry (35) with [redacted] receiving SMA-specific treatment; the treatment status of eight patients is unknown

- To allow development of an appropriate natural history comparator cohort for START, a control population was drawn from external sources, namely the PNCR and NeuroNext studies (3-5). Details of the PNCR and NeuroNext patient populations, and their comparison to the START cohort, are described in Section 6.3.1.1.4

The key baseline characteristics of the patients included in each trial and natural history controls are shown in Table 12 to Table 16.

Table 12: Baseline characteristics of START and natural history control cohorts

Characteristic	START			NeuroNext control (N=16)	PNCR control (N=23)
	Cohort 1 6.7×10^{13} vg/kg (N=3)	Cohort 2 2.0×10^{14} vg/kg[†] (N=12)	All patients (N=15)		
SMN2 copy number	2	2	2	2	2
Age at treatment[‡], months					
Mean (SD)	6.3 (0.75)	3.4 (2.06)	4.0 (2.21)	4.1	29.0[§]
Min, Max	5.9, 7.2	0.9, 7.9	0.9, 7.9	0, 6	2, 171
Sex					
Female, %	66.7	58.3	60.0	50.0	52.2
Male, %	33.3	41.7	40.0	50.0	47.8
Race, %					
White	100	91.7	93.3	93.8	69.6
Other	0	8.3	6.7	6.2	30.4
Ethnicity, %					
Not Hispanic or Latino	100	83.3	86.7	68.7	87.0
Hispanic or Latino	0	16.7	13.3	31.3	13.0
Weight, mean (SD), kg	6.6 (0.56)	5.7 (1.34)	5.9 (1.27)	N/A	11.8 (7.8)
Gestational age at birth, weeks					
n	2	10	12	NA	NA
Mean (SD)	39.0 (1.41)	38.5 (1.43)	38.6 (1.38)	NA	NA
Mean age at symptom onset, months (SD)	1.7 (1.15)	1.4 (1.0)	1.5 (0.99)	NA	3.0 (1.6)
Mean age at diagnosis, days (range)	33 (4–85)	67.8 (1–137)[¶]	–	NA	152 (30–365)
Mean CHOP-INTEND score (SD)[††]	16.3 (10.5)	28.2 (12.3)	25.8 (12.6)[‡‡]	20.3 (11.6)	24.6 (11.6)
Swallowing thin liquid, n (%)					
Yes	0 (0.0)	4 (33.3)	4 (26.7)	NA	NA

Characteristic	START			NeuroNext control (N=16)	PNCR control (N=23)
	Cohort 1 6.7×10^{13} vg/kg (N=3)	Cohort 2 2.0×10^{14} vg/kg† (N=12)	All patients (N=15)		
No	3 (100)	8 (66.7)	11 (73.3)		
Non-oral feeding support, n (%)					
Yes	3 (100)	5 (41.7)	8 (53.3)	7 (43.7)	18 (78.3)
No	0	7 (58.3)	7 (46.7)	9 (56.3)	5 (21.7)
Ventilatory support (invasive/non-invasive), n (%)					
Yes	3 (100)	1 (8.3)§§	4 (26.7)§§	6 (37.5)	12 (52.2)
No	0	11 (91.7)	11 (73.3)	10 (62.5)	11 (47.8)
Familial history of SMA including affected siblings or parent carriers, n (%)					
Yes	1 (33.3)	3 (25.0)	4 (26.7)		
No	2 (66.7)	8 (66.7)	10 (66.7)	NA	NA
Unknown	0	1 (8.3)	1 (6.7)		
Total number of days of prednisolone administration, mean (SD)	47.7 (14.1)¶¶	73.8 (33.0)	68.6 (31.7)	N/A	N/A

Abbreviations: CHOP-INTEND, Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders; NA, not available; N/A, not applicable; SD, standard deviation; SMA, spinal muscular atrophy.

† Direct testing of the actual lot of investigational product used in START by an improved and more fully qualified analytical method (droplet digital PCR) has determined the actual dose received by Cohort 1 to be 3.7 x 10^{13} vg/kg and the actual dose received by Cohort 2 to be 1.1 x 10^{14} vg/kg (the same method has been used to establish an equivalent dose for the IMP in all Phase III trials). ‡ On day of onasemnogene abeparvovec administration in START or enrolment in PNCR and NeuroNext natural history cohorts. § Previously identified patients and newly diagnosed patients were enrolled. Retrospectively enrolled patients included three patients who were 90 months, 116 months and 171 months old at enrolment. All three of these patients were on permanent assisted ventilation at time of enrolment, with daily time spent on BiPAP at enrolment listed as 24 hours, 24 hours and 20 hours, respectively. A further four patients were aged between 28 to 44 months at enrolment; with permanent assisted ventilation reported at enrolment in one of these patients. ¶ Age = (Visit Date - Date of Birth + 1) / 365.25. †† Scores on the CHOP-INTEND scale of motor function range from 0 to 64, with higher scores indicating better function. ‡‡ Data for 'All patients' were calculated using CHOP-INTEND data for all patients (Listing 16.2.6.4-24). §§ Does not include one additional patient in Cohort 2 who was receiving BiPAP at baseline but for whom data was mis-entered at the clinical site. ¶¶ Includes one patient who did not receive prednisolone prophylactically but the corticosteroid began on Day 27.

Table 13: Baseline characteristics of LT-001 (Day 180 update [31 December 2019], study ongoing)

Characteristic	All patients (N=13)
Mean age† at LT-001 baseline visit (SD), years	2.5 (0.52)
Sex	
Female, %	7 (53.8)
Male, %	6 (46.2)
Race, %	
White	12 (92.3)
Other	1 (7.7)
Ethnicity, %	
Not Hispanic or Latino	12 (92.3)
Hispanic or Latino	1 (7.7)
Weight, mean (SD), kg	12.2 (1.4)

Abbreviations: CHOP-INTEND, Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders; SD, standard deviation; SMA, spinal muscular atrophy.
† Age = (Visit Date - Date of Birth + 1) / 365.25.
Source: 31 December 2019 efficacy data cut (data on file) (13).

Table 14: Baseline characteristics of STR1VE-US

Characteristic	N=22
Enrolment status at data cut	Completed
SMN2 copy number	2
Mean age at diagnosis, months (range)	2.6 (0†–5.4)
Mean (range) age at treatment, months‡	3.7 (0.5–5.9)
Mean (range) weight at baseline, kg	5.8 (3.9–7.5)
Mean (range) length/height at baseline, cm	61.3 (51–70)
Sex, n (%)	
Female	12 (54.5)
Male	10 (45.5)
Race, n (%)	
White	11 (50.0)
Other	6 (27.3)
Black or African American	3 (13.6)
Asian	2 (9.1)
Ethnicity, n (%)	
Not Hispanic or Latino	18 (81.8)
Hispanic or Latino	4 (18.2)
Reported feeding support, n (%)	0

Characteristic	N=22
Reported ventilatory support, n (%)	0
Mean (range) score on CHOP-INTEND scale§	32.0 (18–52)
[redacted]	[redacted]

Abbreviations: CHOP-INTEND, Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders.
† Some patient were diagnosed before 1 month of age. Because of rounding, age of diagnosis is reported as "0 months".
‡ Age = (dose date - date of birth + 1)/30.
§ Scores on CHOP-INTEND scale of motor function range from 0 to 64, with higher scores indicating better function.
Source: STR1VE-US clinical study report (16).

Table 15: Baseline characteristics of STR1VE-EU (Day 180 update [31 December 2019], study ongoing)

Characteristic	N=33
Enrolment status at data cut	Completed
SMN2 copy number	2
Mean age at diagnosis, months (range)	[redacted]
Mean (range) age at treatment, months†	[redacted]
Mean (range) weight at baseline, kg	[redacted]
Mean (range) length/height at baseline, cm	[redacted]
Sex, n (%) Female Male	 [redacted] [redacted]
Reported swallowing thin liquid, n (%)	[redacted]
Reported feeding support, n (%)	[redacted]
Reported ventilatory support, n (%)	[redacted]
Mean (range) score on CHOP-INTEND scale	[redacted]‡
[redacted]	[redacted]

Abbreviations: SD, standard deviation; SMA, spinal muscular atrophy.
† Age = (dose date - date of birth + 1)/30.
‡ n=32 – one patient ([redacted]) was dosed at the age of 181 days and was therefore not included for the ITT population.
Source: 31 December 2019 efficacy data cut (data on file) (13).

Table 16: Baseline characteristics of SPR1NT (Day 180 update [31 December 2019], study ongoing)

Characteristic	Cohort 1 Two copies of *SMN2* (n=14)	Cohort 2 Three copies of *SMN2* (n=15)
Enrolment status at data cut	Completed	
Mean age at diagnosis†, months (range)	[redacted]	[redacted]
Mean age‡ (range) at treatment, months	[redacted]	[redacted]
Mean (range) length/height at baseline, cm	[redacted]	[redacted]
Sex, n (%)		
Female	[redacted]	[redacted]
Male	[redacted]	[redacted]
Race, n (%)		
White	[redacted]	[redacted]
Other	[redacted]	[redacted]
Black or African American	[redacted]	[redacted]
Asian	[redacted]	[redacted]
American Indian or Alaska Native	[redacted]	[redacted]
Ethnicity, n (%)		
Not Hispanic or Latino	[redacted]	[redacted]
Hispanic or Latino	[redacted]	[redacted]
Weight, kg (SD)	[redacted]	[redacted]
Reported swallowing thin liquid, n (%)§	[redacted]	[redacted]
Reported feeding support, n (%)§	[redacted]	[redacted]
Reported ventilatory support, n (%)§	[redacted]	[redacted]
Mean (range) score on CHOP-INTEND scale††	[redacted]	[redacted]
Familial history of SMA including affected siblings or parent carriers, n (%)	[redacted]	[redacted]

Abbreviations: CHOP-INTEND, Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders; SD, standard deviation; SMA, spinal muscular atrophy.
† For patients diagnosed in utero, rather than report negative ages age at diagnosis was reported as to 1 day old. Because of rounding, this is reported as "0 months".
‡ Age = (dose date - date of birth + 1).
§ In order to be eligible for enrolment in SPR1NT, patients were required to be asymptomatic, able to swallow thin liquids, and free from ventilatory support.
†† Scores on CHOP-INTEND scale of motor function range from 0 to 64, with higher scores indicating better function.
Source: 31 December 2019 efficacy data cut (data on file) (13).

6.1.5 Provide details of any subgroup analyses that were undertaken in the studies included. Specify the rationale and state whether these analyses were pre-planned or post-hoc.

Whilst no formal subgroup analyses were pre-planned in START, an explorative post-hoc analysis was completed to assess time to independent sitting based on age at treatment. In addition, an explorative scenario is presented in the economic evaluation section (Section 8.2.1.1), in which the motor milestones, overall survival and event-free survival incorporated into the economic model are based on patients treated at ≤3.5 months of age in START and STR1VE-US (with 3.5 months being the median age at dosing across the START [Cohort 2] and STR1VE-US cohorts). Results should be interpreted with an understanding of the caveats of the small sample size and that these analyses was conducted post-hoc.

6.1.6 If applicable, provide details of the numbers of patients who were eligible to enter the study(s), randomised, and allocated to each treatment in an appropriate format.

Details of patients who were screened but did not receive treatment in each trial are presented in Table 17. As of the 31 December 2019 data cut, a total of 99/127 infants screened for inclusion in the clinical trial programme for IV administration of onasemnogene abeparvovec had received treatment.

In START, three of the 16 (18.8%) patients screened for anti-AAV9 antibodies had titres >1:50 at first testing. Two patients were retested following cessation of breast-feeding and reported to have titres of <1:50 and both were enrolled in the study. The remaining patient was excluded due to persistently elevated AAV9 antibody titres.

In STR1VE-US, 4/26 infants were excluded at screening: [redacted]

In STR1VE-EU, 8/41 infants were excluded at screening: five patients had elevated AAV9 titres – [redacted] and also had elevated AAV9 titres, [redacted]. Thus, in total 5/41 patients had elevated AAV9 titres at screening. At the time of the 31 December 2019 data cut, enrolment for STR1VE-EU was complete with a total of 33 patients receiving onasemnogene abeparvovec. One patient ([redacted]) was dosed at the age of 181 days and was therefore not included in the ITT population.

In SPR1NT 14/44 pre-symptomatic infants were excluded at screening. In total, two patients were found to be symptomatic for SMA at screening and were not included in the study. [redacted] two patients were excluded due to elevated AAV9 titres. [redacted]

[redacted]

One patient ([redacted]) was initially tested as having three copies of *SMN2* and enrolled into the three copy cohort of SPR1NT. On repeat testing, the patient was confirmed to have four copies of *SMN2* and was excluded due to the protocol amendment dated 27 September 2018 (36). This patient is enrolled as of 31 December 2019 data cut but excluded from the ITT efficacy population; this patient remains part of the safety population. At the time of data cut (31 December 2019) enrolment for SPR1NT was complete with a total of 30 patients treated with onasemnogene abeparvovec (Cohort 1, n=14; Cohort 2, n=15; 1 patient with four copies of *SMN2*).

Table 17: Screening failures in the onasemnogene abeparvovec clinical trial programme

	Newborns		Infants				All trials total, n (%)
	SPR1NT	Total, n (%)	STR1VE-US	STR1VE-EU	START	Total, n (%)	
Number of patients screened	44	**44 (100)**	26	41	16	**83 (100)**	**127 (100)**
Elevated AAV9 titres	2	**2 (4.5)**	-	5	1	**5 (6.0)**	**7 (5.5)**
Withdrew consent	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Respiratory infection within 4 weeks of screening	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
CMAP <2 mV	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Symptomatic at screening	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Weight below the WHO 3% limit	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Excluded following swallowing test	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Subject transferred to alternative site	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Adverse event	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Expectation of major surgical procedures during the trial assessment period	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Clinically significant abnormalities in haematology or clinical chemistry parameters	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Genetic diagnosis of 2 or 3 copies of *SMN2* not met	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Not up to date on childhood vaccinations	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total number of patients excluded	14†	**14‡ (31.8)**	4	8§	1	**13 (15.7)**	**27 (21.3)**
Total number of patients treated	30‡	**30 (68.2)**	22	33	15	**70 (84.3)**	**100 (78.7)**

Abbreviations: AAV-9, adeno-associated virus subtype 9; N/A, not applicable. Source: AveXis data on file; data extracted 31 December 2019 (13).
† A total of 14 patients were excluded from SPR1NT; patient [redacted] had two reasons for screening failure (CMAP value of <2 mV and symptomatic at screening), patient [redacted] also had two reasons for screening failure (CMAP value of <2 mV and not up to date on childhood vaccinations).
‡ One patient ([redacted]) with four copies of *SMN2* originally included in SPR1NT was excluded due to the protocol amendment dated 27 September 2018 (36). This patient is enrolled as of 31 December 2019 data cut but excluded from the ITT efficacy population; this patient remains part of the safety population.
§ A total of eight patients were excluded from STR1VE-EU at screening; one patient ([redacted]) had two reasons for exclusion at screening[redacted] high AAV9 titres (>1:100).

6.2 *Critical appraisal of relevant studies*

6.2.1 Complete a separate quality assessment table for each study.

Critical appraisals of START and STR1VE-US are presented in Table 18 and Table 19. As per the ERG preferences in the ERG report, the ERG considers it more appropriate to assess the onasemnogene abeparvovec studies using the same tool (i.e. the Newcastle-Ottowa Scale) as used to quality assess the natural history studies (i.e. the studies used as the external control for BSC). Therefore, both START and STR1VE-US have been assessed using the Newcastle-Ottowa Scale. Quality assessments of STR1VE-EU, SPR1NT, or LT-001 are not provided as the studies are ongoing.

Table 18: Quality assessment of START using Newcastle-Ottowa Scale

Study name	Mendell et al. 2017 (8) (NCT02122952)	
Newcastle Ottawa item	**Score**	**Support**
Selection: Representativeness of exposed cohort	*	Somewhat representative of the average SMA patient in the community
Selection: Selection of non-exposed cohort	NA	Single arm study, no non-exposed cohort
Selection: Ascertainment of exposure	*	Secure record; genetically confirmed SMA
Selection: Outcome not present at start of study	*	Assumed that patients requiring PAV were excluded from the study
Comparability: Comparability of cohorts	NA	Single arm study, study only examines exposed cohort
Outcomes: Assessment of outcome	*	Record linkage
Outcomes: Follow-up length	*	All patients 24 months follow-up

Abbreviations: ERG, evidence review group; NA, not applicable; PAV, permanent assisted ventilation; SMA, spinal muscular atrophy.

Table 19: Quality assessment of STR1VE-US using Newcastle-Ottowa Scale

Study name	STR1VE-US (16)	
Newcastle Ottawa item	**Score**	**How is the question addressed in the study?**
Selection: Representativeness of exposed cohort	*	Somewhat representative of the average SMA patient in the community
Selection: Selection of non-exposed cohort	NA	Single arm study, no non-exposed cohort
Selection: Ascertainment of exposure	*	Secure record; genetically confirmed SMA
Selection: Outcome not present at start of study	*	The co-primary efficacy endpoints were the proportion of patients who achieved functional independent sitting for at least 30 seconds at the 18 months of age

		study visit and survival at 14 months of age. By definition, children with SMA type 1 are never able to sit independently
Comparability: Comparability of cohorts	NA	Single arm study, study only examines exposed cohort
Outcomes: Assessment of outcome	*	Record linkage. Defined by the Bayley Scales of Infant and Toddler Development (Version 3), confirmed by video recording, as a patient who sits up straight with the head erect for at least 30 seconds
Outcomes: Follow-up length	*	Days 4 to End of Study at 18 months of age (or early termination)

Abbreviations: ERG, evidence review group; NA, not applicable; PAV, permanent assisted ventilation; SMA, spinal muscular atrophy

6.3 *Results of the relevant studies – clinical trial programme*

6.3.1 Complete a results table for each study with all relevant outcome measures pertinent to the decision problem.

6.3.1.1 START

The efficacy analysis of onasemnogene abeparvovec was carried out in the following SMA type 1 populations:

- ITT analysis set – included all 15 patients who underwent gene replacement therapy via a one-time peripheral IV infusion of onasemnogene abeparvovec
- Full analysis set (FAS) – included all 15 patients who underwent gene replacement therapy via a one-time peripheral IV infusion of onasemnogene abeparvovec and had at least 1 post-infusion visit
- Ability to thrive ITT population – included all 7 patients with bi-allelic deletion of *SMN1* and a baseline CHOP-INTEND score of ≥20 who received an infusion of onasemnogene abeparvovec at 2.0 x 10^{14} vg/kg[6] (therapeutic dose) and who did not require non-oral nutrition prior to gene replacement therapy via a one-time peripheral IV infusion of onasemnogene abeparvovec
- SAS – included any patient who underwent gene replacement therapy via a one-time peripheral IV infusion of onasemnogene abeparvovec

Efficacy analyses were conducted at the following time points:

- The date at which all patients had completed a study visit after reaching 13.6 months of age

[6] Direct testing of the actual lot of IMP used in START by an improved and more fully qualified analytical method has determined the actual dose received by Cohort 2 to be 1.1 x 10^{14} vg/kg. The same method has been used to establish an equivalent dose for the IMP in all Phase III trials.

- When the last enrolled patient had a study visit after reaching 20 months of age
- When all patients completed 24 months of post-dose follow-up

The first two time points were selected to allow a comparison with the external PNCR natural history study of SMA type 1 patients (3), in which it was estimated that only 25% of SMA type 1 patients with 2 copies of *SMN2* would survive ventilation-free to 13.6 months of age and that only 8% would survive ventilation-free to 20 months of age.

Only results from the 24 months post-dose time point are presented as these are the most mature data from START. Results of the efficacy outcomes assessed in START are presented in Table 20.

Table 20: START efficacy results

Outcome	24 months post-dose		
	Cohort 1 (N=3)	Cohort 2 (N=12)	All patients (N=15)
Survived without permanent ventilation, ITT set, % (95% CI[†]; p value[‡])	66.7 (9.4, 99.2; 0.018)	100 (73.54 100; <0.001)	93.3 (68.1, 99.8; <0.001)
Change from baseline in CHOP-INTEND score, FAS	–	+30.7	–
Proportion of patients in the FAS who achieved CHOP-INTEND scores:			
≥40, % (p value[¶])	–	91.7 (<0.001)	–
≥50, % (p value[¶])	–	91.7 (<0.001)	–
≥60, % (p value[¶])	–	33.3 (<0.001)	–
Bayley Scales score, mean (SD)	–	40.3 (3.10)	–
Functional independent sitting (≥30 seconds), % 95% CI[†]; p value[¶])	0	75 (42.8, 94.5; <0.001)	60.0 (32.3, 83.7; <0.001)
Developed significant motor function milestones based on video reviews by external expert, %			
Rolling (back to side from both sides)	0	75.0	60.0
Hold head erect ≥3 seconds, unsupported	0	91.7	73.3
Sits with support	0	91.7	73.3
Sits alone ≥5 seconds[§††]b	0	91.7	73.3
Sits alone ≥10 seconds[§]	0	83.3	66.7
Sits alone ≥15 seconds[§]	0	75.0	60.0
Sits alone ≥30 seconds[§]	0	75.0	60.0
Stands with assistance	0	16.7	13.3
Stands alone	0	16.7	13.3
Walks with assistance	0	16.7	13.3
Walks alone	0	16.7	13.3
Independent of ventilatory support, FAS, % (95% CI[†]; p value[¶])	0	50.0[¶¶] (21.1, 78.9; <0.001)	40.0[¶¶] (16.3, 67.7; <0.001)

Outcome	24 months post-dose		
	Cohort 1 (N=3)	Cohort 2 (N=12)	All patients (N=15)
Maintained the ability to thrive, ability to thrive ITT set, % (95% CI†; p value¶)	0	71.4 (29.0, 96.3; <0.001)	71.4 (29.0, 96.3; <0.001)
Proportion of patients in the SAS receiving non-oral feeding support‡‡, %			
Gastrostomy with Nissen fundoplication	100	33.3	46.7
Gastrostomy without Nissen fundoplication	0	8.3	6.7
Nasogastric	0	8.3	6.7
Nasojejunal	0	25.0	20.0
Gastrostomy with a jejunostomy tube threaded for feeds	0	8.3	6.7

Abbreviations: CI, confidence interval; CHOP-INTEND, Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders; FAS, full analysis set; IMP, investigational medicinal product; ITT, intention-to-treat; SAS, safety analysis set.

Note: Cohort 1 received the low dose onasemnogene abeparvovec (6.7×10^{13} vg/kg) and Cohort 2 received the therapeutic dose of onasemnogene abeparvovec (2.0×10^{14} vg/kg). Direct testing of the actual lot of IMP used in START by an improved and more fully qualified analytical method has determined the actual dose received by Cohort 2 to be 1.1×10^{14} vg/kg. The same method has been used to establish an equivalent dose for the IMP in all Phase III trials.

† Confidence interval from the superiority 1-sided exact binomial test.

‡ Compared with the external natural history estimates of 25% for 13.6 months of age and 8% for 24 months post-dose (3) using a 1-sample exact binomial test.

¶ Compared with zero using a 1-sided exact binomial test. To make computation of the p-value possible, the value of 0.1% was used in place of a literal zero.

§ Patients are included in multiple categories for the "sits alone" milestone. Patients sitting ≥30 seconds are included in the totals for ≥15 seconds, ≥10 seconds, and ≥5 seconds.

†† The source table and listing include a milestone identified as "Sits alone <10 seconds". The external reviewer confirmed that this milestone was defined as "Sits alone ≥5 seconds" and that is how it is labelled here.

‡‡ Patients may be counted more than once in a non-oral feeding category due to changes in non-oral feeding support apparatus or mechanism

¶¶ Does not include 1 additional patient in Cohort 2 who only used BiPAP during illness.

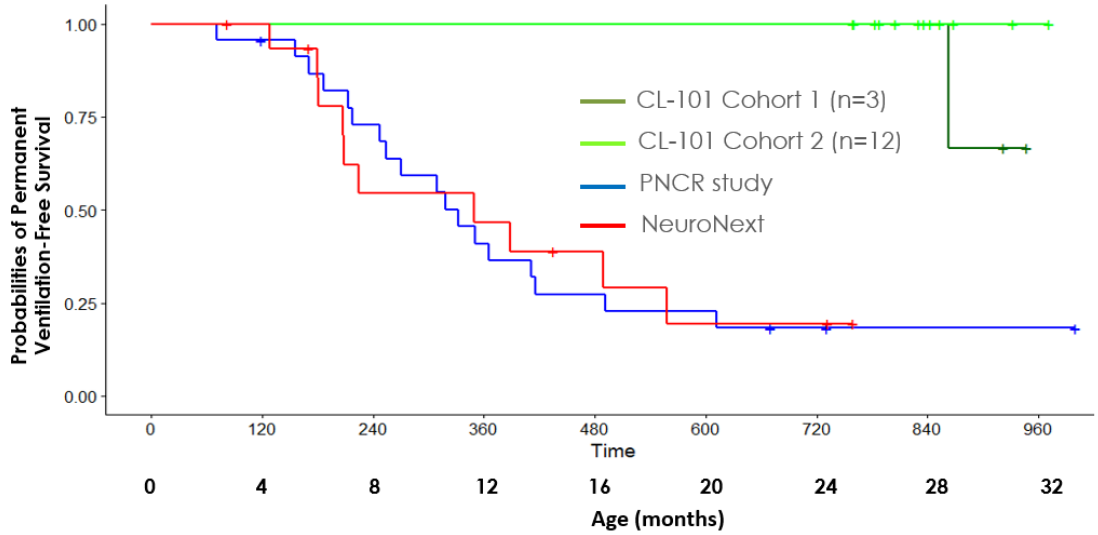
Sustained improvements from baseline to last observation across a range of clinical outcomes were observed in both patient cohorts following treatment with onasemnogene abeparvovec in the START study. It should be noted that patients in Cohort 1 received a lower dose of onasemnogene abeparvovec than those in Cohort 2 (6.7×10^{13} vg/kg versus 2.0×10^{14} vg/kg[7]). Patients in Cohort 1 were also older at the time of administration (6.3 months [range 5.9 to 7.2] versus 3.4 months [range 0.9 to 7.9]), and had greater nutritional and ventilatory support requirements at baseline indicating that they suffered from more advanced disease. As the loss of motor neurons in SMA is irreversible, disease progression results in permanent disability and the differences in baseline variables could therefore have favoured better outcomes in Cohort 2. However, the substantially greater efficacy observed across a broad number of the endpoints in Cohort 2 compared with Cohort 1, including CHOP-INTEND, developmental milestones, and respiratory support, suggest that these baseline differences are unlikely to fully account for the readily apparent greater efficacy of the 2.0×10^{14} vg/kg dose observed in this study.

6.3.1.1.1 Primary efficacy endpoint – survival without permanent ventilation

Onasemnogene abeparvovec administration increased survival for patients with SMA type 1, the primary efficacy endpoint, across all time-points assessed (Figure 3). Survival and survival free of permanent ventilation (alive, without tracheostomy, and not requiring ≥16 hours of ventilatory support per day for ≥2 weeks, absent an acute reversible illness or perioperative) was markedly improved for patients in START compared with patients in natural history cohorts. All patients in START were alive and without permanent ventilation at the final assessment time point of 24 months after dosing, a statistically significant difference compared with the natural history rates estimated from the PNCR and NeuroNext database cohorts (5) (Figure 3 and Table 21 and Table 22). One patient in Cohort 1 required permanent ventilation at approximately 29 months of age (22 months post-dose) for hypersalivation, thus meeting the survival endpoint. Following surgical ligation of the salivary glands, the child's ventilatory requirement subsequently reduced by 25% to below the 16 hours/day threshold.

[7] Direct testing of the actual lot of IMP used in START by an improved and more fully qualified analytical method has determined the actual dose received by Cohort 2 to be 1.1×10^{14} vg/kg. The same method has been used to establish an equivalent dose for the IMP in all Phase III trials.

Figure 3: Ventilation-free survival in START versus PNCR and NeuroNext natural history control



Abbreviations: PNCR, Pediatric Neuromuscular Clinical Research; SMA, spinal muscular atrophy.
Data cut on August 7, 2017.
Natural history: The PNCR and NeuroNext profiles presented are the AveXis datasets used to provide an external control comparator (5). The percentages of patients who were event-free in a study of SMA conducted by the PNCR network included ventilation-free survival measured as time until death or the need for ventilation for at least 16 hours per day for at least 14 consecutive days. In the NeuroNext study, a prospective natural history study in SMA infants with two copies of *SMN2*, survival as defined as alive without tracheostomy.

Table 21: Time to event (death or permanent ventilation) for START and PNCR

	LIFETEST Procedure		
	START, Cohort 2 (N=12)	**PNCR (N=23)†**	**Total (N=35)**
Number of censored and uncensored values			
Reached an event, n	0	18	18
Censored, n (%)	12 (100)	5 (21.74)	17 (48.57)
Statistics for Time to Event (Months)			
Mean (SE)	--	11.9 (1.21)	--
Median	--	11.1	--
Homogeneity of Survival Curves for Time to Event			
Log-Rank Test	Ch-Square= 18.19	p<0.0001	--

Abbreviations: PNCR, Pediatric Neuromuscular Clinical Research; SE, standard error.
† Both the natural history populations reported by Finkel et al. 2014a (3) and the START PNCR external control group (5) were from the PNCR natural history database for SMA. Each population has 23 patients with SMA type 1 and 2 copies of *SMN2,* but one patient differs between these control groups. As a result, the population reported by Finkel et al. 2014a had 19 events but the START PNCR external control group has 18 events.

Table 22: Time to event (death or permanent ventilation) for START and NeuroNext

	LIFETEST Procedure		
	START, Cohort 2 (N=12)	**NeuroNext (N=16)**	**Total (N=28)**
Number of censored and uncensored values			
Reached an event, n	0	10	10
Censored, n (%)	12 (100)	6 (37.50)	18 (64.29)
Statistics for Time to Event (Months)			
Mean (SE)	--	11.8 (1.59)	--
Median	--	11.6	--
Homogeneity of Survival Curves for Time to Event			
Log-Rank Test	Ch-Square= 15.94	p<0.0001	--

Abbreviations: SE, standard error.

6.3.1.1.2 Secondary efficacy endpoints

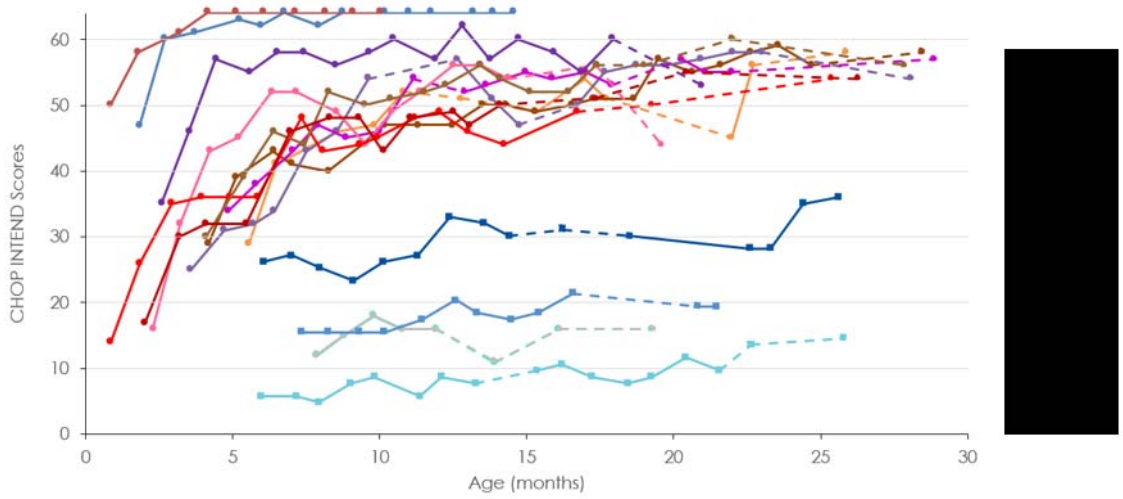
Motor function assessments

The Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders

The change from baseline in the CHOP-INTEND score, an assessment of motor function, was assessed as a secondary efficacy endpoint in START. The absolute and change from baseline in CHOP-INTEND score over time by patient and by cohort through 24 months post-dose is presented in Figure 4 and Figure 5. The mean (SD) CHOP-INTEND score of patients in Cohort 2 at baseline was 28.2 (12.3) points. Mean increases from baseline of 9.8 and 15.4, were reported at 1 and 3 months post gene therapy, respectively (n=12, both p<0.001). At 24 months post onasemnogene abeparvovec administration a mean increase from baseline CHOP-INTEND score of 30.7 was reported (n=6; p value not reported). The mean CHOP-INTEND scores of patients in Cohort 1 also improved (increased) from baseline and were sustained over time.

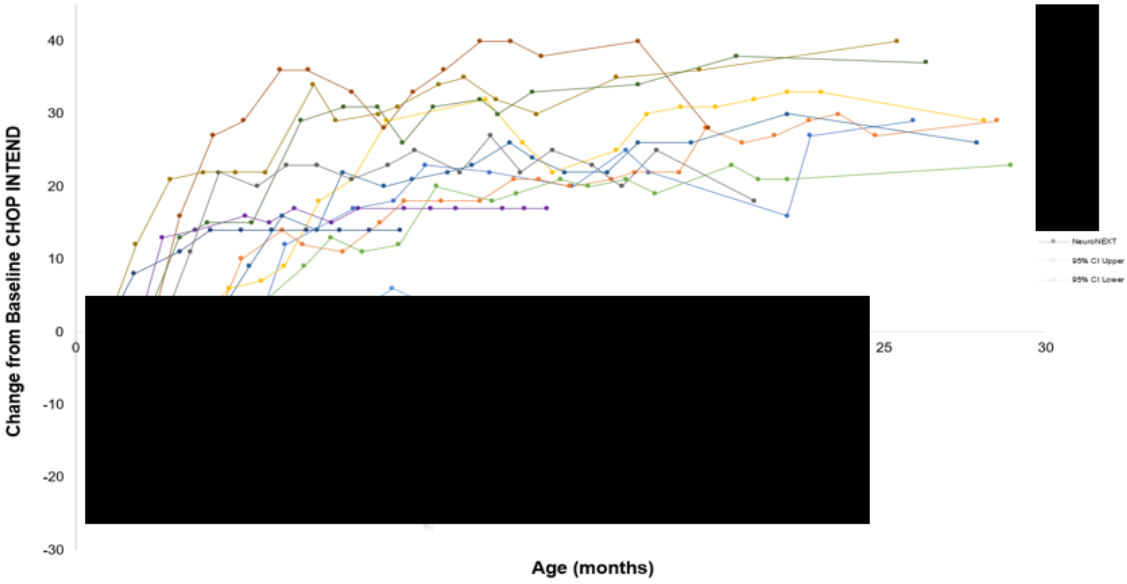
All the patients in Cohorts 1 and 2 had increased scores from baseline on the CHOP-INTEND scale of at least 4 points at their last observation. Further, the average CHOP-INTEND improvement in Cohort 2 patients was substantially greater than 4 points. This 4-point increase is considered a clinically meaningful response to treatment and is a clear deviation from natural history, where, as documented in the NeuroNext natural history study, CHOP-INTEND scores decline after initial diagnosis (4). These results reflect rapid and sustained improvement in motor function and were in contrast to a decline of a mean of more than 10 points between 6 and 12 months of age in the NeuroNext study (Figure 5) (4).

Figure 4: CHOP-INTEND response in START (full analysis set)



Note: Cohort 1 (Patient [redacted], and [redacted]) received the low dose of onasemnogene abeparvovec (6.7×10^{13} vg/kg) and Cohort 2 (Patients [redacted]) received the therapeutic dose of onasemnogene abeparvovec (2.0×10^{14} vg/kg).
Note: Dashed lines denote time between missed or partial CHOP-INTEND assessments and the solid lines denote time between visits when full CHOP-INTEND assessments were conducted.
Abbreviations: CHOP-INTEND, Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders.
Data cut on August 7, 2017

Figure 5: CHOP-INTEND change from baseline by patient in Cohort 2 up to 24 months after onasemnogene abeparvovec infusion (full analysis set) in START and the NeuroNext natural history control cohort (range shown in grey shaded area)



Abbreviations: CHOP-INTEND, Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders.
Data cut on August 7, 2017.

In terms of the achievement of selected CHOP-INTEND threshold scores, the majority of Cohort 2 patients (91.7%) achieved a score ≥40 at 13.6 months of age and 8 (3.3%) achieved a score ≥50, surpassing a threshold effectively never seen amongst patients with SMA type 1 beyond 6 months of age (10). Three patients (25%) achieved CHOP-INTEND scores of ≥60, approaching the ceiling of the CHOP-INTEND scale. At 24 months post-dosing, 91.7% of patients from Cohort 2 achieved CHOP-INTEND scores of ≥50 and 4 patients scored ≥60; 2 patients (16.7%) achieved the maximum score of 64, indicating maximum functional status as measured by the CHOP-INTEND scale.

The improvements in motor function observed in START are in contrast with the complete absence of milestone achievement in natural history cohorts. In the PNCR cohort, no patient achieved a CHOP INTEND score >40 at or after the 6-month visit (with one transient exception) (5). In the NeuroNext cohort, no patient achieved a CHOP INTEND score >33 at or after the 6-month visit, and no patient had an increase in score from Baseline (4). Amongst patients with 2 copies of *SMN2*, a mean decline of 10.7 points was observed between the 6 and 12 months of age visit (5).

Bayley Scales

Four patients from Cohort 2 scored ≥60 on the CHOP-INTEND, and Bayley Scales assessments were initiated per protocol (initial assessments ranging from Day –1 to 24 months post-dosing). Mean (SD) fine motor subset Bayley Scale raw scores for patients in Cohort 2 of START increased from [redacted] between the first and final visit. Mean (SD) gross motor subset raw scores increase from [redacted] between the first and final visit. These increases in Bayley Scale scores reflect gains in motor function not seen amongst patients with SMA receiving BSC alone.

A raw score is a numerical score that reflects how many items the patient can accomplish/gets imputed due to starting position on the Bayley Scales. It should be noted that low or zero raw scores are to be expected of infants with symptomatic SMA type 1 in the gross motor subset. Infants with symptomatic SMA type 1 have a lower independent functional ability for their age when they enrol; thus, sufficient follow-up time is required before treated patients can be expected to achieve the motor milestones as captured in the gross motor subset.

Significant motor function milestones based on independent central review

The development of significant motor function milestones was assessed based on video reviews by an external expert. Compiled video recordings of the CHOP-INTEND, Bayley Scales, submitted home videos, and physical examinations were sent to a central reviewer for independent confirmation of development milestones.

At the 24 months post-dose time point, 91.7% of patients in Cohort 2 were able to hold their head erect without support for ≥3 seconds, sit with support, and sit alone for ≥5 seconds, 75% of patients were able to sit alone for ≥30 seconds, and 16.7% of patients were able to walk alone (Table 23). No patients in Cohort 1 achieved a significant motor milestone, reflecting the more advanced disease of patients in Cohort 1 compared with Cohort 2 prior to onasemnogene abeparvovec administration and the greater efficacy of the therapeutic dose. Data from both the PNCR and NeuroNext natural history studies report that no patients with

SMA type 1 were able to control head, roll over, sit with or without support, stand with assistance or alone, or walk with assistance or alone (5).

Table 23: START: motor milestones and other achievements in Cohort 2 at 24 months post onasemnogene abeparvovec administration versus historical cohorts

Endpoint	Cohort 2 (n=12)	Historical cohorts
Motor milestone achievements, n (%)		
Brings hand to mouth	12 (100)	NR
Controls head	11 (91.7)	0‡
Rolls over†	9 (75.0)	0‡
Sits with assistance	11 (91.7)	0‡
Sits unassisted§		
≥5 seconds	11 (91.7)	0‡
≥10 seconds	10 (83.3)	0‡
≥30 seconds	9 (75.0)	0‡
Stands with assistance	2 (16.7)	0‡
Stands unassisted	2 (16.7)	0‡
Walks unassisted	2 (16.7)	0‡

Abbreviations: n/N, number of patients meeting the criterion/number of patients in the group; NR, not reported; SMA, spinal muscular atrophy; WHO, World Health Organization.
At baseline, none of the patients in Cohort 2 had achieved any of the listed motor milestones, except for bringing a hand to the mouth. During the 24-month study period, the majority of these patients had reached ≥1 major motor milestone. No patients in Cohort 1 are listed, since none attained any motor milestones.
† According to item 20 on the Bayley Scales assessment tool, rolling over is defined as movement of ≥180 degrees both left and right from a position of lying on the back.
‡ Data are from De Sanctis et al. 2016 (30).
§ Sitting unassisted for ≥5 seconds is in accordance with the criteria of item 22 on the Bayley Scales assessment tool gross motor subtest. Sitting unassisted for ≥10 seconds is in accordance with the criteria used in the WHO Multicentre Growth Reference Study. Sitting unassisted for ≥30 seconds defines functional independent sitting and is in accordance with the criteria of item 26 on the Bayley Scales assessment tool gross motor subtest.
Sources: Al-Zaidy et al. 2019 (9); Mendell et al. 2017 (8).

Effect of age at dosing on motor milestone development

In a post-hoc analysis of the effect of age at onasemnogene abeparvovec administration on the motor milestone development of patients treated with the therapeutic dose (n=12), patients treated with onasemnogene abeparvovec at ≤3 months of age achieved the motor milestone of sitting unassisted for ≥5 seconds at a younger median age than patients treated at >3 months of age (12.5 versus 21.6 months, respectively; p=0.0087), even with poor baseline motor function (Table 24) (37). All three patients treated with onasemnogene abeparvovec at ≤3 months of age who had baseline CHOP-INTEND scores >20 (35, 47 and 50) experienced early motor milestone achievement. All three patients treated with onasemnogene abeparvovec at ≤3 months of age who had low baseline CHOP-INTEND scores of <20 (14, 16 and 17) and would therefore generally be expected to have the most severe and rapid disease progression, still experienced profound motor milestone achievement. Among the six patients treated with onasemnogene abeparvovec at

>3 months of age, five patients achieved motor milestones. This exploratory post-hoc analysis suggests that early treatment is key to maximising the efficacy outcomes possible following treatment with onasemnogene abeparvovec.

Table 24: START Phase I/IIa trial: motor milestones in Cohort 2 by age at dosing and baseline CHOP-INTEND scores

	Onasemnogene abeparvovec dosing at <3 months of age		Onasemnogene abeparvovec dosing at >3 months of age (n=6)
	High baseline CHOP-INTEND scores† (n=3)	Low baseline CHOP-INTEND scores† (n=3)	
Age at dosing, months, mean	1.8	1.8	5.1
Motor milestone achievements			
Sits unassisted for ≥5 seconds, n	3	3	5
Median age, months (range)	8.2 (8.0–11.9)	17.6 (13.0–20.5)	21.6 (17.9–27.4)
Sits unassisted for ≥30 seconds, n	3	3	3§
Median age, months (range)	10.0 (8.0–11.9)	22.1 (19.1–22.5)	24.4 (20.3–24.7)
Stands with support			
reached milestone by 24 months of follow-up	2	0	0
reached milestone post-24 months	1	1	1

Abbreviations: CHOP-INTEND, Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders. The CHOP-INTEND scale ranges from 0 to 64, with higher scores indicating better motor function.
† High baseline CHOP-INTEND scores were >20 points and low baseline CHOP-INTEND scores were <20 points.
§ Overall, 5 patients achieved the ability to sit unassisted for ≥30 seconds, including 2 patients who achieved this milestone during long-term follow-up post-24 months at the ages of 3.8 and 3.1 years.
Note: Median and range reflect 24-month follow-up data only.
Source: Lowes et al. 2018a (37).

6.3.1.1.3 Exploratory efficacy endpoints

Pulmonary status

Seven of 15 patients (46.7%) in START required the use of temporary, reversible, invasive ventilatory support (endotracheal tube via mouth/nose) during the study. All were single instances, with the duration of use ranging from 1 to 9 days. Two patients were in Cohort 1 (2/3, 66.7%) and five patients were in Cohort 2 (5/12, 41.7%). Thus, seven patients in Cohort 2 (58.3%) did not require the use of invasive ventilatory support during the study. Temporary invasive ventilatory support was provided either electively when patients had an upper respiratory illness or pneumonia (3/15 patients), or, was planned and used during a procedure or elective evaluation (4/15 patients). In all cases, invasive ventilatory support

was temporary and reversed following resolution of the acute reversible illness or after the conclusion of the procedure or evaluation. No patient received a tracheostomy.

At baseline, five patients (33.3%) required chronic non-invasive ventilatory support (all three patients [100%] in Cohort 1 and 2/12 patients [16.7%] in Cohort 2) while 10 of 12 patients in Cohort 2 (83.3%) were independent of ventilatory support (Table 25). Of the 10 patients in Cohort 2 who did not require non-invasive ventilatory support before dosing with onasemnogene abeparvovec, seven did not require ventilatory support at the 24 months post-dose end of study visit. The three patients who required non-invasive ventilatory support post-dosing but not at baseline had early onset of symptoms in the first month of life and a rapid disease progression characterised by diffuse muscle weakness, respiratory insufficiency, and inability to swallow. The non-invasive ventilatory support was required in the context of viral illnesses and was maintained thereafter.

Overall, although no patients in Cohort 1 or 2 of START needed PAV, all three patients in Cohort 1 and half of patients in Cohort 2 did not meet the 'independence from ventilatory support' outcome. 'Independence from ventilatory support' was defined as: requiring no daily ventilator support/usage at the three efficacy analysis time points, in the absence of acute reversible illness and excluding perioperative ventilation.

Table 25: Decreased pulmonary support in patients in Cohort 2 of START

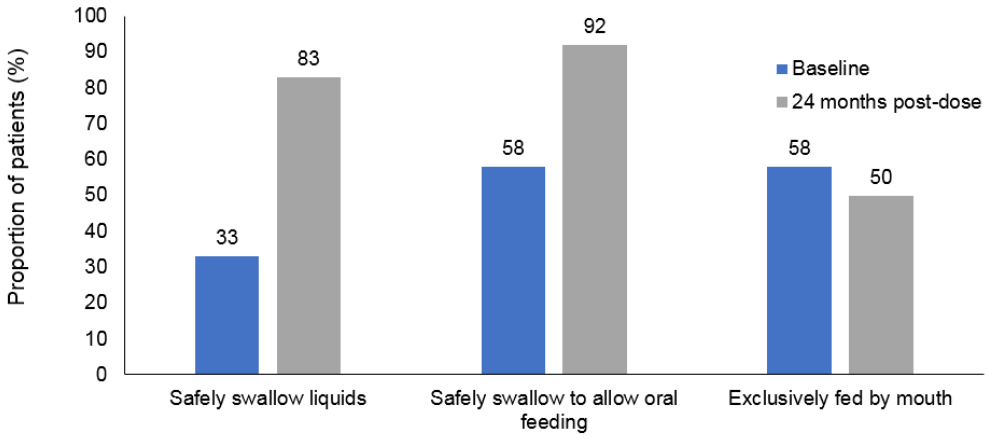
Patients	BiPAP use prior to dosing	Age at last pulmonary assessment (months)	BiPAP use post-dosing in START	Pulmonary event reached in START	BiPAP use in LT-001 at 31 December 2019 data cut
[redacted]	Yes	31.1	Yes	No	Yes
[redacted]	No	28.5	No	No	No
[redacted]	No	26.1	No	No	No
[redacted]	No	28.1	Yes	No	Yes
[redacted]	Yes	26.3	Yes	No	[redacted]
[redacted]	No	28.9	No	No	[redacted]
[redacted]	No	25.3	No	No	No
[redacted]	No	27.7	Yes	No	Yes
[redacted]	No	26.8	No	No	No
[redacted]	No	25.4	Yes†	No	Yes
[redacted]	No	27.9	No	No	No
[redacted]	No	26.3	Yes†	No	Yes†

BiPAP, Bi-level positive airway pressure.
† BiPAP was needed in these infants because of hospitalisations for respiratory infections.
Note: For one patient in Cohort 2 who was receiving BiPAP at baseline, data was mis-entered at the clinical site that the patient did not require ventilatory support prior to administration of onasemnogene abeparvovec.

Nutritional status and swallowing function

At baseline, 5/12 patients in Cohort 2 required non-oral feeding support and only 4/12 (33%) infants in Cohort 2 could swallow thin liquids. The proportion of patients in Cohort 2 who achieved safe swallowing function using thin liquids increased from 33% at baseline to 83% at 24 months post-dosing (Figure 6). The proportion of patients in Cohort 2 able to safely swallow to allow for at least partial oral feeding increased from 58% at baseline to 92% at the end of the follow-up period. All three patients in Cohort 1 required non-oral feeding support at baseline and at 24 months post onasemnogene abeparvovec administration.

Figure 6: Stabilisation or improvement in swallowing function in patients in Cohort 2 in START



Ability to thrive

Patients' ability to thrive was defined by the following: the ability to tolerate thin liquids (as demonstrated through a formal swallowing test), was not receiving nutrition through mechanical support (i.e. feeding tube), and had maintained weight (>3rd percentile for age and gender). Of the 7 patients in Cohort 2 who did not require non-oral nutrition prior to onasemnogene abeparvovec dosing, 71.4% maintained the ability to thrive at 24 months post-dosing. No patients in Cohort 1 met the criteria for demonstrating the ability to thrive.

Ability to speak

The ability of infants treated with onasemnogene abeparvovec to speak was not formally assessed as part of the START protocol. However, a review of the video documentation obtained in START[8] showed that of the 12 patients in Cohort 2, 11 (92%) achieved the ability to speak (9, 38). The precise age/time to speech attainment is not available; the only time point available is at 24 months post-dose (i.e. end of START follow-up). Whilst detailed data are not available for all 11 patients who could speak at the end of START, data from a clinician-led publication (Lowes et al. 2018 (39)) indicates that the language ability (expressive language and receptive language as tested in the Bayley language scale), of

[8] The attainment of the ability to speak for patients in START was determined based upon review of video documentation that demonstrates the ability: speaking is defined as the ability to produce audible consonant sounds consistent with age-appropriate expectations of language development.

patients treated with onasemnogene abeparvovec were in the range of normal childhood development and the authors suggested that these children should be capable of schooling and have the potential for a good quality of life.

Motor neuron function assessment

Motor neuron assessments were conducted at baseline and every 6 months after infusion of onasemnogene abeparvovec.

CMAP

Measurement of CMAP provides information on motor neuron health and the severity of denervation of infants with SMA (Section 6.1.1.1). In healthy infants, CMAP values rise during development before plateauing at adult levels by the end of the first decade; in natural history studies of SMA, CMAP is reduced relative to reference data (3). Changes from baseline in CMAP responses from tibialis anterior-peroneal nerve (peroneal CMAP) and abductor digiti minimi-ulnar nerve (ulnar CMAP) were assessed. At baseline, mean (SD) peroneal and ulnar CMAP amplitude values of [redacted] and 0.74 (1.059) were reported for Cohort 1 and 2, respectively. At 24 months post-dose, patients in Cohort 2 achieved sustained improvements in both peroneal CMAP amplitude (mean change [redacted] increase) and ulnar CMAP amplitude (mean change 0.84 mV, 142% increase). Patients in Cohort 1 also showed improvements in CMAP; at 24 months post-dose, patients in Cohort 1 ([redacted]) achieved an improvement in peroneal CMAP amplitude of [redacted] from a mean (SD) baseline of [redacted]. Ulnar CMAP amplitude decreased from a baseline value of 0.30 (n=1) both at the 12- and 24-month time points (both –0.10 mV, –33%). The observed increases in CMAP amplitudes may be indicative of improved muscle fibre innervation, consistent with the improved motor function observed clinically.

MUNE

MUNE is an electrophysiologic method used to estimate the number of motor neurons innervating a muscle group and to help understand the time course of motor neuron loss in SMA (40) (Section 6.1.1.1). At baseline, MUNE values of [redacted] and [redacted] were reported for patients in Cohort 1 and Cohort 2, respectively. Patients in Cohort 2 achieved improvements in MUNE of [redacted] at 24 months post-dose, indicating no motor neuron loss. Patients in Cohort 1 showed a [redacted] decline from baseline at 24 months after dosing. As MUNE is considered to be an exploratory measure, the physiological relevance to the effects of onasemnogene abeparvovec are currently unknown.

Cognitive function

An assessment of the cognitive function of 7 infants treated with the intended therapeutic dose of onasemnogene abeparvovec reported that all patients scored in the typically developing range on the Bayley Scales cognitive subtest composite score (score range: patients treated with onasemnogene abeparvovec, 90–105; typically developing infants, 90–109) (39). These results indicate that infants with SMA type 1 who received onasemnogene abeparvovec performed similarly to healthy peers (39).

6.3.1.1.4 Comparison of clinical outcomes in START versus natural history

Compared with the patients in START who received the therapeutic dose of onasemnogene abeparvovec (Cohort 2, n=12), a greater proportion of the PNCR natural history control cohort required nutritional (69.6% versus 50.0%) or ventilatory support (78.3% versus 41.7%) over the course of follow-up, indicative of the impact of therapeutic intervention in START (Table 26) (5). Similarly, a greater proportion of the NeuroNext cohort required nutritional and ventilatory support over the course of follow-up (5), an additional indication of the strong impact of therapeutic intervention in START.

In both the PNCR and NeuroNext natural history control cohorts, no child achieved the milestone of sitting with or without support, hands and knees crawling, standing with assistance, walking with assistance, standing alone or walking alone. Within the PNCR cohort, no patient achieved a CHOP-INTEND score of >40 at or after the 6-month visit (with one transient exception). In the NeuroNext cohort, no patient achieved a CHOP-INTEND score of >33 at or after the 6-month visit, and no patient had an increase in score from baseline (5). Amongst patients with 2 copies of *SMN2*, a mean decline of 10.7 points was observed between the 6 and 12 months of age visit (5). The significant milestone achievements and improvements in CHOP INTEND scores observed in START in patients who received the therapeutic dose cohort, contrast sharply with the complete absence of milestone achievement and decline in motor function in the PNCR and NeuroNext natural history control cohorts.

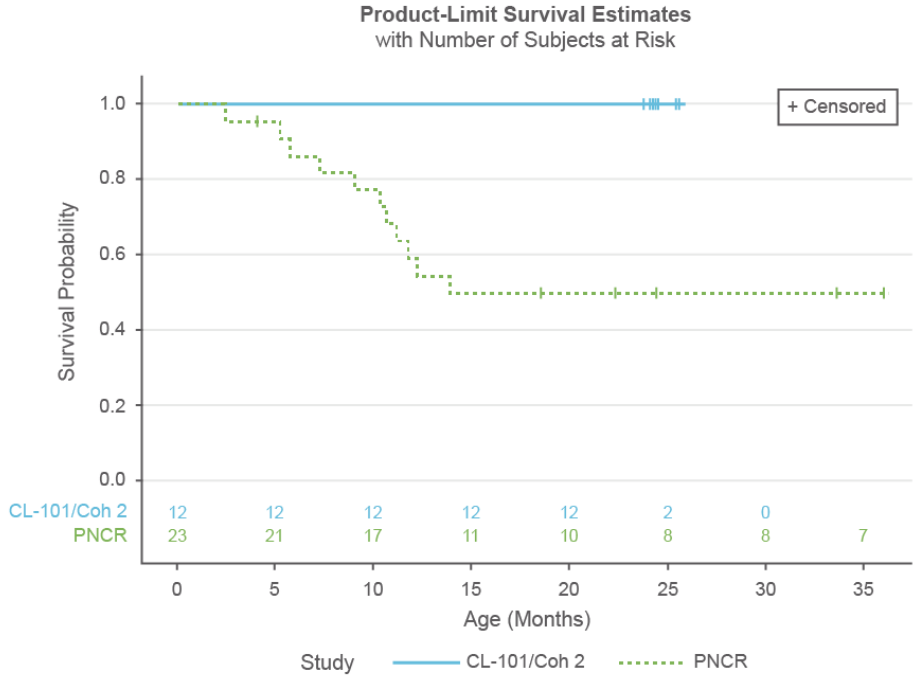
Table 26 and Figure 7–Figure 8 illustrate the markedly improved survival and survival free of permanent ventilation (alive, without tracheostomy, and not requiring ≥16 hours of ventilatory support per day for ≥2 weeks, absent an acute reversible illness or perioperative) in START compared with the PNCR and NeuroNext natural history control cohorts. All 12 patients in the START therapeutic dose cohort remained alive, and none met the definition of requiring permanent ventilation over the course of the 24-month study. Sixteen patients (69.6%) in the PNCR cohort reached the combined endpoint of death or the need for a minimum of 16 hours/day of NIV support for a minimum of 14 continuous days by 13.6 month of age. The data for the NeuroNext cohort reflect tracheostomy-free survival, a less conservative endpoint (a child could receive 24 hours per day of non-invasive support without triggering the combined endpoint, for example). Table 26 also presents the range of ages for death and for reaching the composite survival endpoint (survival free of permanent ventilation) for the PNCR and NeuroNext cohorts.

Table 26: Summary of disease course in the PNCR and NeuroNext natural history cohorts

Variable	Cohort 2 (N=12)	NeuroNext control (N=16)	PNCR control (N=23)
Gastrostomy and ventilation support, n (%)			
Experimental SMA medication used (non-onasemnogene abeparvovec)	0	0	4 (17.4)
Gastrostomy tube placed	6 (50.0)	N/A	16 (69.6)
Ventilation support	5 (41.7)	N/A	18 (78.3)
Motor milestone and motor function achievements, n (%)			
Sit without support for ≥5 seconds	11 (91.7)	0	0
Sit without support for ≥10 seconds	10 (83.3)	0	0
Sit without support for ≥30 seconds	9 (75.0)	0	0
Stand without support	2 (16.7)	0	0
Walk alone	2 (16.7)	0	0
CHOP-INTEND score >40 at any time >6 months of age n (%)	11 (91.7)	0	1 (4.3)
BiPAP or intubation (for ≥16 hours/day and ≥14 days), n (%)	0	N/A	13 (56.5)
Age reached, months, mean (SD)			10.2 (4.9)
Intubation, n (%)	0	2 (12.5)	NA
Age reached, months, mean (SD)		12.1 (8.8)	
Mortality or ventilation outcome at 14 months			
Mortality, n (%)	0	7 (43.8)	7 (30.4)
Age at death, months, mean (SD)		7.9 (3.1)	7.7 (3.5)
Composite of mortality or ventilation, n (%)	0	8 (50.0)	16 (69.6)
Age at composite of mortality or ventilation, months, mean (SD)		7.7 (2.3)	8.8 (3.3)
Mortality or ventilation outcome – all data			
Mortality, n (%)	0	8 (50.0)	11 (47.8)
Age at death, months, mean (SD)		8.9 (4.1)	33.1 (53.1)
Composite of mortality or ventilation, n (%)	0	10 (62.5)	18 (78.3)
Age at composite of mortality or ventilation, months, mean (SD)		9.6 (4.8)	9.8 (4.4)

Abbreviations: BiPAP, bi-level positive airway pressure; CHOP-INTEND, Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders; NA, not available; SMA, spinal muscular atrophy; PNCR, Pediatric Neuromuscular Clinical Research; SMA, spinal muscular atrophy.
Sources: PNCR NeuroNext report (5).

Figure 7: Overall survival in START (Cohort 2) vs PNCR



Note: The X axis is truncated to 36 months and does not show the two 'late' deaths in PNCR; one death occurred at 88 months of age and one death at 179 months of age. Both infants with a 'late' death were enrolled retrospectively (i.e. age at enrolment of 44 months for patient who died at 88 months of age; age at enrolment of 171 months for patient who died at 179 months of age), and are events in the ventilation-free survival analyses.

Figure 8: Ventilation-free survival in START (Cohort 2) vs PNCR

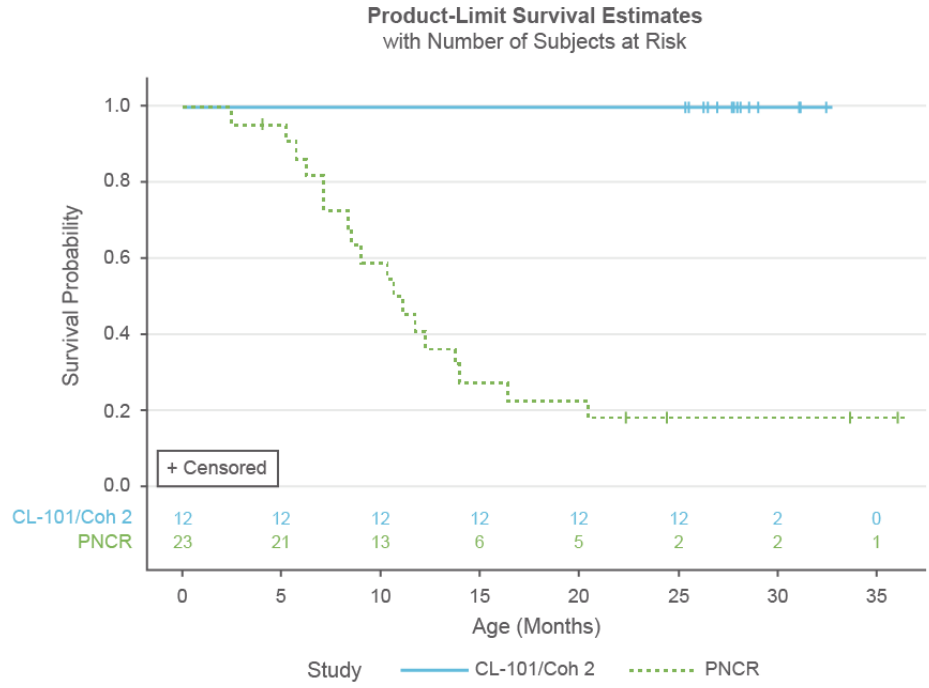


Figure 9: Overall survival in START (Cohort 2) vs NeuroNext

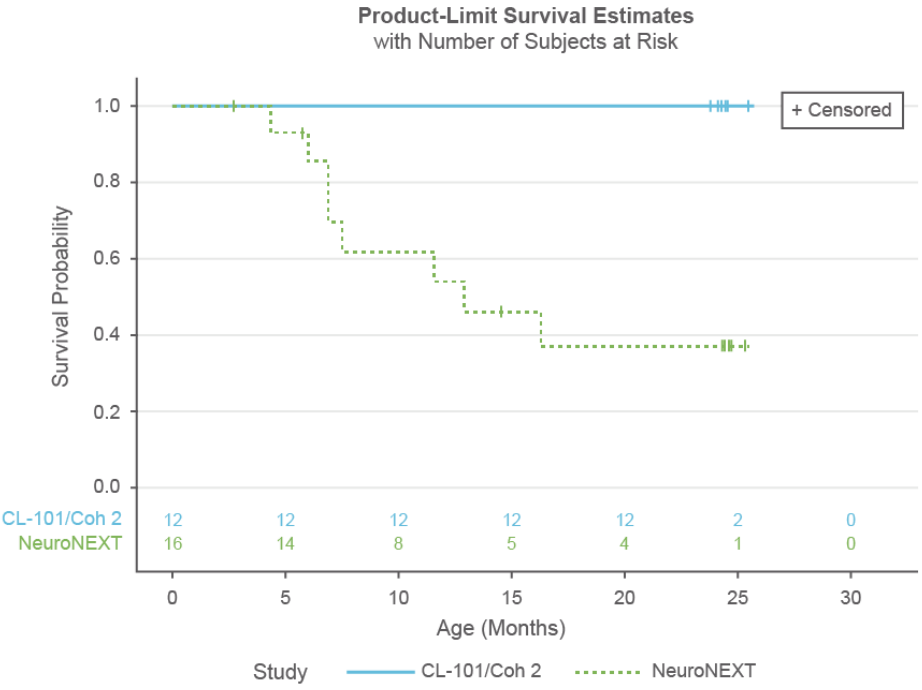
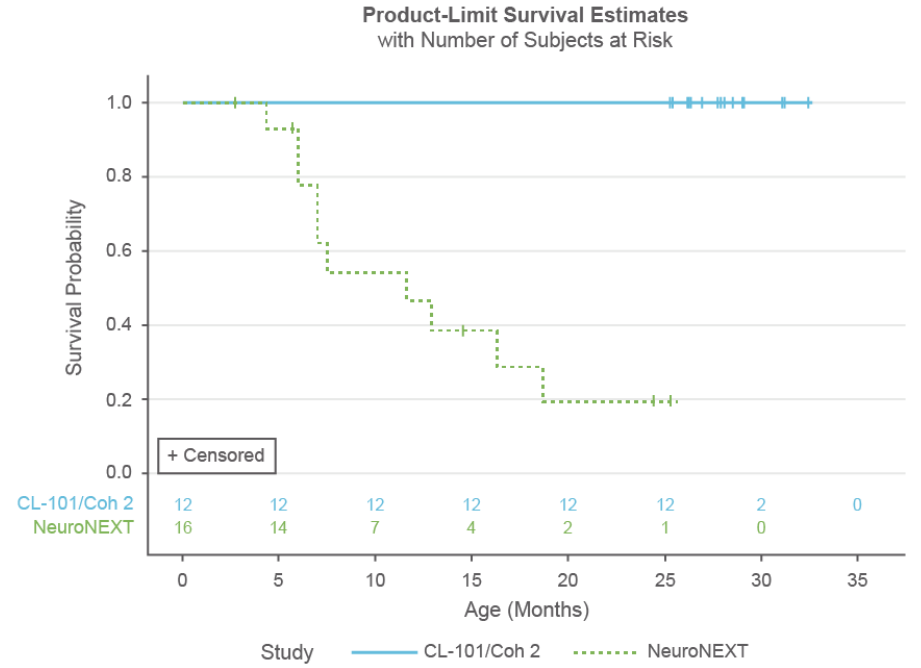


Figure 10: Ventilation free survival in START (Cohort 2) vs NeuroNext



6.3.1.2 LT-001

Study LT-001 is an ongoing, long-term follow-up study of patients who received onasemnogene abeparvovec in START. In total, 13/15 patients from START are enrolled in LT-001 (three patients from Cohort 1 [low dose] and 10 patients from Cohort 2 [therapeutic dose]). Between the 31 May 2019 and the 31 December 2019 data cut, there have been nine new clinical visits.

The 100% event-free survival rate achieved at the end of START, which has never been observed in natural history studies, is being maintained in LT-001; at the data cut all patients in Cohort 2 were alive and free from permanent ventilation. In addition, five of the 10 enrolled Cohort 2 patients (50.0%) require no respiratory support and one Cohort 2 patient requires respiratory support only when ill (Table 25). Thus, 6 of 10 enrolled Cohort 2 patients (60.0%) require no regular, daily respiratory support. The median age of Cohort 2 at the data cut was 4.5 years (range: 4.3–5.6). At the data cut, two of the three patients (66.7%) in the lower dose Cohort 1 remain free of permanent ventilation; the oldest patient treated with onasemnogene abeparvovec in Cohort 1 is now 6.2 years old.

Results from LT-001 show that patients treated with the therapeutic dose of onasemnogene abeparvovec in START (Cohort 2) are maintaining milestones, as well as gaining new milestones. No patients in START (Cohort 2) have lost motor milestones and [redacted] patients have gained new motor milestones during LT-001 follow-up (Table 27):

- **Two new video-confirmed milestones:** Two patients gained the milestone of ‘stands with assistance’ ([redacted] home video, clinician assessment, and central reviewer confirmed; [redacted] home video and central reviewer confirmed) compared with the end of START

[redacted]

The maintained and/or new milestones observed in all (10/10) Cohort 2 patients enrolled in LT-001 have not previously been reported in natural history studies of patients with SMA type 1.

It should be noted that all 15 patients (100%) completed the 24-month follow-up period post treatment with onasemnogene abeparvovec of START without receiving any additional SMA-targeted therapies (such as nusinersen). The use of other SMA-targeted therapies (e.g. nusinersen) is permitted for patients enrolled in LT-001. Nusinersen use data are available for all 13 enrolled patients (100%) at the baseline visit and for 11 patients (84.6%) at the 1-year follow-up visit (Table 27). As of the 31 Dec 2019 data cut, nusinersen treatment was ongoing in seven of the 13 enrolled patients (53.8%). Nusinersen is documented as having been used in all three patients (100%) enrolled in Cohort 1 treated with the low dose of onasemnogene abeparvovec and this is reported as ongoing. Four of 10 patients (40.0%) who received the higher dose in Cohort 2 and who enrolled in LT-001 have been started on nusinersen and this is reported as ongoing. The reasons for initiation of nusinersen therapy

are not recorded in LT-001; treatment with nusinersen may have been initiated as a result of parental requests to see if the children could achieve additional benefit from nusinersen following treatment with onasemnogene abeparvovec, which was an investigational therapy at the time of administration to patients in START. The limited dataset does not allow conclusions on the additional benefit of nusinersen in LT-001 or lack thereof. Patient [redacted] stopped nusinersen use on 13 August 2018 and then re-started on 12 February 2019. Of note, patients [redacted] and [redacted] who achieved the video-confirmed milestone of 'stands with assistance' were not receiving nusinersen treatment at any point.

These results continue to indicate that a one-time IV administration of onasemnogene abeparvovec at the therapeutic dose in START has continued to provide prolonged and durable efficacy. Patient developmental milestones and survival have been maintained and two new video-confirmed milestones have been achieved without the use of nusinersen. The durability of onasemnogene abeparvovec efficacy has been demonstrated over the long term; at the data cut the median age of patients treated with onasemnogene abeparvovec in START (Cohort 2) was 4.5 years (range: 4.3–5.6).

Table 27: Highest development milestone achievement in START and LT-001 and nusinersen usage (as of 31 December 2019)

Patient	Maximum significant milestone achieved in START[†]	START end visit date	LT-001 baseline visit date	New maximum significant milestone achieved in LT-001		Nusinersen usage in LT-001			
				Central reviewer video-confirmed	Clinician assessed	Start date	Usage at LT-001 baseline visit	Usage at LT-001 1-year visit	Usage at LT-001 2-year visit
Cohort 1 (low dose)									
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cohort 2 (therapeutic dose)									
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]						
[redacted]	[redacted]	[redacted]	[redacted]						
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Patient	Maximum significant milestone achieved in START†	START end visit date	LT-001 baseline visit date	New maximum significant milestone achieved in LT-001		Nusinersen usage in LT-001			
				Central reviewer video-confirmed	Clinician assessed	Start date	Usage at LT-001 baseline visit	Usage at LT-001 1-year visit	Usage at LT-001 2-year visit
[redacted]									
[redacted]									
[redacted]									

Abbreviations: Apr, April; Dec, December; Feb, February; Jun, June; N/A, not applicable; Nov, November; secs, seconds; Oct, October; Sep, September.
Cells highlighted in green denote patients who have achieved an additional motor milestone during LT-001 either by central reviewer video confirmation or by clinician assessment at study visits.
† Sitting unassisted definitions were: ≥5 seconds as per item 22 of the Bayley-III Scales gross motor subtest, ≥10 seconds as per the World Health Organization (WHO) criteria, and ≥30 seconds as per item 26 of the Bayley-III Scales gross motor subtest.
‡ The Year 1 visit date is not reported in the data on file listing 16.2.3, however, the status of nusinersen treatment was reported as ongoing as of the 31 December 2019 data cut.
§ The data listing describes milestone as “Sits alone <10 seconds”. The external reviewer confirmed that this milestone was defined as “Sits alone ≥5 seconds” and that is how it is labelled here.
¶ Reported at baseline visit. Sits unassisted ≥30 seconds as per item 26 of the Bayley-III Scales gross motor subtest. Listing 16.2.5, List of Clinician Assessed Milestones Reported, 31 December 2019.
†† Patient [redacted] stopped nusinersen use on 13 August 2018 and then re-started on 12 February 2019.
‡‡ Patient also described as ‘sitting without support for ≥15 seconds’ per the Nationwide Children’s Hospital (NCH) definition in the Gross Motor Skills checklist in START Listing 16.2.15-24.
§§ Reported at Year 1 visit. [redacted]. Listing 16.2.5, List of Clinician Assessed Milestones Reported, 31 December 2019.
¶¶ As reported in: Listing 16.2.1 Listing of Clinician Assessed Milestones Reported.
Note: Listing 16.2.1 does not state the time period for milestone attainment, however, milestones are defined in the LT-001 protocol, with sitting unassisted defined as item 26 in the Bayley-III Scales gross motor subtest.

6.3.1.3 STR1VE-US

The results of the efficacy analysis of onasemnogene abeparvovec in STR1VE-US are presented for the ITT and safety populations. Analyses were carried out in the following populations:

- Intent-to-treat population (ITT): symptomatic patients with biallelic-deletion mutations of *SMN1* (exon 7/8 common homozygous deletions) and two copies of *SMN2* without the known gene modifier mutation (c.859G>C) who receive an IV infusion of onasemnogene abeparvovec at <180 days of age
- Efficacy completers population:
    - All treated patients who reach 14 months of age for the survival endpoint or 18 months of age for the endpoint of achievement of functional independent sitting, OR
    - All treated patients who meet discontinuation criteria, discontinue the study due to an AE or experience death
- All enrolled population: the all enrolled population will consist of all patients who receive an IV infusion of onasemnogene abeparvovec. Analyses of endpoints in this population are considered descriptive
- Safety population: the safety analysis population will consist of all patients who receive an IV infusion of onasemnogene abeparvovec. All safety analyses will be conducted on the safety analysis population

6.3.1.3.1 Survival and permanent ventilation

Of the 22 enrolled patients enrolled in STR1VE-US, 21 patients (95.5%) survived >10.5 months without permanent ventilation, 20 patients (90.9%) survived event-free to ≥13.6 months, and 20 patients (90.9%) had survived event-free at 18 months of age (Figure 11).

In total, 19 of the 22 patients (86.4%) enrolled in STR1VE-US completed the study. Two of the 22 patients (9.1%) enrolled in the study discontinued prior to 13.6 months of age. One patient ([redacted]) died at age 7.8 months due to respiratory failure that was not considered related to onasemnogene abeparvovec. One patient ([redacted]) discontinued (withdrew consent) at 11.9 months of age; this patient required ≥16 hours of non-invasive BiPAP ventilator support for ≥14 consecutive days, prior to discontinuation. The patient met the ventilatory endpoint on Study Day 176 (age 11 months). One additional patient [redacted]) was discontinued at the age of 18 months, before the Month 18 end of study visit, due to an adverse event of respiratory distress (not considered related to study drug). As this patient did not complete an end of study visit (Month 18 or early termination), they are included in the patients who withdrew from the study. Since this patient was alive and did not require permanent ventilation at 18 months of age, they are also included as having survived without permanent ventilation at 18 months of age.

These results are unprecedented compared with the 50% and 25% survival without permanent ventilatory support (as defined in the study protocol) at 10.5 and 13.6 months of

age, respectively, reported in the published natural history PNCR dataset (3) (Figure 12); these data suggest that onasemnogene abeparvovec has a significant therapeutic benefit in prolonging ventilation-free survival in patients with SMA type 1.

Figure 11: Event-free survival in STR1VE-US (Safety population)

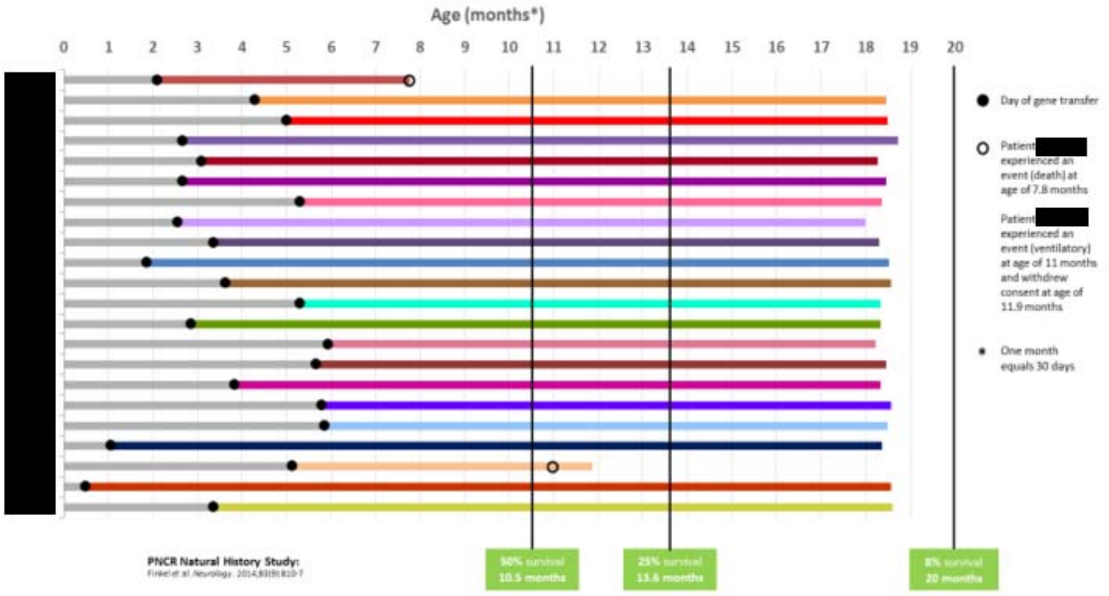
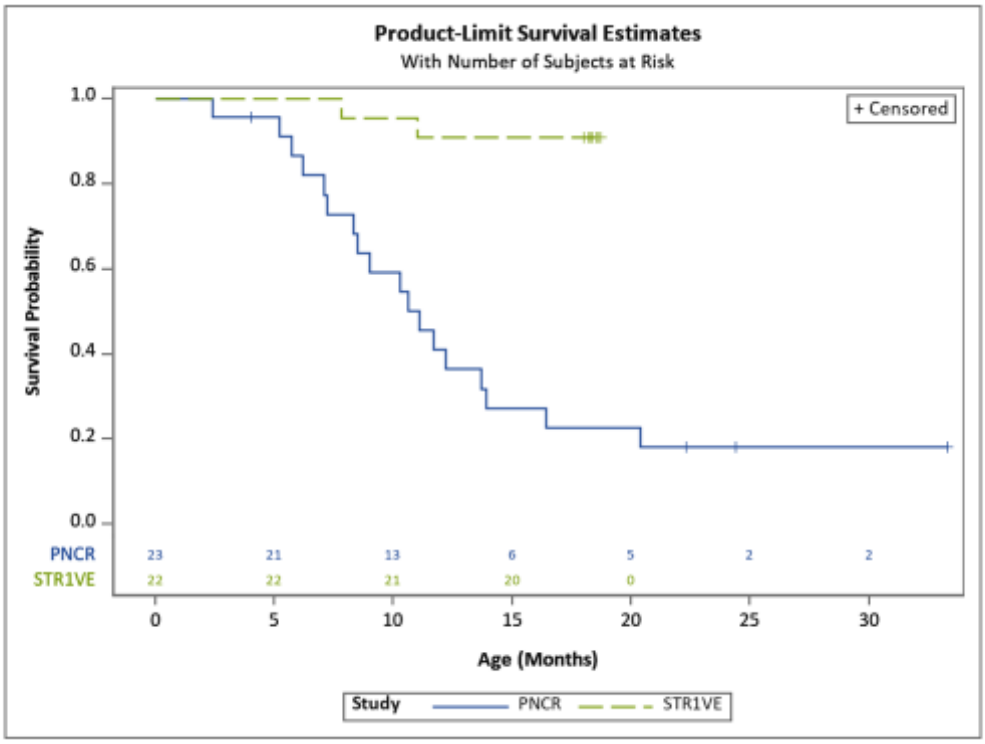


Figure 12: Kaplan-Meier plot for event-free survival in STR1VE-US



Natural history: The PNCR and NeuroNext profiles presented are the AveXis datasets used to provide an external control comparator (5).

6.3.1.3.2 Milestones based on video review

The video-confirmed developmental milestones for patients in STR1VE-US at 18 months of age are summarised in Table 28.

Video-confirmed milestones that were achieved as defined by the Bayley gross motor scale included 17 patients (of 20[9], 85.0%) that achieved head control, 13 patients (59.0%) that achieved rolls from back to sides, and 14 patients (63.6%) that achieved sits without support for ≥30 seconds[10]. Fourteen patients (63.6%) achieved the video-confirmed milestone of sitting without support for support for ≥10 seconds[11]. As the criterion for sitting ≥10 seconds is from WHO and is rated differently than the criterion for sitting without support ≥30 seconds from the Bayley Scales, the proportion of patients achieving each milestone at a given timepoint may not be equivalent. In addition, one patient (4.5%; Patient [redacted]) achieved the motor milestones of crawls, pulls to stand, stands with assistance, walks with assistance, stands alone, and walks alone as defined by the Bayley gross motor scale. This patient was initially categorised by the Investigator as asymptomatic and later re-classed as symptomatic due to the absence of patellar function.

In addition, through 18 months of age, 19 patients (86.4%) achieved motor milestone(s), confirmed by independent central video review. Two patients were capable of holding their heads erect at baseline. After receiving onasemnogene abeparvovec, an additional 17 patients achieved the motor milestone of holding head erect, 13 patients achieved the motor milestone of turning from back to side, and 14 patients achieved the motor milestone of sitting alone for ≥30 seconds (Bayley definition) and for ≥10 seconds (WHO definition) (as observed by independent video assessments).

From the WHO Multicentre Growth Reference Study, the 99th percentile of the achievement of sitting without support is 9.2 months (Figure 2) (28). For the 14 patients in STR1VE-US that achieved the milestone of independent sitting for ≥30 seconds, the median age when this milestone was first demonstrated was 12.6 months (range 9.2 to 18.6 months). The milestone of independent sitting for ≥30 seconds was confirmed for 13 patients at the 18-month visit (co-primary endpoint, p<0.0001). One patient ([redacted]) achieved the milestone of sitting independently for ≥30 seconds at 16 months of age, but this milestone was not confirmed at the 18 months of age visit. [redacted]

Infants with SMA type 1 in natural history studies are never able to sit independently (3, 29, 41). These results are remarkable in that while motor milestone development in children with SMA type 1 treated with onasemnogene abeparvovec may be slightly delayed compared with healthy population equivalents (6), they are achievable.

[9] Two of 22 patients were able to hold head erect for ≥3 seconds without support at screening visit.

[10] Bayley Scales Gross Motor subset item #26: Child sits alone without support for ≥30 seconds.

[11] WHO definition: child sits up straight with head erect for ≥10 seconds; child does not use hands or arms to balance body or support position.

Table 28: Video confirmed developmental milestones at 18 months of age in STR1VE-US (ITT population)

Milestone achieved	n (%) (N=22)
Holds head erect for ≥3 seconds without support†‡	17 (85.0)
Turns from back to both right and left sides§	13 (59.0)
Sits alone without support for ≥30 seconds¶	14 (63.6)
Sits independently for ≥10 seconds††	14 (63.6)
Crawls‡‡	1 (4.5)
Pulls to stand§§	1 (4.5)
Stands with assistance¶¶	1 (4.5)
Stands alone†††	1 (4.5)
Walks with assistance‡‡‡	1 (4.5)
Walks alone§§§	1 (4.5)

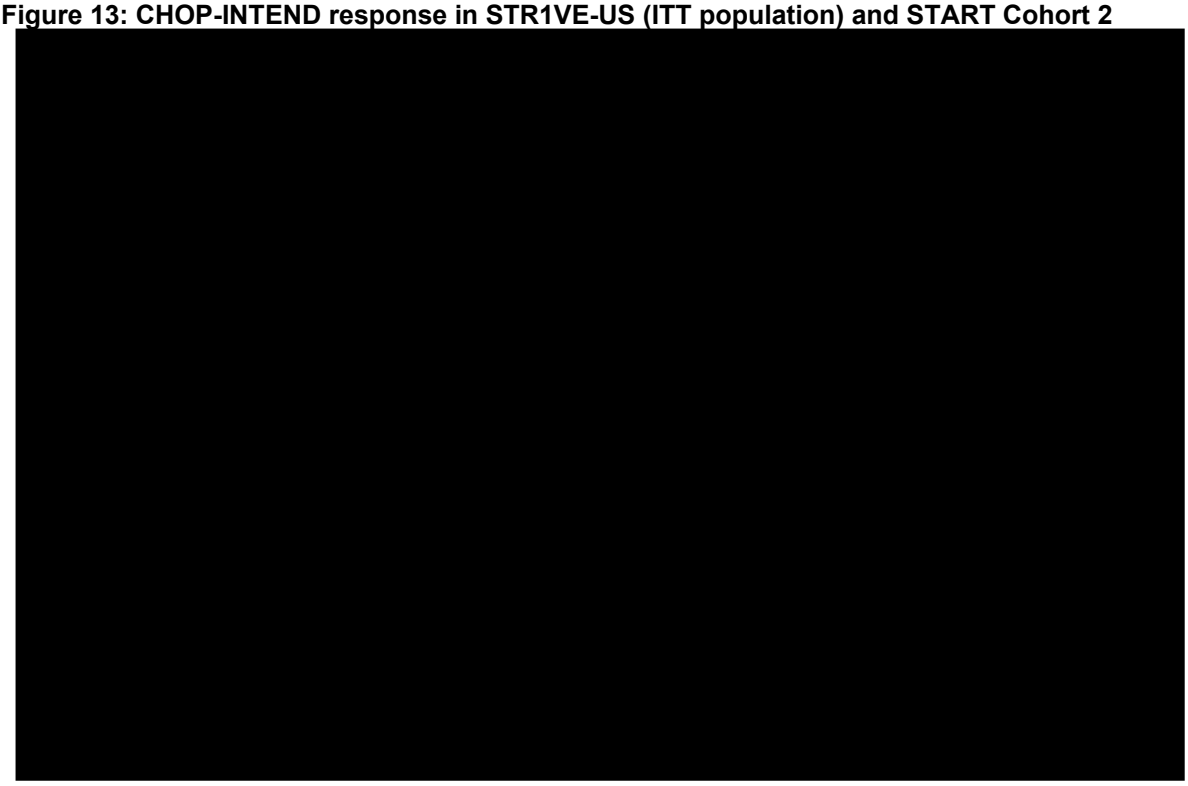
† Two patients who were able to hold head erect for ≥3 seconds without support at screening visit are not included.
‡ Bayley Scales gross motor subtest item #4: Child holds head erect for at least 3 seconds without support.
§ Bayley Scales gross motor subtest item #20: Child turns from back to both right and left sides.
¶ Bayley Scales gross motor subtest item #26: Child sits alone without support for at least 30 seconds.
†† WHO MGRS definition: Child sits up straight with head erect for at least 10 seconds. Child does not use arms or hands to balance body or support position.
‡‡ Bayley Scales gross motor subtest item #34: Child makes forward progress of at least 5 feet by crawling on hands and knees.
§§ Bayley Scales gross motor subtest item #35: Child raises self to standing position using chair or other convenient object for support
¶¶ Bayley Scales gross motor subtest item #33: Child supports his or her own weight for at least 2 seconds, using your hands for balance only.
††† Bayley Scales gross motor subtest item #40: Child stands alone for at least 3 seconds after you release his or her hands.
‡‡‡ Bayley Scales gross motor subtest item #37: Child walks by making coordinated, alternated stepping movements.
§§§ Bayley Scales gross motor subtest item #43: Child takes at least 5 steps independently, displaying coordination and balance.

6.3.1.3.3 The Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders

All 22 patients (100%) had at least 3 months of CHOP-INTEND data post onasemnogene abeparvovec administration. The mean (SD) baseline CHOP-INTEND score was 32.0 (9.69). Rapid improvements in motor function were observed following treatment with onasemnogene abeparvovec, as demonstrated by improvements in the CHOP-INTEND scores by age, presented in Figure 13 alongside the results from START and the NeuroNext natural history cohort, for comparison. The mean (SD) increases (improvement) from baseline to visit Month 1 (n=22), Month 3 (n=22), and Month 6 (n=20) after onasemnogene abeparvovec administration were 6.9 (5.35), 11.7 (6.40), and 14.6 (7.04) points, respectively.

Twenty-one patients (95.5%) achieved or maintained a CHOP-INTEND score ≥40, 14 (63.6%) achieved or maintained a score ≥50, and 5 patients (22.7%) achieved a score ≥60. These CHOP-INTEND scores are remarkable, as patients with SMA type 1 receiving BSC almost never achieve a CHOP-INTEND score of ≥40 and show a mean decline in score over time (3, 4).

Figure 13: CHOP-INTEND response in STR1VE-US (ITT population) and START Cohort 2



6.3.1.3.4 Bayley Scales

The gross and fine motor subtests of the Bayley Scales were administered at baseline and then monthly in STR1VE-US. Early improvements in the fine and gross motor function of infants with SMA type 1 treated with onasemnogene abeparvovec were observed across the study (Figure 14 and Figure 15).

By the age of 18 months, most patients had seen an improvement, in most cases marked improvement, in performance on both the Bayley Scales gross motor and fine motor

subtests. At the 18 months of age visit, the mean (SD) change from baseline in the fine motor subtest raw scores was [redacted]. The mean (SD) change from baseline in the gross motor subtest raw scores was [redacted] at the 18 months of age visit. It should be noted that low or zero raw scores are to be expected of infants with symptomatic SMA type 1 in the gross motor subset. This also, to an extent, reflects a normal developmental perspective, with younger children having lower gross motor scores (i.e. motor milestones) compared to older children i.e. low or zero gross motor scores in younger children are expected. Infants with symptomatic SMA type 1 have a lower independent functional ability for their age when they enrol; thus, sufficient follow-up time is required before treated patients can be expected to achieve the motor milestones as captured in the gross motor subset.

On the Bayley scale, mean (SD) changes from baseline scores of [redacted], [redacted] and [redacted] were observed for the subscales of cognitive assessments, expressive communication and receptive communication respectively. All were within the range of normally developing children at all timepoints.

The improved Bayley Scales motor function scores over time relate to patients being reported to achieve tasks in the Bayley Scales motor subsets such as turning the pages of a book [redacted], scribbling spontaneously [redacted], thrusting arms in play [redacted], placing coins in a slot [redacted], and grasping foot with hand [redacted]; numbers reflect item achievement at any visit post onasemnogene abeparvovec administration. Assessment of the Bayley Scales cognitive domain demonstrated that patients could find hidden objects, identify pictures, and recognise caregivers, amongst other achievements. Similarly, assessment of the Bayley Scale receptive and expressive communication subsets showed that patients treated with onasemnogene abeparvovec in STR1VE-US could react to sounds in the environment, respond to a person's voice, vocalise mood, use words to make wants known, combine words and gesture, and understand inhibitory words.

Figure 14: Bayley Scales fine motor subset raw score over time in STR1VE-US (ITT population)

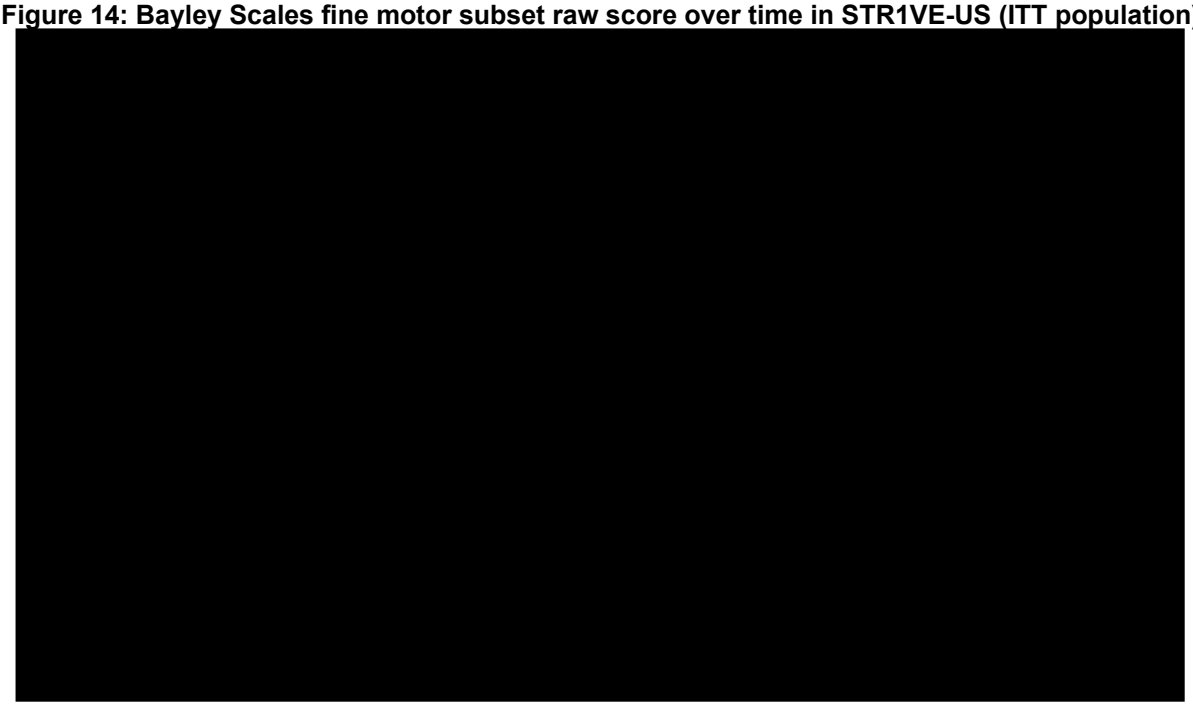
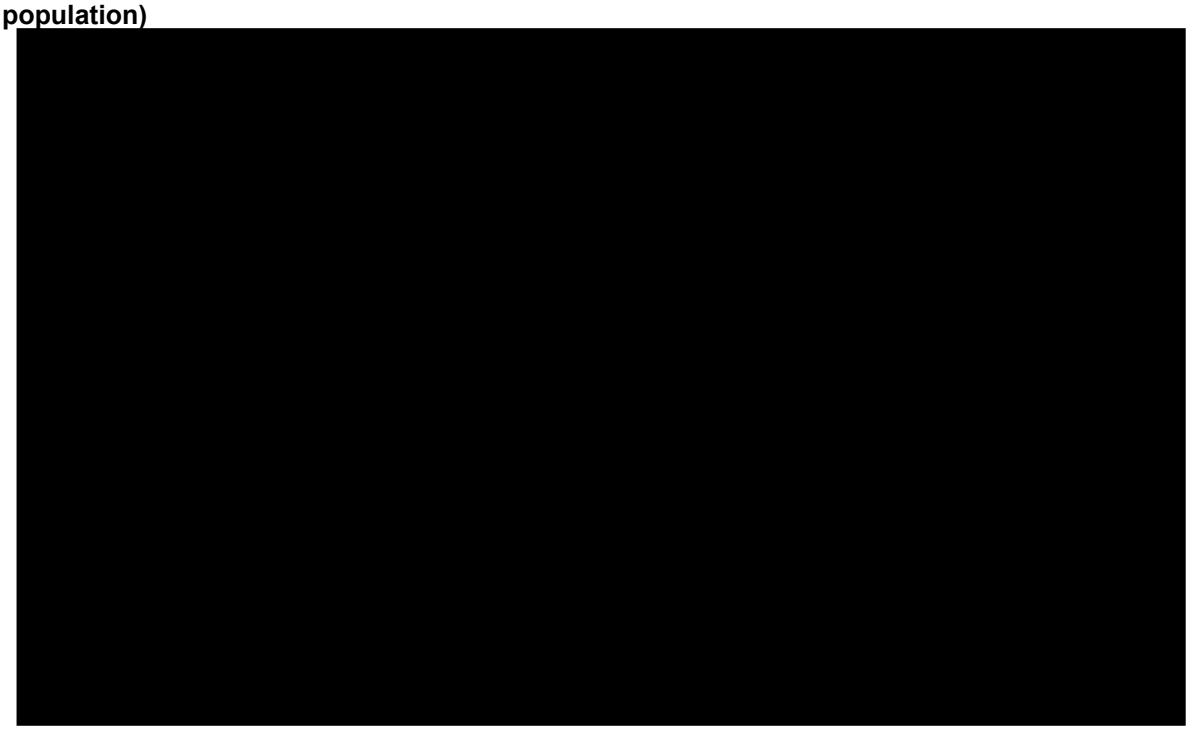


Figure 15: Bayley Scales gross motor subset raw score over time in STR1VE-US (ITT population)



6.3.1.3.5 Non-invasive and invasive ventilatory support

No patients required non-invasive ventilatory support at baseline in STR1VE-US. **At the 18 months of age end of study visit 18 of 22 patients (81.8%) were independent of ventilatory support** (as assessed by Trilogy BiPAP data; co-secondary endpoint, p<0.0001). Further, **15 of 22 patients (68.1%) did not require any non-invasive ventilatory support at any point during STR1VE-US**.

Five patients required BiPAP during the study and two patients had other non-invasive ventilatory support (Table 29); patient [redacted] had post-treatment continuous positive airway pressure (CPAP) and patient [redacted] had non-invasive ventilatory support using a Cuirass device during the study. Patients [redacted], and [redacted] did have transient use of endotracheal tube via mouth or nose but all were related to either peri-operative use or an adverse event; all were successfully extubated.

At the end of the study, four patients were reported not to have achieved independence of ventilatory support (as assessed by Trilogy BiPAP data); two patients had Trilogy data at or after 18 months of age ([redacted] and [redacted]) and two patients withdrew from the study prior to 18 months of age ([redacted] and [redacted]).

After onasemnogene abeparvovec administration, one patient ([redacted]) met the definition for permanent, non-invasive or invasive ventilatory support (as assessed by the Trilogy BiPAP data) Study Day 176 (age 11.0 months); this patient withdrew consent on Study Day 203 (age 11.8 months).

Table 29: Summary of ventilatory support in STR1VE-US (Safety population)

Patient number	Ventilatory support during STR1VE-US	Ongoing at last visit
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]

6.3.1.3.6 Swallowing and feeding support

In infants with severe SMA treated with BSC the development of tongue and swallowing weakness increases swallowing and feeding difficulty over time, and leads to weight loss, pulmonary aspiration and the need for mechanical feeding (3, 33, 34).

At baseline, all patients in STR1VE-US were able to swallow thin liquids and none required feeding support (Table 14). **Fifteen (15) of 22 patients (68.1%) received no non-oral feeding support at any time during the study – i.e. were exclusively fed by mouth**. Seven patients (31.8%) received non-oral feeding support at some point during the study and are summarised in Table 30. Of these, four patients had intermittent or transient feeding support during the study and were not receiving non-oral feeding support at the end of the study. **A total of 19 of 22 patients (86.3%) were feeding without mechanical support at the end of the study (or early termination).** Two patients had gastrostomy-tube placement ([redacted] and [redacted]) and were receiving feeding support at the end of the study or withdrawal from the study. One patient discontinued prematurely from the study ([redacted], death) and feeding support was ongoing at the time of withdrawal.

Table 30: Summary of feeding support in STR1VE-US (Safety population)

Patient number	Feeding support	Ongoing at end of study	Number of days of feeding support (not ongoing)
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]

Patient number	Feeding support	Ongoing at end of study	Number of days of feeding support (not ongoing)
	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]

Abbreviations: NA, not applicable; ND, nasoduodenal; NG, nasogastric; NJ, nasojejunal.
† Patient [redacted] discontinued from the study due to a fatal adverse event of respiratory arrest on Study Day 171 at the age of 7.8 months.

6.3.1.3.7 Ability to thrive

The ability to thrive at 18 months of age was a co-secondary endpoint defined as the ability to tolerate thin liquids, does not receive nutrition through mechanical support, and maintains weight consistent with age. The results of the analysis show that nine of 22 patients (40.9%) met the ability to thrive criteria at 18 months of age (Table 31). Of note, 12 of 22 patients (54.5%) could swallow effectively (tolerate thin or very thin liquids) at the age of 18 months. The seven other patients who had formal swallow tests at 18 months of age had normal or functional swallow, but for consistencies other than thin or very thin liquids at or after 18 months of age (Patients [redacted]). Thus, these seven patients are not included in the total number of patients who could tolerate thin liquids at 18 months of age. Fourteen of 22 patients (63.6%) were maintaining weight consistent with age at 18 months of age. Patients who did not receive nutrition through mechanical support (e.g., feeding tube) or other non-oral method were considered to be not requiring feeding through mechanical support. Nineteen of 22 patients (86.4%) did not require nutrition through mechanical support.

Table 31: Proportion of patients with the ability to thrive at 18 months of age in STR1VE-US (ITT population)

Subitems comprising the ability to thrive at 18 months of age	N = 22
Ability to tolerate thin liquids, n (%)	12 (54.5)
Does not receive nutrition through mechanical support, n (%)	19 (86.4)
Maintains weight consistent with age, n (%)	14 (63.6)
Maintain ability to thrive at 18 months of age	
n (%)	9 (40.9)
97.5% confidence interval†	18.6, 66.4
p-value†	<0.0001

† p-value and 97.5% confidence interval are from a one-sided exact binomial test.

6.3.1.4 STR1VE-EU

The results of the efficacy analysis of onasemnogene abeparvovec in STR1VE-EU are presented for the ITT and safety population. Analyses were carried out in the following populations:

- Intent-to-treat (ITT) population: patients with bi-allelic deletion mutations of *SMN1* (exon 7/8 common homozygous deletions) and two copies of *SMN2* without the known gene modifier mutation (c.859G>C) who receive an IV infusion of onasemnogene abeparvovec at less than 180 days of age. All primary and secondary efficacy analyses and subgroup analyses will be conducted on the ITT population
- Ability to thrive ITT population: symptomatic patients with bi-allelic deletion mutations of *SMN1*, two copies of *SMN2* without the genetic modifier (c.859G>C), intact swallowing and receiving no enteral (mechanical) nutrition at baseline, who receive an IV infusion of onasemnogene abeparvovec and have at least one post-baseline efficacy evaluation. This population will be utilised to calculate the proportion of patients with the ability to thrive
- Efficacy completers population:
    - All treated patients who reach 14 months of age, OR
    - All treated patients who meet discontinuation criteria, discontinue the trial due to an AE or death
- All enrolled population: all patients who receive an IV infusion of onasemnogene abeparvovec. Analyses of endpoints in this population are considered descriptive
- Safety population: all patients who receive an IV infusion of onasemnogene abeparvovec. All safety analyses will be conducted on the safety analysis population

6.3.1.4.1 Survival and permanent ventilation

At the time of 31 December data cut (13), enrolment for STR1VE-EU was complete with a total of 33 patients receiving onasemnogene abeparvovec. The study was ongoing and the median duration of follow-up at last visit was 11.9 months (range: 1.8–15.4); the median age of patients at last visit was 15.4 months (range: 6.9–18.6). One patient (3.0[redacted]was dosed at the age of 181 days and was therefore not included for the ITT population.

[redacted]

[redacted]

Figure 16: Event-free survival in STR1VE-EU (31 December 2019 data cut) (Safety population)

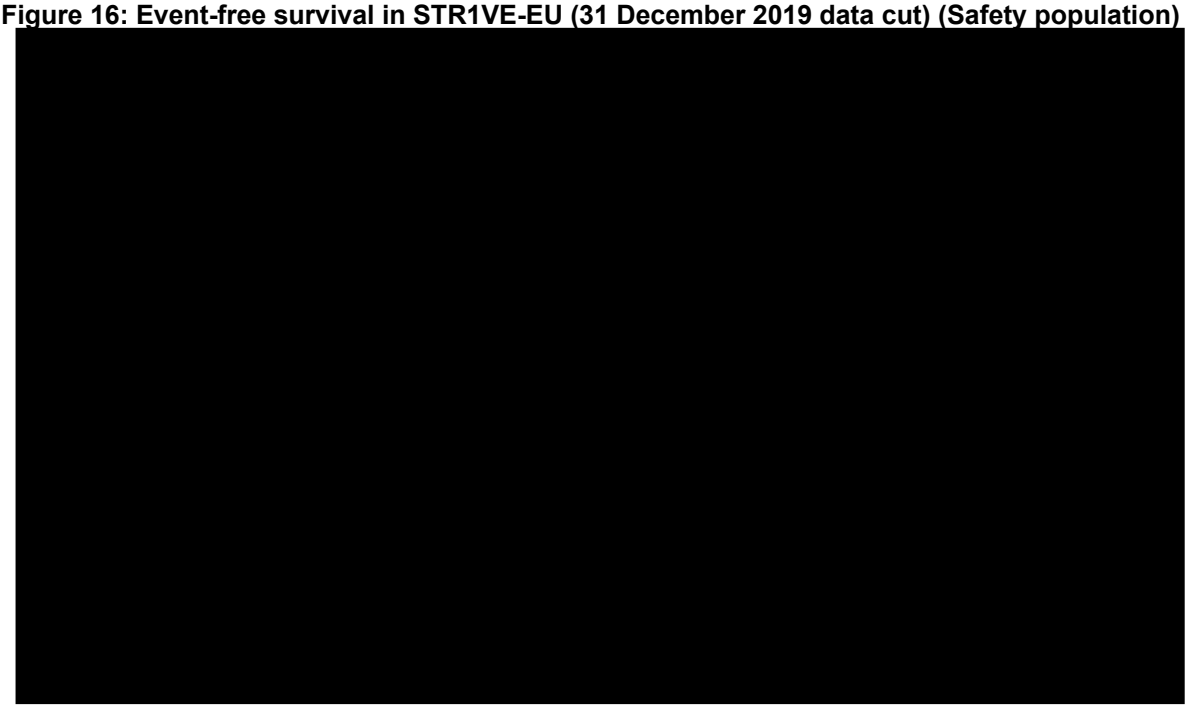


Figure 17: Kaplan-Meier plot for event-free survival in in STR1VE-EU (31 December 2019 data cut) (Safety population)

Natural history: The PNCR and NeuroNext profiles presented are the AveXis datasets used to provide an external control comparator (5).

6.3.1.4.2 Motor milestones based on video review

The video-confirmed developmental milestones achieved in STR1VE-EU are summarised in Table 32. At their last visit prior to the 31 December 2019 data cut, patients in STR1VE-EU were between 6.9 and 18.6 months of age. Thirty-one of the 32 patients (96.9%) in the ITT population were above 9.2 months of age, which is the 99th percentile of the achievement of sitting without support (28).

[redacted]

[redacted]

[12] Bayley Scales gross motor subtest Item #4: Child holds head erect for at least 3 seconds without support

[13] Bayley Scales gross motor subtest Item #20: Child turns from back to both right and left sides.

[14] Bayley Scales Gross Motor subset item #26: Child sits alone without support for ≥30 seconds.

[15] WHO definition: Child sits up straight with head erect for ≥10 seconds; child does not use hands or arms to balance body or support position

[16] Bayley Scales gross motor subtest Item #33: Supports weight. Child supports his or her own weight for at least 2 seconds, using your hands for balance only.

[17] WHO MGRS definition: Child stands in upright position on both feet, holding onto a stable object (e.g., furniture) with both hands without leaning on it. The body does not touch the stable object, and the legs support most of the body weight. Child thus stands with assistance for at least 10 seconds

[18] WHO MGRS definition: Child alternately moves forward or backward on hands and knees. The stomach does not touch the supporting surface. There are continuous and consecutive movements, at least 3 in a row.

[19] Bayley Scales gross motor subtest Item #34: Child makes forward progress of at least 5 feet by crawling on hands and knees.

[20] Bayley Scales gross motor subtest item #37: Child walks by making coordinated, alternated stepping movements.

Table 32: Video confirmed developmental milestones in STR1VE-EU (31 December 2019 data cut) (ITT population)

Milestone achieved	n (N=32)
Holds head erect for ≥3 seconds without support†	[redacted]
Turns from back to both right and left sides‡	[redacted]
Sits alone without support for ≥30 seconds§	[redacted]
Sits independently for ≥10 seconds¶	[redacted]
Crawls at least 5 feet††	[redacted]
Crawls at least 3 movements‡‡	[redacted]
Stands with assistance – supports weight for at least 2 seconds§§	[redacted]
Stands with assistance – holding stable object¶¶	[redacted]
Walks with assistance†††	[redacted]
Follow-up	
Median (range) duration of follow-up at last visit, months	11.9 (1.8–15.4)
Median (range) age at last visit, months	15.4 (6.9–18.6)

† Bayley Scales gross motor subtest Item #4: Child holds head erect for at least 3 seconds without support. ‡ Bayley Scales gross motor subtest Item #20: Child turns from back to both right and left sides. § Bayley Scales gross motor subtest Item #26: Child sits alone without support for at least 30 seconds. ¶ WHO MGRS definition: Child sits up straight with head erect for at least 10 seconds. Child does not use arms or hands to balance body or support position. †† Bayley Scales gross motor subtest Item #34: Child makes forward progress of at least 5 feet by crawling on hands and knees. ‡‡ WHO MGRS definition: Child alternately moves forward or backward on hands and knees. The stomach does not touch the supporting surface. There are continuous and consecutive movements, at least 3 in a row. §§ Bayley Scales gross motor subtest Item #33: Supports weight. Child supports his or her own weight for at least 2 seconds, using your hands for balance only. ¶¶ WHO MGRS definition: Child stands in upright position on both feet, holding onto a stable object (e.g., furniture) with both hands without leaning on it. The body does not touch the stable object, and the legs support most of the body weight. Child thus stands with assistance for at least 10 seconds. ††† Bayley Scales gross motor subtest item #37: Child walks by making coordinated, alternated stepping movements.
Note: Patient [redacted] was dosed at 181 days of age and is not included in the ITT population; this patient had not achieved any motor milestones as of the 31 December 2019 data-cut.

6.3.1.4.3 The Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders

As of the 31 December 2019 data cut, 29/32 patients (90.6%) had at least 3 months of CHOP-INTEND data post onasemnogene abeparvovec administration. Figure 18 illustrates CHOP-INTEND scores overtime of infants in STR1VE-EU by age (and not by the amount of time after the administration of onasemnogene abeparvovec).

[redacted]

Figure 18: CHOP-INTEND response in STR1VE-EU (31 December 2019 data cut) (ITT population)

6.3.1.4.4 Bayley Scales

The gross and fine motor subsets of the Bayley Scales were administered at baseline and then monthly beginning with Visit 6 in STR1VE-EU. Thirty patients (93.8%) had ≥3 months of Bayley Scales data (range of 1 to 15 months of data) at the most recent data cut. Improvement in performance was observed in both the Bayley Scales gross motor and fine motor subsets raw scores (Figure 19 and Figure 20[redacted] Infants with symptomatic SMA type 1 have a lower independent functional ability for their age when they enrol; thus, sufficient follow-up time is required before treated patients can be expected to achieve the motor milestones as captured in the gross motor subset.

Figure 19: Bayley Scales fine motor subtest raw scores in STR1VE-EU (31 December 2019 data cut) (ITT population)

[redacted]

Figure 20: Bayley Scales gross motor subset raw scores in STR1VE-EU (31 December 2019 data cut) (ITT population)

6.3.1.4.5 Non-invasive and invasive ventilatory support and feeding support

Individual patient feeding support data for infants in STR1VE-EU are summarised in Table 33.

Table 33: Summary of feeding support during study STR1VE-EU 31 December 2019 data cut) (safety population)

Patient number	Feeding support	Feeding support started before onasemnogene abeparvovec administration (study day)	Number of days of feeding support (ongoing at data cut)
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: NA, not applicable; NR, not reported; NG, nasogastric; PEG, percutaneous endoscopic gastrostomy.
† Patient [redacted] received feeding support for 106 days prior to onasemnogene abeparvovec administration (study day -109 to -3).

[redacted] patients in STR1VE-EU required permanent ventilatory support as of the most recent data cut. A total of [redacted] of 33 patients [redacted] required non-invasive ventilatory support during the study; eight of these patients required the support at baseline. After administration of onasemnogene abeparvovec, [redacted] patients [redacted] required BiPAP support. BiPAP support was given prophylactically to [redacted] patients, for rhinovirus infection in [redacted], and due to progression of SMA without acute cause in [redacted]. [redacted] developed respiratory distress and hypoxic-ischaemic encephalopathy and died (see Section 6.4.2.5). This patient was intubated on Study Day 17 until the time of death on Study Day 53.

6.3.1.5 SPR1NT

SPR1NT is an ongoing study in infants with genetically diagnosed and pre-symptomatic SMA; efficacy results obtained to date are presented separately for Cohort 1 (infants with two copies of *SMN2* that meet the ITT criteria) and Cohort 2 (infants with three copies of *SMN2* that meet the ITT criteria). In order to be eligible for enrolment in SPR1NT, infants were required to have genetically determined SMA defined by bi-allelic deletion of *SMN1* with two or three copies of *SMN2,* be asymptomatic, ≤6 weeks of age at the time of gene replacement therapy, able to swallow thin liquids, and free from ventilatory support. Enrolment for SPR1NT was completed on 8 November 2019; a total of 30 patients enrolled in the study. Fourteen patients with two *SMN2* copies were enrolled in Cohort 1 and 15 patients with three *SMN2* copies were enrolled in Cohort 2. Pre-symptomatic patients with four copies of *SMN2* were included in the original SPR1NT protocol but later removed as per protocol amendment dated 27 September 2018 (36); one patient [redacted]) with four copies of *SMN2* originally included in SPR1NT was excluded due to the protocol amendment. This patient is neither accounted as a participant of Cohort 2 nor part of the ITT population, but this patient remains in the Safety Population.

The efficacy analyses of onasemnogene abeparvovec in SPR1NT are presented for the ITT and safety populations. Analyses were carried out in the following populations:

- Intent-to-treat population (ITT): all enrolled patients with bi-allelic *SMN1* deletions and two or three copies of *SMN2* without the *SMN2* gene modifier mutation (c.859G>C) who receive onasemnogene abeparvovec.
- Efficacy Completers Population: a subset of the ITT population consisting of all patients who are given an onasemnogene abeparvovec injection and who complete an end of study visit relevant for their assigned cohort (based upon *SMN2* copy number). Patients who terminate early due to other reasons will not be included in the efficacy completers population
- All enrolled population: all patients enrolled who receive onasemnogene abeparvovec. Unless specified otherwise, this set will be used for patient listings and for summaries of patient disposition
- Safety population: all patients who are given an onasemnogene abeparvovec injection. The safety population will be used for all analyses of safety endpoints and for the presentation of patients in all patient listings

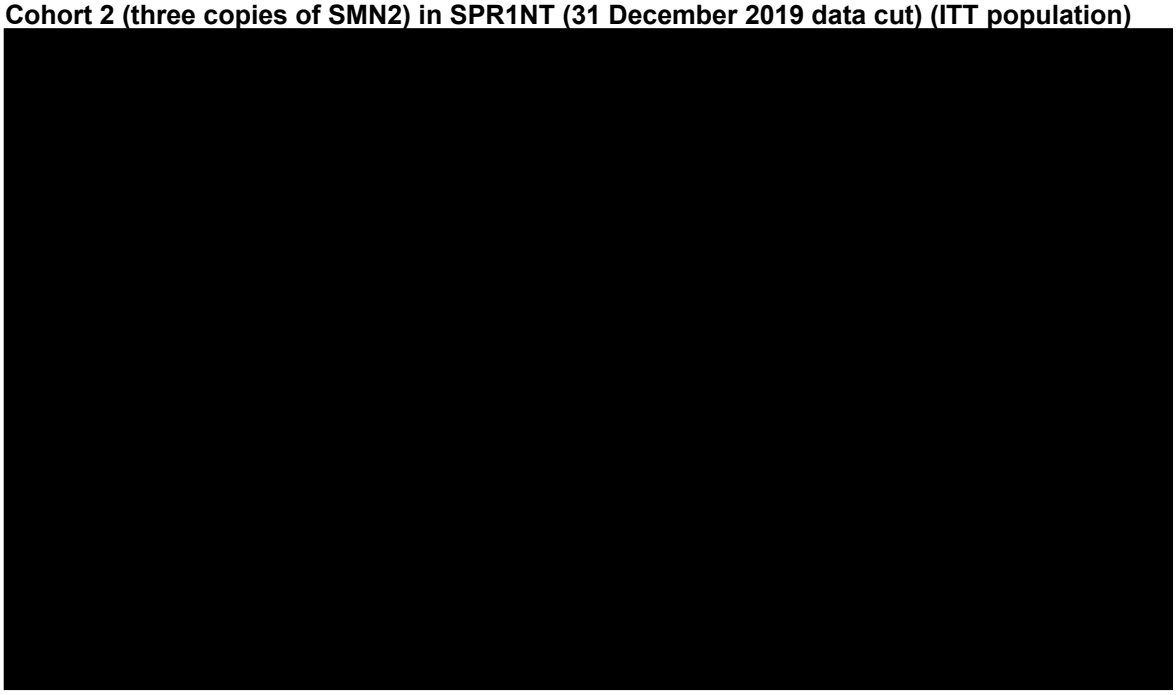
6.3.1.5.1 Survival and permanent ventilation

All patients in SPR1NT were alive and free of permanent ventilation as of their last study visit prior to the 31 Dec 2019 data cut (Figure 21–Figure 23). For patients in Cohort 1 (2 x *SMN2*), the median duration of follow-up at last visit was 9.9 months (range: 5.1–18.0), and the median age of patients at last visit was 10.5 months (range: 6.0–18.6). For patients in Cohort 2 (3 x *SMN2*), the median duration of follow-up at last visit was 9.0 months (range: 2.0–13.9), and the median age of patients at last visit was 9.6 months (range: 3.3–15.1).

Figure 21: Event-free survival in Cohort 1 (two copies of *SMN2*) in SPR1NT (31 December 2019 data cut) (ITT population)

Figure 22: Event free survival in Cohort 2 (three copies of *SMN2*) in SPR1NT (31 December 2019 data cut) (ITT population)

Figure 23: Kaplan-Meier plot for event free survival in Cohort 1 (two copies of *SMN2*) and Cohort 2 (three copies of SMN2) in SPR1NT (31 December 2019 data cut) (ITT population)

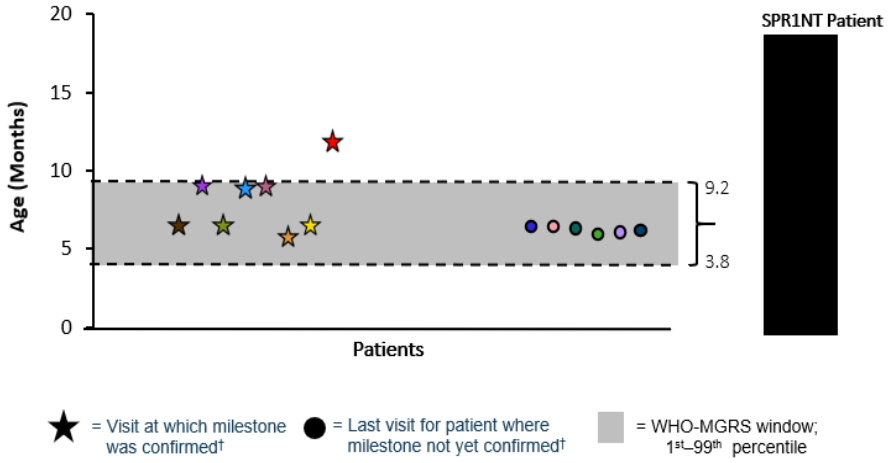


Natural history: The PNCR and NeuroNext profiles presented are the AveXis datasets used to provide an external control comparator (5).

6.3.1.5.2 Video confirmed motor milestones

The video-confirmed motor milestones of infants in Cohort 1 of SPR1NT are summarised in Table 34. The primary efficacy endpoint for patients in Cohort 1 is the proportion of patients achieving sitting for ≥30 seconds[21] at any visit up to 18 months of age. The WHO Multicentre Growth Reference Study established that sitting without support in healthy children develops between 3.8 and 9.2 months of age (1st–99th percentiles) (28). As of their last visit before the 31 December 2019 data cut, 8 (of 14) patients in Cohort 1 achieved the video-confirmed primary efficacy endpoint of sitting without support for ≥30 seconds (achieved between 5.7 and 11.8 months of age); seven patients achieved this milestone within the expected WHO age range of <9.2 months (Figure 24 and Table 34). Seven of these eight patients (all except [redacted]) also achieved sitting without support according to the WHO Multicentre Growth Reference Study definition[22]. The six patients in Cohort 1 who could not sit at the data cut were all younger than 9.2 months of age; further follow-up time is required to assess if the milestone of sitting without support is reached within an age appropriate window. All Cohort 1 patients older than 9.2 months of age are sitting without support as confirmed by video assessment.

Figure 24: Achievement of the primary endpoint of sitting without support for ≥30 seconds in Cohort 1 (two copies of *SMN2*) in SPR1NT (31 December 2019 data cut)



† Milestone achievement assessed at the time of study visit. Visits occur every 3 months.
WHO-MGRS: World Health Organization Multicentre Growth Reference Study Group (28).

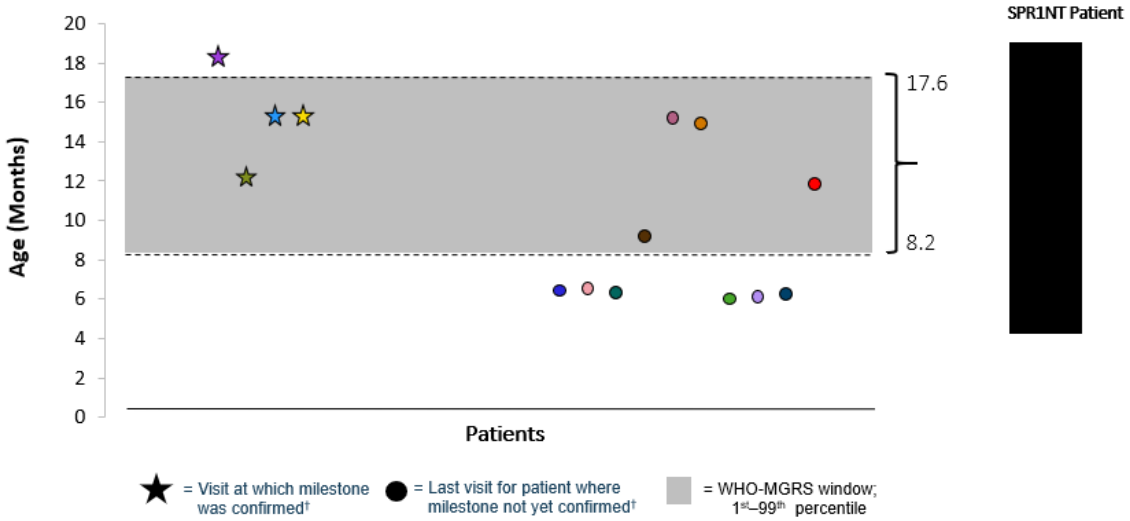
Cohort 1 patients achieved the additional video-confirmed Bayley Scales gross motor milestones of standing alone and walking alone. Standing alone typically develops between 6.9 and 16.9 months of age (1st–99th percentiles) and walking alone develops between 8.2 and 17.6 months of age(1st–99th percentiles). Twelve (12/14; 85.7%) patients were younger than 16.9 months and 12 patients were younger than 17.6 months as of their last visit prior to the 31 December 2019 data cut. [redacted] Cohort 1 patients achieved the milestone of standing alone, and four also achieved the milestone of walks alone according to WHO

[21] Bayley Scales Gross Motor subset item #26: Child sits alone without support for ≥30 seconds.

[22] WHO definition: child sits up straight with head erect for ≥10 seconds; child does not use hands or arms to balance body or support position

Multicentre Growth Reference Study definitions (Figure 25). The remaining Cohort 1 patients would not be expected to stand alone or walk alone as they have not yet passed through the typical windows of achievement to develop these milestones (28).

Figure 25: Achievement of walking independently (WHO definition) in Cohort 1 (two copies of *SMN2*) in SPR1NT (31 December 2019 data cut)



† Milestone achievement assessed at the time of study visit. Visits occur every 3 months.
WHO-MGRS: World Health Organization Multicentre Growth Reference Study Group (28).

[redacted] patients in Cohort 1 stood alone for ≥3 seconds according to the Bayley Scales definition at [redacted] of age, prior to the close of the normal developmental window for standing alone at 16.9 months. [redacted] Cohort 1 patients walked alone according to the Bayley Scales definition at [redacted] of age, prior to the close of the normal developmental window for walking alone at 17.6 months. [redacted] achieved both standing alone and walking alone at [redacted] months of age, outside the typical developmental window for both milestones.

Table 34: Video confirmed developmental milestones (ITT population) in Cohort 1 (two copies of *SMN2*) in SPR1NT (31 December 2019 data cut)

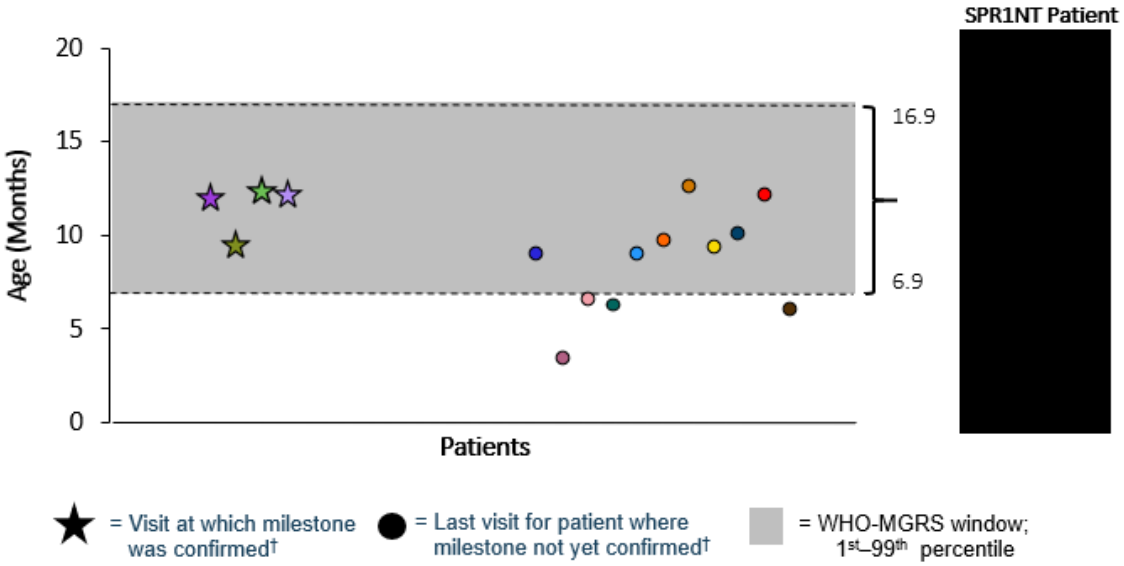
Milestone achieved		n (%) (N=14)
Holds head erect for ≥3 seconds without support†		[redacted]
Turns from back to both right and left sides‡		[redacted]
Sits alone without support for ≥30 seconds§		8 (57.1)
Sits alone without support for ≥10 seconds¶		[redacted]
Crawls at least 5 feet††		[redacted]
Crawls at least 3 movements‡‡		[redacted]
Stands with assistance	Supports own weight for ≥2 seconds§§	[redacted]
	Stands holding a stable object¶¶	[redacted]
Pulls to stand†††		[redacted]
Stands alone	≥3 seconds ‡‡‡	[redacted]
	≥10 seconds§§§	[redacted]
Walks with assistance	Bayley Scales¶¶¶	[redacted]
	WHO MGRS††††	[redacted]
Walks alone	Bayley Scales‡‡‡‡	[redacted]
	WHO MGRS§§§§	4 (28.6)
Follow-up		
Median (range) duration of follow-up at last visit, months		[redacted]
Median (range) age at last visit, months		[redacted]

† Bayley Scales gross motor subtest item #4: Child holds head erect for ≥3 seconds without support. ‡ Bayley Scales gross motor subtest item #20: Child turns from back to both right and left sides. § Bayley Scales Gross Motor subset item #26: Child sits alone without support for ≥30 seconds. ¶ WHO definition: child sits up straight with head erect for ≥10 seconds; child does not use hands or arms to balance body or support position. †† Bayley Scales gross motor subtest item #34: Child makes forward progress of at least 5 feet by crawling on hands and knees. ‡‡ WHO definition: Child alternately moves forward or backward on hands and knees. The stomach does not touch the supporting surface. There are continuous and consecutive movements, at least 3 in a row. §§ Bayley Scales gross motor subtest Item #33: Supports weight. Child supports his or her own weight for ≥2 seconds, using your hands for balance only. ¶¶ WHO definition: Child stands in upright position on both feet, holding onto a stable object (e.g. furniture) with both hands without leaning on it. The body does not touch the stable object, and the legs support most of the body weight. Child thus stands with assistance for ≥10 seconds. ††† Bayley Scales gross motor subtest item #35: Child raises self to standing position using chair or other convenient object for support. ‡‡‡ Bayley Scales gross motor subtest item #40: Child stands alone for at least 3 seconds after you release his or her hands. §§§ WHO MGRS definition: Standing alone. Child stands in upright position on both feet (not on the toes) with the back straight. The legs support 100% of the child's weight. There is no contact with a person or object. Child stands alone for at least 10 seconds. ¶¶¶ Bayley Scales gross motor subtest item #37: Child walks by making coordinated, alternated stepping movements. †††† WHO MGRS definition: Walking with assistance Child is in upright position with the back straight. Child makes sideways or forward steps by holding onto a stable object (e.g. furniture) with 1 or both hands. One leg moves forward while the other supports part of the body weight. Child takes at least 5 steps in this manner. ‡‡‡‡ Bayley Scales gross motor subtest item #43: Child takes at least 5 steps independently, displaying coordination and balance. §§§§ WHO MGRS definition: Walking alone Child takes at least 5 steps independently in upright position with the back straight. One leg moves forward while the other supports most of the body weight. There is no contact with a person or object.

The video-confirmed motor milestones of infants in Cohort 2 of SPR1NT are summarised in Table 35. As of their last visit, four (of 15) 3-copy *SMN2* patients in the ITT population achieved the video-confirmed primary efficacy endpoint of standing without support[23] (Figure 26). [redacted] of these four patients also achieved standing alone according to the WHO Multicentre Growth Reference Study definition[24]. Additionally, [redacted] of the 3-copy *SMN2* patients in the ITT population achieved the video-confirmed secondary efficacy endpoint of walking alone assessed using the Bayley Scale definition[25]. These patients also achieved walking alone according to the WHO Multicentred Growth Reference Study definition at the same visits and ages (Figure 27). One additional patient ([redacted]) also achieved walking alone according to the WHO Mulitcentre Growth Reference Study definition at 12.4 months of age at the Age 12 Months visit.

At the time of their last visit, all (100%) of the 3-copy patients were less than 16.9 months of age, the 99th percentile for development of standing alone. In addition, all (100%) of the 3-copy patients were less than 17.6 months of age, the 99th percentile for development of walking alone (28).

Figure 26: Achievement of the primary endpoint of standing without support in Cohort 2 (three copies of *SMN2*) in SPR1NT (31 December 2019 data cut)



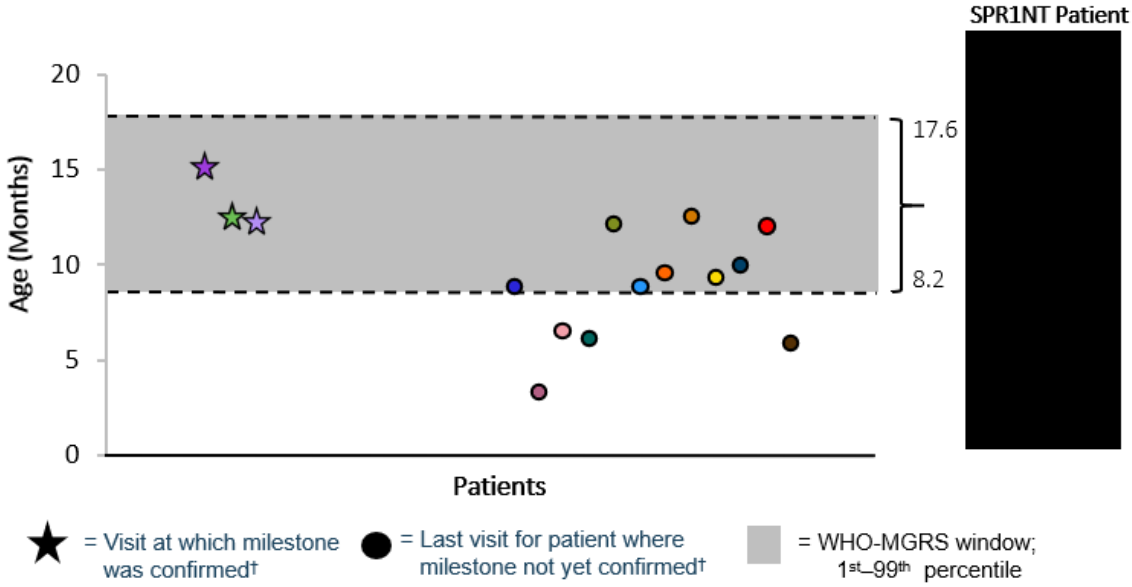
† Milestone achievement assessed at the time of study visit. Visits occur every 3 months.
WHO-MGRS: World Health Organization Multicentre Growth Reference Study Group (28).

[23] Bayley Scales gross motor subtest item #40: Child stands alone for at least 3 seconds after you release his or her hands.

[24] WHO MGRS definition: Standing alone. Child stands in upright position on both feet (not on the toes) with the back straight. The legs support 100% of the child's weight. There is no contact with a person or object. Child stands alone for at least 10 seconds.

[25] Bayley Scales gross motor subtest item #43: Child takes at least 5 steps independently, displaying coordination and balance.

Figure 27: Achievement of walking independently (WHO definition) in Cohort 2 (three copies of *SMN2*) in SPR1NT (31 December 2019 data cut)



† Milestone achievement assessed at the time of study visit. Visits occur every 3 months.
WHO-MGRS: World Health Organization Multicentre Growth Reference Study Group (28).

[redacted] patients with three copies of *SMN2* were video-confirmed to have achieved sits without support for ≥30 seconds. [redacted] achieved sitting without support prior to 9.2 months of age, the 99th percentile for development of this motor milestone. The other [redacted] patients achieved sitting without support between the age of 9.3 and 12.0 months. Of the remaining [redacted] infants in Cohort 2 who have yet to sit without support, four are younger than 9.2 months of age and one is older than 9.2 months of age. A total of [redacted] patients with three copies of *SMN2* achieved sitting without support for ≥10 seconds according to the WHO Multicentre Growth Reference Study definition.

Table 35: Video confirmed developmental milestones (ITT population) in Cohort 2 (three copies of *SMN2*) in SPR1NT (31 December 2019 data cut)

Milestone achieved		n (%) (N=15)
Holds head erect for ≥3 seconds without support†		[redacted]
Turns from back to both right and left sides‡		[redacted]
Sits alone without support for ≥30 seconds§		[redacted]
Sits alone without support for ≥10 seconds¶		[redacted]
Crawls at least 5 feet††		[redacted]
Crawls at least 3 movements‡‡		[redacted]
Stands with assistance	Supports own weight for ≥2 seconds§§	[redacted]
	Stands holding a stable object¶¶	[redacted]
Pulls to stand†††		[redacted]
Stands alone	≥3 seconds‡‡‡	4 (26.7)
	≥10 seconds§§§	[redacted]
Walks with assistance	Bayley Scale¶¶¶	[redacted]
	WHO MGRS††††	[redacted]
Walks alone	Bayley Scale‡‡‡‡	[redacted]
	WHO MGRS§§§§	3 (20.0)
Follow-up		
Median (range) duration of follow-up at last visit, months		[redacted]
Median (range) age at last visit, months		[redacted]

† Bayley Scales gross motor subtest item #4: Child holds head erect for ≥3 seconds without support. ‡ Bayley Scales gross motor subtest item #20: Child turns from back to both right and left sides. § Bayley Scales Gross Motor subset item #26: Child sits alone without support for ≥30 seconds. ¶ WHO definition: child sits up straight with head erect for ≥10 seconds; child does not use hands or arms to balance body or support position. †† Bayley Scales gross motor subtest item #34: Child makes forward progress of at least 5 feet by crawling on hands and knees. ‡‡ WHO definition: Child alternately moves forward or backward on hands and knees. The stomach does not touch the supporting surface. There are continuous and consecutive movements, at least 3 in a row. §§ Bayley Scales gross motor subtest Item #33: Supports weight. Child supports his or her own weight for ≥2 seconds, using your hands for balance only. ¶¶ WHO definition: Child stands in upright position on both feet, holding onto a stable object (e.g. furniture) with both hands without leaning on it. The body does not touch the stable object, and the legs support most of the body weight. Child thus stands with assistance for ≥10 seconds. ††† Bayley Scales gross motor subtest item #35: Child raises self to standing position using chair or other convenient object for support. ‡‡‡ Bayley Scales gross motor subtest item #40: Child stands alone for at least 3 seconds after you release his or her hands. §§§ WHO MGRS definition: Standing alone. Child stands in upright position on both feet (not on the toes) with the back straight. The legs support 100% of the child's weight. There is no contact with a person or object. Child stands alone for at least 10 seconds. ¶¶¶ Bayley Scales gross motor subtest item #37: Child walks by making coordinated, alternated stepping movements. †††† WHO MGRS definition: Walking with assistance Child is in upright position with the back straight. Child makes sideways or forward steps by holding onto a stable object (e.g. furniture) with 1 or both hands. One leg moves forward while the other supports part of the body weight. Child takes at least 5 steps in this manner. ‡‡‡‡ Bayley Scales gross motor subtest item #43: Child takes at least 5 steps independently, displaying coordination and balance. §§§§ WHO MGRS definition: Walking alone Child takes at least 5 steps independently in upright position with the back straight. One leg moves forward while the other supports most of the body weight. There is no contact with a person or object.

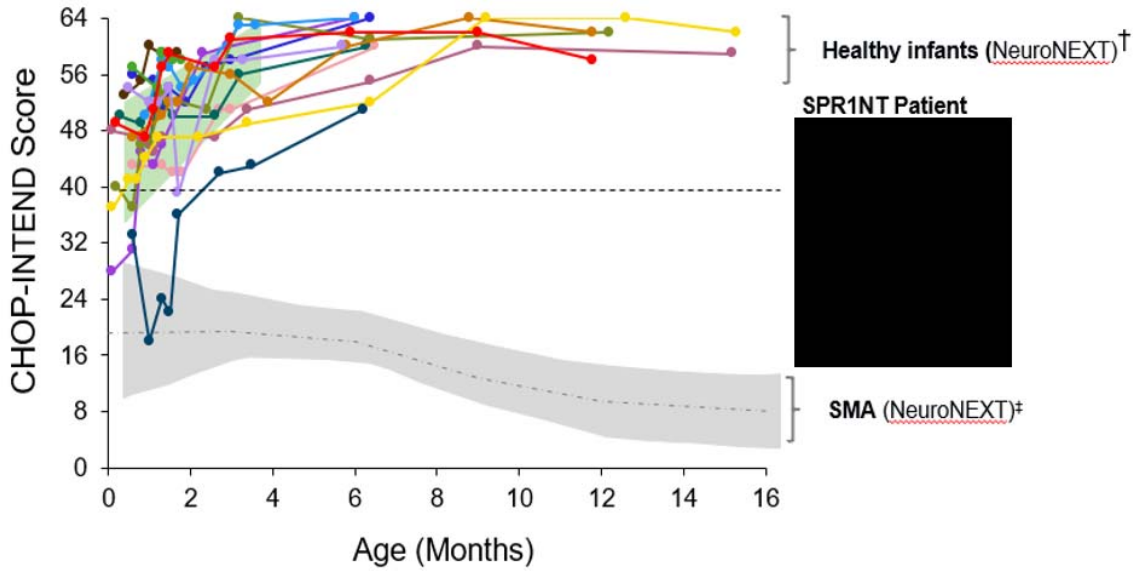
6.3.1.5.3 The Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders

As per the protocol, CHOP-INTEND data was only assessed in Cohort 1 individuals with 2 copies of *SMN2*. The mean (SD) baseline CHOP-INTEND score was 46.1 (8.77). The mean (SD) increases (improvement) from baseline to Month 1 (n=14), Month 3 (n=9), and Month 6 (n=7) after dosing were 3.9 (8.28), 12.1 (9.87), and 16.3 (10.06) points, respectively. Figure 28 illustrates CHOP-INTEND scores overtime by age juxtaposed with the results of healthy controls.

All 14 patients in the 2 *SMN2*-copy cohort (100%) achieved a CHOP-INTEND score ≥50 by 6 months of age, and 13 patients (92.9%) achieved a CHOP-INTEND score ≥58 by 9 months of age. Twelve (12) patients (85.7%) have achieved CHOP-INTEND scores ≥60 as of the 31 December 2019 data cut. Nine patients (64.3%) achieved three consecutive CHOP-INTEND scores ≥58, and these patients will not undergo additional CHOP-INTEND examinations as per protocol. One of these nine patients, [redacted], achieved this with scores of 59, 58, and 58, and therefore will not have a further opportunity to demonstrate a CHOP-INTEND score ≥60.

These CHOP-INTEND scores are remarkable, in that patients with SMA type 1 receiving BSC in historical controls from the NeuroNext study never improved, and never achieved CHOP-INTEND scores ≥40 at any point during the first 24 months of life (4).

Figure 28: CHOP-INTEND response in Cohort 1 (two copies of *SMN2*) in SPR1NT (31 December 2019) (ITT population) and juxtaposed healthy infants



† The NeuroNext CHOP-INTEND score estimate for healthy infants is a model-based estimate of motor function in healthy infants. The green shaded area denotes the 95% CI around the estimate (42).
‡ The NeuroNext SMA data are model-based estimates of an SMA cohort excluding *SMN2* >2. The grey shaded area denotes the 95% CI around the estimate.
Dotted line at CHOP-INTEND score of 40: A score ≥40 is beyond that reported in the literature for maximum transiently achieved function amongst symptomatic patients with SMA type 1 beyond 6 months of age (1).

6.3.1.5.4 Bayley Scales

The gross and fine motor subtests of the Bayley Scales were administered at baseline, 1 month after receiving onasemnogene abeparvovec, and every 3 months beginning at 3 months of age in SPR1NT. Results of the fine and gross motor subtests raw scores for the 14 infants with two copies of *SMN2* enrolled in Cohort 1 of SPR1NT are illustrated by patient in Figure 29 and Figure 30, respectively.

Ten (10) patients (71.4%) had ≥3 months of Bayley Scales data (range of 3 to 18 months of data). [redacted] In the gross motor subtest, the mean (SD) raw score of 2-copy *SMN2* patients improved by 0.9 (1.94) points at Month 1 (n=14), 16.6 (4.37) points at Month 6 (n=8), 29.3 (10.84) points at Month 12 (n=4), and 33.5 (9.40) points at Month 15 (n=4) post onasemnogene abeparvovec administration.

Figure 29: Bayley Scales fine motor subtest raw score over time in Cohort 1 of SPR1NT (two copies of *SMN2*) (31 December 2019) (ITT population)

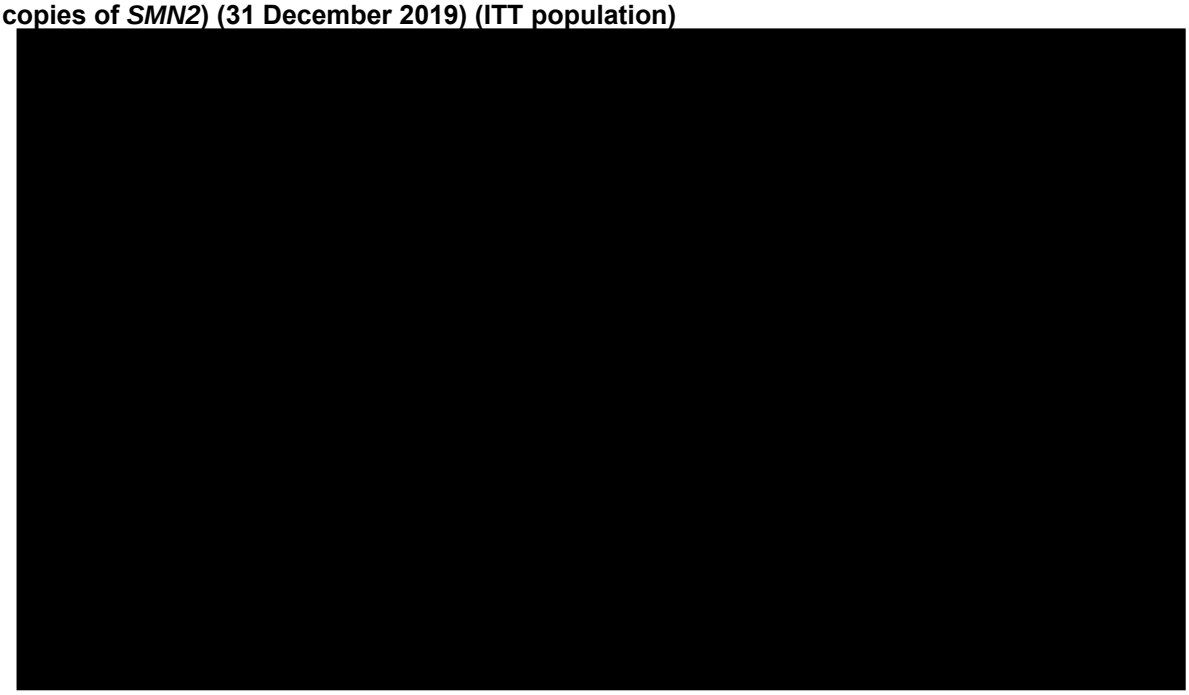
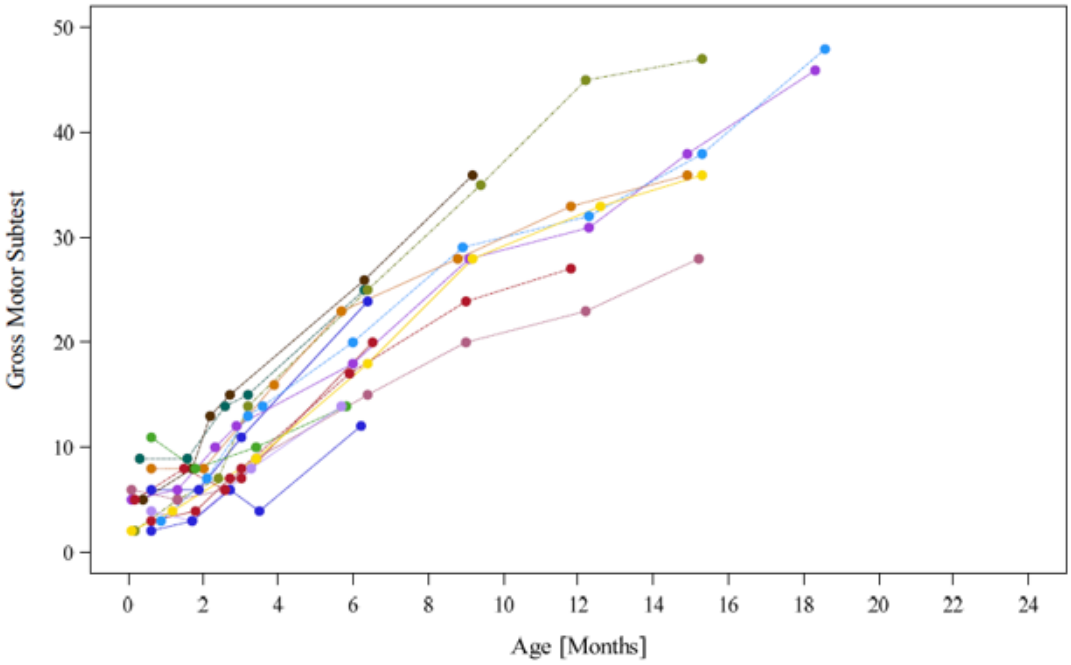


Figure 30: Bayley Scales gross motor subtest raw score over time in Cohort 1 of SPR1NT (two copies of *SMN2*) (31 December 2019) (ITT population)



[redacted]

Bayley raw scores are transformed into scaled scores using a formulated table. The scaled score reflects performance according to age as compared with healthy children of the same age. The mean score is 10, with standard deviation of ±3 points; thus, approximately 97% of children tested will fall within 2 standard deviations of the mean (scores 4–16). In the absence of treatment with onasemnogene abeparvovec, few children with SMA type 1 would ever achieve a raw score greater than zero on the gross motor subtest, and therefore they would never achieve a scaled score greater than 1 (the lowest possible scaled score) on the gross motor subtest.

In the 2-copy *SMN2* cohort in SPR1NT, seven patients (of 14; 50%) have Bayley gross motor subtest scaled scores within 2 SD of the mean for age (i.e., scaled score ≥4) at their most recent visit prior to the 31 December 2019 data cut. All (14 of 14; 100%) patients in the 2-copy *SMN2* cohort have Bayley fine motor scaled scores within 2 SD of the mean for age (i.e.. scaled score ≥4) at their most recent visit prior to the 31 December 2019 data cut. Therefore, seven of 14 (50%) infants in the 2-copy *SMN2* cohort in SPR1NT have gross motor performance similar to that of healthy peers, and 14 of 14 (100%) have fine motor performance similar to normal fine motor development as of their most recent visit prior to the data cut.

Results of the fine and gross motor subtests of the 15 patients in Cohort 2 (three copies of *SMN2*) of SPR1NT are presented by patient in Figure 31 and Figure 32, respectively. All patients (100%) had at least 2 months of Bayley Scales data (range of 1 to 14 months of data). The Month 11 visit is the last visit for which more than one observation is available.

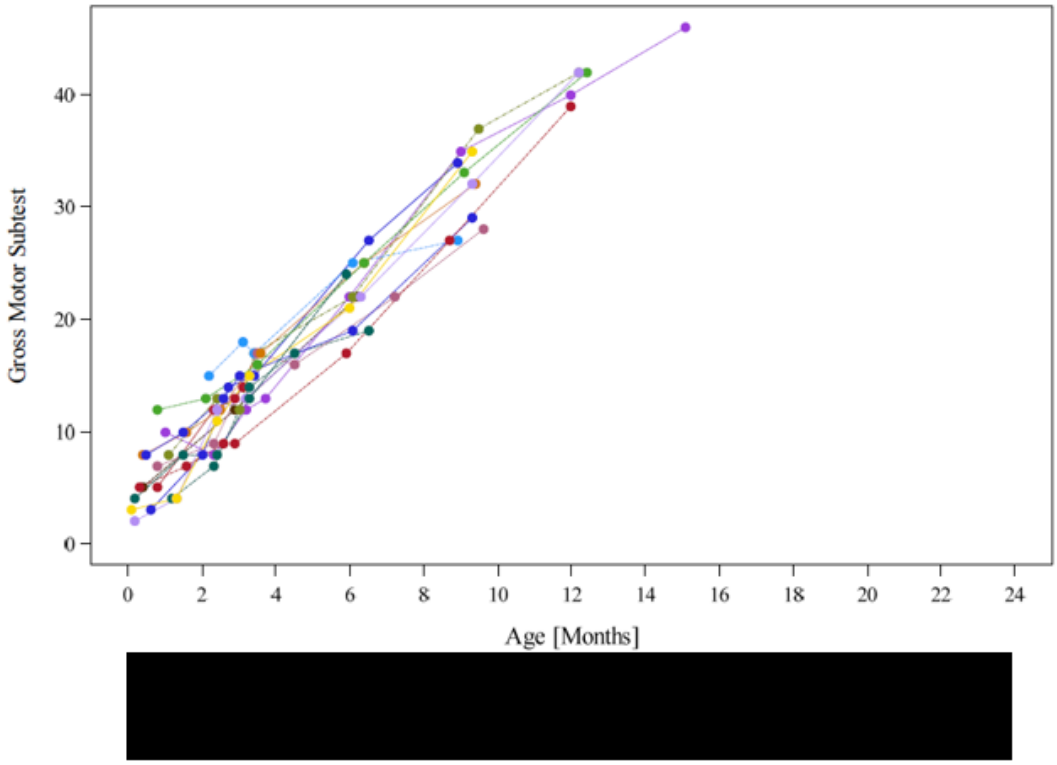
Only one patient has had Month 12 and Month 14 visits as of the 31 December 2019 data cut.

[redacted]In the gross motor subtest, 3-copy *SMN2* patients improved their mean (SD) raw score by 2.6 (2.26) points at Month 1 (n=13), 17.5 (4.42) points at Month 6 (n=6), and 32.0 (2.31) at Month 11 (n=4) post-dose.

Figure 31: Bayley Scales fine motor subtest (raw score) score over time in Cohort 2 (three copies of *SMN2*) in SPR1NT (31 December 2019) (ITT population)

[redacted]

Figure 32: Bayley Scales gross motor subtest (raw score) score over time in Cohort 2 (three copies of *SMN2*) in SPR1NT (31 December 2019) (ITT population)



In the 3-copy *SMN2* cohort, all 15 patients (of 15; 100%) have Bayley gross motor subtest scaled scores within 2 SD of the mean for age (i.e. scaled score ≥4) at their most recent visit prior to the 31 December 2019 data cut. Fourteen (14; of 15; 93.3%) patients in the 3-copy *SMN2* cohort have Bayley fine motor scaled scores within 2 SD of the mean for age (i.e. scaled score ≥4) at their most recent visit prior to the 31 December 2019 data cut.

Therefore, 15 of 15 (100%) of 3 copy *SMN2* patients have gross motor performance similar to same-age peers, and 14 of 15 (93.3%) patients have fine motor performance similar to same-age peers as of their most recent visit prior to the data cut.

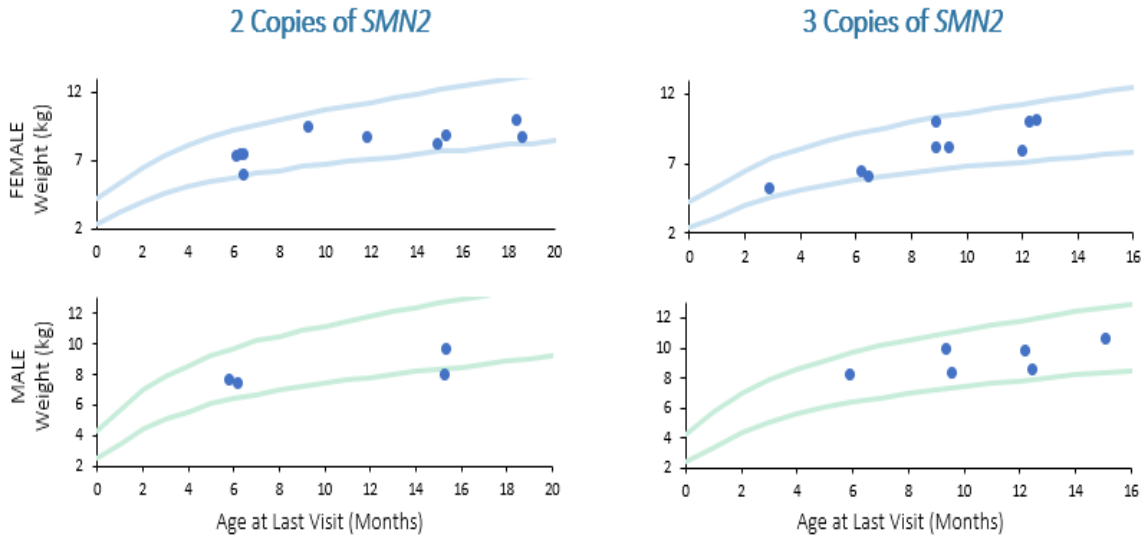
6.3.1.5.5 Non-invasive and invasive ventilatory support and normal feeding support

In order to be eligible for enrolment in SPR1NT, infants were required to be asymptomatic, able to swallow thin liquids, and free from ventilatory support. Swallowing is formally assessed at screening, and every 6 months starting at 6 months of age. At the 31 December 2019 data cut, 29 of 30 patients (96.7%) had completed at least their 6-month swallow evaluation and 14 (46.7%) had competed at least their 12-month swallow evaluation (including eight infants in Cohort 1 [2 x *SMN2*], six infants in Cohort 2 [3 x *SMN2*], and one 4 x *SMN2* copy patient).

Except for patient 304-002-001, for whom normal swallow was not noted at their 6-month swallow evaluation, all patients had normal swallow at all timepoints. No patients in the study required feeding support and most remained within the normal weight range (Figure 33).

As of the 31 December 2019 data cut, no patients in SPR1NT required ventilatory support of any kind, including no non-invasive ventilatory support, invasive ventilatory support, cough assist, or BiPAP.

Figure 33: Weight of infants treated with onasemnogene abeparvovec in SPR1NT (31 December 2019) (ITT population)



Note: The blue and green lines correspond to the 3rd through 97th percentile of weight-for-age values for female and male patients, respectively, based on child growth standards from the World Health Organization (24).

6.3.1.6 Efficacy conclusions

One-time administration of onasemnogene abeparvovec to patients with SMA type 1 with two copies of *SMN2* in the completed START and STR1VE-US studies resulted in survival rates and the achievement of developmental milestones not observed in infants with SMA type 1 in natural history studies. Improvement in motor function was further demonstrated for the therapeutic dose by the rapid (as early as 1-month post dosing) and statistically significant increases in mean CHOP-INTEND scores in both START and STR1VE-US. In addition, in both studies patients were free of nutritional and ventilatory support at the end-of-study visit and maintained the ability to thrive, in contrast to patients with SMA type 1 treated with BSC alone in natural history studies (3). The results of START and STR1VE-US support the efficacy of onasemnogene abeparvovec for a period of 2 years after dosing and at 18 months of age, respectively, across multiple endpoints, outcomes which are drastically different from the motor and bulbar decline and death associated with the natural history of SMA (3, 4, 30).

The durability of response to onasemnogene abeparvovec has been further confirmed in the long-term follow-up study LT-001. The results of LT-001 to date indicate that a one-time IV administration of onasemnogene abeparvovec at the therapeutic dose provides prolonged and durable efficacy in infants with SMA type 1 for durations longer than 5 years post gene therapy administration (up to and including 61.9 months). For those patients enrolled in LT-001 who received the therapeutic dose of onasemnogene abeparvovec in START (n=10), at the 31 December 2019 data cut (13) all patients were alive with no worsening of ventilatory or nutritional function compared with the end of START. All patients (10/10) have either maintained all previously attained milestones in START or gained new milestones (two

patients, [redacted] and [redacted] who were not receiving nusinersen treatment at any point, gained the video-confirmed milestone of stands with assistance). The maintained and new milestones achieved by patients originating from Cohort 2 of START have not previously been observed in infants with SMA type 1. The infants treated with onasemnogene abeparvovec in STR1VE-US are expected to reach additional milestones during longer follow up consistent with results from the START study.

The most recent interim results from the ongoing STR1VE-EU and SPR1NT studies continue to demonstrate the rapid and substantial clinical efficacy of onasemnogene abeparvovec across multiple endpoints, including survival, developmental motor milestones and motor function, and swallowing abilities. The data from SPR1NT also supports the use of onasemnogene abeparvovec in pre-symptomatic patients with two or three copies of *SMN2*. Patients in SPR1NT achieved higher (maximal or near maximal) CHOP-INTEND scores more quickly than patients in STR1VE-EU and STR1VE-US and do not need ventilatory or feeding support, further supporting the hypothesis that early intervention has the greatest potential to achieve maximum therapeutic benefit.

In conclusion, based on the consistent evidence of rapid and substantial efficacy across endpoints and clinical trials and the continuing high unmet medical need in the severe and life-threatening disease, onasemnogene abeparvovec significantly improves the clinical outcomes of infants with SMA type 1 and pre-symptomatic patients with up to three copies of *SMN2,* reducing infant death rates and enabling developmental achievements never seen with BSC.

6.4 *Adverse events*

6.4.1 Provide details of the identification of studies on adverse events, study selection, study methodologies, critical appraisal and results.

Adverse events (AE) are recorded throughout the onasemnogene abeparvovec clinical development programme; the identification, study details, methodologies and efficacy results of the onasemnogene abeparvovec trials are presented in Sections 6.1-0.

Safety results as of 31 December 2019 from four studies are provided in this update:

- STR1VE-US
- STR1VE-EU
- SPR1NT
- LT-001 (extension of START)

In all four studies, onasemnogene abeparvovec was administered intravenously or studied in a long-term follow-up trial (LT-001 or LT-002).

Although the results of START have already been submitted to NICE and have not changed since the original company submission, the safety results from START are also included in this submission appendix to provide a single, consolidated document that contains all onasemnogene abeparvovec clinical trial data.

6.4.2 Provide details of all important adverse events reported for each study.

6.4.2.1 Overall adverse event experience

As of the 31 December 2019 data cut, 100 patients received an IV infusion of onasemnogene abeparvovec in START, STR1VE-US, STR1VE-EU, and SPR1NT; baseline characteristics of patients treated with onasemnogene abeparvovec are reported in Section 6.1.3. Of the 97 patients who received the therapeutic dose, 96 (99%) experienced at least one treatment-emergent adverse event (TEAE) and 56 patients (58%) were reported to have a TEAE considered by the investigator to be related to onasemnogene abeparvovec (Table 36). A total of 45 patients (46%) had at least 1 SAE, and 39 patients (40%) had at least one TEAE that was Grade 3 severity or higher. At the therapeutic IV dose, the most frequently reported TEAEs considered related to onasemnogene abeparvovec across START, STR1VE-US, STR1VE-EU, and SPR1NT (≥5%) were transaminases increased (12.4%); aspartate aminotransferase increased (9.3%); and vomiting, alanine aminotransferase increased, and hypertransaminasemia (all 8.2%). Two patients (2.1%), one in STR1VE-US and one in STR1VE-EU, were discontinued due to TEAEs that resulted in death.

Table 36: Overview of TEAEs for START, STR1VE-US, STR1VE-EU and SPR1NT (31 December 2019 data cut)

TEAEs	START			STR1VE-US n (%) (N=22)	STR1VE-EU n (%) (N=33)	SPR1NT n (%) (N=30†)	All patients n (%) (N=100)	Therapeutic dose n (%) (N=97)
	Cohort 1 Low dose n (%) (N=3)	Cohort 2 Therapeutic dose n (%) (N=12)	All patients n (%) (N=15)					
Patients with ≥1 TEAE	3 (100)	12 (100)	15 (100)	22 (100)	32 (97.0)	30 (100)	99 (99.0)	96 (99.0)
TEAE ≥Grade 3 severity	3 (100)	10 (83.3)	13 (86.7)	10 (45.5)	13 (39.4)	6 (20.0)	42 (42.0)	39 (40.2)
TEAEs related to study treatment‡	1 (33.3)	3 (25.0)	4 (26.7)	12 (54.5)	24 (72.7)	17 (56.7)	57 (57.0)	56 (57.7)
Serious TEAEs	3 (100)	10 (83.3)	13 (86.7)	10 (45.5)	19 (57.6)	6 (20.0)	48 (48.0)	45 (46.4)
TEAE causing study discontinuation	0	0	0	2 (9.1)	1 (3.0)¶	0	3 (3.0)	3 (3.1)
TEAE resulting in death	0	0	0	1 (4.5)§	1 (3.0)¶	0	2 (2.0)	2 (2.1)

Abbreviations: TEAE, treatment emergent adverse event.
† The safety data reported from SPR1NT as of the 31 December 2019 data cut includes 14 patients with two copies of *SMN2*, 15 patients with three copies of *SMN2*, and one patient with 4 copies of *SMN2*.
‡ Adverse events were considered related to treatment if the event is classified as unknown, possibly, probably or definitely related to study treatment.
§ Patient [redacted] died due to respiratory arrest considered unrelated to onasemnogene abeparvovec by the Investigator.
¶ Patient [redacted] discontinued the study due to AEs of respiratory distress and hypoxic-ischaemic encephalopathy in death.
Source: 31 December 2019 Safety Update (14).

6.4.2.2 START

Of the 15 patients treated in START, all (100%) experienced at least one TEAE. Four patients (27%) had a TEAE considered by the Investigator to be related to onasemnogene abeparvovec, with 13 patients (87%) experiencing SAEs. The most frequently reported TEAEs were upper respiratory tract infection (73.3%), pyrexia (53.3%), vomiting (53.3%), constipation (46.7%), pneumonia (46.7%), gastroesophageal reflux disease (40.0%), and nasal congestion (40.0%). No event resulted in study discontinuation or death.

Four patients were reported to have TEAEs of increased liver transaminase, alanine aminotransferase, aspartate aminotransferase, liver function, or hepatic enzymes related to onasemnogene abeparvovec; two of these events in two patients were SAEs (transaminases increased). All adverse events were clinically asymptomatic and resolved during the observation period. No adverse events of cardiac toxicity or thrombocytopenia were reported. No sensory abnormalities suggestive of dorsal root ganglia cell inflammation were reported in START.

6.4.2.3 LT-001

In LT-001, only SAEs and AESIs (gene therapy-related AEs; liver function enzyme elevations; new incidences of a malignancy or hematologic disorder, and new incidences or exacerbations of pre-existing neurologic or autoimmune disorders, and sensory abnormalities suggestive of dorsal root ganglionopathy) are being collected. Onasemnogene abeparvovec was not administered in LT-001, as these patients received study drug in START. Eight of the 13 patients (61.5%) enrolled to the study experienced at least 1 TEAE (Table 37). No patients had a TEAE considered by the Investigator to be related to onasemnogene abeparvovec. No TEAE resulted in study discontinuation. No patient deaths were reported in LT-001.

No clinically significant events of cardiac toxicity or sensory abnormalities suggestive of dorsal root ganglia cell inflammation were reported.

Table 37: Overview of patients with TEAEs in LT-001 (31 December 2019 data cut)

	Cohort 1 6.7×10^{13} vg/kg n (%) (N=3)	**Cohort 2 2.0×10^{14} vg/kg n (%) (N=10)**	**All patients n (%) (N=13)**
Patients with ≥1 TEAE	1 (33.3)	7 (70.0)	8 (61.5)
TEAE ≥ Grade 3 severity	1 (33.3)	7 (70.0)	8 (61.5)
Serious TEAEs	1 (33.3)	7 (70.0)	8 (61.5)
TEAEs related to study treatment†	0	0	0
TEAE causing study discontinuation	0	0	0
TEAE resulting in death	0	0	0

Abbreviations: TEAE, treatment emergent adverse event.
† Adverse events were considered related to treatment if the event is classified as unknown, possibly, probably or definitely related to study treatment.
Source: 31 December 2019 Safety Update (14).

6.4.2.4 STR1VE-US

All 22 patients (100%) treated with an IV infusion of onasemnogene abeparvovec in STR1VE-US had experienced at least 1 TEAE by the end of the study (Table 36). The most frequently reported TEAEs were pyrexia (54.5%), upper respiratory tract infection (50.0%), constipation (40.9%), and scoliosis (40.9%). Most were not serious and were considered by the Investigator to be unrelated to onasemnogene abeparvovec. Twelve patients (54.5%) had a TEAE considered by the Investigator to be related to onasemnogene abeparvovec, ten patients (45.5%) had treatment-emergent SAEs. Two patients discontinued prematurely from the study due to SAEs; one patient ([redacted]) died due to a TEAE of respiratory arrest and one patient ([redacted]) discontinued due to a TEAE of respiratory distress. Neither event was considered by the Investigator as related to onasemnogene abeparvovec.

Seven patients were reported to have TEAEs of increased liver transaminase, alanine aminotransferase, aspartate aminotransferase, liver function, or hepatic enzyme. All events were considered by the Investigator as related to treatment, and three events in two patients were SAEs ([redacted]: alanine aminotransferase increased, aspartate aminotransferase increased, [redacted]: transaminases increased). Eight patients (36.4%) had events in the thrombocytopenia category, four of which were considered by the Investigator as related to onasemnogene abeparvovec (Patients [redacted], and [redacted]).

No clinically significant events of cardiac toxicity (e.g. events were considered not clinically significant if they were events such as tachycardia, bradycardia, or pre-existing congenital heart defects) were reported.

Thirteen events in 5 patients (22.7%) were reported within the Nervous System Disorders category; none of the events were sensory in nature, therefore, none were assessed to be suggestive of dorsal root ganglia cell inflammation. Many of the events (e.g. tongue fasciculations, tremor and hypotonia) are commonly associated with SMA, and likely reflect signs and symptoms of the underlying disease.

6.4.2.5 STR1VE- EU

Of the 33 infants treated onasemnogene abeparvovec in STR1VE-EU, 32 (97.0%) experienced at least 1 TEAE by the 31 December 2019 data cut. The most frequently reported TEAEs were pyrexia (19 patients; 57.6%); hypertransaminasemia (27.3%); vomiting (24.2%), upper respiratory tract infection (24.2%), respiratory tract infection (18.2%), gastroenteritis (15.2%); and constipation, diarrhoea, pneumonia, transaminases increased, cough, and hypertension (12.1%). Nineteen patients (57.6%) had an SAE during the study, and four patients (12.1%) had a severe TEAE considered by the Investigator to be related to onasemnogene abeparvovec. One patient discontinued from the study due to a TEAE of respiratory distress and hypoxic-ischaemic encephalopathy that resulted in death: this was due to an event of hypoxic-ischemic encephalopathy due to respiratory distress due to underlying SMA as per the autopsy report. The events of respiratory distress and hypoxic-ischemic encephalopathy were considered unrelated to onasemnogene abeparvovec by the Investigator.

Liver related adverse events were reported in 16 patients, including hepatic steatosis, hypertransaminasemia, and increased transaminases, alanine aminotransferases, aspartate

aminotransferases, gamma-glutamyl transferases, and hepatic enzyme. Of these, two events in one patient ([redacted]) were considered serious. This patient also experienced a serious thrombocytopenia event, assessed as being possibly related to onasemnogene abeparvovec by the Investigator, and was accompanied by multi-organ system failure from respiratory distress. All other hepatic adverse events were considered non-serious and related to onasemnogene abeparvovec.

No clinically significant events of cardiac toxicity or sensory abnormalities suggestive of dorsal root ganglia cell inflammation were reported.

6.4.2.6 SPR1NT

As of the 31 December 2019 data cut, all 30 infants treated with onasemnogene abeparvovec in SPR1NT experienced at least one TEAE. Seventeen patients (57%) had a TEAE considered by the Investigator to be related to onasemnogene abeparvovec, with six patients (20%) experiencing SAEs. The most frequently reported TEAEs were pyrexia (30%), upper respiratory tract infection (23%), constipation (17%), and nasopharyngitis (17%). Most were not serious and considered by the Investigator to be unrelated to onasemnogene abeparvovec. No adverse events resulted in study discontinuation or death.

Seven patients were reported to have liver related adverse events: increased transaminases (Patients [redacted]), increased alanine aminotransferase (Patient [redacted]), increased aspartate aminotransferase(Patient [redacted]), liver function increased (Patients [redacted]), or increased hepatic enzymes (Patient [redacted]). While all were considered related, none was serious, nor were any accompanied by clinical symptoms. In general, an increase in transaminases occurred in most patients during the first month after treatment and declined thereafter. One patient experienced transient thrombocytopenia and one patient experienced platelet count decreased, which resolved without any sequelae.

No clinically significant events of cardiac toxicity or sensory abnormalities suggestive of dorsal root ganglia cell inflammation were reported.

6.4.3 Provide a brief overview of the safety of the technology in relation to the scope.

The safety outcomes noted in the NICE scope were mortality and adverse effects of treatment. In total, of 97 patients treated with the therapeutic dose of onasemnogene abeparvovec in START, STR1VE-US, STR1VE-EU, SPR1NT, 93 (95.8%) were alive and free from permanent ventilation as of the 31 December 2019 data cut. Two treatment-emergent deaths were reported in clinical trials: one due to a TEAE of respiratory arrest that the investigator considered unrelated to onasemnogene abeparvovec and one due a TEAE of respiratory distress and hypoxic-ischemic encephalopathy, both of which were considered unrelated to onasemnogene abeparvovec by the investigator.

Of the 97 patients who received the therapeutic dose of onasemnogene abeparvovec, 56 patients (58.0%) were reported to have a TEAE considered by the Investigator to be related to onasemnogene abeparvovec. The onasemnogene abeparvovec SmPC (43) specifies that liver function, platelet counts, and cardiac troponin-I levels must be monitored

following treatment to assess the immune response to the AAV9 capsid. To dampen the immune response, immunomodulation with corticosteroids (prednisolone) is recommended. As all patients that received onasemnogene abeparvovec had anti-AAV9 titres at or below 1:50 before onasemnogene abeparvovec administration, no relationship has been established between high anti-AAV9 antibody titres and the potential for adverse reactions or efficacy parameters.

Overall, onasemnogene abeparvovec has been shown to have a monitorable and manageable safety profile when administered to clinically diagnosed patients with symptoms of SMA and pre-symptomatic patients with up to three copies of the *SMN2* gene in the completed START and STR1VE-US trials and in ongoing clinical studies (STR1VE-EU, SPR1NT, and LT-001). In the context of the substantial and urgent unmet medical needs of patients with the most severe form of SMA, the safety and efficacy data currently available strongly support a positive benefit risk relationship for a single IV administration of 1.1×10^{14} vg/kg onasemnogene abeparvovec for the treatment of patients with 5q SMA with a bi-allelic mutation in the *SMN1* gene and up to three copies of the *SMN2* gene.

6.5 *Real-world evidence*

RESTORE is a prospective, long-term registry initiated by AveXis, of patients who have been diagnosed with SMA. Patients are enrolled to the RESTORE registry from multiple sources, including existing SMA consortia (e.g. Cure SMA and TREAT-NMD), the onasemnogene abeparvovec US managed access programme and expanded access program. Patients are also recruited to RESTORE from the onasemnogene abeparvovec clinical trial programme.

The RESTORE registry captures data from patients with SMA who have received various different therapies including some who have switched from one active therapy to another. The study will enrol at least 500 patients with SMA in clinical practice in the US, UK, France, Germany, Italy, Spain, and other countries, including approximately 20% of patients treated with existing or investigational treatments. The primary objective of the RESTORE registry is to assess contemporary SMA treatments, including effectiveness, short and long-term safety, and overall patient survival. Secondary objectives include the assessment of HCRU, caregiver burden, and changes in patient functional independence over time. The outputs from the registry will include the pulmonary and nutritional requirements of patients, assessments of motor function, hospitalisations, AEs, and caregiver burden and QoL. The registry collates data for patients every 6 months until the 24-month visit and then annually for up to 15 years or until death, whichever is sooner.

RESTORE enrols patients with SMA, genetically confirmed on or after 24 May 2018. The current evidence base includes data collected between 25 September 2018 and 31 January 2020. As of 31 January 2020, [redacted] patients were enrolled into the RESTORE registry (35). The demographics of [redacted] patients enrolled in RESTORE for whom information on SMA treatment regimen was available are presented in Table 38. SMA treatments reported to have been administered to patients in RESTORE included onasemnogene abeparvovec and nusinersen. The median age of infants at the time of enrolment into the registry was [redacted] and the median age of patients at the 31 January 2020 data cut was [redacted] At the 31 January 2020 data cut, [redacted]

The current enrolment in the RESTORE registry reflects a range of SMA patient types and treatment regimens. However, the small number of patients to date, short, variable duration of follow-up, and lack of clinical outcomes data at the time of the cut, prevent in-depth assessment of the efficacy of treatments for SMA. It is anticipated that over time, with longer durations of follow-up and increased participants, RESTORE will provide data for evaluating the effectiveness of treatments for SMA including over the longer term.

Table 38: Demographics of patients treated with onasemnogene abeparvovec and enrolled in RESTORE (31 January 2020, study ongoing)

Characteristic	Treatment-evaluable patients ([redacted])
Sex, n (%)	[redacted]
Female	[redacted]
Male	[redacted]
SMN2 copy number, n (%)	[redacted]
1	[redacted]
2	[redacted]
3	[redacted]
4	[redacted]
SMA type, n (%)	[redacted]
Pre-symptomatic	[redacted]
1	[redacted]
2	[redacted]
3	[redacted]
SMA function status, n (%)	[redacted]
Non-sitter	[redacted]
Sitter	[redacted]
Standing	[redacted]
Walking	[redacted]
Age at first treatment, n (%)	[redacted]
0–6 months	[redacted]
>6–24 months	[redacted]
>24 months	[redacted]
Age at confirmation/assent into registry, months (range) ([redacted])	[redacted]
Age at 31 January 2020, months (range) ([redacted])	[redacted]

Abbreviations: SD, standard deviation; SMA, spinal muscular atrophy; SMN, survival motor neuron.

6.6 *Interpretation of clinical evidence*

6.6.1 Provide a statement of principal findings from the clinical evidence highlighting the clinical benefit and any risks relating to adverse events from the technology. Please also include the Number Needed to Treat (NNT) and Number Needed to Harm (NNH) and how these results were calculated.

The current clinical evidence base shows that infants with SMA type 1 treated with onasemnogene abeparvovec in START and STR1VE-US have unprecedented survival to date in comparison with natural history controls (8, 9, 13). All patients in START who received a one-time therapeutic dose of onasemnogene abeparvovec were alive and free from permanent ventilation at the end of the study (24 months post dose) and 90.9% (20/22) survived without permanent ventilatory support to 18 months of age in STR1VE-US[26] (9, 10, 13). Thus, the rate of ventilation-free survival at 18 months of age for START and STR1VE-US is 94.1% (32/34).These outcomes are in contrast to the survival rates reported in a UK natural history study that 50% of patients with SMA type 1 die before 1 year of age and also that reported in a US natural history study that only 8% of infants with SMA type 1 were alive without permanent ventilation at 20 months of age (3, 44).

In addition, patients in START and STR1VE-US achieved improvements in motor function not previously observed in patients with SMA type 1 treated with BSC alone. At the end of START (24 months post dosing), 91.7% of patients were able to hold their head erect without support, 75.0% were able to sit alone for ≥30 seconds, 16.7% were able to walk unassisted, 71.4% maintained the ability to thrive, 58.3% were entirely free from ventilation support, and 91.7% of patients were able to speak (9, 10). At the completion of STR1VE-US (18 months of age), 14 infants (63.6%) reached the milestone of sitting independently for ≥30 seconds; this milestone was confirmed for 13 patients at the 18-month visit (co-primary endpoint). In addition, one patient (4.5%) could walk alone, nine infants (40.9%) maintained the ability to thrive, and 18 infants (81.8%) were independent of ventilatory support at 18 months of age. These are notable achievements as infants with symptomatic SMA type 1 receiving BSC do not show improvement in motor function after initial disease presentation and never sit independently (3, 4). The maintenance of the ability to swallow at the end of START and STR1VE-US is also indicative of significant improvement compared with the normal clinical course of infants with SMA type 1 treated with BSC alone (30, 45). Similarly, the absence of a need for permanent ventilation indicates a significant benefit of onasemnogene abeparvovec in both studies (3). Assessment of the language and cognitive abilities of infants in START and STR1VE-US using the Bayley scale indicate that patients

[26] One patient ([redacted]) was discontinued at the age of 18.0 months in STR1VE-US, before the Month 18 end of study visit, due to an adverse event of respiratory distress (not considered related to study drug). Since this patient was alive and did not require permanent ventilation at 18 months of age, they are also included as having survived without permanent ventilation at 18 months of age.

treated with onasemnogene abeparvovec were in the range of normal childhood development.

The rapid and statistically significant increase from baseline in mean CHOP-INTEND scores in babies treated with the therapeutic dose of onasemnogene abeparvovec in START and STR1VE-US provide further evidence of improvement in motor function. In addition, START included observations of substantial benefits in survival, motor function, and developmental milestone achievements relative to natural history cohorts (5), which were particularly striking for several patients treated at younger ages (Section 6.3.1.1.2). This analysis suggests that early treatment before extensive neurodegeneration has occurred is key to maximizing the efficacy outcomes possible following treatment with onasemnogene abeparvovec.

In currently available long-term follow-up, the survival, motor function, developmental motor milestones, and ventilatory and nutritional endpoints achieved in START are being maintained, and in some cases further improved upon, in LT-001. The oldest patient treated with the therapeutic dose of onasemnogene abeparvovec in START (Cohort 2) is now 5.6 years old. No patients who received the therapeutic dose of onasemnogene abeparvovec have lost motor milestones gained in START and four patients have gained new motor milestones: for example, two patients in Cohort 2 (who have only received onasemnogene abeparvovec and no other SMA-targeted therapies) have gained the video-confirmed motor milestone of standing with assistance. Infants in STR1VE-US are also expected to reach additional milestones during longer follow up in LT-002, consistent with results from the LT-001.

Similarly to START and STR1VE-US, the interim results from the ongoing clinical study STR1VE-EU show that overall survival remains high in infants treated with onasemnogene abeparvovec with [redacted] of infants alive and free from permanent ventilation at the 31 December 2019 data cut. In addition, rapid and substantial clinical improvements in motor milestones and motor function have been observed. The interim results from STR1VE-EU demonstrate that the efficacy of onasemnogene abeparvovec is generalisable to European healthcare systems; however, additional follow-up data is required to determine the full extent of treatment outcomes in this study.

The most recent interim data from SPR1NT supports the exceptional impact of early treatment with onasemnogene abeparvovec in infants with two or three copies of *SMN2* prior to the onset of SMA symptoms. To date, all (29/29, 100%) infants in SPR1NT are alive and free from permanent assisted ventilation, no patients are receiving ventilatory or nutritional support and over half of patients are sitting without support (for ≥30 seconds) (Section 6.3.1.5). In most cases, motor milestones are being attained within normal developmental windows, indicating that patients treated with a one-time administration of onasemnogene abeparvovec are following a similar motor developmental path to the general population. The data obtained from SPR1NT support that early intervention is key to achieve maximum therapeutic benefit for infants with SMA, regardless of their ultimate anticipated disease course.

The ability to sit independently (and potentially stand and walk), breathe without ventilatory requirement, swallow, and speak are critical functional needs that would potentially allow a

child affected by SMA type 1 to attend school, maintain functional and social independence, and participate more fully in society. Onasemnogene abeparvovec represents an innovative and potentially transformative treatment which will not only represent a step-change in the management of SMA type 1, but may entirely revolutionise the treatment of infants with this disease. Infants who would otherwise die under BSC and who would never be able to sit, walk, or talk could have dramatically extended life expectancies and may be able to achieve physical independence from their caregivers. This is particularly true for children diagnosed at the pre-symptomatic stage of the disease, for whom the prospect of dramatic gains is greatest. Treatment with onasemnogene abeparvovec could also have a transformative effect for caregivers, who would otherwise have reduced QoL as a result of the burden of caring for a severely ill child with SMA type 1 and then losing their child in early infancy.

Overall, the data continue to support the efficacy of IV onasemnogene abeparvovec for the treatment of newly diagnosed children with SMA type 1 and in infants diagnosed pre-symptomatically with up to three copies of the *SMN2*. These data demonstrate clinically meaningful improvements in all endpoints tested compared with historical controlled data for children with SMA who were not treated. In addition, this update supports the premise that a single IV administration of onasemnogene abeparvovec provides prolonged and durable efficacy with a manageable safety profile.

6.6.2 Provide a summary of the strengths and limitations of the clinical-evidence base of the technology.

The clinical development programme for onasemnogene abeparvovec comprises of Phase I–III clinical trials in patients with SMA. To date, clinical data are available from two completed studies (START and STR1VE-US) and three that are ongoing (STR1VE-EU, SPR1NT, and LT-001). Data are not currently available from the additional long-term follow-up study, LT-002, which will enrol patients from studies including but not limited to SPR1NT, STR1VE-EU and STR1VE-US. The current clinical evidence for onasemnogene abeparvovec has demonstrated the important benefits of this disease-modifying treatment versus BSC with clinically meaningful improvements reported for all outcomes assessed, including survival without permanent ventilation, motor function, developmental motor milestones, ventilatory and nutritional endpoints, and developmental outcomes including speech (Section 0). In total, of 97 patients treated with the therapeutic dose of onasemnogene abeparvovec in START, STR1VE-US, STR1VE-EU, SPR1NT, 93 (95.8%) were alive and free from permanent ventilation as of the 31 December 2019 data cut.

The follow-up time for the Phase III trials STR1VE-US (completed) and STR1VE-EU (ongoing) for patients with symptomatic SMA type 1 is up to 18 months of age, in contrast to START (Phase I/IIa trial) which followed patients up to 24 months post-dose (to approximately 30 months of age). Despite these caveats, these efficacy data presented for STR1VE-US and STR1VE-EU provides confirmation that a single dose of onasemnogene abeparvovec has therapeutic benefit in rapidly improving motor function and prolonging ventilation-free survival in patients with symptomatic SMA type 1, in contrast with the observations from natural history studies.

While the START trial monitored patients for 24 months following a one-time administration of onasemnogene abeparvovec, the follow-up study LT-001 provides long-term evidence which demonstrates the durable effects of this disease-modifying treatment. The results of LT-001 to date indicate that a one-time IV administration of onasemnogene abeparvovec at the therapeutic dose provides prolonged efficacy for durations longer than 5 years (up to 61.9 months) post gene therapy administration (13). Although the long-term efficacy of onasemnogene abeparvovec beyond this time-frame is currently unknown, long-term efficacy and safety follow-up will be performed for LT-001 until 15 years after treatment or until death, whichever is sooner (11). Similarly, the STR1VE-US, STR1VE-EU, and SPR1NT studies have follow-up times of 18 (STR1VE-US, STR1VE-EU, SPR1NT Cohort 1) or 24 (SPR1NT Cohort 2) months of age. However, patients are offered enrolment to LT-002 which will assess the long-term efficacy of onasemnogene abeparvovec until 15 years after treatment. In addition, AveXis has established a global patient registry (RESTORE) to follow patients who receive onasemnogene abeparvovec in clinical practice, which will provide further long-term data. This registry will also address the long-term persistence of the onasemnogene abeparvovec transgene; data on this are currently limited to the survival and sustained motor milestone response of patients in LT-001 and preclinical data. Evidence for AAV-mediated gene persistence can also be drawn from studies in different, but relevant pre-clinical models e.g. behavioural recovery and stable transgene expression of genes for dopamine-synthesising enzymes has been reported for 15 years post AAV vector-mediated gene delivery in a primate model of Parkinson's disease (46). In a mouse model of SMA, gene therapy resulted in survival of greater than 250 days, compared with control-treated animals who did not survive past 22 days; this suggests continued expression (47). In addition, gene therapy vector-derived DNA and RNA were detected in tissues from mice examined at 24 weeks post-injection, indicating persistence of expression (48).

START was designed as a Phase I/IIa safety trial (N=15), where an open-label dose-escalation design in a small patient population is typical, and despite the small size of the patient population, a clear and unequivocal benefit of treatment with onasemnogene abeparvovec was demonstrated compared with natural history controls. To support the robustness of clinical evidence from START, a greater number of patients are enrolled in Phase III trials (STR1VE-EU, STR1VE-US, SPR1NT), with a total of 100[27] patients now dosed with a one-time IV infusion of onasemnogene abeparvovec. Further, the patients enrolled to the ITT populations of STR1VE-US and STR1VE-EU had similar baseline characteristics to patients in START; all patients had two copies of *SMN2* without the gene modifier mutation (c.859G>C), symptom onset at <6 months of age, a similar age at onasemnogene abeparvovec administration, and similar baseline CHOP-INTEND scores (Section 6.1.3). There were differences between study populations in race and nutritional/ventilatory support requirements at baseline. Overall, the evidence available from the Phase III trials demonstrates that the survival and motor milestone efficacy outcomes originally shown in START are reproducible in larger, multicentre trials (Section 6.3.1). The results from SPR1NT also provide confirmation of the efficacy of onasemnogene abeparvovec in a broader infant population than that included in START, including patients

[27] 100 patients across the studies included in this submission: START n = 15 (12 receiving therapeutic dose); STR1VE-US n = 22; STR1VE-EU n = 33; SPR1NT n = 30 (including one 4 x *SMN2* patient).

treated prior to the onset of SMA symptoms and with different copy numbers of *SMN2* (n=14 with 2 copies; n=15 with 3 copies; n=1 with 4 copies).

START and the Phase III clinical trials of onasemnogene abeparvovec have a single arm open-label trial design. Given the extremely poor prognosis of patients who did not receive treatment in natural history studies (see original company submission Section 6) and the unprecedented efficacy and the safety profile observed in the START trial, it was considered unethical to include placebo patients in further onasemnogene abeparvovec trials. In addition, as nusinersen was not available when the clinical development programme for onasemnogene abeparvovec was designed, thus, no head-to-head study could have been conducted at that time. The single arm design used in the onasemnogene abeparvovec clinical trial programme was also discussed and agreed with regulators during protocol assistance discussions.

Due to the single arm design of the trials, well characterised datasets from the SMA natural history studies (i.e. the PNCR and NeuroNext) were identified as appropriate for use as historical controls (5). Comparisons with historical controls may be considered as a limitation as perceived treatment effects can be overestimated, particularly when standards of care improve over time or when there is a variable natural history (49). Despite differences in methodology, geographical location, and study populations, the PNCR and the NeuroNext studies show consistency in mortality, ventilatory requirement, motor function, and milestone achievement with the European experience described in recent papers by Wadman et al. 2017 (29) and De Sanctis et al. 2018 (50), as well as studies from the UK (44, 51), Poland and Germany (52), France (53), the US (54) and Hong Kong (55). In addition, although there are differences between the onasemnogene abeparvovec study populations and the PNCR and NeuroNext natural history control cohorts which may indicate that the patients in the PNCR cohort could have less severe disease (as expressed by the older age of the included patients), the potential bias this creates i.e. these patients are expected to experience the event earlier, is not in favour of onasemnogene abeparvovec. The efficacy of onasemnogene abeparvovec was also evident in analyses versus the sub-cohorts of PNCR and NeuroNext historical control datasets, when using a matched-subject approach. Therefore, SMA type 1 patients from the PNCR and NeuroNext datasets are considered to be appropriate comparators for the patients treated with onasemnogene abeparvovec. The generalisability of the extracted PNCR and NeuroNext natural history control cohorts to the UK SMA type 1 patient population treated with BSC was confirmed at the UK Clinical Advisory Board (May 2019) (56).

A greater range in baseline CHOP-INTEND scores was reported in onasemnogene abeparvovec studies (START Cohort 1: 6–27; Cohort 2: 12–50; STR1VE-US: 18–52; STR1VE-EU; 14–55; SPR1NT Cohort 1:28–57) compared with those reported in the PNCR (5–40) and NeuroNext (10–33) natural history control cohorts. These differences may indicate that some infants in the onasemnogene abeparvovec studies had less severe disease than infants in the natural history controls. However, as the infants included in START, STR1VE-US, and STR1VE-EU were proactively identified for the studies, they were likely to have been diagnosed at an earlier stage of disease progression than those in natural history controls, explaining the differences in baseline CHOP-INTEND scores. This is supported by the observation that the baseline CHOP-INTEND scores in onasemnogene abeparvovec clinical trials were in line with those reported for the sham-control group in

ENDEAR (presented in graph format only: approximate range of 10 to 50) (57). Similarly, infants enrolled in SPR1NT were pre-symptomatic newborn patients expected to develop SMA who were ≤6 weeks old at the time of gene replacement therapy and baseline CHOP-INTEND assessment. As clinical practice in England is moving towards earlier symptom recognition and earlier diagnosis due to the increasing awareness of SMA (in part due to the recent licensing of treatment options), the patient population in the onasemnogene abeparvovec clinical trial programme is expected to be representative of the infants that would receive this gene therapy in clinical practice in England.

Given the novel status of onasemnogene abeparvovec, the long-term duration of expression of the transgene is unknown. An opportunity to assess SMN expression following administration of onasemnogene abeparvovec was provided by the unfortunate death of one patient in the ongoing STR1VE-US trial (Section 6.4.2.4) and one patient in STR1VE-EU (Section 6.4.2.5) (12, 58). Widespread biodistribution of the onasemnogene abeparvovec genome and expression of the construct across the CNS and in the peripheral tissues and organs, including the heart and liver, was demonstrated (12, 59). These human data support that onasemnogene abeparvovec crosses the blood brain barrier following systemic administration, with substantial targeting and expression of SMN protein in key cellular targets such as CNS and muscle cells (12, 59). Preclinical data also support the expectation of long-term gene expression following administration of onasemnogene abeparvovec. In a mouse model of SMA, gene therapy resulted in survival of greater than 250 days, compared with control-treated animals who did not survive past 22 days; this suggests continued expression (47). Gene therapy vector-derived DNA and RNA were detected in tissues from mice examined at 24 weeks post-injection, indicating persistence of expression (48). Intravenous administration of onasemnogene abeparvovec is able to restore *SMN* expression to motor neurons that lack a functional *SMN1* gene, thereby addressing the genetic root cause of SMA (12, 59).

Administration of AAV9 vector may represent a potential adverse immune response risk for patients with high levels of pre-existing antibodies against the AAV9 capsid. In the clinical trials studying IV administered onasemnogene abeparvovec, patients were required to have an anti-AAV9 antibody titer of ≤1:50 prior to treatment. Thus, there has not been an exploration of any relationship between higher anti-AAV9 antibody titres and the potential for adverse reactions.

6.6.3 Provide a brief statement on the relevance of the evidence base to the scope. This should focus on the claimed patient- and specialised service-benefits described in the scope.

The onasemnogene abeparvovec evidence base directly addresses the following outcomes set out in the NICE scope: mortality, need for non-invasive or invasive ventilation, motor function, respiratory function, complications of SMA, and adverse effects of treatment in infants with SMA type 1.

Health-related quality of life (HRQoL) was included in the NICE scope but is not considered in the current clinical evidence base. Quality of life utilities for infants are extremely difficult to gain a consensus on due to difficulties in receiving reliable feedback from infants or parents

regarding the quality of life. HRQoL cannot be directly measured in infants with SMA type 1 and would rely on proxy reported measures. While HRQoL was not included in the onasemnogene abeparvovec clinical trial programme, AveXis has sourced values from the literature to estimate the HRQoL of infants with SMA type 1 and conducted an exploratory UK utilities elicitation study (presented in Section 7.1). Given the extreme difficulties in obtaining reliable HRQoL data in SMA type 1 patients, and their caregivers, it may be appropriate to place more consideration to other, more robust outcomes from the clinical evidence base including the unprecedented survival outcomes observed.

6.6.4 Identify any factors that may influence the external validity of study results to patients in routine clinical practice.

The aetiology and pathology of SMA type 1 are consistent globally, therefore, the clinical data presented in this submission and the efficacy and safety conclusions based on the data are applicable to infants with SMA type 1 in England. It is likely that increasing awareness of SMA and the availability of new treatments will incentivise rapid diagnosis and treatment. A key factor which may influence results in clinical practice is how early treatment is administered, as the loss of motor neurons and resulting muscle atrophy is irreversible, therefore, the earlier patients are diagnosed and treated, the lower the burden of symptoms and the better the expected clinical outcomes. The average age of SMA type 1 diagnosis in the nusinersen EAP, which provides an approximation of UK clinical practice, was 2.6 months (60). The mean age at diagnosis of infants enrolled to START was 2.25 months (range: 0.0–4.6). In STR1VE-US and STR1VE-EU, the mean age of infants at SMA diagnosis was 2.64 months (range: 0.0–5.4) and 2.63 months (range: 0.9–5.2), respectively. The mean age at SMA diagnosis of the pre-symptomatic infants enrolled in SPR1NT was 0.24 months (range: 0.0–0.9) (13). AveXis is committed to working with HCPs to improve education and awareness of SMA and the available treatments to ensure early diagnosis followed by rapid treatment, to enable the achievement of optimal clinical outcomes for infants with this condition. As healthcare systems are moving to adopt newborn screening for SMA it can be expected that the clinical outcomes following one-time gene therapy will more closely correspond to those seen in pre-symptomatic babies in SPR1NT rather than in symptomatic children treated in START and STR1VE-US.

6.6.5 Based on external validity factors, describe any criteria that would be used in clinical practice to select patients for whom the technology would be suitable.

In England, the proposed positioning of onasemnogene abeparvovec is for the treatment of children with SMA type 1 and pre-symptomatic infants with a genotype predictive of SMA type 1 (i.e. those with up to three copies of the SMN2 gene).

This positioning is supported by strong evidence from the AveXis clinical trial programme, with n=67 SMA type 1 and n=29 pre-symptomatic SMA patients with up to three copies of *SMN2* treated with a one-time administration of the therapeutic dose of onasemnogene abeparvovec.

Based on this target patient population, the criteria used in clinical practice for the diagnosis of infants with SMA type 1 would remain as per current established clinical practice – (diagnostic pathway described in Section 6.1.2 of the original company submission). As clinical practice in England is moving towards earlier symptom recognition and earlier diagnosis due to the increasing awareness of SMA (in part due to the recent licensing of an active treatment), the patient population in the onasemnogene abeparvovec clinical trial programme is expected to be representative of the infants that would receive this gene therapy in clinical practice in England. The interim results presented from SPR1NT provide an indication of the clinical outcomes that could be achieved by infants with SMA type 1 when a newborn screening programme for SMA is introduced in England.

With respect to the target SMA patient population of those diagnosed pre-symptomatically with up to three copies of the *SMN2* gene, it is recognised that newborn screening is not currently established clinical practice in England. Very few patients are currently being diagnosed pre-symptomatically as a result of newborn genetic testing referral, initiated due to a sibling history of SMA. As the benefits of onasemnogene abeparvovec and other existing SMA-targeted treatments become known, it is expected that newborn screening will be introduced in the UK in the future, which is an initiative currently being adopted across many European healthcare systems.

7 Measurement and valuation of health effects

Quality-of-life data used in cost-effectiveness analysis

7.1 *Please summarise the values you have chosen for your cost-effectiveness analysis in the following table. Justify the choice of utility values, giving consideration to the reference case.*

7.1.1 Base case – health state utility values

The base case patient health state utility values used in the revised cost-effectiveness model are drawn from the recent US ICER assessment of SMA therapies and UK expert clinical advice independently sourced by the NICE ERG. These values are presented in Table 39 and were derived from multiple sources:

- **E state [0.000]:** The utility value of 0.000 for the E state (permanent assisted ventilation) is sourced from the 'ERG-preferred base case' assumptions in the interim ERG report for this appraisal (61). Clinical expert advice sourced independently by the ERG, indicated that the E state should have a lower utility value than the D state.

- **D state [0.190]:** The utility value of 0.190 for the D state is adopted in the US ICER assessment. It is sourced from Thompson et al. 2017 (62), which is a cross-sectional study of individuals with SMA in Europe; investigators collected parent-proxy–assessed quality of life using the EuroQol-5 Dimensions (EQ-5D) 3-level version. The mean utility value for patients with SMA type 1 in the UK was 0.190 (n=7 parent-proxy assessments).

- **C state [0.600]:** The utility value of 0.600 for the C state (sits unassisted) is adopted in the US ICER assessment. It is sourced from the ERG report evaluating the nusinersen submission for NICE. Tappenden et al. 2018 (63) reported utilities elicited (these estimates were described as 'not preference-based') from the clinical experts who advised the ERG, who were asked to provide plausible utility estimates for the different health states

- **B state [general population]:** The utility for the B state (walks unassisted) and A state (within broad range of normal development) are sourced from general population utilities presented in Table 40, and calculated annually as per the well-established methodology of Ara and Brazier (64) using the equation below. The sex coefficient used is male= 41.7% as per the demographics of patients enrolled in Cohort 2 of START. It is noted that proportion of males in the pooled cohort across the START and STR1VE-US trials is slightly higher (44.1%), but this amend has not been applied in the revised economic model. The impact on the ICER of changing the male coefficient from 41.7% to 44.1% is negligible (base case ICER decreases by £34). Table 41 presents examples utility values using this approach; all annual ages between 0–100 are not included in Table 49 for brevity sake.

Utility (EQ-5D) = 0.9508566 + (0.0212126 x male) – (0.0002587 x age) – (0.0000332 x age^2)

- Notably, the base case cost-effectiveness model adopted by US ICER also included additional utility benefits – often referred to as 'on-treatment utility' – in the treatment arms (onasemnogene abeparvovec and nusinersen) for achieving interim milestones such as head control, rolling, standing, crawling, etc. The US ICER implemented these on-treatment utilities as an additional utility of 0.1 and 0.05 compared with BSC in the non-sitting and sitting health states, respectively. The interim milestones (i.e. head control, rolling, crawling and standing with/without assistance) and other non-motor milestone features that may be achieved with pharmacotherapy (e.g. improvements in talking and non-verbal communication, fine motor control and learning etc.) The updated base case analysis includes an on-treatment utility benefit assumed in the treatment arms to account for achieving such 'intra-health state' benefits of treatment. The following on-treatment utilities increments are applied in both treatment arms (onasemnogene abeparvovec and nusinersen) in the base case analysis:

  D state: on treatment utility of 0.1

  C state: on treatment utility of 0.05

  This amend to include on-treatment utilities as part of the base case also reflects the 'ERG-preferred base case' assumptions described in the interim ERG report for this appraisal (61).

These utility values have been chosen for the base case as:

- They were considered most appropriate by the US ICER independent assessment group and/or the clinical experts advising the ERG for this appraisal
- The D state uses utilities sourced via EQ-5D, which is the preferred measure of HRQoL in the NICE reference case
- They were deemed plausible according to a UK clinical advisory board (May 2019)
- Measuring robust utility values in babies and young children is exceptionally challenging, even more so in the rare disease setting. The NICE reference case states when it is not possible to obtain measurements of HRQoL directly from patients, data should be obtained from the person who acts as their carer (typically parents in the case of SMA type 1) in preference to healthcare professionals; in the base case parent-proxy EQ-5D values were sourced for the D state

Table 39: Summary of patient utility values used in the base case cost-effectiveness analysis

State	Description	Utility value	Reference	Justification
E state	Permanent assisted ventilation	0.000	Interim ERG report. Edwards et al. 2020 (61)	• Input amended to match 'ERG-preferred base case' assumption • Informed by UK expert clinical advice, sourced by the ERG for this appraisal
D state	Not sitting	0.190	Thompson et al. 2017 (62)	• Approach taken by US ICER • Uses parent-proxy via EQ-5D-3L for UK-specific SMA type 1 population
C state	Sits unassisted	0.600	Tappenden et al. 2018 (63)	• Approach taken by US ICER • Informed by UK expert clinical advice, sourced by an independent group (NICE ERG)
B state	Walks unassisted	General population	Ara and Brazier 2010 (64)	• Approach taken by US ICER, adapted to UK general population
A state	Broad range of normal development			

Abbreviations: ERG, Evidence Review Group; NICE, National Institute for Health and Care Excellence; EQ-5D-3L, 3-level EuroQol 5-dimension; SMA, spinal muscular atrophy; UK, United Kingdom; US ICER, United States Institute for Clinical and Economic Review.

Table 40: General population utilities used for A state and B state

Description	Reference	Justification
Annual age-related utility using the following equation: $EQ\text{-}5D = 0.9508566 + (0.0212126 \times 0.417) - (0.0002587 \times age) - (0.0000332 \times age^2)$	Calculation as reported in Ara and Brazier 2010 (64)	Walking unassisted by 2 years of age is reflective of normal development, as per the WHO reported windows of motor milestone achievement in healthy children. Therefore, general population utility values are applied for the B state and A state

Abbreviations: EQ-5D, EuroQol 5-dimension; WHO, World Health Organization.

Table 41: Example calculated age-adjusted general population utilities for A state and B state

Age	Utility value
10 years	0.9538
20 years	0.9412
30 years	0.9221
40 years	0.8962
50 years	0.8638
60 years	0.8247
70 years	0.7789
80 years	0.7265

7.1.2 Scenario analysis – health state utility values

Alternative published sources

Utilities from three alternative studies identified as part of the HRQoL SLR were assessed for incorporation as scenario analyses:

1) PedsQL from CHERISH (nusinersen later-onset SMA clinical trial) mapped to EQ-5D-Y (62). PedsQL data was mapped to the EQ-5D-Y using a published algorithm by Khan et al. 2014 (65)

2) A case vignette study that assessed clinician-proxy–assessed (n=5) EQ-5D-Y (62)

3) A cross-sectional study of individuals with SMA in European countries collected parent-proxy–assessed EQ-5D-3L. Values from UK respondents (n=7) are used only (62)

Further details of each study and a justification for why these were not use in the base case are provided in Table 42 below.

UK *de novo* utilities study

Prior to the publication of the US ICER report there was a lack of robust utility values, with face validity, which could be used to populate the *de novo* cost-effectiveness model, hence AveXis undertook a *de novo* UK utilities elicitation study (66). Further details of this study are in the UK utilities elicitation report (66). The full critique of this study and the justification for why it is not used in the base case is described in the original company submission (Section 10.1.9) and is summarised in Table 42 below.

Caregiver disutilities

Due to substantial physical disability resulting from SMA type 1, babies with this disease require high levels of physical support and constant supervision from carers. The carers of babies with SMA type 1 have to make difficult treatment choices (i.e. whether to pursue an invasive treatment regimen for a child with respiratory function deterioration) and deal with uncertainty in the life expectancy or functional status of the infant (67-69). In addition, carers experience isolation due to limitations in their ability to socialise and engage in activities

outside of the home; and pressure on family finances from lost income or changes in career goals or employment related to time spent attending treatment and caring for the extra needs of the child (67-69). Whilst it is well accepted that SMA has a substantial effect on the HRQoL of parents, caregivers and families, robust UK quantitative caregiver utility data for the SMA population are lacking.

Methods for performing economic evaluations including caregiver burden are still under development, and currently there are no formally accepted mechanisms of including caregiver disutilities due to bereavement and loss of a child. Furthermore, learnings from other recent evaluations of SMA therapies indicate that incorporating caregiver HRQoL into economic evaluations has limitations, for example:

- US ICER did not include HRQoL burden associated with caregivers in their base case or scenario analyses, stating that incorporating caregiver burden may lead to counter-intuitive results due to prolonged negative productivity effects and unknown HRQoL effects on caregivers when children who need care live longer
- Committee discussions in the nusinersen single technology appraisal (STA) concluded that caregiver utility should be considered in decision making but that quantifying it was extremely difficult

Due to the lack of robust SMA-specific UK caregiver utility data, and for the methodological limitations described, the impact of caregiver HRQoL is assessed as an explorative scenario only. This explorative scenario applies a disutility for caregivers that varies by the health state of the patient, drawing data from a proxy, but related, disease – spina bifida. Spina bifida was chosen as an appropriate proxy disease as it shares several characteristics with SMA, for example, it afflicts very young babies and severely impacts the motor function and ambulation of patients. A study by Tilford et al. 2005 (70) compared Quality of Well-Being (QWB) scale data from the primary caregivers of children aged 0–17 years (n=98) with spina bifida versus a control sample of parents of non-disabled/unaffected children (n=49). Spina bifida children were categorised into three disability levels according to the location of the child's lesion: 1) sacral, 2) lower lumbar and 3) thoracic. When comparing caregivers of spina bifida patients to the control caregiver sample, the 'spill over' disutility of spina bifida caregivers are reported as: -0.03, -0.03 and -0.08 for the sacral, lower lumbar and thoracic lesion groups respectively. Values were calculated using the method described by Wittenberg et al. 2013 (71). These caregiver disutilities are incorporated into the exploratory scenario analysis as follows: -0.08 for caregivers of a child in the E state (permanent assisted ventilation) or D state (not sitting) and -0.03 for a child in the C state (sits unassisted).

Table 42: Summary of alternative patient utility values

Health state†	CHERISH: PedsQL mapped to EQ-5D-Y (Thompson et al. 2017)		Lloyd: Clinician-proxy Case Vignette EQ-5D-Y (Lloyd et al. 2017)		European study: Parent-proxy EQ-5D-3L, UK reports only (Thompson et al. 2017)		UK utilities elicitation study using TTO (AveXis, UK utilities report)	
	Health state	**Utility value**	**Health state**	**Utility value**	**Health state**	**Utility value**	**Health state**	**Utility value**
E state	SMA type 2: Worsened (from baseline)	0.730	SMA type 1: Requires ventilation	-0.33	SMA type 1	0.190	Permanent assisted ventilation	[redacted]
D state	SMA type 2: Stabilisation of baseline function	0.756	SMA type 1: Baseline	-0.12	SMA type 1	0.190	Not sitting	[redacted]
C state	SMA type 2: Moderate improvement	0.764	SMA type 1: Reclassified as SMA type 2†	-0.04	SMA type 2	0.100	Sits unassisted	[redacted]
B state	SMA type 2: Walks unaided	0.878	SMA type 1: Reclassified as SMA type 3‡	0.71	SMA type 3	0.540	Walks unassisted	[redacted]
A state	N/A	General pop.§	N/A	General pop.‡§	N/A	General pop.§	N/A	General pop.§
Justification for exclusion from the base case	The mapping described by Kahn et al 2014 has several methodological limitations: for example, it was conducted in a population that differed considerably (school children aged of 11 to 15 years) to SMA type 1 babies. In addition, the values seem implausibly high; for example, it seems unlikely that for an individual who requires PAV would be considered as being three quarters of that of an individual in perfect health		The study uses clinician-proxy assessment, which is less preferred to parent-proxy assessments, as per the NICE reference case. In addition, the study reported a negative utility (a health state worse than death) for 'reclassified SMA type 2'. A negative utility value for the C state (sits unassisted) lacks face validity and was deemed implausible by UK clinical experts (UK advisory board, May 2019)		Whilst this study uses parent-proxy assessment, which is preferred to clinician-proxy assessments, the results for the SMA type 2 group (used as proxy for the C state [sit unassisted]) lack face validity, as they are lower than the utility value reported for SMA type 1 patients who fail to achieve any milestones. Due to this lack of face validity, a scenario using values reported for SMA type 2 and 3 groups from this study is also not formally modelled		When using the utility values from this study, the overall estimates of discounted QALYs for both the BSC arm (-0.536 QALYs) and nusinersen [redacted] QALYs) are negative – see Section 8.5.2.1. This result lacks face validity, in that this suggests that both UK standard of care (BSC) and a recently approved pharmacotherapy (nusinersen) results in patients losing QoL despite receiving treatment	

Abbreviations: BSC, best supportive care; EQ-5D-3L, 3-level EuroQol-Five Dimension; EQ-5D-Y, EuroQol-Five Dimension youth; N/A, not applicable; NICE, National Institute of Health and Care Excellence; PAV: permanent assisted ventilation; pop., population; QALY, quality-adjusted life-year; SMA, spinal muscular atrophy; TTO, ; UK, United Kingdom.
† Where possible, it was decided to use available utility data of type 1 patients behaving as type 2, rather than type 2 has a proxy. These are patients that have been treated, so type 1 patients who can sit, which is similar to our model. ‡ Where possible, it was decided to use available utility data of type 1 patients behaving as type 3, rather than type 2 proxy walkers. These are patients that have been treated, so type 1 patients who can walk, which is similar to our model. Baseline is D state and they can transition to B state.
§ Identified studies did not included an A state. The A state (within broad range of normal development) is assumed to have HRQoL equivalent to the UK general population.

7.2 *If clinical experts assessed the applicability of values available or estimated any values, please provide the following details:*

- ***the criteria for selecting the experts***
- ***the number of experts approached***
- ***the number of experts who participated***
- ***declaration of potential conflict(s) of interest from each expert or medical speciality whose opinion was sought***
- ***the background information provided and its consistency with the totality of the evidence provided in the submission***
- ***the method used to collect the opinions***
- ***the medium used to collect opinions (for example, was information gathered by direct interview, telephone interview or self-administered questionnaire?)***
- ***the questions asked***
- ***whether iteration was used in the collation of opinions and if so, how it was used (for example, the Delphi technique).***

The utility value for the C state (sits unassisted) and the E state (permanent assisted ventilation) in the base case were informed by UK expert clinical advice, sourced independently by the ERG for the nusinersen STA appraisal (63) and by the ERG for this ongoing appraisal (61), respectively.

As described in Section 8.2.5, UK expert clinicians and patient advocacy experts assessed the different options for utilities, reporting the following consensus:

- It is plausible for the D and E health states to be associated with negative health state utility values (i.e. considered worse than death)
- It is implausible for the C state to be associated with a negative health state utility value
- The concept of an average QoL score for each health state in the model is nonsensical as SMA is a heterogeneous disease that impacts very young infants and the impact on the patient, caregiver and family is very individual/environment-specific
- Of the health state utility values options shown, the US ICER values were the most plausible but there should be a differentiation between the values for E and D states (i.e. the E state value should be lower than the D state value)

7.3 *Please define what a patient experiences in the health states in terms of HRQL. Is it constant or does it cover potential variances?*

HRQoL changes over time as patients transition between different model health states. Potential variances with respect to 'intra-health state' benefits that patients may incur as a result of treatment in the D state and C state are accounted for by applying 'on-treatment' utility in the base case, as described in Section 7.1.1.

As the values used for the base case patient utilities values are sourced from published sources external to AveXis, that employed parent-proxy (62) (D state) or clinician-proxy (61, 63) (E state and C state) assessments, details of the full questions/elicitation technique/vignettes used are lacking to be able assess whether the assessments captured a single timepoint 'snap shot' or also accounted for the potential variation that may occur to a patient in a given health state over time. Due to a lack of robust quantitative data informing how HRQoL may change over time on an 'intra-health state' basis, patient health state utilities remain constant for the lifetime horizon of the model.

7.4 *Please clarify whether HRQL is assumed to be constant over time. If not, provide details of how HRQL changes with time.*

Only the general population utilities for the B state and A state vary by age; all other utilities stay constant for the lifetime horizon of the model. General population utilities were adjusted by age, using published methods as described in Section 7.1.1.

8 Economic analysis

8.1 *Description of the de novo cost-effectiveness analysis*

In line with the final scope, BSC is used as a comparator in the cost-effectiveness analysis of onasemnogene abeparvovec.

The cost-effectiveness results of onasemnogene abeparvovec versus nusinersen are not presented in this updated submission, as nusinersen is no longer considered a comparator for this appraisal. As the revised economic model Excel file (.xlsm) submitted to NICE still includes a nusinersen arm, for completion, the methods and inputs sections relating to the nusinersen arm of the economic model are described.

8.1.1 Patients

8.1.1.1 What patient group(s) is (are) included in the cost-effectiveness analysis?

In the original company submission, only clinical data from START (Cohort 2, n=12) were available. Since then, the STR1VE-US (n=22) trial has completed and data have become available. Therefore, the economic model has been updated with pooled data from both the START and STR1VE-US trials (see Section 8.2.1.1 for more detail), and the pooled cohort (n=34) is used for the base case analysis presented in this updated submission.

The patient group included in the cost-effectiveness analysis is infants with 5q spinal SMA with a bi-allelic mutation in the *SMN1* gene and a clinical diagnosis of SMA type 1 based on the enrolled cohorts of the available completed clinical trials (START and STR1VE-US). The modelled population includes those:

- with two copies of the *SMN2* gene
- with the onset of SMA symptoms at age ≤6 months
- who are symptomatic at baseline

8.1.2 Technology and comparator

8.1.2.1 Provide a justification if the comparator used in the cost-effectiveness analysis is different from the scope.

In line with the final scope, BSC is used as a comparator in the cost-effectiveness analysis.

Intervention

- Onasemnogene abeparvovec: administered as a single-dose intravenous infusion. It should be administered with the syringe pump administered as a single intravenous

infusion with a slow infusion of approximately 60 minutes at a dose of $1.1x10^{14}$ vg/kg[28], in addition to BSC

- No stopping rules exist for onasemnogene abeparvovec, as it is a one-time treatment administered via a single IV infusion.

Comparator

- BSC: standard respiratory, gastrointestinal, and nutritional care for patients with SMA, delivered via an multidisciplinary team (MDT)

Although no longer considered a comparator, the updated economic model Excel file (.xlsm) submitted to NICE with this updated submission still contains a nusinersen arm defined as: Nusinersen by intrathecal use by lumbar puncture, in addition to BSC. The nusinersen arm incorporates a dosing schedule as per the SmPC (72) and a stopping rule as per the terms of the NICE MAA for nusinersen (73):

- Patients discontinue nusinersen in the E state (permanent assisted ventilation)
- Patient discontinue due to an annual risk of withdrawal (3%) in the D state and C state
    - The annual risk of withdrawal accounts for discontinuation due to reasons of patient/caregiver preferences [e.g. decision to avoid further hospital attendance], inability to administer nusinersen by intrathecal administration because of spinal fusion surgery or a worsening in motor function
    - The rate of annual risk of withdrawal (3%) is from ENDEAR (proportion achieving a 4-point worsening in CHOP-INTEND) and reported withdrawal rates (n=3/95 withdrew treatment) from the nusinersen UK/Ireland EAP

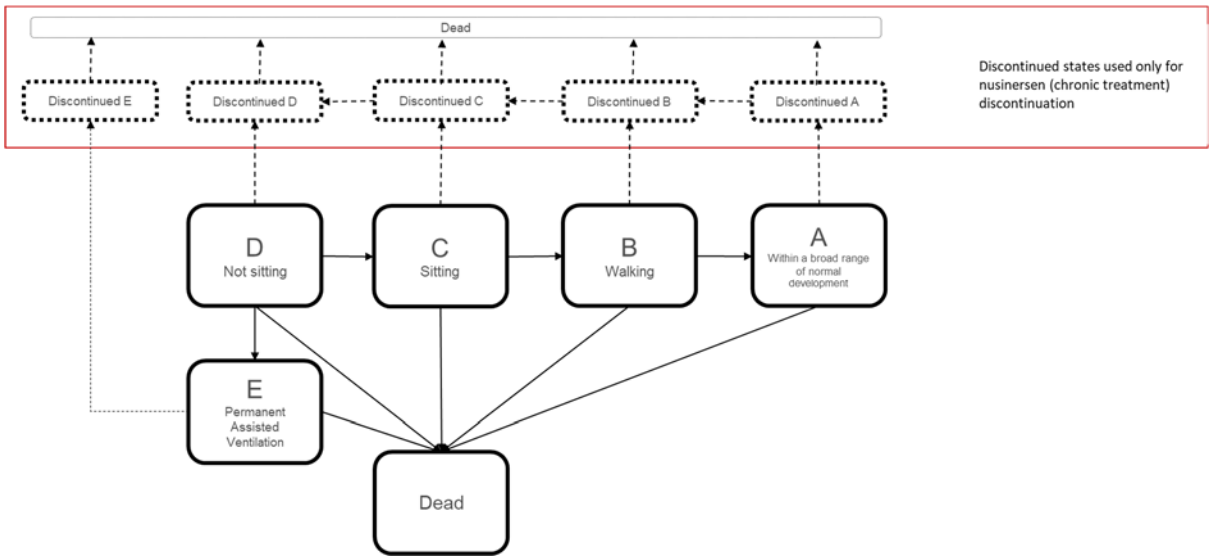
8.1.3 Model structure

8.1.3.1 Provide a diagram of the model structure you have chosen.

The cost-effectiveness model is a cohort Markov state-transition model. The structure of the model is shown in Figure 34.

[28] Equivalent to the dose received by Cohort 2 in START as determined by direct product testing with improved analytical methods. Direct testing of the actual lot of IMP used in START by an improved and more fully qualified analytical method has assigned a value of 1.1×10^{14} vg/kg to the actual dose received by Cohort 2. The same method has been used to establish an equivalent dose for the IMP in the completed STR1VE-US trial and all ongoing Phase III trials.

Figure 34: Model schematic



Health States	
A	Within a broad range of normal development
B	Walks independently
C	Sits independently
D	Cannot sit independently
E	Requires Permanent Assisted Ventilation

Health states

The model health states differ based on the motor function milestones achieved by the patient, the need for permanent assisted ventilation, and time to death. The model includes two health states that reflect the natural history of SMA type 1: D state (not sitting) and E state (permanent assisted ventilation). Three higher functioning health states are possible for patients in the pharmacotherapy-treated arms: C state (sits unassisted), B state (walks unassisted), and A state (within a broad range of normal development) (Table 43). Whilst the health states are broadly defined by the motor function milestone achieved, each health state also captures the likely associated symptoms and complications of SMA, which are described in Section 8.1.3.4.

Table 43: Functional status across health states

State	Clinical features
A	Within a broad range of normal development
B	Walks unassisted
C	Sits unassisted
D	Not sitting
E	Requires permanent assisted ventilation

Abbreviations: SMA, spinal muscular atrophy.

Other motor function milestones such as head control, rolling, crawling, and standing with/without assistance were not modelled as explicit health states as these data were not available for all model arms; as such, these milestones represent potential 'intra-health state' clinical benefits or disease progression, if gained or lost, respectively. In addition, other 'intra-health state' clinical benefits that may be achieved as a result of pharmacotherapy treatment are not formally modelled via explicit health or tunnel states, such as:

- an improvement in an attained motor milestone (e.g. ability to sit, stand or walk unassisted for longer period prior to fatigue)
- reduction in time spent on ventilatory support
- improvements in talking and non-verbal communication (e.g. smiling and eye contact)
- improvements in fine motor control (e.g. ability/strength to operate a joystick on a wheelchair, use of a tablet computer or use of utensils for feeding)
- learning to write or being able to go through the education system
- greater independence and self-care ability

These health benefits associated with such 'intra-health state' improvements are incorporated into the model by applying on-treatment utilities to the D state and C state in the base case.

Transitions

The model consists of two parts: 1) a short-term model concordant with observed clinical trial data, and 2) a long-term extrapolation model. Observed clinical outcomes are captured in the model by moving treated patients into higher functioning health states; higher functioning health states are associated with longer survival, higher QoL, and lower HCRU costs. Patients can only be in one state at a time (mutually exclusive) and all patients must be captured in a state (mutually exhaustive).

At model baseline, all patients are in the D state (not sitting). At the end of each model cycle (every 6 months for the first 3 years, then annually), patients can transition into a new health state or stay in the same health state. A 6-monthly model cycle was chosen in the first three years, to allow changes in childhood development and milestone achievement to be adequately captured. Patients transition to higher health states when they attain motor milestones (sits unassisted or walks unassisted). Transition to the E state (permanent assisted ventilation) in the model was only possible for patients who did not have any motor function milestones (i.e. those in the D state [not sitting]). For E state patients, both overall survival and permanent ventilation-free survival (described as event-free survival) were modelled. Patients who achieved motor function milestones (sits unassisted, walks unassisted or within broad range of normal development) were not considered to be at risk of transitioning to permanent assisted ventilation, and as such, could only transition to death.

In the base case analysis, it is assumed that the motor function milestones achieved at the end of follow-up in the clinical trials were sustained until death (i.e. patients stay in the same motor function milestone-based health state at the end of the short-term model until death). Backwards transitions, i.e. regression from higher functioning health states to worse functioning health states are only applicable for patients that discontinue nusinersen (discontinuation does not apply to onasemnogene abeparvovec as it requires a one-time, single IV administration).

A technical consideration when pooling the data from the START and STR1VE-US trials for use in the revised economic model is the difference in follow-up periods of each respective trial. START followed patients to 24 months post-dose (approximately 30 months of age), whereas STR1VE-US captured outcome data only up to 18 months of age[29]. Due to the relatively short follow-up period of STR1VE-US (up to 18 months of age), the revised economic evaluation presented includes the base case assumption that from the STR1VE-US cohort, there will be one additional independent sitter and one additional independent walker between 18 months and 30 months of age. Please see Section 8.2.1.1 for more details.

[29] The End of Study visit must occur within 0 to 14 days after the date on which the patient reaches 18 months of age (or early termination).

8.1.3.2 Justify the chosen structure in line with the clinical pathway of care.

The model framework was conceptualised with clinical experts (see Section 8.1.3.3), drawing on frameworks developed for other SMA pharmacotherapies and models for similar rare genetic neuromuscular disorders, such as Duchenne's muscular dystrophy. In addition, using a five functioning health state model framework (from permanent assisted ventilation [E state] to within broad range of normal development [A state]) that applies a short-term (observed data) and a long-term (extrapolation) modelling period, is broadly aligned to the model structure chosen by the US ICER institute, who recently published an assessment of SMA therapies (74).

Prior to the development of disease-modifying therapies for SMA type 1, patients would never achieve motor milestones, such as sitting unassisted, and would experience rapid, progressive deterioration and mortality without permanent assisted ventilation, typically by the age of 2 years. With the development of innovative therapies, children with SMA type 1 now have the potential to attain motor milestones, which correlate with improved functionality, HRQoL and survival. The economic model consequently considers these outcomes by including health states aligned with motor milestone development.

The model structure captures the main drivers of costs, mortality and HRQoL associated with SMA type 1 to ensure that the natural history of SMA type 1 is modelled accurately. In addition, the model uses SMA type 2 and SMA type 3 populations managed with BSC only as proxies for SMA type 1 pharmacotherapy-treated patients' resource utilisation, survival and outcomes in higher functioning health states (C state [sits unassisted] and B state [walks unassisted]), as under BSC, SMA type 1 patients would never reach such health states.

A *de novo* UK HCRU study with n=16 UK clinical experts (see Section 8.3.1.1), was conducted by AveXis to determine the HCRU costs associated with BSC, to ensure the model accurately captured the current UK clinical pathway of care for SMA patients (75). Aligned to the expert advice provided and literature searched, the model structure accounts for the following costs associated with BSC:

- Consultations with the MDT responsible for the care of SMA patients (e.g. neuromuscular specialists, respiratory physicians, physiotherapists, nutritionists, nurses [community and hospital based] etc.)
- Hospitalisations (accident and emergency department [A&E] and overnight admissions)
- Pharmacotherapies for treatment of SMA-related symptoms and comorbidities
- Tests, devices and surgeries – including those required for ventilatory and nutritional support
- Community and social care services (including personal and respite care)
- Patient and caregiver out of pocket costs (via an additional scenario analysis only)

8.1.3.3 Provide a list of all assumptions in the model and a justification for each assumption.

The model is underpinned by three foundational assumptions:

1. **Onasemnogene abeparvovec will have a lifelong duration of effect**

    a. The missing/dysfunctional *SMN1* gene is replaced and normal gene biology is restored, which results in long-term motor neuron survival for innervation and the development functioning neuromuscular junctions and skeletal muscles

    Justification: The results of LT-001 to date indicate that a one-time IV administration of onasemnogene abeparvovec at the therapeutic dose provides prolonged efficacy for durations longer than 5 years (up to 61.9 months) post gene therapy administration (13). In addition, the mechanism of action of onasemnogene abeparvovec results in the delivery of a stable, functioning *SMN* gene that remains in non-mitotic cells indefinitely and enables continuous and sustained SMN protein expression, eliminating the need for repeat administration of onasemnogene abeparvovec. Evidence from animal models also support the prolonged duration of effect of onasemnogene abeparvovec (47, 48)

2. **Survival is improved in correlation with motor function milestone achievement, and life expectancy can be estimated using proxies**

    a. The model uses long-term survival data (observed and extrapolated) for untreated SMA patients who sit unassisted (SMA type 2 used as proxy) and walk unassisted (SMA type 3 used as proxy) to predict survival for pharmacotherapy-treated SMA type 1 patients who achieve motor milestones

    Justification: The use of proxy long-term survival data in the model was the approach adopted in the US ICER independent analysis of the comparative clinical effectiveness and value of onasemnogene abeparvovec and nusinersen for SMA (74) and was considered appropriate by participants in the UK clinical advisory board (56)

3. **Costs and utilities for each motor milestone group can be estimated using proxies**

    a. The model base case uses UK HCRU costs and utilities for SMA patients receiving BSC only who sit unassisted (SMA type 2 used as proxy) and walk unassisted (SMA type 3 used as proxy) to predict the costs and utilities of pharmacotherapy-treated SMA type 1 patients who achieve motor milestones

    Justification: The use of proxy long-term survival data in the model was the approach adopted in the US ICER independent analysis of the comparative clinical effectiveness and value of onasemnogene abeparvovec and nusinersen for SMA (74) and was considered appropriate by participants in the UK clinical advisory board (56)

These assumptions were considered acceptable by key opinion leader (KOL) expert advisors consulted during model conceptualisation (Section 8.2.5). In addition, these underpinning assumptions were accepted for use by the independent US ICER in their recent assessment of SMA pharmacotherapies (74). A full list of assumptions, justification and sources used in the model is provided in Table 44.

Table 44: Base Case Model assumptions

#	Intervention(s)	Assumption and rationale	Source(s)and justification(S)	Management of uncertainty
Treatment benefit				
1	Onasemnogene abeparvovec	Onasemnogene abeparvovec will have a lifelong duration of effect, because the missing/dysfunctional *SMN1* gene is replaced and normal gene biology is restored. Motor function milestones achieved at the end of follow-up in START and STR1VE-US are sustained until death. Due to the relatively short follow-up period of STR1VE-US (up to 18 months of age), the revised economic evaluation presented includes a base case assumption that from the STR1VE-US cohort, there will be one additional independent sitter and one additional independent walker between 18 months and 30 months of age. Please see Section 7.2.1.1 for more details	KOL model conceptualisation UK clinical advisory board (56) (Section 8.2.5) US ICER (74) Section 8.2	Use of modelled scenario analyses that uses empirical data only from STR1VE-US, i.e. employs no extrapolation of milestone outcomes between 18 months to 30 months of age
2	Onasemnogene abeparvovec	Children who were observed walking unassisted (B state) during START and STR1VE-US before 2 years of age are transitioned to the A state (within broad range of normal development) at 5 years of age. Walking independently by 2 years of age is reflective of normal development, as per the WHO reported windows of motor milestone achievement in healthy children	UK clinical advisory board (56) (Section 8.2.5) WHO Motor Development Study (24)	The ERG-preferred base case is to apply B state costs to the A state (essentially no A state for the model). This approach is adopted in the revised economic model base case.
3	Nusinersen†	Duration of effect continues while patients continue treatment with nusinersen; motor function milestones achieved in SHINE (Day 578) are sustained until death, whilst patients remain on treatment	SHINE (76) US ICER (74) Section 8.2	As a proportion of patients in ENDEAR had a 4-point worsening in CHOP-INTEND whilst on nusinersen, this is considered a conservative assumption and therefore not probed further
4	Onasemnogene abeparvovec and nusinersen†	The model uses UK HCRU costs and utilities for SMA type 2 and SMA type 3 patients managed with BSC alone as proxy for pharmacotherapy-treated SMA type 1 patients:	KOL model conceptualisation UK clinical advisory board (56) (Section 8.2.5)	Use of modelled scenario analyses where different sources for utilities are used

#	Intervention(s)	Assumption and rationale	Source(s)and justification(S)	Management of uncertainty
		• C state (sits unassisted) is assumed to have HCRU costs and utilities of SMA type 2 patients managed with BSC • B state (walks unassisted) is assumed to have HCRU costs of SMA type 3 patients managed with BSC and utilities of the general population (base case) • A state (within normal range of development) is assumed to have the same HCRU costs as B state (i.e. costs of untreated SMA type 3 patients) and utilities of the general population Based on the above assumptions applied for B and A states, it is assumed that the two states have the same associated costs and utilities in the updated economic model base case.	US ICER, C and B states (74) Interim ERG report. Edwards et al. 2020 (61) Sections 7.1, 8.2.5, and 8.3.1.1	Use of additional scenario analyses where different sources for HCRU costs are used
5	Onasemnogene abeparvovec and nusinersen†	Observed milestone attainment data are incorporated into the short-term model using a conservative approach, as the milestones attained in the trials (START/STR1VE-US or ENDEAR/SHINE) are 'offset' by a cycle when incorporated into the model: patients observed achieving a motor milestone during a model cycle are transitioned in the next model cycle. For example, if a patient was observed to sit unassisted at 9 months of age in a clinical trial (i.e. during cycle 2 [6 to 12 months of age]), they would not contribute to the transition probability of moving from the D state (not sitting) to the C state (sits unassisted) until cycle 3 (12 to 18 months of age).	KOL expert opinion – model conceptualisation Section 8.2	Use of an additional scenario analysis where this conservative model 'offset' is not applied to milestone outcomes
6	All interventions	All base case pairwise analyses use naïve, unanchored comparisons. There are no head-to-head trials comparing onasemnogene abeparvovec to comparators, and sample sizes are limited to conduct robust matched, adjusted indirect comparisons or simulated treatment comparisons. Thus, the model makes no adjustment for differences in patient characteristics between the studies	Unanchored ITC (see Section 9.8.1 in the original company submission)	-

#	Intervention(s)	Assumption and rationale	Source(s)and justification(S)	Management of uncertainty
Loss of treatment effect				
7	Nusinersen†	Regression from higher functioning health states to worse functioning health states is only applicable for patients who discontinue nusinersen. Nusinersen is a chronic therapy with a CSF half-life of around four to six months; therefore, treatment effect is no longer maintained after cessation of therapy. It is assumed the annual probability of regression through the health states is 90%	Nusinersen SmPC (72) Section 8.2 KOL opinion – model conceptualisation	-
Survival				
8	Onasemnogene abeparvovec	The revised economic model base case applies 100% survival in the first 5 cycles (up to 30 months of age) for the C and B states, to reflect the empirical survival data available for sitting and walking patients treated with onasemnogene abeparvovec from START and STR1VE-US. This is in line with the 'ERG-preferred base case' described in the interim ERG report for this appraisal	Interim ERG report. Edwards et al. 2020 (61) Section 8.2	
9	Onasemnogene abeparvovec and nusinersen†	Survival is improved in correlation with motor milestone achievement, and life expectancy can be estimated using proxies. Pharmacotherapy-treated SMA type 1 patients who are in the: • C state (sits unassisted) are assumed to have a life expectancy like that of SMA type 2 patients managed by BSC • B state (walks unassisted) are assumed to have a life expectancy like that of SMA type 3 patients managed by BSC, which is equivalent to the general population • A state (within broad range of normal development) are assumed to have a life expectancy of the general population	KOL opinion – model conceptualisation UK clinical advisory board (56) (Section 8.2.5) US ICER, C and B states (74) Section 8.2	Use of modelled scenarios to probe more optimistic survival in C state, whereby general population survival is assumed

<table>
<tr><th>#</th><th>Intervention(s)</th><th>Assumption and rationale</th><th>Source(s)and justification(S)</th><th>Management of uncertainty</th></tr>
<tr><td>10</td><td>Onasemnogene abeparvovec and nusinersen†</td><td>After the observed trial periods, patients who remain in the D state (not sitting) are assumed to follow natural history survival and permanent ventilation-free survival (EFS) curves, in the absence of long-term evidence of continued survival benefit for non-sitting pharmacotherapy-treated SMA type 1 patients. The revised economic model base case uses a survival limit of 48 months in the D state for both the pharmacotherapy arms and the BSC arm, which reflects the ‘ERG-preferred’ base case described in the interim ERG report for this appraisal</td><td>Interim ERG report. Edwards et al. 2020 (61)
Section 8.2</td><td>Four different sources for natural history in the D state are provided
Model functionality, which allows the user to amend the survival limit in the D state for each treatment arm individually and independently from one another</td></tr>
<tr><td colspan="5">HCRU costs</td></tr>
<tr><td>11</td><td>Onasemnogene abeparvovec</td><td>It is assumed the HCRU costs required for the one-time IV administration of onasemnogene abeparvovec (including pre-infusion baseline tests, AAV9 antibody testing [to be funded by AveXis], pre-, peri- and post-infusion monitoring) are captured in the existing NHS reference codes of PR01 and AA25. This assumption is based on UK clinical expert advice that the one-time IV infusion with onasemnogene abeparvovec will require one pre-infusion visit at a secondary/tertiary neuromuscular centre followed by a two-night, three-day elective stay at a highly specialised infusion centre</td><td>UK clinical advisory board (56) (Section 8.2.5)
Resource identification (Section 8.3.2.2)</td><td>Use of additional scenario analyses to assess significantly higher (10-fold) administration costs</td></tr>
<tr><td>12</td><td>All treatment arms</td><td>For the purposes of estimating health state HCRU costs, it is assumed patients receive ventilatory support under the following different healthcare settings:
<table>
<tr><th>Ventilation group</th><th>Paediatric intensive care</th><th>High dependency</th><th>Home-based</th></tr>
<tr><td>Patients on NIV <16 hours per day</td><td>5%</td><td>5%</td><td>90%</td></tr>
<tr><td>Patients on NIV >16 hours per day</td><td>15%</td><td>15%</td><td>70%</td></tr>
</table></td><td>UK clinical advisory board (56) (Section 8.2.5)
Sections 8.2 and 8.3.2.2</td><td>Use of additional scenario analysis using alternative sources for HCRU costs</td></tr>
</table>

#	Intervention(s)	Assumption and rationale	Source(s)and justification(S)	Management of uncertainty
		Tracheostomy patients 10% 30% 60%		
Discontinuation				
13	Nusinersen†	To reflect the MAA stopping rule, patients discontinue nusinersen in the E state (permanent assisted ventilation) or due to an annual risk of withdrawal (3%). The annual risk of withdrawal accounts for discontinuation due to reasons of patient/caregiver preferences [e.g. decision to avoid further hospital attendance], inability to administer nusinersen by intrathecal administration because of spinal fusion surgery or a worsening in motor function. The rate of annual risk of withdrawal (3%) is from ENDEAR (proportion achieving a 4-point worsening in CHOP-INTEND) and reported withdrawal rates (n=3/95 withdrew treatment) from the nusinersen UK/Ireland EAP.	Nusinersen MAA (73) Nusinersen SmPC (72) Nusinersen UK/Ireland EAP (60) Section 8.2	Model functionality, which allows the user to amend discontinuation rates and rules

#	Intervention(s)	Assumption and rationale	Source(s)and justification(S)	Management of uncertainty
Utilities				
14	Onasemnogene abeparvovec and nusinersen†	Improved clinical outcomes for pharmacotherapy-treated patients versus patients on BSC translates into greater HRQoL. Although the interim milestones (e.g. head control, rolling, crawling and standing with/without assistance) and non-motor milestone features that may be achieved with pharmacotherapy (e.g. improvements in talking and non-verbal communication, fine motor control and learning etc.) are not modelled as explicit health states, according to the 'ERG-preferred' base case, an on-treatment utility benefit is assumed in both pharmacotherapy arms to account for achieving benefits of treatment. The following on-treatment utility increments are applied in the base case analysis: • D state: 0.1 (as per US ICER assumptions) • C state: 0.05 (as per US ICER assumptions)	US ICER (74) Interim ERG report. Edwards et al. 2020 (61) Section 7.1	Use of additional scenario analysis that apply different on-treatment utility increments
15	Onasemnogene abeparvovec and nusinersen†	Disutilities associated with adverse events or administration of treatments were not included in the model. Given the nature of SMA, it is difficult to separate utilities due to treatment from the complications associated with SMA, which are already accounted for in the health state utility values. As such, separate disutilities for adverse events or administration procedures are not included in the model	US ICER (74) Section 7.1	

Abbreviations: AAV, adeno-associated virus; BSC, best supportive care; CHOP-INTEND, Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders; CSF, cerebrospinal fluid; EAP, early access plan; ERG, Evidence Review Group; HCRU, healthcare resource utilisation; HSUV, health state utility value; US ICER, US Institute for Clinical and Economic Review; ITC, indirect treatment comparison; IV, intravenous; KOL, key opinion leaders; MAA, managed access agreement NIV, non-invasive ventilation; OS, overall survival; QoL, quality of life; SMA, spinal muscular atrophy; SmPC, summary of product characteristics; SMN, spinal moto neuron; UK, United Kingdom; US, United States; WHO, World Health Organization.

† The cost-effectiveness results of onasemnogene abeparvovec versus nusinersen are not presented in this updated submission, as nusinersen is no longer considered a comparator for this appraisal. As the revised economic model Excel file (.xlsm) submitted to NICE still includes a nusinersen arm, for completion, the methods and inputs sections relating to the nusinersen arm of the economic model are described

8.1.3.4 Define what the model's health states are intended to capture.

Whilst the health states primarily capture the major motor function milestones achieved by patients, they are also intended to capture the likely associated complications and features of SMA (Table 45).

Table 45: Functional status across health states

State	Motor features	Additional features
A	Within a broad range of normal development	• Within a broad range of normal development
B	Walks unassisted	• No breathing difficulties • Number and severity of chest infections similar to a typically developing child of the same age • Does not require a feeding tube – few difficulties swallowing, is able to eat and, for instance, swallow water • Talking ability similar to that of a typically developing child of the same age
C	Sits unassisted	• May have breathing problems and sometimes require NIV • Development of chest infections more frequently than a typically developing child of the same age • Some difficulties with eating and swallowing but able to swallow thin liquids and take some food by mouth • Risk of choking • Temporary placement of a gastric tube may be required • Requires help moving • Can talk, but ability to speak will deteriorate over time
D	Not sitting	• Experiences breathing problems and requires regular NIV for a number of hours every night or during the day • Development of chest infections more frequently than a typically developing child of the same age • Difficulties feeding and swallowing • High risk of choking • Only able to swallow thick fluids • Fed by a feeding tube (gastrostomy) surgically placed directly into the stomach • Requires moving regularly to prevent sores • Unable to talk, but can make sounds and cry
E	Permanent assisted ventilation	• Require 24-hour non-invasive ventilation • May require a tracheostomy if NIV is not working well • Require gastrostomy to be surgically placed directly into the stomach due to difficulty feeding and swallowing

State	Motor features	Additional features
		• High risk of choking • Require moving regularly to prevent sores • Develop chest infections more often than healthy children of the same age • Unable to talk, but can make sounds and cry

Abbreviations: NIV, non-invasive ventilation.

8.1.3.5 Describe any key features of the model not previously reported. A suggested format is presented below in table D4.

Table 46: Key features of model not previously reported

Factor	Chosen values	Justification	Reference
Time horizon of model	Lifetime horizon.	SMA type 1 is a progressive, lifelong, life-limiting disease and patients will continue to need management and/or treatment for the whole of their lives. NICE guidance states that model time horizons should be long enough to capture all benefits of the treatment.	NICE guide to the methods of technology appraisal 2013 (77)
Discount of 3.5% for costs	3.5%	In line with NICE guidance.	NICE guide to the methods of technology appraisal 2013 (77)
Perspective (NHS/PSS)	NHS and PSS in England	In line with NICE guidance.	NICE guide to the methods of technology appraisal 2013 (77)
Cycle length	6-month cycles for first 3 years, 12-month cycles for remainder of model	A 6-monthly model cycle was chosen in the first three years, to allow changes in childhood development and milestone achievement to be adequately captured.	KOL opinion – model conceptualisation

Abbreviations: KOL, key opinion leader; NHS, National Health Service; PSS, personal and social services; SMA, spinal muscular atrophy.

8.2 *Clinical parameters and variables*

8.2.1 Describe how the data from the clinical evidence were used in the cost-effectiveness analysis.

8.2.1.1 Motor function milestone achievement

Onasemnogene abeparvovec

For the updated base case, motor milestone attainment data has been derived from the two completed trials – START and STR1VE-US – and pooled into one dataset (hereinafter referred to as the 'POOLED' dataset). The POOLED dataset has been estimated by summing up the number of patients attaining a milestone in the same cycle from each trial. This increased the total patient number used for the pooled dataset to 34 patients (START, Cohort 2: 12 patients; STR1VE-US: 22 patients).

A technical consideration when pooling the data from the START and STR1VE-US trials for the revised economic model is the difference in follow-up periods of each respective trial.

START followed patients to 24 months post-dose (approximately 30 months of age), whereas STR1VE-US captured outcome data only up to 18 months of age[30]. There is evidence to support that using an 18-month age timepoint as the basis for estimating maximum milestone attainment would result in an underestimate of the potential benefit from onasemnogene abeparvovec. For this reason, the economic evaluation presented includes a base case assumption that from the STR1VE-US cohort, there will be one additional independent sitter and one additional independent walker between 18 months and 30 months of age. Table 47 below indicates the proportion of patients who 'sit alone' and 'walk alone' in STR1VE-US based on empirical data (up to 18 months of age) versus the base case assumption (up to 30 months of age) used in the revised base case:

Table 47: Milestone outcomes in STR1VE-US: Empirical versus model base case assumption

	STR1VE-US, N=22¶ Empirical, n (%) By 18 months of age	**STR1VE-US, N=22¶ Base case assumption, n (%) By 30 months of age**
Non-sitters†	8 (36.4%)	7 (31.8%)
Sits alone‡	14 (63.6%)††	15 (68.2%)††
Walks alone§	1 (4.5%)	2 (9.1%)

† Includes one patient who died aged 7.7 months and one patient who met the permanent-assisted ventilation event endpoint aged 11 months.
‡ Bayley Scales gross motor subtest item #26: Child sits alone without support for at least 30 seconds
§ Bayley Scales gross motor subtest item #43: Child takes at least 5 steps independently, displaying coordination and balance
¶ Numbers and percentages across the three rows are greater than N=22 and 100%, respectively, since patients can attain multiple milestones. For example, the patients who can walk alone can also sit alone
††For one patient in STR1VE-US the milestone of sits unassisted ≥30 seconds was not confirmed at the end of study 18 month visit but was observed at the 16-month and 17-month visit. This patient did sit unassisted for ≥5 seconds at the 18-month visit (as recorded in the Bayley Scale assessment, gross motor item #22).

The appropriateness of including additional milestone attainment between 18 months and 30 months of age for the STR1VE-US cohort in the base case model was tested at an internal clinical expert steering committee (March 2020). The conclusions of this internal clinical expert steering committee indicated that it is highly unlikely that the milestone attainment at 18 months of age in STR1VE-US is representative of the final outcomes patients may achieve; additional long-term follow-up is required to establish further milestone attainment after 18 months of age. Therefore, it was considered plausible that further milestones will be attained after 18 months of age based on the following observations:

- STR1VE-US stopped when patients reached 18 months of age[30], which is only just past the upper limit of the WHO window for walking independently in normal childhood development (17.6 months is the 99th percentile for walking independently (24)). This (18 months of age) is too strict a threshold at which to expect all

[30] The End of Study visit must occur within 0 to 14 days after the date on which the patient reaches 18 months of age (or early termination).

symptomatic SMA type 1 patients treated with onasemnogene abeparvovec to have achieved all gross motor milestones by

- START data showed that patients continue to develop key gross motor milestones (sitting alone and walking alone) beyond 18 months of age. In START, 5 patients sat unassisted after 18 months of age and 2 patients walked unassisted after 18 months of age
    - START and STR1VE-US data showed that symptomatic SMA type 1 patients achieve gross motor milestones, but these are 'delayed' compared with WHO windows or normal childhood development: In START, the median age at sitting alone and walking alone was 17.1 months (range: 8.0 – 30.8 months) and 19.3 months (range: 18.9 – 19.6 months, respectively.
    - In STR1VE-US, the median age at sitting alone was 12.6 months (range: 9.2 – 18.6 months)
    - As STR1VE-US stopped when patients reached 18 months of age, it is likely later or 'delayed' milestones will not be fully captured and hence a trial stopping at 18 months of age is likely to underestimate the overall maximum milestones attained by patients
- Although the internal clinical experts consulted with described that using a single baseline characteristic or clinical outcome to predict future milestone attainment is not feasible based on the current data available, notable characteristics of the STR1VE-US cohort that provide support that additional patients may go on to sit alone and walk alone between 18 months and 30 months of age include:
    - At 18 months of age, one of the non-sitters ([redacted]) had a CHOP INTEND score of 58. This score (of 58) is above the mean CHOP INTEND score (of 52) at the first visit at which independent sitting was observed in the n=14 who sat alone during STR1VE-US (range: 41–64)
    - Data from the onasemnogene abeparvovec clinical trial programme indicate the earlier the treatment, typically the better the outcomes observed in children with SMA. Among the non-sitters and non-walkers at 18 months of age, one non-sitter ([redacted]) and one non-walker ([redacted]) received gene replacement therapy at less than 2 months of age
    - Two of the non-sitters ([redacted]) at 18 months of age had achieved other notable milestones of head control and rolls from back to side
- The clinical experts noted that of the patients who achieved independent sitting by 18 months of age, but not independent walking, none had achieved the interim milestones of crawls, pulls to stand or standing with assistance, which may lead to an interpretation that patients 'plateaued' in terms of milestone attainment. However, the classification used to define milestones in the trial are 'strict' in that patients had to comply with the exact criteria in the specified Bayley Scales item for each milestone. These binary measurements of milestone attainment do not capture when patients are moving towards attaining a particular milestone. Furthermore, the attainment of

these milestones requiring core and limb strength is likely to be 'delayed' in treated symptomatic SMA type 1 patients compared with healthy peers, and hence follow up after 18 months of age is required to capture the full extent of treatment benefit.

Whilst it is clinically expected that STR1VE-US patients will attain additional outcomes after 18 months of age, it is difficult to predict the exact number of additional sitters and additional walkers from a single baseline characteristic or observed clinical outcome. Therefore, a conservative approach is taken: the presented base case assumption includes the minimum number of additional milestones in the 'sits alone' and 'walks alone' category after 18 months of age, i.e. it includes one additional independent sitter and one additional independent walker. Furthermore, these additional milestones are assumed to occur at the last cycle of the short-term model – i.e. between 24 months and 30 months of age, which equates to between 30 to 36 months of age (model cycle 6) due to the milestone 'offset' approach, which is described below.

It should be noted that no assumptions/extrapolations are made to the milestone data observed in START when these are pooled with the STR1VE-US cohort and incorporated into the revised model. Table 49 describes the POOLED milestone data used in the revised model base case.

A conservative approach is used to incorporate motor milestone attainment data into the short-term model, as the milestones attained in POOLED are 'offset' by a cycle when incorporated into the model: patients observed achieving a motor milestone during a model cycle are transitioned in the next model cycle. For example, if a patient was observed to sit unassisted at 9 months of age (i.e. during cycle 2 [6 to 12 months of age]), they would not contribute to the transition probability of moving from the D state (not sitting) to the C state (sits unassisted) until cycle 3 (12 to 18 months of age). Table 49 describes how the POOLED dataset are 'offset' and subsequently modelled in the economic analysis. As a result of using this 'offset' approach when incorporating motor milestones from the POOLED dataset into the model, it is appropriate for the short-term model time horizon for motor milestone attainment to be up to cycle 6 (up to 36 months of age), i.e. 6 months longer than the observed data in START (up to 30 months of age) and STR1VE-US (up to 18 months of age). AveXis considers this approach as conservative because milestone attainment is being modelled as occurring at a later age than was observed in both trials. A scenario analysis is also presented during which this conservative 'offset' is not applied to milestone data in the model, please see Section 8.5.2.2.

The definition used for 'sitting unassisted' when incorporating milestones from START into the POOLED base case analysis is 'sitting unassisted for ≥5 seconds in accordance with the criteria of item 22 on the Bayley-III assessment tool gross motor subtest'. This outcome was chosen as attainment was confirmed through video review by an external reviewer. The threshold of sitting alone for ≥30 seconds was not chosen as the clinical outcome for independent sitters from START for the model as two patients ([redacted] and [redacted]) would no longer contribute to the modelled cohort who reside in the C state (sits unassisted) and hence remain in the D state (non-sitting). This was considered by the company to be an overly pessimistic scenario as:

- Patient [redacted] subsequently achieved [redacted]

- Patient [redacted] during START achieved the milestone of 'sits unassisted for ≥10 seconds' in accordance with the WHO Multicentre Growth Reference Study criteria: '*Child sits up straight with head erect for at least 10 seconds. Child does not use arms or hands to balance body or support position'*. In addition, patient [redacted] has subsequently achieved [redacted]

The definition used for 'sitting unassisted' when incorporating milestones from STR1VE-US into the POOLED base case analysis is 'sitting unassisted for ≥30 seconds in accordance with the criteria of item 26 on the Bayley-III assessment tool gross motor subtest'. This outcome was chosen as it is the co-primary endpoint of STR1VE-US and this outcome was one of the milestones confirmed through video review by an external reviewer.

No extrapolation of motor milestone achievements from the short-term model to the long-term model is assumed, i.e. motor function milestones achieved at the end of follow-up in START and STR1VE-US (including the additional sitter and additional walker of the STR1VE-US base case assumption) are sustained until death. Limiting motor milestone achievement (i.e. forward transitions to higher functioning health states) to the first 6 model cycles after treatment with onasemnogene abeparvovec can be considered conservative, as continued improvement in motor function has been observed in LT-001 (long-term follow-up of START), after 24 months post-treatment (see Section 6.3.1.2).

Children who were observed walking unassisted (B state) before 2 years of age during START and STR1VE-US are transitioned to the A state (within a broad range of normal development) at 5 years of age. Walking independently by 2 years of age is reflective of normal development, as per the WHO reported windows of motor milestone achievement in healthy children (28). It should be noted that in the updated base case analysis, all HCRU costs and clinical outcomes (utilities and survival) associated with the B state (walks unassisted) and A state (within broad range of normal development) are the same. This approach aligns to the 'ERG-preferred base case' as reported in the interim ERG report.

In order to explore different scenarios of milestone achievements after treatment with onasemnogene abeparvovec, scenario analyses have been included in the model based on data and assumptions from the START and STR1VE-US trials. Table 48 describes these scenarios in detail, with results presented Section 8.5.2.2.

Table 48: Exploratory scenarios of milestone achievements after treatment with onasemnogene abeparvovec

Scenario	Explanation/Justification
Use of POOLED dataset, but with only one additional sitter compared with empirical data in STR1VE-US after 18 months of age. The additional sitter sits between 24 - 30 months of age and therefore moves to sitting in cycle ending 36 months This is more conservative than the base case	In STR1VE-US, one additional patient who can sit unassisted sits between 24–30 months of age and therefore moves to C state in cycle ending 36 months
Use of POOLED dataset, but with only one additional walker compared with empirical data in STR1VE-US after 18 months of age. The additional walker walks between 24–30 months of age and therefore moves to walking in cycle ending 36 months This is more conservative than the base case	In STR1VE-US, one additional patient who can walk unassisted walks between 24–30 months of age and therefore moves to B state in cycle ending 36 months
Use of POOLED dataset but use of the empirical data only from STR1VE-US. i.e. it assumes there are no additional patients who can sit or walk unassisted in STR1VE-US after 18 months of age This is more conservative than the base case and is the most conservative approach	No additional milestones are observed after 18 months of age for STR1VE-US patients
Use of POOLED dataset, but with 4 new patients who can sit unassisted and 4 new patients who can walk unassisted in STR1VE-US (half in cycle ending 30 months; half in cycle ending 36 months) This is less conservative than the base case	In STR1VE-US, two of the additional patients who can sit unassisted, and two of the additional patients who can walk unassisted walk between 18 -24 months of age, and therefore move to C and B states in cycle ending 30 months, respectively. In addition, two of the additional patients who can sit unassisted sit, and two of the additional patients who can walk unassisted walk between 24–30 months of age, and therefore move to C and B states in cycle ending 36 months, respectively.
Use of the POOLED dataset, but the conservative 'offset' is not applied to milestone data in the model This is less conservative than the base case	Milestones are incorporated into the model, as they were observed in clinical trials. For example, if a patient sits at 9 months old, they would transition to the sitting health state in cycle 2 (between 6 and 12 months of age)
Milestones, overall survival and event-free survival are based on those treated at ≤3.5 months of age in START and STR1VE-US (n=17)	Of those treated at or before 3.5 months of age across START and STR1VE-US, n=14/17 (82.4%) sat independently of which n=3/17 (17.6%) also walked independently Of those treated at or before 3.5 months of age across START and STR1VE-US, one patient died and no patients went on to permanent assisted ventilation (OS = 94.1% and EFS = 94.1%)
Milestone achievement based on START trial data	Milestone achievement is according to observed data in START as shown in Table 50

Table 49: Proportions of patients achieving motor milestones in the POOLED data versus 'offset' data for those that are alive and event-free†

Cycle	Age at end of cycle (mo.)	Observed‡ Inclusive of the base case assumption: one additional sitter and one additional walker in STR1VE-US						'Offset' modelled§ Inclusive of the base case assumption: one additional sitter and one additional walker in STR1VE-US					
		Not sitting		Sitting but not walking¶††		Walking		Not sitting		Sitting but not walking¶††		Walking	
		n	%	n	%	n	%	n	%	n	%	n	%
1	6	34	100.0%	0	0.0%	0	0.0%	34	100.0%	0	0.0%	0	0.0%
2	12	24	75.0%	8	25.0%	0	0.0%	32	100.0%	0	0.0%	0	0.0%
3	18	13	40.6%	18	56.3%	1	3.1%	24	75.0%	8	25.0%	0	0.0%
4	24	9	28.1%	20	62.5%	3	9.4%	13	40.6%	18	56.3%	1	3.1%
5	30	6	18.8%	22	68.8%	4	12.5%	9	28.1%	20	62.5%	3	9.4%
6	36	N/A‡‡	N/A‡‡	N/A‡‡	N/A‡‡	N/A‡‡	N/A‡‡	6	18.8%	22	68.8%	4	12.5%

Abbreviations: mo., month; N/A, not applicable.

† Proportions achieving milestones are calculated based on those who are alive and event-free.

‡ Date at milestone attainment is sourced from the START CSR 'Listing 16.2.6.6-24 Development Milestones Observed All Patients' and converted to age using patients' date of birth. For two patients ([redacted] and [redacted]) in START date at milestone attainment was not available in this listing; therefore, the date of milestone attainment was imputed using the date of the last study visit for these two patients. For STR1VE-US, age at milestone attainment is taken from 'Listing 16.2.6.1 Listing of Age at which Central Confirmed Developmental Milestones first achieved'. 'Observed' data also includes the base case assumption of one additional sitter and one additional walker in the STR1VE-US cohort between 24–30 months of age, as per the described base case assumption of the revised model

§ The motor milestones attained in START and STR1VE-US have been 'offset' by a model cycle in the modelled data. For example, if a patient was observed to sit unassisted at 9 months of age (i.e. during cycle 2 [6 to 12 months of age]), they would not contribute to the transition probability of moving from the D state (not sitting) to the C state (sits unassisted) until cycle 3 (12 to 18 months of age). Different green shading in the table has been used to show how the milestones in START and STR1VE-US are 'offset' by a model cycle in the modelled data.

¶ Sitting unassisted for ≥5 seconds is in accordance with the criteria of item 22 on the Bayley-III assessment tool gross motor subtest for START; sitting unassisted for ≥30 seconds is in accordance with the criteria of item 26 on the Bayley-III assessment tool gross motor subtest for STR1VE-US.

†† For one patient in STR1VE-US the milestone of sits unassisted ≥30 seconds was not confirmed at the end of study 18 month visit but was observed at the 16-month and 17-month visit. This patient did sit unassisted for ≥5 seconds at the 18-month visit (as recorded in the Bayley Scale assessment, gross motor item #22).

‡‡ Data are described as not available since the maximum follow-up period for the POOLED data was 24-months post dose (i.e. mainly up to 30 months of age).

Table 50: Proportions of patients achieving motor milestones in START (Cohort 2) data versus 'offset' modelled data†

Cycle	Age at end of cycle (mo.)	Observed‡						'Offset' modelled§					
		Not sitting		Sitting but not walking¶		Walking		Not sitting		Sitting but not walking¶		Walking	
		n	%	n	%	n	%	n	%	n	%	n	%
1	6	12	100.0%	0	0.0%	0	0.0%	12	100.0%	0	0.0%	0	0.0%
2	12	10	83.3%	2	16.7%	0	0.0%	12	100.0%	0	0.0%	0	0.0%
3	18	6	50.0%	6	50.0%	0	0.0%	10	83.3%	2	16.7%	0	0.0%
4	24	3	25.0%	7	58.3%	2	16.7%	6	50.0%	6	50.0%	0	0.0%
5	30	1	8.3%	9	75.0%	2	16.7%	3	25.0%	7	58.3%	2	16.7%
6	36	N/A††	N/A††	N/A††	N/A¶††	N/A††	N/A††	1	8.3%	9	75.0%	2	16.7%

Abbreviations: mo., month; N/A, not applicable.

†Proportions achieving milestones are calculated based on those who are alive and event-free, which in START is 100%.

‡ Date at milestone attainment is sourced from the START CSR 'Listing 16.2.6.6-24 Development Milestones Observed All Patients' and converted to age using patients' date of birth. For two patients ([redacted] and [redacted]) date at milestone attainment was not available in this listing; therefore, the date of milestone attainment was imputed using the date of the last study visit for these two patients.

§ The motor milestones attained and observed in START have been 'offset' by a model cycle in the modelled data. For example, if a patient was observed to sit unassisted at 9 months of age (i.e. during cycle 2 [6 to 12 months of age]), they would not contribute to the transition probability of moving from the D state (not sitting) to the C state (sits unassisted) until cycle 3 (12 to 18 months of age). Different green shading in the table has been used to show how the milestones observed in START are 'offset' by a model cycle in the modelled data.

¶ Sitting unassisted for ≥5 seconds is in accordance with the criteria of item 22 on the Bayley-III assessment tool gross motor subtest.

†† Data are described as not available since the follow-up period for START was 24-months post dose (i.e. mainly up to 30 months of age).

Best supportive care

No patients in the BSC arm are assumed to achieve any motor function milestones (e.g. sits unassisted or walks unassisted) at any time points in accordance with the observed data from natural history studies including:

- NeuroNext, Kolb et al. 2017 (4)
- PNCR, Finkel et al. 2014a (3)
- PNCR, De Sanctis et al. 2016 (30)
- NeuroNext and PNCR databases (5) described in Section 9.4.3.1 in the original company submission, and
- Sham-control arm in ENDEAR (57)

Nusinersen

The data on proportions of nusinersen patients achieving motor function milestones at different time points were based on observed data from SHINE (long-term follow up of ENDEAR). Castro et al. 2018 (78) reported the proportion of patients achieving sitting at different time points, which are presented in Table 51.

With different numbers of patients at risk at each time point, and as the published data on proportion sitting independently is presented as percentages, multiple steps were followed to estimate the proportions of nusinersen patients sitting at the different time points:

- The numbers of patients sitting at each time point were estimated and were rounded to the nearest integer (value ‘A’)
- The number of patients at risk (value ‘B’) were approximated from ventilation-free survival estimates from the digitized KM curve at each time point (78)
- The integer values representing the number of patients sitting (value ‘A’) were divided by the number of patients at risk (value ‘B’) at each time point to estimate the proportions of patients sitting (value ‘C’)

The proportions of patients sitting (value ‘C’) were then used to calculate proportions in each motor function milestone health state at each time point (Table 52). An underlying assumption is that patients who continue nusinersen treatment do not lose milestones gained. Therefore, the proportion of patients achieving sitting unassisted at Day 578 from SHINE is used from cycle 4 onwards, as the proportion achieving this milestone decreased between Day 578 and Day 689 according to data reported in Castro et al. 2018. As per the description provided for how observed milestone data from START and STR1VE-US are ‘offset’ by a model cycle when calculating transition probabilities, the same approach is taken when calculating transition probabilities from observed milestone data from SHINE in the model – please see Table 53 for the resulting ‘offset’ transition probabilities.

Table 51: Proportions of patients achieving motor milestones on nusinersen

Input		Baseline	Day 64	Day 183	Day 302	Day 394	Day 578	Day 689
SHINE data								
Patients with available data, n		81	70	65	51	48	31	17
% Achieved independent sitting†		0%	1%	5%	10%	15%	29%	24%
Calculations								
A	**Independent sitting, n**	0	1	3	5	7	9	4
B	**Alive and ventilation-free patients, n**	81	71	57	45	45	39	39
C	**% of alive and ventilation free sitting independently**	0.00%	1.41%	5.26%	11.11%	15.56%	23.08%	10.26%

† Time spent unassisted not reported. In ENDEAR, independent sitting included HINE-2 score categories: stable sit and pivots (rotates).
Source: Castro et al. 2018 (78). Sources of 'A','B' and 'C' described above in text.

Table 52: Calculated proportions of patients achieving motor milestones on nusinersen

Cycle	Visit (Day)	Approx. age at end of cycle (mo.)‡	Not sitting	Sitting but not walking	Walking
			%	%	%
1	1	6	100.00%	0.00%	0.00%
2	183	12	94.74%	5.26%	0.00%
3	394	18	84.44%	15.56%	0.00%
4	548†	24	76.92%	23.08%	0.00%
5	730	30	76.92%	23.08%§	0.00%
6	913	36	76.92%	23.08%§	0.00%

† Use data reported from SHINE at day 578.
‡ Based on a mean age at first dose of 5.4 months.
§ An underlying assumption is that patients who continue nusinersen treatment do not lose milestones gained. Therefore, the proportion of patients achieving sitting unassisted at Day 578 from SHINE is used from cycle 4 onwards.

Transition probabilities

Transition probabilities between health states were based on the proportion of patients estimated to be sitting unassisted or walking unassisted. The probability of transitioning to a higher functional health state (D state to C state or C state to B state) was calculated using the number of patients who newly achieved motor milestones before the start of each cycle as the numerator and the number of patients in the outgoing state in the previous cycle as the denominator (Table 53).

The model accounts for milestones gained during a cycle in the next full cycle, i.e. calculations are "offset" so that patients are transitioned in the following cycle. This is a conservative approach when assigning motor milestones to cycles. For example, if a patient achieved a motor milestone at age 19 months, that patient only appears as having achieved the milestone for the cycle beginning age 24 months.

Table 53: Transition probabilities for onasemnogene abeparvovec for alive and event-free patients

Cycle	Age at end of cycle (mo.)	Onasemnogene abeparvovec		
		D to C	C to B	B to A
1	6	0.00%	0.00%	0.00%
2	12	0.00%	0.00%	0.00%
3	18	25.00%	0.00%	0.00%
4	24	45.83%	12.50%	0.00%
5	30	30.77%	11.11%	0.00%
6	36	33.33%	5.00%	0.00%
7	48	0.00%	0.00%	0.00%
8	60	0.00%	0.00%	0.00%
9	72	0.00%	0.00%	100.00%†

† Children who were observed walking unassisted (B state) during START and STR1VE-US before 2 years of age who are transitioned to the A state (within broad range of normal development) at 5 years of age. As noted previously, in the revised economic model B state is equivalent to A state in terms of costs and outcomes.

8.2.1.2 Motor function milestone loss

Onasemnogene abeparvovec

Onasemnogene abeparvovec patients do not regress (i.e. lose milestones) in the base case, as per the observed data from START and STR1VE-US. To date, there has been no loss of previously attained milestones for patients who received the therapeutic dose of onasemnogene abeparvovec in START as part of LT-001 (long-term follow-up of START), in which the oldest patient is 5.6 years at the latest data cut (31 December 2019). Furthermore, there is no evidence of the loss of milestones in interim analysis from other ongoing Phase III trials for onasemnogene abeparvovec.

Best supportive care

Transitions associated with loss of milestones (C state to D state and B state to C state) are not included for the BSC arm in the model, as SMA type 1 patients receiving BSC never attain motor milestones in the first place.

Nusinersen

Duration of effect continues while patients remain on treatment with nusinersen and motor function milestones achieved in SHINE (Day 578) are sustained until death. Patients only regress (i.e. lose milestones) if they discontinue nusinersen. Nusinersen is a chronic therapy with a cerebrospinal fluid (CSF) half-life of around four to six months; therefore, treatment effect is no longer maintained after cessation of therapy. It is assumed the annual probability of regression through the health states is 90% for patients that discontinue nusinersen. As described above, this (90%) regression rate is based on CMAP and MUNE values from untreated (i.e. who have not received pharmacotherapy) SMA type 1 patients, which are <10% of normal values (79).

To reflect the nusinersen MAA stopping rule (73), all patients discontinue nusinersen in the E state (permanent assisted ventilation) or due to an annual risk of withdrawal (3%) in the D state and C state. The annual risk of withdrawal accounts for discontinuation due to reasons of patient/caregiver preferences [e.g. decision to avoid further hospital attendance], inability to administer nusinersen by intrathecal administration because of spinal fusion surgery or a worsening in motor function. The rate of annual risk of discontinuation in D state and C state is modelled as 3%. This rate is from taken from data reported in ENDEAR (72) (i.e. 3% of the cohort were reported as achieving a 4-point worsening in CHOP-INTEND) and reported withdrawal rates (n=3/95 withdrew treatment) from the nusinersen UK/Ireland EAP (60).

8.2.1.3 Survival

Survival in each health state is based on observed data and extrapolated survival curves from clinical trials and natural history studies. The sources for survival data for each health state and by treatment arm are described in Table 54 for the base case. Detailed methods used for fitting parametric survival curves to the observed data to extrapolate survival beyond trial and study periods are described in Section 8.2.2.1.

Onasemnogene abeparvovec

In the short-term model for patients in the onasemnogene abeparvovec arm, the observed 24 months post-dose (up to 30 months of age) POOLED dataset from START and STR1VE-US were used directly in the D state. As STR1VE-US patients only provide survival data up to 18 months of age, they are censored from survival curves in the short-term model from 18 months to 30 months of age. Of the pooled N=34 patients from START and STR1VE-US, one patient died, and one patient met the permanent assisted ventilation event endpoint. In the long-term model (i.e. cycle 6 onwards), the parametric natural history curves from the BSC survival data were appended to the clinical trial data beyond the trial period for the onasemnogene abeparvovec arm in the D state. The updated base case assumes a 48 months survival limit in the D state (which can be adjusted separately in each arm of the updated model) in response to the 'ERG-preferred base case' described in the interim ERG report for this appraisal.

In the updated base case, according to the 'ERG-preferred base case' assumptions, 100% survival is modelled in the C state (sits unassisted), B state (walks unassisted) and A state (within broad range of normal development) for cycles 0–5 (i.e. up to 30 months of age) as per the observed data during the follow-up period of START, prior to the respective survival curves for each health state being used from cycle 6 onwards in the long-term model.

Nusinersen

In the short-term model for patients in the nusinersen arm, the observed 34 months post initial dose (modelled as up to 36 months of age) data from SHINE were used directly. In the long-term model, the parametric natural history curves from the BSC survival data were appended to the clinical trial data beyond the trial period for the nusinersen arm in the D state – details are described in Section 8.2.2.1.

Best supportive care

As START and STR1VE-US were single-arm trials, an external natural history control data set is required to model the BSC arm. The comparison made to BSC in the model is an unanchored, naïve comparison and therefore, as no adjustment has been made for differences (known or unknown) in trial populations or differences in study effects, caution is required in any interpretation of results. It should be noted, however, that the eligibility criteria for START and STR1VE-US were very similar with respect to the genetic profile of the SMA type 1 patients enrolled (age at symptom onset <6 months, 2 x *SMN2* copy number) and respiratory function (oxygen saturation levels ≥95% in START and ≥96% in STR1VE-US) and that despite the small sample sizes in all clinical trials used, the analysis performed was the best feasible with the data available at the time.

Four studies reporting the natural history of SMA type 1 patients – including overall survival and event (permanent ventilation)-free survival outcomes – were identified as part of the SLR (see Section 9.3.1 in the original company submission):

- NeuroNext study, as reported in Kolb et al. 2017 (4) and the AveXis external control database (5)
- PNCR study, as reported by Finkel et al. 2014a (3) and the AveXis external control database (5)
- Sham-control arm of the ENDEAR (57)
- Single site, longitudinal study, as reported by Finkel et al. 2014b (80)

For the model base case, the NeuroNext (n=16 with *SMN2* copy x 2) natural history cohort was chosen to inform overall survival and event-free survival for BSC in the D state (non-sitting) as:

- The study is prospective in design
- The study closely resembled the entry criteria for START and STR1VE-US with respect to age and baseline function
- NeuroNext was an external control data set used as part of the EMA regulatory filing for onasemnogene abeparvovec, and hence detailed clinical effectiveness data are described in Section 9.6.1.1 in the original company submission
- Individual patient-level data were available for NeuroNext as part of the external database made available from NeuroNext to AveXis, permitting development of Kaplan-Meier (KM) curves ('disaggregated' and 'aggregated') for the observed period and for onward parametric curve fitting, without reliance on the digitisation of figures
- The genetic profile of NeuroNext (n=16), START and STR1VE-US were equivalent: all patients had bi-allelic deletions of *SMN1* exon 7, *SMN2* copy x 2 and confirmation of exclusion of the *SMN2* modifier mutation c.859G>C
- The generalisability of NeuroNext to the UK SMA type 1 population treated with BSC was confirmed as the UK Clinical Advisory Board (May 2019) (56)

However, the NeuroNext study had a narrower definition for permanent ventilation (defined as time to permanent invasive ventilatory [intubation] only) when compared with START and

STR1VE-US (4). As such, the narrower endpoint of the NeuroNext study does not capture patients who transition to permanent non-invasive ventilation and may underestimate the number of patients transitioning to the E state. Therefore, three alternative sources for overall survival and event-free survival of BSC in the D state are provided as modelled scenario analyses:

- AveXis external control PNCR database, n=23 (5)
- The sham-control arm of ENDEAR, n=41 (Finkel et al. 2017 (57))
- PNCR database plus Italian centre, n=26 (De Sanctis et al. 2016 (30))

Details about the natural history studies used to inform the base case and scenario analyses are further described in Table 55**.** The study reported by Finkel et al. 2014b (80) identified in the SLR was not included as a scenario analysis due to is limitations in design (single site in the US) and small sample size (n=7). The De Sanctis et al. 2016 publication (30), which was identified during full text screening as part of the SLR, was included as a scenario as it is more recent (patients enrolled between 2010 and 2014) thus, may be a better reflection of current standard of care with a higher reported use of ventilatory support and is a multi-country study including a European perspective (includes US and Italy centres). Also, as the De Sanctis et al. 2016 study did not limit inclusion based on *SMN2* copy number, this study is reflective of the real world, mixed genetic profile of SMA type 1 patients, with respect to *SMN2* copy number. It is reported that most patients with SMA type 1 have two copies of *SMN2* (73.4%), with the remaining minority having one or three copies (81).

Table 54: Sources of survival data – base case

Transition	Onasemnogene abeparvovec	Nusinersen	BSC
D to death	**Short-term model, observed data** Ages 0–30 months: POOLED data from START and STR1VE-US (8, 10, 16) **Long-term model, extrapolated data** Ages 30+ months: projected survival using parametric curves fitted to natural history data used for BSC (NeuroNext†)	**Short-term model, observed data** Ages 0–36 months: SHINE trial (78) **Long-term model, extrapolated data** Ages 36+ months: projected survival using parametric curves fitted to natural history data used for BSC (NeuroNext†)	**Short-term model, observed data** Ages 0–24 months: NeuroNext† **Long-term model, extrapolated data** Ages 24+ months: projected survival using fitted parametric curve to observed data from NeuroNext†
D to E	**Short-term model, observed data** Ages 0–30 months: POOLED data from START and STR1VE-US (8, 10, 16) **Long-term model, extrapolated data** Ages 30+ months: projected permanent ventilation-free survival using parametric curves fitted to natural history data used for BSC (NeuroNext†)	**Short-term model, observed data** Ages 0–36 months: SHINE trial (78) **Long-term model, extrapolated data** Ages 36+ months: projected permanent ventilation-free survival using parametric curves fitted to natural history data used for BSC (NeuroNext†)	**Short-term model, observed data** Ages 0–24 months: NeuroNext† **Long-term model, extrapolated data** Ages 24+ months: projected permanent ventilation-free survival using fitted parametric curve to observed data from NeuroNext†
E to death	**Short-term and long-term model:** E state patients requiring PAV are assumed to have long-term survival consistent with an observational study of SMA type 1 patients with tracheostomy or NIV (defined as continuous NRA, including non-invasive ventilation and mechanically assisted cough is the study) published by Gregoretti et al. 2013 (82). For the base case, observed data based on only patients with NIV has been used. The parametric function fitted to the observed data is used for the entire model time horizon, even during the observed period of the study (Section 8.2.2.1)		
C to death	**Short-term and long-term model:** The survival for SMA type 1 patients that can sit unassisted is modelled from the long-term survival of the 52-year prospective and retrospective study of SMA type 2 patients, as reported by Zerres et al. 1997 (83). The parametric function fitted to the observed data is used for the entire model time	**Short-term and long-term model:** The survival for SMA type 1 patients that can sit unassisted is modelled from the long-term survival of the 52-year prospective and retrospective study of SMA type 2 patients, as reported by Zerres et al. 1997 (83). The parametric function fitted to the observed data is	N/A – patients on BSC never reach C state

Transition	Onasemnogene abeparvovec	Nusinersen	BSC
	horizon, except in the first five model cycles (up to 30 months of age), when 100% survival has been modelled according to 'ERG-preferred base case' assumptions	used for the entire model time horizon, even during the observed period of the study	
B/A to death	In the first five model cycles (up to 30 months of age), 100% survival has been modelled according to 'ERG-preferred base case' assumptions. From cycle 6,the survival for SMA type 1 patients that can walk unassisted is modelled based on general population survival from the 2014–2016 UK National Life tables (84)	The survival for SMA type 1 patients that can walk unassisted is modelled based on general population survival from the 2014–2016 UK National Life tables (84)	N/A – patients on BSC never reach A/B state

Abbreviations: BSC, best supportive care; N/A, not applicable; NIV, non-invasive ventilation; NRA, non-invasive respiratory muscle aid; PAV, permanent assisted ventilation; SMA, spinal muscular atrophy.

† NeuroNext cohort as reported in AveXis external control database (n=16 patients with *SMN2* copy x 2) is selected as the data source for BSC in the base case (5).

Table 55: Sources of survival data for BSC – D state, base case and scenario analysis

Characteristic	Base case	Scenario analysis		
	NeuroNext† (5) AveXis external control database	**PNCR‡ (5) AveXis external control database**	**ENDEAR Sham-control Finkel et al. 2017a (57)**	**PNCR De Sanctis et al. 2016 (30)**
Size, n	16	23	41	26
Definition of PAV	Intubation only	Tracheostomy or ≥16 hours of respiratory assistance per day continuously for ≥14 days in the absence of an acute, reversible illness or a perioperative state	Tracheostomy or ventilatory support for ≥16 hours per day for >21 continuous days in the absence of an acute reversible event	Tracheostomy or NIV (time on non-invasive ventilatory support not described)

Characteristic	Base case	Scenario analysis		
	NeuroNext† (5) AveXis external control database	**PNCR‡ (5) AveXis external control database**	**ENDEAR Sham-control Finkel et al. 2017a (57)**	**PNCR De Sanctis et al. 2016 (30)**
Genetic profile	Homozygous deletion of exon 7 in the *SMN1* gene Two copies of the *SMN2* gene Exclusion of the *SMN2* gene modifier mutation c.859G>C	Homozygous deletion of exon 7 in the *SMN1* gene Two copies of the *SMN2* gene	Homozygous deletion or mutation in the *SMN1* gene Two copies of the *SMN2* gene	Homozygous deletion of exon 7 in the *SMN1* gene *SMN2* copy number not reported
Region(s)	US	US	US and Germany	US and Italy
Enrolment years	2012 to 2014	2005 to 2009	2014 to 2015	2010 to 2014
Length of follow-up	24 months	36 months§	13 months (394 days)	24 months
Key results at study end				
Dead, n (%)	8 (50.0)	11 (47.8)	16 (39.0)	12 (46.2)
Dead or PAV, n (%)	10 (62.5)	18 (78.3)	28 (68.3)	24 (92.3)
Alive and PAV, n (%)	2 (12.5)	7 (30.4)	12 (29.3)	12 (46.2)
Alive and ventilation-free, n (%)	6 (37.5)	5 (21.7)	13 (31.7)	2 (7.7)

Abbreviations: BSC, best supportive care; NIV, non-invasive ventilation; PAV, permanent assisted ventilation; SMN, survival motor neuron; US, United States.
† NeuroNext cohort as reported in AveXis external control database (n=16 patients with *SMN2* copy x 2).
‡ PNCR cohort as reported in AveXis external control database (n=23 patients with *SMN2* copy x 2).
§ Previously identified patients and newly diagnosed patients were enrolled. Retrospectively enrolled patients included three patients who were 90 months, 116 months and 171 months old at enrolment; all three of these patients were on permanent assisted ventilation at time of enrolment, with daily time spent on BiPAP at enrolment listed as 24 hours, 24 hours and 20 hours, respectively. A further four patients were aged between 28 to 44 months at enrolment; with permanent assisted ventilation reported at enrolment in one of these patients.

8.2.1.4 Utilities

Full details and justification for the patient health state utility values used in the base case and scenario analyses are described in Section 7.1. For completion, base case values are shown again below in Table 56.

Table 56: Summary of patient utility values used in the base case

State	Description	Utility value	Standard Error	Reference
E state	Permanent assisted ventilation	0.000	0.0000	'ERG-preferred base case' (61)
D state	Not sitting	0.190	0.0095	Thompson et al 2017 (62)
C state	Sits unassisted	0.600	0.0300	Tappenden et al 2018 (63)
B state	Walks unassisted	General population		Ara and Brazier 2010 (64)
A state	Broad range of normal development			

To match the 'ERG-preferred base case' reported in the interim ERG report for this appraisal (61), the updated base case analysis includes an on-treatment utility benefit assumed in the treatment arms to account for achieving 'intra-health state' benefits of treatment. The following on-treatment utilities increments are applied in both treatment arms (onasemnogene abeparvovec and nusinersen) in the base case analysis:

- D state: on treatment utility of 0.1 (as applied in the US ICER base case)
- C state: on treatment utility of 0.05 (as applied in the US ICER base case)

8.2.2 Are costs and clinical outcomes extrapolated beyond the study follow-up period(s)? If so, what are the assumptions that underpin this extrapolation and how are they justified?

8.2.2.1 Clinical outcomes extrapolation – survival

For all survival data, parametric survival curves were fitted to the empirical data to extrapolate survival and calculate transition probabilities using published methods (85). All reconstructions of individual patient data and fitting of parametric curves were conducted using the R software package 'flexsurv' procedure (details of R code used can be found in the 'Survival_R_Code' tab of the executable model) using published methods (86, 87).

Selection of models for survival modelling was informed by methods described in the NICE decision support unit (DSU) report 14 (88) and technical review by ERG as part of this appraisal. Goodness-of-fit was assessed by the following methods:

- Statistically via Akaike information criterion (AIC) and Bayesian information criterion (BIC)

- Visual inspection

Parametric curves fitted to the survival data included exponential, log-normal, log-logistic, Weibull, generalized gamma, and Gompertz curves. The parametric models with the lowest AIC and BIC were used for all parametric curves but for OS and EFS curves in the D state, for which curves were selected based on 'ERG-preferred base case' assumptions (61). All curves were accelerated failure time curves. Following guidance in NICE DSU 14 (88), the same types of parametric models were used for onasemnogene abeparvovec and nusinersen within a health state, i.e. generalised Gamma distributions were used for C state OS in both the nusinersen and onasemnogene abeparvovec arms. To avoid long curve tails leading to clinically implausible survival, curves were terminated based on observed life expectancy, input from clinical expert opinion or based on 'ERG-preferred base case' assumptions. The specific parametric models used in the base case model are shown in Table 57.

Table 57: Summary of survival curves used for the trial periods and beyond (base case)

Survival curve	Model used for trial period	Model used beyond trial period (after 30 months of age)
State E – all arms	Exponential	Exponential
State D – BSC OS (aggregated and disaggregated curves)	Kaplan-Meier (Empirical)	Weibull
State D – BSC EFS	Kaplan-Meier (Empirical)	Weibull
State D – Onasemnogene abeparvovec OS	Kaplan-Meier (Empirical)	Weibull†
State D – Onasemnogene abeparvovec EFS	Kaplan-Meier (Empirical)	Weibull†
State D – Nusinersen OS	Kaplan-Meier (Empirical)	Weibull†
State D – Nusinersen EFS	Kaplan-Meier (Empirical)	Weibull†
State C – Onasemnogene abeparvovec OS	Generalised Gamma	Generalised Gamma
State C – Nusinersen OS	Generalised Gamma	Generalised Gamma
State B and A – Onasemnogene abeparvovec OS	National Life Tables	National Life Tables (84)
State B and A – Nusinersen OS	National Life Tables	National Life Tables (84)

Abbreviations: BSC, best supportive care; EFS, event-free survival; OS, overall survival.
† Uses aggregated and disaggregated curves from natural history trial (NeuroNext) beyond the trial period

E state (permanent assisted ventilation) – All arms

For the model base case analysis, E state patients requiring permanent assisted ventilation are assumed to have long-term survival consistent with an observational study of SMA type 1 patients in Italy with NIV (n=31) (defined as continuous non-invasive respiratory muscle aid [NRA], including non-invasive ventilation and mechanically assisted cough is the study) published by Gregoretti et al. 2013 (82). Maximum survival is set to 16 years.

Because there are no data suggesting that patients who receive disease-modifying treatment experience improved survival after experiencing respiratory insufficiency, it was assumed that all patients in the E state would experience the same survival function with no adjustment by treatment arm.

It is noted that in the NRA group, Gregoretti et al 2013 states that seven patients (7/31 [22.6%]) went on to receive tracheostomy, but it is not clear whether these patients are included in the survival estimates in the NRA curve. However, these data are used to define the proportion receiving tracheostomy (22.6%) versus non-invasive ventilation (77.4%) for calculating health care resource utilisation costs for the E state.

These inputs and assumptions match those described in the 'ERG-preferred base case' in the interim ERG report for this appraisal (61).

The parametric function fitted to the observed data is used for the entire model time horizon, even during the observed period of the observational trial. This approach is to avoid over-fitting the model to the study population observed in Gregoretti et al. 2013 (82) and to ensure that transition probabilities remained relatively constant over time.

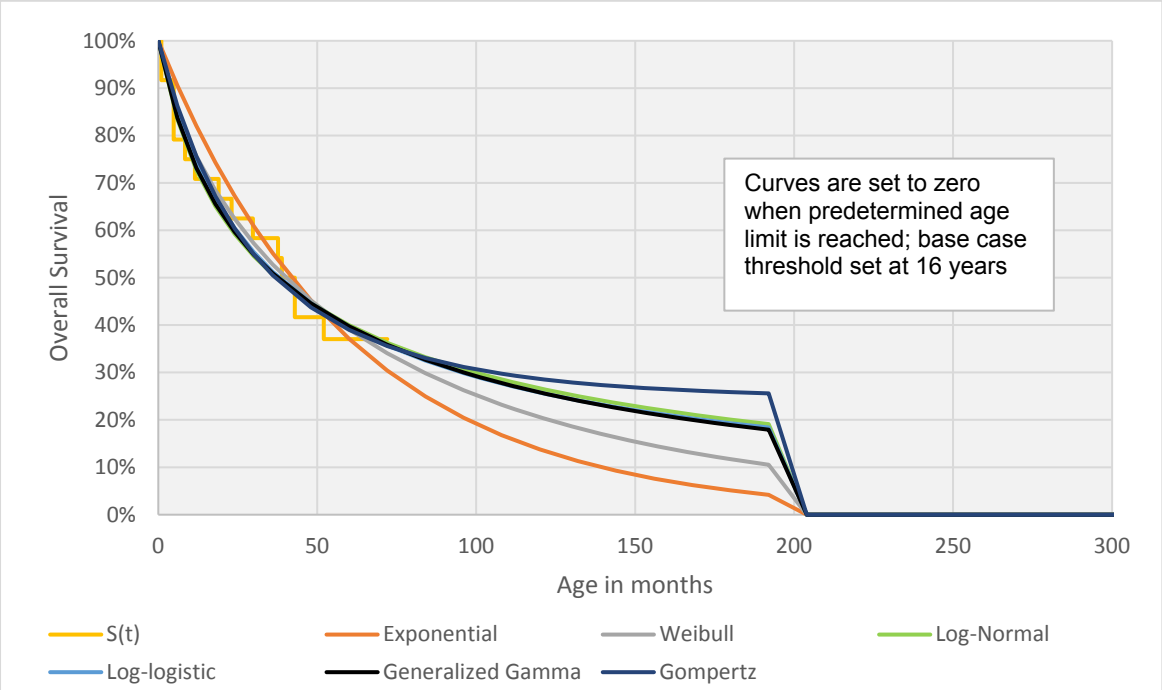
The mathematically best fitting curves were the exponential (lowest BIC) and the log-normal (lowest AIC) curve. To match the 'ERG-preferred base case', the exponential curve was selected for the updated base case, however this curve slightly plateaued and was deemed to be clinically implausible. To maintain clinically plausible results, the fitted curve is truncated at 16 years. The parametric models are visualised below in Figure 35. AIC and BIC values for survival curves assessed in the E state are shown below in Table 58.

Table 58: Assessment of curve fits for the E state

Parametric model	AIC	BIC
Exponential	155.09	156.27
Weibull	155.40	157.76
Log-Normal	154.97	157.33
Log-Logistic	155.25	157.61
G.Gamma	156.96	160.49
Gompertz	155.44	157.80

Abbreviations: AIC, Akaike information criterion; BIC, Bayesian information criterion.

Figure 35: E state overall survival (all treatment arms)



It should be noted that using the NIV only ('NRA arm') KM data from Gregoretti et al. 2013 (82) to inform overall survival in the E state, means the impact/use of tracheostomy on the survival of SMA type 1 patients is not captured in the model and therefore does not reflect current clinical practice in England: AveXis understands that, whilst the use of tracheostomy to provide permanent assisted ventilation in patients with SMA type 1 is not used in all patients as part of BSC in England, there is still some use of tracheostomy as part of clinical practice. For example, data from a recent early access programme for nusinersen indicated that of those receiving permanent assisted ventilation (NIV >16 hours/day or tracheostomy) at baseline prior to receipt of pharmacotherapy, 13% (n=3/23) had a tracheostomy (89). Similarly, SMA UK registry data indicates that of the SMA type 1 patients receiving ventilatory support, 16% (n=3/19) had a tracheostomy (90). It should be noted that these UK data on tracheostomy usage only provide a single timepoint or 'snapshot', and hence may not be fully reflective of the total proportion of SMA type 1 patients who go on to receive a tracheostomy for permanent assisted ventilation over their lifetime.

D state (non-sitting) – BSC

In the base case, overall survival and event-free survival for BSC in the D state was based on the NeuroNext natural history trial (4, 5), using 24-month follow-up data for 16 patients with 2 copies of the *SMN2* gene, as per the data described in Section 9.4.3.1 of the original company submission.

The Kaplan-Meier (KM) data were used directly for the observed 24 months study period. To extrapolate survival beyond the follow-up period, parametric survival curves were fitted to the generated KM curve of the empirical data. The mathematically best fitting curve was the generalised gamma curve, however, according to the 'ERG-preferred base case' assumptions, the Weibull curve was used for the D to Death transition. To avoid implausibly long survival predicted by long parametric curve tails, the model interface for the D state

includes a user input survival threshold, measured as “select an age at which survival in the D state is set to zero” in the BSC arm. This interface can be found on the model tab titled ‘D_Survival_BSC’ in cell J112. The base case analysis uses ‘4 years’ as the maximum overall survival age in the D state in the BSC arm.

Overall survival in the D state is adjusted for patients who are not on permanent assisted ventilation: i.e. overall survival in the D state is ‘adjusted/disaggregated’ are per the following terms:

- All patients in a given natural history dataset are included in overall survival calculations at the start (from cycle 0) because they are not on permanent assisted ventilation on entry into the model;
- Once a patient receives permanent assisted ventilation they are censored from the cohort (censored from both the numerator and the denominator) contributing to OS calculations
- This approach allows the model to use as much of each natural history dataset as possible, before censoring patients on permanent assisted ventilation from OS calculations in the D state;
- The result of this approach is that patients will only contribute to overall survival in the D state if they are alive and are not on permanent assisted ventilation
- This approach ensures that overall survival in the D state is not artificially increased by the survival of patients receiving permanent assisted ventilation

Once the survival function was calculated, transition probabilities were calculated using the method set out in Briggs et al. 2006 (91):

$$Tp(tu) = 1 - S(t) / S(t-u)$$[31]

AIC and BIC values for survival curves assessed in the D state for BSC are shown below in Table 59. The parametric models are visualised below in Figure 36.

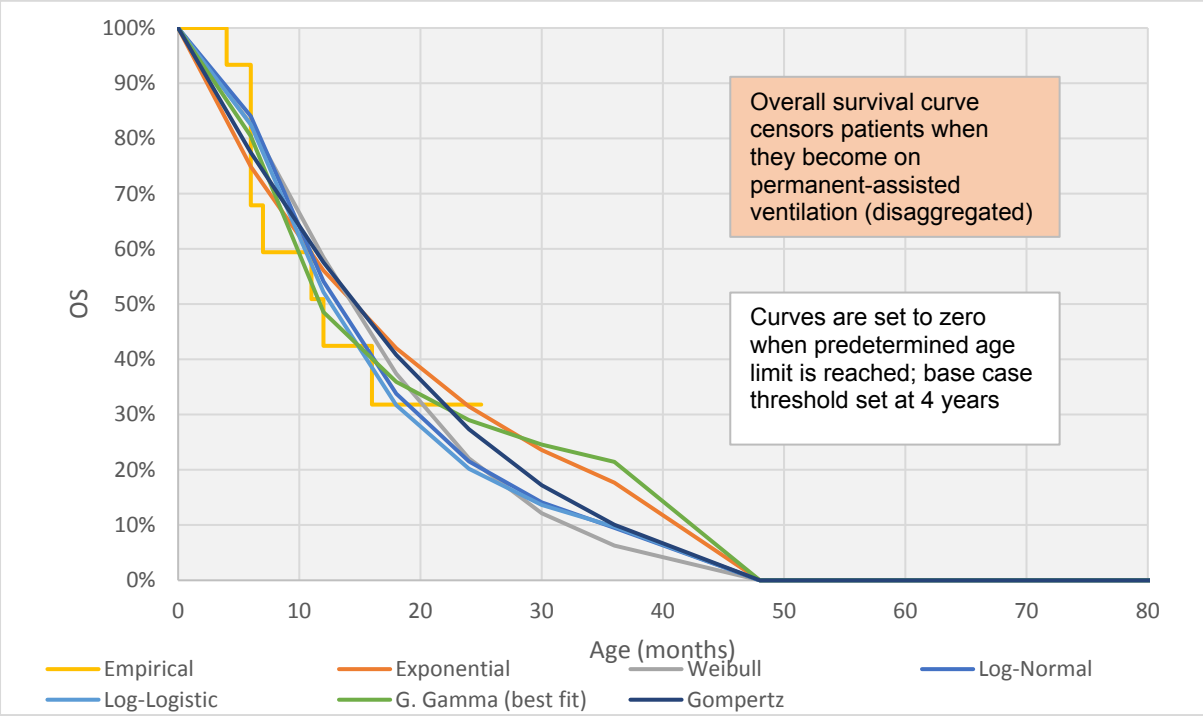
Table 59: Assessment of curve fits for D state OS: BSC

Parametric model	NeuroNext	
	AIC	BIC
Exponential	66.52	67.29
Weibull	66.76	68.31
Log-Normal	64.15	65.69
Log-Logistic	64.84	66.39
G.Gamma	62.62	64.94
Gompertz	68.32	69.87

Abbreviations: AIC, Akaike information criterion; BIC, Bayesian information criterion.

[31] Where S(t) is survival at time t, and u is the length of the cycle.

Figure 36: D state overall survival for BSC (NeuroNext)



To calculate the probability that a patient will transition from D state (non-sitting) to E state (permanent assisted ventilation), an EFS KM curve was generated using the time to the event "Permanent Endotracheal Intubation" (4, 5). However, in order to estimate the correct probability of transition from D state to E state, an OS KM curve needed to be generated that was not adjusted for patients who are not on permanent assisted ventilation (unlike the OS KM curve for the D state to death transition described above). Therefore, for this OS KM curve, death events of all patients were included and censoring only occurred when patients were lost to follow-up (i.e. patients on permanent assisted ventilation were not censored). This additionally generated 'aggregated' OS KM curve allowed to estimate the probability of patients transitioning from D state to E state alone following the method below.

According to the 'ERG-preferred base case' assumptions, the Weibull curve was used for the D state to E state (permanent assisted ventilation) or D state to Death transition; the associated transition probability was calculated using the Briggs method applied to the EFS function. The probability of transitioning from D state to the E state (permanent assisted ventilation) alone was calculated as follows:

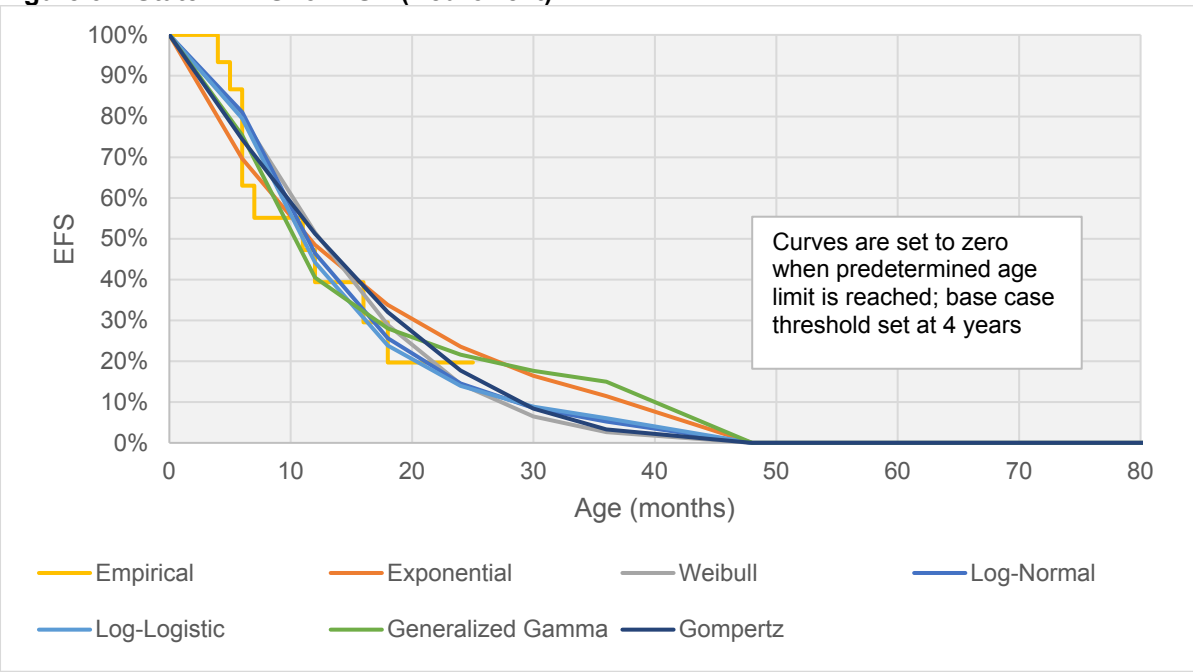
TP (PAV) = TP (Death or PAV) – TP (Death) AIC and BIC values for EFS curves assessed in the D state for BSC are shown below in Table 60. The parametric models are visualised below in Figure 37.

Table 60: Assessment of curve fits for the D state EFS: BSC

Parametric model	NeuroNext	
	AIC	BIC
Exponential	78.19	78.96
Weibull	77.56	79.11
Log-Normal	74.63	76.18
Log-Logistic	75.33	76.87
G.Gamma	72.93	75.25
Gompertz	79.56	81.10

Abbreviations: AIC, Akaike information criterion; BIC, Bayesian information criterion.

Figure 37: State D EFS for BSC (NeuroNext)



The final overall survival and event-free survival functions for BSC in the D state are shown Figure 38.

Figure 38: State D, fitted overall survival and event-free survival curves for BSC (NeuroNext)

D state (non-sitting) – treatment arms

For patients in the onasemnogene abeparvovec arm, the empirical KM survival data were used directly for the observed 24 months post-dose (approximately 30 months of age) data from the START and STR1VE-US trials. As STR1VE-US patients only provide survival data up to 18 months of age, they are censored from survival curves in the short-term model from 18 months to 30 months of age in the POOLED model. For patients in the nusinersen arm, the empirical KM survival data were used directly for the observed 34 months post initial dose (modelled as up to 36 months of age) from ENDEAR/SHINE.

Beyond the observed trial periods, extrapolations were generated based on the parametric models used for the BSC arm (i.e. NeuroNext in the base case); i.e. after the observed trial periods patients who remain in the D state (non-sitting) are assumed to follow the natural history curve, in the absence of long-term evidence of continued survival benefit for non-sitting pharmacotherapy-treated SMA type 1 patients. The parametric natural history curves from the BSC survival data were appended to the clinical trial data beyond the trial period. This process was performed separately for both the overall survival and event-free survival.

It should be noted that the same survival limit applied to the BSC arm (4 years) was applied to the onasemnogene abeparvovec arm in the updated base case to align to the 'ERG preferred base case'. Feedback from the ERG stated that a survival benefit for onasemnogene abeparvovec in the D state may not be unreasonable due to interim milestones being achieved, such as head control and rolling, compared with BSC. However, as there are limited data to substantiate the survival benefit, the ERG preferred to set the survival limit (truncation point) for the OS curve of the D state for the onasemnogene abeparvovec arm to 4 years, to match the BSC arm. Thus, the revised economic model base case uses a survival limit of 4 years in the D state for both the onasemnogene abeparvovec and BSC arms. Functionality has been added to the model to allow amending the survival limits for each arm individually.

The overall survival and event-free survival curves for onasemnogene abeparvovec are shown below in Figure 39, Figure 40 and Figure 41. The overall survival and event-free survival curves for nusinersen are not shown for brevity, as nusinersen is no longer a relevant comparator for this appraisal. However, survival curves for the nusinersen arm can be found in the tab 'D_Survival_Nsn' of the model file. No AIC and BIC data are available for these curves directly as they are composites of the empirical KM data (from observed trial periods) and parametric model extrapolations based on the BSC data.

Figure 39: State D overall survival for onasemnogene abeparvovec (KM followed by parametric models based on NeuroNext in the base case)

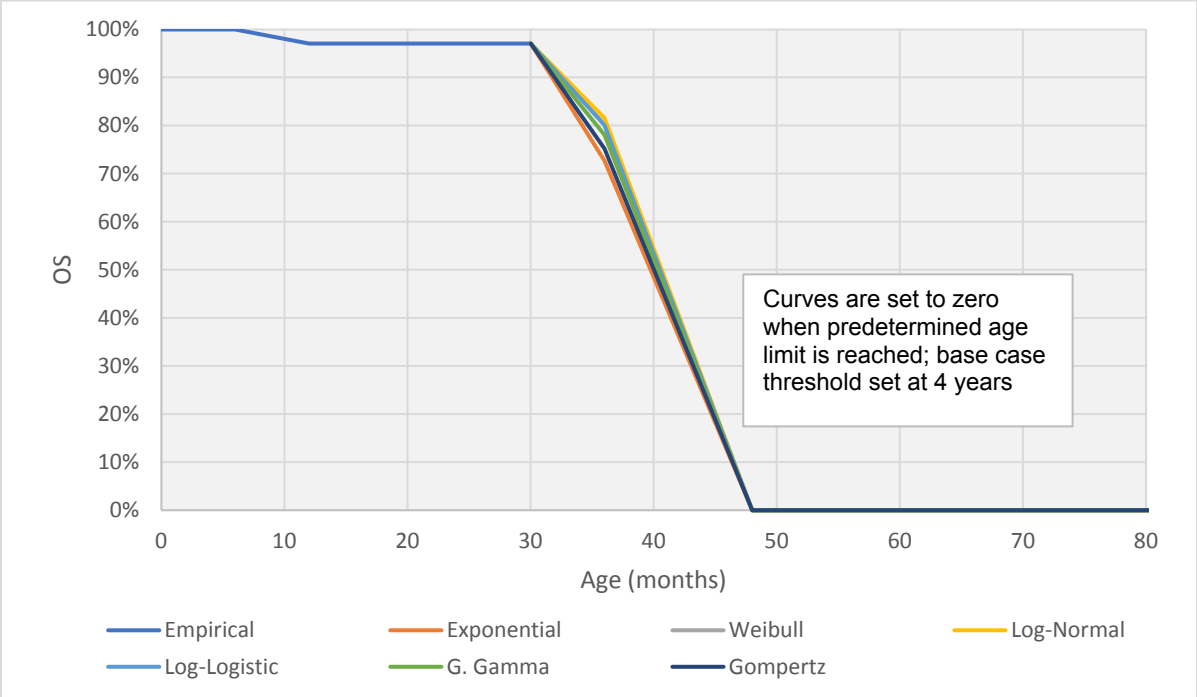


Figure 40: State D EFS for onasemnogene abeparvovec (KM followed by parametric models based on NeuroNext in the base case)

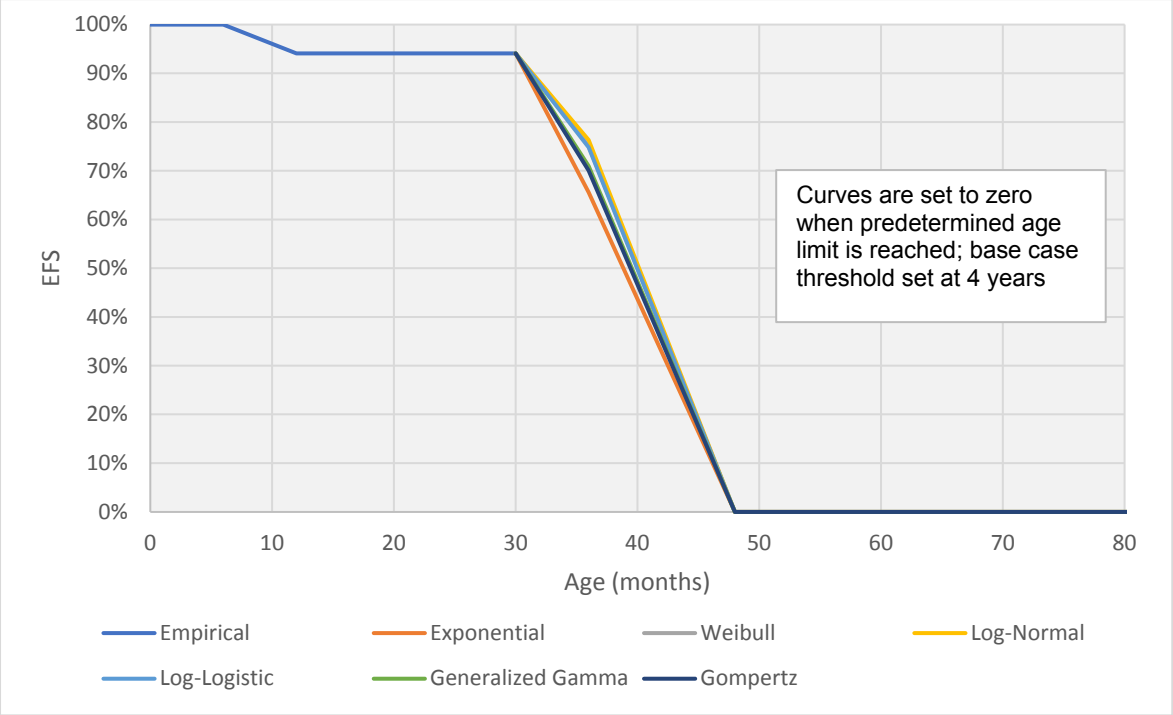
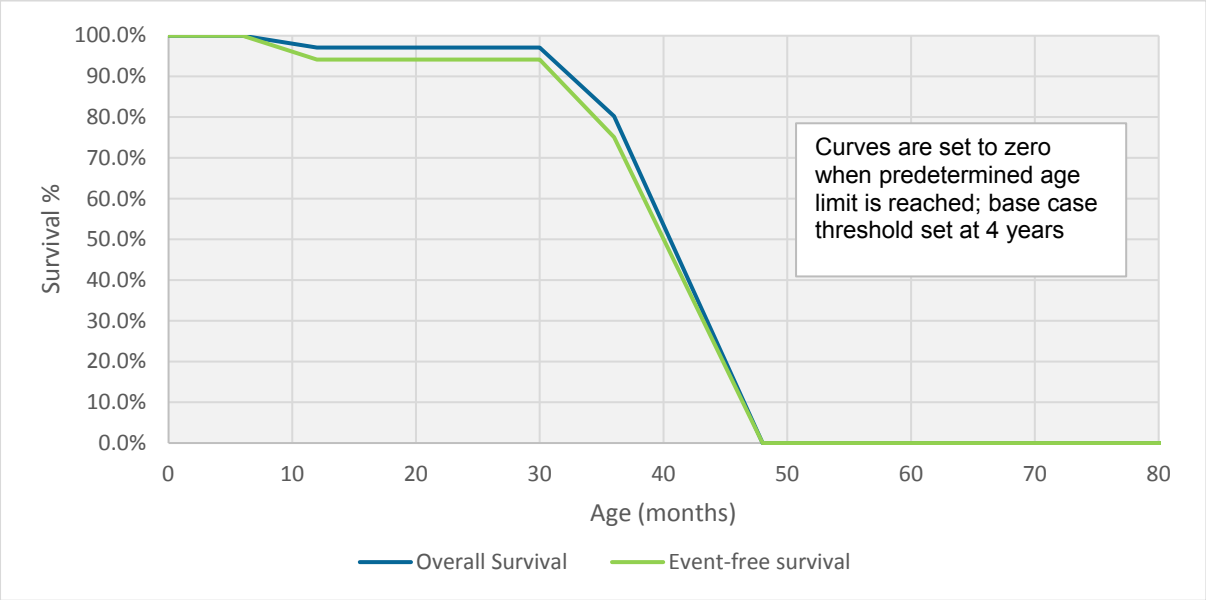


Figure 41: State D, overall survival and event-free survival curves for onasemnogene abeparvovec



C state (sits unassisted) – treatment arms

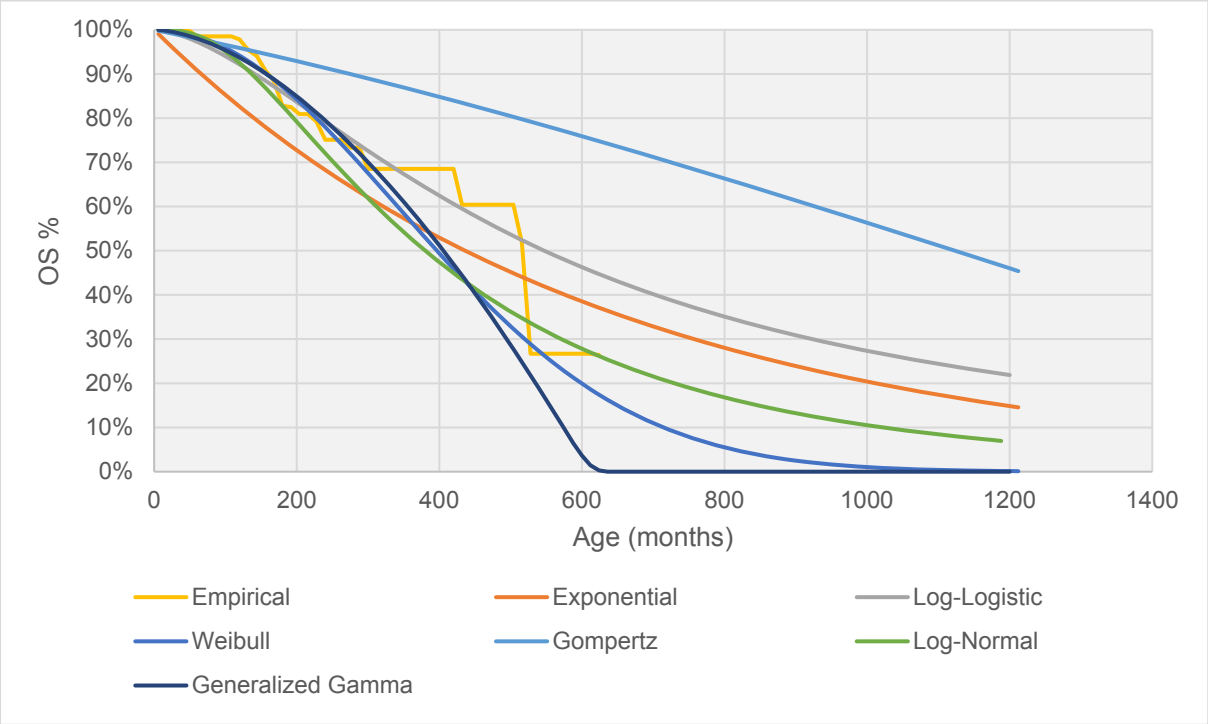
As a result of the underpinning assumption of the model that survival is improved in correlation with motor milestone achievement, and life expectancy can be estimated using proxies, SMA type 1 patients treated with onasemnogene abeparvovec or nusinersen are modelled to experience survival consistent with the natural history of SMA type 2 patients managed with BSC for those in the C state (sits unassisted). The survival for SMA type 1 patients that can sit unassisted is modelled from the long-term survival of the 52-year prospective and retrospective genetic study of SMA type 2 patients, as reported by Zerres et al. 1997 (83). The individual patient data were reconstructed using published methods (86, 87). Survival was projected with parametric estimation using the generalised gamma curve (best fit). Goodness-of-fit is shown in terms of the AIC and BIC in Table 61 and shown visually in Figure 42. The parametric function fitted to the observed data is used for the entire model time horizon, even during the observed period of the study. This approach is to avoid over-fitting the model to the study population observed and to ensure that transition probabilities remained relatively constant over time.

Table 61: Assessment of curve fits for health state C

Parametric model	AIC	BIC
Exponential	1151.27	1154.66
Weibull	1093.97	1100.76
Log-Normal	1103.72	1110.50
Log-Logistic	1131.50	1138.28
G.Gamma	1087.90	1098.08
Gompertz	1263.74	1270.53

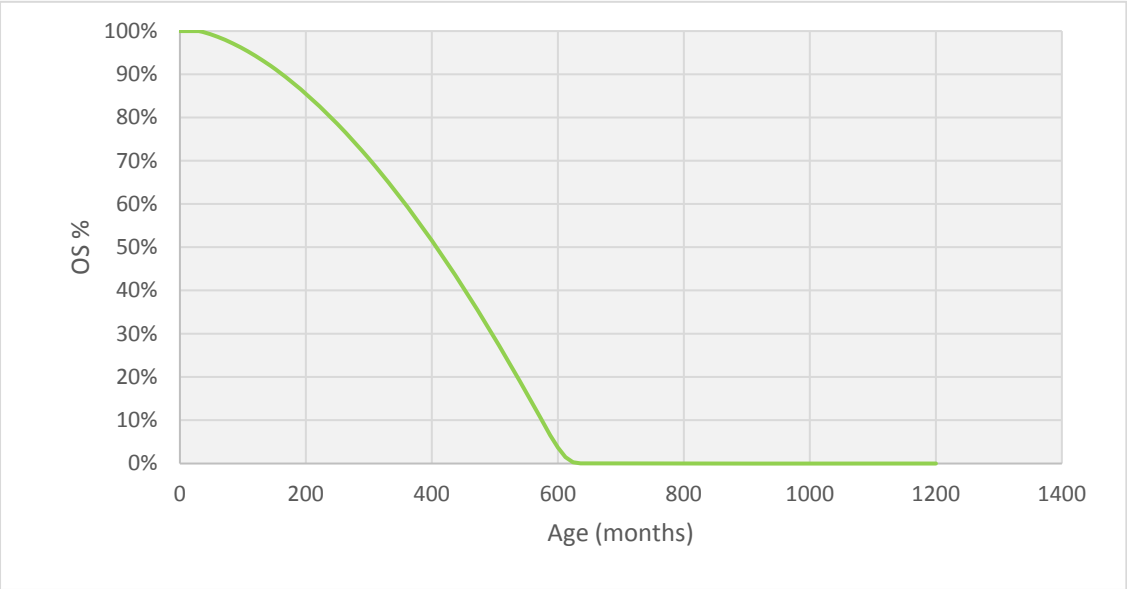
Abbreviations: AIC, Akaike information criterion; BIC, Bayesian information criterion.

Figure 42: State C overall survival parametric survival models based on data from Zerres et al. 1997 (63)



The original model used the fitted survival curves for the entire duration of the model from Zerres et al 1997 and general population mortality tables for the C state ('sits unassisted') and B state ('walks unassisted'), respectively. In this approach, the modelled cohort is subject to a mortality risk in all cycles, which contrasts with the empirical data from START and STR1VE-US in which patients who sit unassisted and walk unassisted have a 100% survival for up to 24 months post-dose (circa 30 months of age) and 18 months of age, respectively. The revised economic model base case applies 100% survival in the first 5 cycles (up to 30 months of age) for the C and B states, to reflect the empirical survival data available for sitting and walking patients treated with onasemnogene abeparvovec. This aligns to the 'ERG-preferred base case' assumptions. From cycle 6 onwards, the generalised gamma curve fitted to the data from Zerres et al. 1997 (63) has been used. While for nusinersen, the fitted generalised gamma curve was applied for the entire time horizon. Figure 43 shows the modelled overall survival in C state for the onasemnogene abeparvovec arm. The C state survival curve for the nusinersen arm can be found in the tab 'C_Survival' of the model file.

Figure 43: State C, overall survival curves for onasemnogene abeparvovec



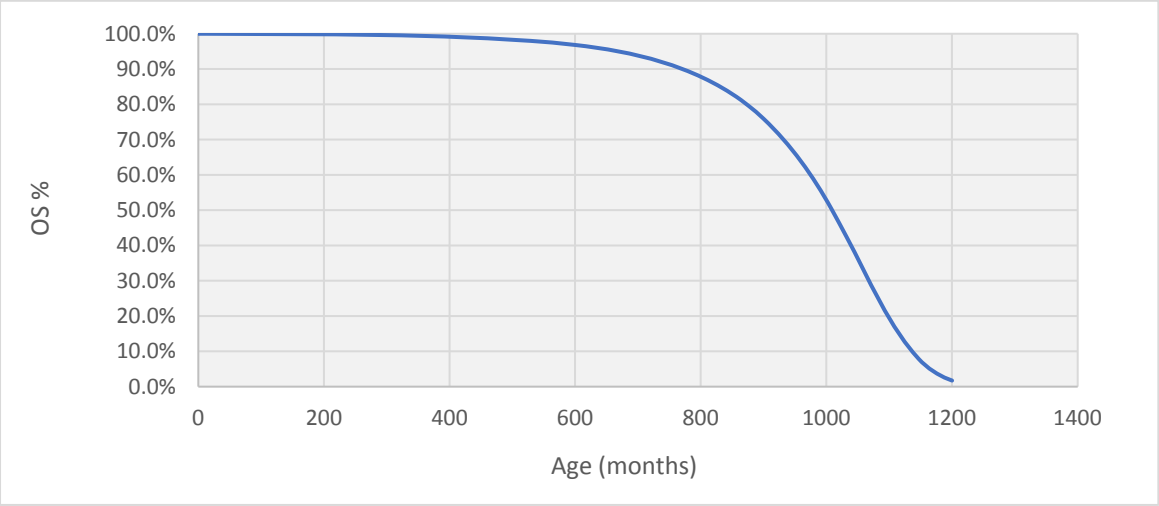
B state (walks unassisted) and A state (within broad range of normal) – treatment arms

Patients who could walk unassisted were assumed to have survival consistent with the natural history of SMA type 3 patients, which is reported to not significantly differ from the survival of the general population (83).

Thus, for both the B state (walks unassisted) and A state (within broad range of normal development) SMA type 1 patients treated with onasemnogene abeparvovec or nusinersen are modelled to experience survival consistent that of the general population. However, for onasemnogene abeparvovec, it has been assumed for the first five model cycles (up to 30 months of age) that the survival is 100% in both B and A states to match the 'ERG-preferred base case' assumptions; please see description above.

To estimate survival in these health states the 2014–2016 UK life tables were used to determine the probability of death in each cycle (84). The survival curve for these health states for onasemnogene abeparvovec arm is shown below in Figure 44. The B/A state survival curve for the nusinersen arm can be found in the tab 'B_A_Survival' of the model file.

Figure 44: B state and A state overall survival for onasemnogene abeparvovec



8.2.2.2 Cost extrapolations

All health state costs are constant; the same annual costs for a given health state in cycle 1 persist for the life time horizon of the model.

8.2.3 Were intermediate outcome measures linked to final outcomes (for example, was a change in a surrogate outcome linked to a final clinical outcome)? If so, how was this relationship estimated, what sources of evidence were used and what other evidence is there to support it?

As described in Section 8.2.1, the clinical outcomes (motor milestone achievement, mortality and the need for permanent ventilation) observed in trials were used directly in the short-term model for both the treatment arms and the BSC arm. The exception to this approach, is that the revised economic evaluation presented includes a base case assumption that from the STR1VE-US cohort, there will be one additional independent sitter and one additional independent walker between 18 months and 30 months of age, of which empirical data are currently not available since STR1VE-US only followed patients up to 18 months of age. Please see Section 8.2.1.1 for the rationale and evidence supporting this assumption.

For the long-term model, a key assumption is that motor milestone achievement (i.e. the ability to sit unassisted or walk unassisted) in pharmacotherapy-treated SMA type 1 patients is linked to a better overall survival beyond trial follow-up periods; overall survival in the C state (sits unassisted), B state (walks unassisted) and A state (within broad range of normal population) are drawn from proxy populations. This relationship between improvements in motor function and a long-term survival benefit in pharmacotherapy-treated SMA type 1 patients was considered suitable as part of the recently published US ICER model (74). In addition, use of proxy populations to model overall survival in the C state, B state and A state was deemed reasonable as part of a recent UK clinical advisory board (see Section 8.2.5.2).

8.2.4 Were adverse events included in the cost- effectiveness analysis? If appropriate, provide a rationale for the calculation of the risk of each adverse event.

Given the nature of SMA, it is difficult to separate AEs due to treatment from complications associated with SMA itself, which are already accounted for in the health state costs and health state utility values. As such, the costs and disutilities of AEs were not included in the model.

8.2.5 Provide details of the process used when the sponsor's clinical advisers assessed the applicability of available or estimated clinical model parameter and inputs used in the analysis.

8.2.5.1 Model conceptualisation

To obtain external expert opinion on the appropriateness of the cost-effectiveness model structure, AveXis consulted ten international experts including clinical experts (paediatric neurologists and respiratory physicians with experience in treating SMA), external academic health economists and an expert physician associated with an SMA patient advocacy group.

The objective of the model conceptualisation expert engagement was to design the most appropriate model framework for SMA type 1; opinions were collated via group telephone or group email exchange. The key conceptualisation questions posed to the experts included:

- The model structure:
    - The use of two health states that reflect the natural history of SMA type 1 – D state (not sitting) and E state (permanent assisted ventilation) – and three higher functioning health states for patients in the pharmacotherapy-treated arms: C state (sits unassisted), B state (walks unassisted), and A state (within a broad range of normal development)
    - The use of natural history SMA type 2 and SMA type 3 populations managed with BSC only as proxy (for mortality and HCRU costs) for pharmacotherapy-treated SMA type 1 infants, who can sit unassisted and walk unassisted, respectively
- Rules associated with transition probabilities:
    - Only patients in the D state (not sitting) could transition to the E state (permanent assisted ventilation)
    - Patients in all other functional health states can only regress to death

8.2.5.2 UK clinical advisory board

Objectives

The objectives of the UK clinical advisory board were to:

- Discuss the key areas of uncertainty related to the clinical effectiveness of onasemnogene abeparvovec
- Explore any heterogeneity of health outcomes and benefits within SMA type 1
- Validate key assumptions underpinning the draft cost-effectiveness model
- Discuss the key areas of uncertainty related to the draft cost- effectiveness model

Criteria for selecting experts

For inclusion in the UK clinical advisory board, clinical experts were required to have expertise in treating SMA in the UK using BSC. In addition, some delegates also had experience of:

- Referring and/or treating patients with nusinersen via the nusinersen UK EAP
- Referring and/or treating infants with onasemnogene abeparvovec via UK clinical trials centres involved in ongoing clinical trials
- Experience of using gene therapies to treat neuromuscular disorders

In total nine clinical experts and three representatives from patient organisations were invited; all attended except two clinical experts who declined due to clinical commitments.

Experts

The healthcare professionals known to AveXis to have specialist clinical experience of SMA in the UK were contacted and were asked for their availability to participate in an advisory board. Seven clinical experts and three representatives from patient organisations were able to take part in the advisory board:

[redacted]

[redacted]

Remuneration and conflict of interest

Each participant received an honorarium at Fair Market Value funded by AveXis to cover the time required to prepare for the advisory board (pre-reading) and time to attend at the advisory board. All participants signed a ‘no conflicting work’ statement.

Methods

Before the advisory board pre-reading materials were circulated to each participant, which included clinical trial data from the Phase I clinical trial for onasemnogene abeparvovec (START) and key clinical trial publications on comparators (BSC and nusinersen).

During the advisory board, context slides were presented (92) and questions discussed by the group. Discussion points and group consensuses were recorded in report format (56).

Questions

Full details of all questions asked are provided in a data on file reference (92). Key questions and consensus results are presented in Table 62.

Table 62: Key questions and consensus results UK clinical advisory board (May 2019)

Question	Consensus
Natural history of SMA type 1	
AveXis plans to submit an effectiveness assessment of onasemnogene abeparvovec in SMA type 1 as one group. Is this reasonable, or do subtypes (1A, 1B, 1C) need to be considered?	In clinical practice, infants with SMA type 1 are considered as a single population in terms of treatment decision making. SMA type 1 can be classified as infants with symptom onset at ≤6 months of age
Does the estimate (30–39 new cases of SMA type 1 per year in the England) align to your clinical experience/knowledge of the SMA type 1 population in England?	The initial reaction to the estimate of 30–39 incident SMA type 1 patients / year in England was that this number might be low, but on reflection of the numbers shared in the room from local centres and learnings from the EAP, this number is realistic. These estimates are supported by real world evidence from the nusinersen EAP which reports that in its last year of operation, 32 babies were diagnosed with SMA type 1 and treated with nusinersen in England (personal communication; [redacted], Paediatric Neurologist).
Generalisability of US natural history cohorts to the SMA type 1 population in England	
Are the US natural history cohorts (NeuroNext and PNCR) generalisable to the SMA type 1 population in England?	Yes, broadly the US natural history cohorts (NeuroNext and PNCR) are generalisable to the English SMA type 1 population
	The group noted that motor milestone achievements are not influenced by NIV; NIV only has an impact on life expectancy in SMA type 1 patients
Clinical effectiveness of onasemnogene abeparvovec versus best supportive care	
How representative is the CL-101 (START), Cohort 2 of the SMA type 1 population in England?	It is likely that Cohort 2 in START will be generalisable to 'future' SMA type 1 patients in England, as clinical practice is moving towards earlier symptom recognition and earlier diagnosis due to the increasing awareness of SMA. Remarks were raised about the generalisability of Cohort 2 from START to the England SMA type 1 population, specifically: • Patient 8: It is unlikely a patient would be treated this late (7.9 months) with onasemnogene abeparvovec in clinical practice in England • Patient 6 and 10: In current clinical practice, the diagnosis of symptomatic SMA type 1 patients with a CHOP-INTEND scores of >45 at baseline is unlikely

Question	Consensus
Clinical effectiveness of onasemnogene abeparvovec versus nusinersen	
	Some caution was raised relating to the comparison between onasemnogene abeparvovec and nusinersen based on currently available data. Certain participants stated that their instinct is that onasemnogene abeparvovec is the better of the two treatments with respect to clinical outcomes; however, robust evidence to support this perception is lacking at present
	If considering route and method of administration, then onasemnogene abeparvovec has a clear advantage relative to nusinersen
	The speed of response (as inferred by CHOP-INTEND) relative to natural history is an advantage for onasemnogene abeparvovec/potential limitation for nusinersen
Draft NICE model: economic inputs and assumptions	
Onasemnogene abeparvovec restores normal biology and is assumed to have a lifetime effect for the model base case. What is your view of this assumption?	The model base case assumption is correct that onasemnogene abeparvovec addresses the primary biological problem in SMA type 1 i.e. lack of a functional *SMN1* gene
If a pessimistic scenario was to be modelled, what proportion of patients after being treated with onasemnogene abeparvovec would you model to lose milestones each year after 24 months?	It is very difficult to predict how onasemnogene abeparvovec treated patients may regress in the absence of long-term data; the base case should be adhered to in which milestones achieved with onasemnogene abeparvovec are maintained in the lifetime, and hence are not lost
Children who were observed walking unassisted during clinical trials before age 2 are transitioned to 'within a broad range of normal range of development' (A state) at 5 years of age. What is your view of this assumption?	Children diagnosed and treated early in their disease course with onasemnogene abeparvovec could go on to meet the 'normal' description i.e. they could attend school, participate in family life, etc
Based on your clinical experience, what is the maximum age an SMA patient has been kept on permanent ventilation until? Is 22 years, as reported by Bach et al publication, a plausible maximum age?	It is rare for patients with SMA type 1 who receive permanent ventilation to reach the age reported by Bach. However, a clinical expert reported two cases of permanent ventilated SMA type 1 patients in England who are in their 20's, thus the estimate from Bach is appropriate as an absolute maximum
SMA type 1 children who achieve motor milestones (sitting unassisted and beyond – i.e. health states C, B and A) will not follow the deteriorating trajectory of SMA type 1 natural history.	The use of proxy SMA subtypes is not ideal; but it was recognised to be the best possible approach in the absence of long-term data for onasemnogene abeparvovec-treated patients

Question	Consensus
In the absence of clinical trial data, other SMA types and the general population are used as proxies/surrogates: • Sitting (C state) = survival of untreated SMA type 2 • Walking (B state) = survival of untreated SMA type 3 • Normal (A state) = survival of general population What is your view on this approach to using proxies for survival?	
Are any of the negative health state valuations plausible?	It is plausible for the D and E health states to be associated with negative health state utility values (i.e. considered worse than death)
	It is implausible for the C state to be associated with a negative health state utility value
	The concept of an average QoL score for each health state in the model is nonsensical as SMA is a heterogeneous disease that impacts very young infants and the impact on the patient, caregiver and family is very individual/environment-specific
What is your view on the health state utility values used by US ICER?	Of the health state utility values options shown, the US ICER values were the most plausible but there should be a differentiation between the values for E and D states (i.e. the E state value should be lower than the D state value)
SMA type 1 children who achieve motor milestones (sitting and beyond – i.e. health states C, B and A) will not follow the deteriorating trajectory of SMA type 1 natural history. In the absence of clinical trial data, other SMA types and the general population are used as proxies/surrogates for HCRU costs: • Non-sitting (D state) = costs of an SMA type 1 • Sitting (C state) = costs of an SMA type 2 • Walking (B state) = costs of an SMA type 3 • Normal range (A state) = zero SMA-related costs; patients are expected to be in the 'normal' range of development What is your view on this approach to using proxies for healthcare resource utilisation costs?	The use of proxies for healthcare resource utilisation costs is reasonable

<table>
<tr><th>Question</th><th>Consensus</th></tr>
<tr><td>What proportion of each ventilation group are treated across the four healthcare settings, based on best supportive care of SMA patients in England?</td><td>
<table>
<tr><th>Ventilation group</th><th>Paediatric intensive care</th><th>High dependency</th><th>Children's ward</th><th>Home-based</th><th>Total check</th></tr>
<tr><td>Patients on NIV >16 hours per day</td><td>15%</td><td>15%</td><td>0</td><td>70%</td><td>100%</td></tr>
<tr><td>Patients on NIV <16 hours per day</td><td>5%</td><td>5%</td><td>0</td><td>90%</td><td>100%</td></tr>
<tr><td>Tracheostomy patients</td><td>10%</td><td>30%</td><td>0</td><td>60%</td><td>100%</td></tr>
</table>
Most infants with SMA type 1 who receive ventilatory support (permanent or non-permanent) would be home-based in England</td></tr>
<tr><td colspan="2">Service redesign for SMA type 1 in England</td></tr>
<tr><td>Positioning of onasemnogene abeparvovec relative to nusinersen</td><td>There is no biological justification to continue or start treatment with nusinersen following administration of onasemnogene abeparvovec</td></tr>
<tr><td>What might the clinical care pathway including onasemnogene abeparvovec look like?</td><td>The one-time IV infusion with onasemnogene abeparvovec will typically require one pre-infusion visit at a secondary/tertiary neuromuscular centre followed by a two-night, three-day elective stay at a highly specialised infusion centre. It was noted by patient representatives that travelling with ill children is a huge burden which should be avoided/minimised as much as possible as part of service redesign</td></tr>
</table>

Abbreviations: CHOP-INTEND, Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders; EAP, early access programme; NICE, National Institute of Health and Care Excellence; NIV, non-invasive ventilation; PNCR, Pediatric Neuromuscular Clinical Research; SMA, spinal muscular atrophy; SMN, survival motor neuron; UK, United Kingdom; US ICER; United States Institute for Clinical and Economic Review.

Data aggregation

No formal data aggregation took place. After each discussion/question, a summary of the advice shared was summarised verbally to the group to reach a consensus statement in response to each topic.

8.2.6 Summarise all the variables included in the cost-effectiveness analysis. Provide cross-references to other parts of the submission. A suggested format is provided in table D5 below.

A summary of the input variables for the model are shown in Table 63.

Table 63: Summary of model input variables

Variable	Base case value	Range, SE or 95% CI (distribution)	Source	Section(s)
Discounting				
Discount rate (costs)	3.5%	N/A for PSA 0% – 5% used in additional scenario analyses	NICE guide to the methods of technology appraisal 2013 (77)	8.1.3.5 8.4.3.2
Discount rate (outcomes)	3.5%	N/A for PSA 0% – 5% used in additional scenario analyses		
Costs				
Annual SMA care costs				
E state: drug costs	£680	SE: £135.98 (Gamma)	UK HCRU study (75); NHS 2018/19 National Cost Collection data (93)	8.3.1.1
E state: medical tests	£645	SE: £129.07 (Gamma)		
E state: medical visits	£3,153	SE: £630.61 (Gamma)		
E state: hospitalisations	£200,247	SE: £40,049.49 (Gamma)		
E state: GP & emergency	£325	SE: £64.96 (Gamma)		
E state: health materials	£3,172	SE: £634.42 (Gamma)		
E state: social services	£49,994	SE: £9,998.72 (Gamma)		
D state: drug costs	£919	SE: £183.87 (Gamma)		
D state: medical tests	£873	SE: £174.53 (Gamma)		
D state: medical visits	£4,264	SE: £852.71 (Gamma)		
D state: hospitalisations	£63,516	SE: £12,703.16 (Gamma)		
D state: GP & emergency	£439	SE: £87.84 (Gamma)		

Variable	Base case value	Range, SE or 95% CI (distribution)	Source	Section(s)
D state: health materials	£4,027	SE: £805.34 (Gamma)		
D state: social services	£27,896	SE: £5,579.28 (Gamma)		
C state: drug costs	£743	SE: £148.56 (Gamma)		
C state: medical tests	£651	SE: £130.13 (Gamma)		
C state: medical visits	£2,509	SE: £501.88 (Gamma)		
C state: hospitalisations	£37,336	SE: £7,467.27 (Gamma)		
C state: GP & emergency	£183	SE: £36.52 (Gamma)		
C state: health materials	£2,079	SE: £415.88 (Gamma)		
C state: social services	£18,598	SE: £3,719.52 (Gamma)		
B state: drug costs	£939	SE: £187.86 (Gamma)		
B state: medical tests	£533	SE: £106.60 (Gamma)		
B state: medical visits	£2,217	SE: £443.31 (Gamma)		
B state: hospitalisations	£452	SE: £90.50 (Gamma)		
B state: GP & emergency	£73	SE: £14.67 (Gamma)		
B state: health materials	£592	SE: £118.42 (Gamma)		
B state: social services	£2,952	SE: £590.40 (Gamma)		
A state: drug costs;	£939	SE: £187.86 (Gamma)	‘ERG-preferred base case’ assumption Interim ERG report (61)	8.3.1.1
A state: medical tests	£533	SE: £106.6055.31 (Gamma)		
A state: medical visits	£2,217	SE: £443.31379.75 (Gamma)		
A state: hospitalisations	£452	SE: £903.50 (Gamma)		
A state: GP & emergency	£73	SE: £14.6711 (Gamma)		

Variable	Base case value	Range, SE or 95% CI (distribution)	Source	Section(s)
A state: health materials	£592	SE: £118.4213 (Gamma)		
A state: social services	£2,952	SE: £590.40 (Gamma)		
Onasemnogene abeparvovec costs				
Onasemnogene abeparvovec drug acquisition cost	£1,795,000	Fixed in PSA SE: 20% (£334,900) in DSA	UK list price	8.3.3.2
Onasemnogene abeparvovec administration cost	£2,803	SE: £560.51 (Gamma)	2018/19 National Cost Collection data (93); Weighted average of codes relating paediatric nervous system disorders and cerebral degenerations or miscellaneous disorders of nervous system (EL- PR01A-E and EL - AA25C-G)	8.3.3.3
Nusinersen costs‡				
Technology acquisition cost, per vial	£75,000	Fixed in PSA SE: 20% (£15,000) in DSA	UK list price, BNF (94)	8.3.3.3
Inpatient lumbar puncture				
Aged ≤5 years	£1,545	SE: £309.07 (Gamma)	NHS 2018/19 National Cost Collection data (93) (Codes: EL - HC72C; EL - HC72B; EL - HC72A)†	8.3.3.3
Aged 6–18 years	£1,327	SE: £265.32 (Gamma)		
Aged ≥19 years	£815	SE: £162.95 (Gamma)		
Outpatient lumbar puncture				
Aged ≤5 years	£224	SE: £44.81 (Gamma)	NHS 2018/19 National Cost Collection data (93) (Codes: OPROC - HC72C, service code 421; (OPROC - HC72B, service code 421; OPROC - HC72A, service code 400)†	8.3.3.3
Aged 6–18 years	£220	SE: £43.95 (Gamma)		
Aged ≥19 years	£315	SE: £62.97 (Gamma)		

Variable	Base case value	Range, SE or 95% CI (distribution)	Source	Section(s)
Day case lumbar puncture				
Aged ≤5 years	£1,224	SE: £244.70 (Gamma)	NHS 2018/19 National Cost Collection data (93) (Codes: DC - HC72C; DC - HC72B; DC - HC72A)†	8.3.3.3
Aged 6–18 years	£891	SE: £178.23 (Gamma)		
Aged ≥19 years	£565	SE: £112.91 (Gamma)		
% of patients having an elective inpatient procedure (all age groups)	40%	Sampled from a Dirichlet distribution using a 4:3:3 ratio	Assumption, NICE nusinersen STA (76)	8.3.3.3
% of patients having an outpatient procedure (all age groups)	30%			
% of patients having a day case procedure (all age groups)	30%			
Nusinersen discontinuation‡				
Proportion of arm discontinuing nusinersen in E state	100%	Fixed in PSA and DSA	Nusinersen MAA (73)	8.2.1.2
Proportion of arm discontinuing nusinersen in C and D states	3%	SE: 0.6% (Beta)	Nusinersen MAA (73), nusinersen SmPC (72) and nusinersen UK/Ireland EAP (60)	8.2.1.2
Rate of milestone loss for patients that discontinue nusinersen in C and D states	90%	SE: 0.18 (Beta)	Assumption	8.2.1.2
Quality of life adjustments				
Utility: E state	0.000	SE: 5% (0.0000) (Gamma) in PSA	‘ERG-preferred base case’ assumption (61) Interim ERG report	7.1
Utility: D state	0.190	SE: 5% (0.0095) (Gamma) in PSA	Thompson et al. 2017 (62)	

Variable	Base case value	Range, SE or 95% CI (distribution)	Source	Section(s)
Utility: C state	0.600	SE: 5% (0.0300) (Gamma) in PSA	US ICER (74)	
Utility B/A state: % male in equation	0.417	SE: 5% (0.0209) (Beta) in PSA	Ara and Brazier 2010 (64)	7.1
Utility B/A state: equation intercept	0.9508566	SE: 5% (0.0475) (Beta) in PSA		
Utility B/A state: equation sex coefficient	0.0212126	SE: 5% (0.0011) (Beta) in PSA		
Utility B/A state: equation age coefficient	0.0002587	SE: 5% (0.000013) (Beta) in PSA		
Utility B/A state: equation age^2 coefficient	0.0000332	SE: 5% (0.000002) (Beta) in PSA		
On-treatment utility increment: D state - onasemnogene abeparvovec and nusinersen‡	0.100	SE: 5% (0.0050) (Beta) in PSA	'ERG-preferred base case' assumption (61) Interim ERG report US ICER (74)	7.1
On-treatment utility increment: C state - onasemnogene abeparvovec and nusinersen‡	0.050	SE: 5% (0.0025) (Beta) in PSA		
Survival limits				
Survival limit (years) for E state	16	SE: 20% (Gamma)	Assumption	8.2.2.1
Survival limit (years) for D state - BSC	4	SE: 20% (Gamma)	'ERG-preferred base case' assumption (61) Interim ERG report	8.2.2.1
Survival limit (years) for D state - onasemnogene abeparvovec	4	SE: 20% (Gamma)		8.2.2.1
Survival limit (years) for D state - nusinersen‡	4	SE: 20% (Gamma)		8.2.2.1
Survival curve parameters – shown for base case				
E state OS: Exponential distribution: lambda	0.0165	Cholesky decomposition	Parametric curve fitted to observed 'NRA' (NIV-only) data in Gregoretti et al. 2013 (82)	8.2.2.1

Variable	Base case value	Range, SE or 95% CI (distribution)	Source	Section(s)
			and selected based on 'ERG-preferred base case' assumption (61)	
D state OS (disaggregated): Weibull: lambda	0.0131	Cholesky decomposition	Parametric curve fitted to observed data in NeuroNext, which has been 'adjusted/disaggregated' for those on PAV (5) and selected based on 'ERG-preferred base case' assumption (61)	8.2.2.1
D state OS (disaggregated): Weibull: gamma	1.4938			
D state OS (aggregated): Weibull: lambda	0.0172	Cholesky decomposition	Parametric curve fitted to observed data in NeuroNext (5)	8.2.2.1
D state OS (aggregated): Weibull: gamma	1.3259			
D state EFS: Weibull: lambda	0.0140	Cholesky decomposition		8.2.2.1
D state EFS: Weibull: gamma	1.5506			
C state: generalised gamma: mu	6.35646	Cholesky decomposition	Parametric curve fitted to observed data in Zerres et al. 1997 (83)	8.2.2.1
C state: generalised gamma: sigma	0.11002			
C state: generalised gamma: q	5.35602			
B state and A state: survival curve	See model sheet: B_A_Survival	N/A	Office for National Statistics 2018 (84)	8.2.2.1

Abbreviations: BNF, British National Formulary; BSC, best supportive care; CI, confidence interval; DSA, deterministic sensitivity analysis; EAP, early access programme; EFS, event-free survival (permanent ventilation-free survival); ERG, Evidence Review Group; GP, general practitioner; HCRU, health care resource utilisation; MAA, managed access agreement; N/A, not applicable; NHS, National Health Service; NICE, National Institute for Health and Care Excellence; NIV, non-invasive ventilation; NRA, non-invasive respiratory aid ; OS, overall survival; PAV, permanent assisted ventilation; PSA, probabilistic sensitivity analysis; SE, standard error; STA, single technology appraisal; SmPC, summary of product characteristics; UK, United Kingdom; US ICER, United States Institute for Clinical and Economic review.

† Code costs rounded to nearest pound.

‡ Cost-effectiveness results of onasemnogene abeparvovec versus nusinersen are not presented in this revised submission, as nusinersen is no longer considered a comparator for this appraisal. As the revised economic model submitted to NICE still includes a nusinersen arm, for completion, the methods and inputs sections relating to the nusinersen arm of the economic model are described.

8.3 *Resource identification, measurement and valuation*

8.3.1 NHS costs

8.3.1.1 Describe how the clinical management of the condition is currently costed in the NHS in terms of reference costs and the payment by results (PbR) tariff.

A UK HCRU study using in-depth telephone interviews with UK clinical experts (n=16) was conducted (February 2019 – April 2019) to ensure the model accurately captured the current UK clinical pathway of care for SMA patients. As HCRU costs for SMA type 2 and SMA type 3 are being used as proxy for pharmacotherapy-treated SMA type 1 patients who can sit unassisted (C state) and walk unassisted (B state) milestones, respectively, the current management of SMA in multiple types (SMA type 1, type 2 and type 3) was sought via the UK HCRU study. Full details of the study are provided in the UK HCRU study report (75), but in summary:

Clinical experts

The n=16 clinical experts included: [redacted]

Methods

Each clinical expert took part in an individual, in-depth telephone interview, which was semi-directive to explore SMA clinical management overall, specific HCRU was quantified using a prepared data summary sheet (Excel). Weighted means of proportions of patients using specific resources, frequency and where relevant, duration, of each type of resource used were calculated. The total patients seen in the past 12 months was calculated as the aggregate number of SMA patients seen by the clinical experts reporting on this resource over the last 12 months, and the number of patients using this resource was calculated using the prevalence of this resource use reported by each clinical expert for their own patients. The prevalence per resource use was calculated using the total number of patients seen by all clinical experts interviewed, per SMA type, as a denominator [redacted] The mean prevalence was based on responses from clinical experts who were considered the most likely to use or prescribe a type of resource – described as ‘Scenario 3’ in UK HCRU report (75). Thus, in some instances a modification in the denominator for the calculation of mean prevalence according to the number of patients seen by only the relevant clinical experts was required.

Unit costs sources

Multiple sources for unit costs were used to calculate costs associated with the HCRU identified:

- For consultations, inpatient hospitalisations and A&E visits the main source of unit costs was the NHS 2018/19 National Cost Collection data (93) and the Personal Social Services Research Unit (PSSRU) Costs of Health and Social Care 2019 report (95)
- For resources related to pharmacological therapy, Prescription Cost Analysis (PCA) England data, 2018 were used (96). When different formulations were available for a medication, a weighted average of different formulations deemed suitable for the target population was used, with weights equal to the total number of units distributed in 2017–18.
    - Technology costs and administration costs for nusinersen – although reported by as a HCRU for some SMA type 1 patients in the UK HCRU study – are handled separately in the model as part of the comparator costs (see Section 8.3.3.3) and hence, are not included as part of the health state HCRU costs.
- For resources related to laboratory tests, respiratory tests/evaluations, orthopaedic devices, surgeries and respiratory devices sources included:
    - NHS 2018/19 National Cost Collection data (93)
    - NHS England Orthotic services, Local tariffs for direct access (97)
    - NICE Motor neuron disease: assessment and management guideline [NG42] (98)
    - Several published articles and NHS buyer's guides/information leaflets

Full details of the unit costs applied per healthcare resource, including the specific reference codes and sources used, are provided in the supplementary Excel reference appendices to the UK HCRU report (75). A summary of costs for SMA is shown in Table 64.

Table 64: Summary of costs for SMA from the UK HCRU study

	Mean resource use per quarter	Mean resource use per year
D state (SMA type 1)		
Consultations	[redacted]	[redacted]
Data hospitals	[redacted]	[redacted]
Pharmacological therapy†	[redacted]	[redacted]
Tests (I), devices (I), surgeries	[redacted]	[redacted]
Tests (II), devices (II), nutrition	[redacted]	[redacted]
Total	[redacted]	[redacted]
C state (SMA type 2 as proxy)		
Consultations	[redacted]	[redacted]
Data hospitals	[redacted]	[redacted]
Pharmacological therapy	[redacted]	[redacted]

Tests (I), devices (I), surgeries	[redacted]	[redacted]
Tests (II), devices (II), nutrition	[redacted]	[redacted]
Total	[redacted]	[redacted]
B state (SMA type 3 as proxy)		
Consultations	[redacted]	[redacted]
Data hospitals	[redacted]	[redacted]
Pharmacological therapy	[redacted]	[redacted]
Tests (I), devices (I), surgeries	[redacted]	[redacted]
Tests (II), devices (II), nutrition	[redacted]	[redacted]
Total	[redacted]	[redacted]

Abbreviations: HCRU, healthcare resource utilisation; SMA, spinal muscular atrophy.
† Nusinersen drug costs and administration costs are removed, as these are handled separately in the model as part of the comparator costs (see Section 8.3.3.3) and hence, are not included as part of the health state HCRU costs.

A limitation of the UK HCRU study is that the clinical expert sample did not include palliative care or intensive care/high dependency specialists, and only included one expert (health visitor) with expertise of the community and social care setting. As such, HCRU associated with such specialisms may not be fully captured. Therefore, the costs calculated in the HCRU study were adjusted using resource costs reported by Noyes et al. 2006 (99). The Noyes study provides detailed costs associated with ventilator-dependent children in the UK under different healthcare settings including home-based, high-dependency units and intensive care units. The proportion of patients receiving care in a home-based, high-dependency and intensive care setting was sourced from UK clinical experts and described in Table 65.

Table 65: Healthcare settings of UK SMA patients by ventilatory status

Ventilation group	Intensive care	High dependency	Home-based
Patients on NIV <16 hours per day	5%	5%	90%
Patients on NIV >16 hours per day	15%	15%	70%
Tracheostomy patients	10%	30%	60%

Abbreviations: NIV, non-invasive ventilation; SMA, spinal muscular atrophy; UK, United Kingdom.
Source: UK advisory board (May 2019) (56).

The proportion of patients requiring NIV <16 hours per day for each health state is estimated based on the prevalence of using non-invasive ventilatory aids (BiPAP NIPPY, Breas) as reported in the UK HCRU study:

- D state (SMA type 1): 16% non-ventilated; 84% NIV <16 hours/day
- C state (SMA type 2): 44% non-ventilated; 66% NIV <16 hours/day
- B state (SMA type 3): 80% non-ventilated; 20% NIV <16 hours/day

Costs for the E state (permanent assisted ventilation) were derived from the Noyes et al. 2006 study (99), as a permanently assisted ventilation cohort was not captured in the UK

HCRU study. Patients in the E state are either on permanent invasive ventilation (i.e. tracheostomy) or receiving NIV >16 hours / day. To align with the 'ERG-preferred base case' assumptions (61), the proportions in these two categories for the purposes of calculating resource utilisation were derived from an SMA type 1 cohort in Italy, receiving non-invasive respiratory aid (NRA) (Gregoretti et al. 2013 (82)). It is noted that in the NRA group, Gregoretti et al 2013 states that seven patients (7/31 [22.6%]) went on to receive tracheostomy. Thus, for calculating resource costs in the E state it is assumed:

- n=24/31 (77.4%) receive NIV >16 hours/day
- n=7/31 (22.6%) have a tracheostomy

Full details how the E state, D state, C state and B state HCRU costs were adjusted or calculated using costs reported by Noyes et al. 2006 (99) and the aforementioned proportions for healthcare settings and ventilatory status were provided in Appendix 7 of the original company submission. Furthermore, calculations can be observed in the 'MedicalCostCalculator' tab of the model Excel file.

In the original model, patients who walk independently are transitioned to the A state after 5 years of age, after which they incur zero SMA-related health care costs. The ERG's clinical experts stated that it is not unreasonable to expect that a patient who is able to walk independently would develop normally, however, there is no evidence that patients who have achieved the ability to walk will incur no additional costs compared with a healthy individual of the same age. The 'ERG-preferred base case' assumption is to apply B state costs to the A state (essentially no A state for the model). This approach is adopted in the revised economic model base case. The resulting health sate costs used in the base case are described in Table 66.

Table 66: Annual SMA-care related costs used in the cost-effectiveness base case

Cost category	**SMA type 1**		**SMA type 2 as proxy**	**SMA type 3 as proxy**	**SMA related costs**
Health state	**E**	**D**	**C**	**B**	**A**
Drugs	£680	£919	£743	£939	£939
Medical tests	£645	£873	£651	£533	£533
Medical visits	£3,153	£4,264	£2,509	£2,217	£2,217
Hospitalisations	£200,247	£63,516	£37,336	£452	£452
GP and Emergency	£325	£439	£183	£73	£73
Health material	£3,172	£4,027	£2,079	£592	£592
Social services	£49,994	£27,896	£18,598	£2,952	£2,952
Total	**£258,216**	**£101,934**	**£62,099**	**£7,759**	**£7,759**

Abbreviations: GP, general practitioner; SMA, spinal muscular atrophy; UK, United Kingdom.

8.3.2 Resource identification, measurement and valuation studies

8.3.2.1 Provide a systematic search of relevant resource data for the NHS in England. Include a search strategy and inclusion criteria, and consider published and unpublished studies.

As described in the original company submission, a systematic literature review was undertaken to identify cost and resource use associated with SMA type 1. However, the cost and resource use values used in the model were identified as per the methods described in Section 8.3.1.1.

8.3.2.2 Provide details of the process used when clinical advisers assessed the applicability of the resources used in the model.

As per section 8.3.1.1, the *de novo* UK HCRU study included aggregated data from n=16 clinical experts to estimate HCRU costs associated with the management of SMA. Details of the recruitment and inclusion criteria used to select the clinical experts are provided in the UK HCRU study report (75).

At a recent UK clinical advisory board – see Section 8.5.1.2 for details – experts provided the consensus that the use of proxies for HCRU costs is reasonable (e.g. SMA type 2 HCRU costs can be used to estimate the HCRU associated with a SMA type 1 baby who can sit unassisted). It was also during this advisory board, consensus was provided on the healthcare settings (intensive care, high dependency or home-based) in which SMA patients receive care, based on their ventilatory status (NIV <16 hours/day, NIV>16 hours/day and tracheostomy).

8.3.3 Technology and comparators' costs

8.3.3.1 Provide the list price for the technology.

The list price for onasemnogene abeparvovec is £1,795,000.

8.3.3.2 If the list price is not used in the de novo cost- effectiveness model, provide the alternative price and a justification.

Not applicable

8.3.3.3 Summarise the annual costs associated with the technology and the comparator technology (if applicable) applied in the cost effectiveness model. A suggested format is provided in tables D6 and D7. Table D7 should only be completed when the most relevant UK comparator for the cost analysis refers to another technology. Please consider all significant costs associated with treatment that may be of interest to commissioners.

The total cost associated with the technology per patient for onasemnogene abeparvovec is £1,797,803 (Table 67).

Table 67: Costs per treatment/patient associated with the technology (onasemnogene abeparvovec) in the cost-effectiveness model

Items	Value	Source
Price of the technology per treatment/patient	£1,795,000	List price for onasemnogene abeparvovec.
Treatment administration cost	£2,803	NHS 2018/19 National Cost Collection data (93) Weighted average of codes relating paediatric nervous system disorders and cerebral degenerations or miscellaneous disorders of nervous system (EL- PR01A-E and EL - AA25C-G)
Total cost per treatment/patient	**£1,797,803**	Calculation

Abbreviations: NHS, National Health Service; US, United States.

The technology and administration costs applied in the nusinersen arm of the model can be found in the model tab 'NusinersenCosts'.

Annual SMA care (i.e. HCRU) costs are not included in the total calculated costs for the technologies but are included in the model as health state costs. All costs for BSC are included in health state costs and have zero 'technology' costs.

8.3.4 Health-state costs

8.3.4.1 If the cost- effectiveness model presents health states, the costs related to each health state should be presented in table D8. The health states should refer to the states in section 12.1.6. Provide a rationale for the choice of values used in the cost- effectiveness model.

Table 68 shows the cost categories that are applied to each of the health states in the model. Section 8.2.6 and section 8.3.1.1 shows the unit cost data used in the model, and, for those costs which are cycle dependent, shows how the values were derived. Total costs by health state are shown in Section 8.5.1.9.

Table 68: List of health states and associated costs in the cost-effectiveness model

Cost categories	Health State				
	E Permanent assisted ventilation	**D Not sitting**	**C Sits unassisted**	**B Walks unassisted**	**A Within broad range of development**
Technology	Onasemnogene abeparvovec: all patients receive gene therapy at baseline Nusinersen: all patients receive drug unless discontinued; patients who move to E state do not receive nusinersen				
Technology administration	Onasemnogene abeparvovec: all patients incur administration costs at baseline. As the technology is a one-time, single IV administration, no ongoing administration costs are incurred Nusinersen: all patients incur drug administration costs per dose, which is for lifetime unless the patient discontinues or dies. Patients who move to the E state do not receive nusinersen and do not incur administration costs				

Cost categories	Health State				
	E Permanent assisted ventilation	D Not sitting	C Sits unassisted	B Walks unassisted	A Within broad range of development
SMA treatment costs	E state costs in each cycle times probability patient is in the cycle	D state costs in each cycle times probability patient is in the cycle	C state costs in each cycle times probability patient is in the cycle	B state costs in each cycle times probability patient is in the cycle	A state costs in each cycle times probability patient is in the cycle†

†To align the base case with 'ERG-preferred base case' assumptions, A state costs have been assumed to be the same as B state costs.

8.3.5 Adverse-event costs

8.3.5.1 Complete table D9 with details of the costs associated with each adverse event included in the cost- effectiveness model. Include all adverse events and complication costs, both during and after longer-term use of the technology.

All patients in onasemnogene abeparvovec clinical studies were treated with prophylactic oral prednisolone, except for the first patient enrolled into START, who developed elevated transaminases >20 x the upper limit of normal, which appeared to respond to prednisolone. However, since the cost of prednisolone is minor, no AEs are included in the cost-effectiveness model in terms of cost or health impacts.

For nusinersen, as no serious AEs were reported in either arm of ENDEAR and no AEs were considered by trial investigators to be related to treatment in ENDEAR (76), AEs were excluded from consideration in the model. Adverse events associated with lumbar puncture (e.g. headache and back pain) were observed but the incidence and severity of these were consistent with events expected to occur with lumbar puncture. In addition, these events could not be assessed because of the limited communication abilities in the infant population treated with nusinersen.

8.3.6 Miscellaneous costs

8.3.6.1 Describe any additional costs and cost savings that have not been covered anywhere else (for example, PSS costs, and patient and carer costs). If none, please state.

In the opinion of AveXis, the model captures all of the major costs and cost savings that arise with the introduction of onasemnogene abeparvovec in England as part of the base case. Note that the potential impact on family and patient income/out of pockets expenses from the introduction of the technology is addressed as explorative scenarios in the answers to questions 10.1, 10.3, and 10.4.

8.3.6.2 Are there any other opportunities for resource savings or redirection of resources that it has not been possible to quantify?

No other opportunities for NHS/PSS resource savings outside of those explored in answers to questions 10.1, 10.3, and 10.4 have been identified.

8.4 *Approach to sensitivity analysis*

8.4.1 Has the uncertainty around structural assumptions been investigated? State the types of sensitivity analysis that have been carried out in the cost- effectiveness analysis.

No. However, extensive sensitivity analyses and scenario analyses are conducted, as described in Section 8.4.3 to determine the impact on the results of varying key model assumptions and parameters.

8.4.2 Was a deterministic and/or probabilistic sensitivity analysis undertaken? If not, why not? How were variables varied and what was the rationale for this? If relevant, the distributions and their sources should be clearly stated.

Yes. Deterministic, probabilistic, and scenario-based sensitivity analyses were undertaken. The variables used, together with the range of the variation (upper and lower values) and the method used, are summarised in Section 8.4.3.

8.4.3 Complete table D10.1, D10.2 and/or D10.3 as appropriate to summarise the variables used in the sensitivity analysis.

8.4.3.1 Values used in the one-way sensitivity analysis

The values used in the one-way sensitivity analysis are shown below in Table 69. The value of each variable was adjusted by +/- 20%.

Table 69: Variables used in one-way deterministic sensitivity analysis

Category	Variable	Base case	Low value	High value
Annual SMA-care health state costs	E state: drug costs	£680	£544	£816
	E state: medical tests	£645	£516	£774
	E state: medical visits	£3,153	£2,522	£3,784
	E state: hospitalisations	£200,247	£160,198	£240,297
	E state: GP & emergency	£325	£260	£390
	E state: health materials	£3,172	£2,538	£3,807
	E state: social services	£49,994	£39,995	£59,992
	D state: drug costs	£919	£735	£1,103
	D state: medical tests	£873	£698	£1,047
	D state: medical visits	£4,264	£3,411	£5,116
	D state: hospitalisations	£63,516	£50,813	£76,219
	D state: GP & emergency	£439	£351	£527
	D state: health materials	£4,027	£3,221	£4,832
	D state: social services	£27,896	£22,317	£33,476
	C state: drug costs	£743	£594	£891
	C state: medical tests	£651	£521	£781
	C state: medical visits	£2,509	£2,008	£3,011
	C state: hospitalisations	£37,336	£29,869	£44,804
	C state: GP & emergency	£183	£146	£219
	C state: health materials	£2,079	£1,664	£2,495
	C state: social services	£18,598	£14,878	£22,317

Category	Variable	Base case	Low value	High value
	B state: drug costs	£939	£751	£1,127
	B state: medical tests	£533	£426	£640
	B state: medical visits	£2,217	£1,773	£2,660
	B state: hospitalisations	£452	£362	£543
	B state: GP & emergency	£73	£59	£88
	B state: health materials	£592	£474	£710
	B state: social services	£2,952	£2,362	£3,542
	A state: drug costs	£939	£751	£1,127
	A state: medical tests	£533	£426	£640
	A state: medical visits	£2,217	£1,773	£2,660
	A state: hospitalisations	£452	£362	£543
	A state: GP & emergency	£73	£59	£88
	A state: health materials	£592	£474	£710
	A state: social services	£2,952	£2,362	£3,542
Onasemnogene abeparvovec costs	Onasemnogene abeparvovec list price	£1,795,000	£1,436,000	£2,154,000
	Onasemnogene abeparvovec administration cost	£2,803	£2,242	£3,363
Nusinersen costs and administration costs[†]	Technology acquisition cost, per vial	£75,000	£60,000	£90,000
	Inpatient lumbar puncture: Aged ≤5 years	£1,545	£1,236	£1,854
	Inpatient lumbar puncture: Aged 6–18 years	£1,327	£1,061	£1,592
	Inpatient lumbar puncture: Aged ≥19 years	£815	£652	£978
	Outpatient lumbar puncture: Aged ≤5 years	£224	£179	£269
	Outpatient lumbar puncture: Aged 6–18 years	£220	£176	£264

Category	Variable	Base case	Low value	High value
	Outpatient lumbar puncture: Aged ≥19 years	£315	£252	£378
	Day case lumbar puncture: Aged ≤5 years	£1,224	£979	£1,468
	Day case lumbar puncture: Aged 6–18 years	£891	£713	£1,069
	Day case lumbar puncture: Aged ≥19 years	£565	£452	£677
Nusinersen discontinuation rate and rate of milestone loss†	Proportion of arm discontinuing nusinersen in C state	3.0%	2.4%	3.6%
	Proportion of arm discontinuing nusinersen in D state	3.0%	2.4%	3.6%
	Rate of milestone loss for patients that discontinue nusinersen: state C	90.0%	72.0%	100.0%
	Rate of milestone loss for patients that discontinue nusinersen: state D	90.0%	72.0%	100.0%
Quality of Life adjustments	Utility: E state	0.000	0.000	0.000
	Utility: D state	0.190	0.152	0.228
	Utility: C state	0.600	0.480	0.720
	Utility B and A state: % male in Ara Brazier equation	41.7%	33.36%	50.04%
	Utility B and A state: Ara Brazier equation intercept	0.951	0.761	1.000
	Utility B and A state: Ara Brazier sex coefficient	0.021	0.01697	0.02546
	Utility B and A state: Ara Brazier age coefficient	0.00026	0.000207	0.0003104
	Utility B and A state: Ara Brazier age squared coefficient	0.00003	0.0000266	0.000398
	On-treatment utility increment: D state - onasemnogene abeparvovec and nusinersen†	0.100	0.080	0.120
	On-treatment utility increment: C state - onasemnogene abeparvovec and nusinersen†	0.050	0.040	0.060
Survival limits	Survival limit (years) for E state	16.0	12.8	19.2
	Survival limit (years) for D state - BSC	4.0	3.2	4.8

Category	Variable	Base case	Low value	High value
	Survival limit (years) for D state - onasemnogene abeparvovec	4.0	3.2	4.8
	Survival limit (years) for D state - nusinersen†	4.0	3.2	4.8

Abbreviations: GP, general practitioner; SMA, spinal muscular atrophy.

† Cost-effectiveness results of onasemnogene abeparvovec versus nusinersen are not presented in this revised submission, as nusinersen is no longer considered a valid comparator for this appraisal. As the revised economic model submitted to NICE still includes a nusinersen arm, for completion, the methods and inputs sections relating to the nusinersen arm of the economic model are described.

8.4.3.2 Values used in other sensitivity analyses

AveXis examined the impact of varying the underlying data and assumptions in the model on the onasemnogene abeparvovec versus BSC ICER; the data values and sources explored included:

Discount rates:

- Costs and effects at 0%;
- Costs and effects at 5%;
- Costs at 0%, effects at 5%;
- Costs at 5%, effects at 0%;
- Costs and effects at 1.5%.

Cost assumptions:

- Replacing the base case health state costs with the 'Real World Evidence (RWE)' costs presented at the nusinersen NICE third appraisal committee meeting (ACM3) (60). Values used were:
    - 'SMA type 1' costs of £148,214 for the E state and D state (i.e. using the doubled SMA type 1 costs)
    - 'SMA type 2' costs of £68,322 used as a proxy for the C state
    - 'SMA type 3' costs of £21,765 used as a proxy for the B state (and A state)
- SMA type 3 costs from RWE presented at nusinersen ACM3 applied to the A state and B state patients, other health state costs remain as base case
- Pessimistic scenario that the costs of onasemnogene abeparvovec administration are 10X greater than the base case of £2,803 (i.e. £28,030);

Utility values:

- On-treatment utilities (i.e. an additional utility of 0.1 compared with BSC in the D state and an additional utility of 0.05 compared with BSC in the C state) are applied in the base case, to accommodate the 'ERG-preferred base case' assumptions: *Interim milestones that maybe achieved with the use of onasemnogene abeparvovec are considered by the ERG's clinical experts to have an impact on a patient's quality of life. Consequently, the ERG considers the inclusion of on-treatment utility values based on values reported in the US ICER report should be included to account for these benefits of treatment.* Scenarios applied to the on-treatment utilities included:
    - Analysis as above but with lower "on-treatment" utilities than used by US ICER. A value of 0.05 was added to the D state (not sitting) and a value of 0.025 was added to the C state (sits unassisted)

    - Analysis as above but with higher “on treatment” utilities than used by US ICER. A value of 0.15 was added to the D state (not sitting) and a value of 0.075 was added to the C state (sits unassisted)

- The base case values for the C, D and E states were substituted with the utility values derived from the mapping of the PedsQL score in the CHERISH nusinersen study to EQ-5D-Y as described in Section 7.1.2: values for these states were 0.878 (B state), 0.764 (C state), 0.756 (D state) and 0.730 (E state);

- The base case values for the C, D and E states were substituted with the utility values derived from the Lloyd et al 2017 Clinician-proxy Case Vignette study as described in Section 7.1.2: values for these states were 0.710 (B state), -0.04 (C state), -0.12 (D state) and -0.33 (E state);

- The base case values for the B, C, D and E states were substituted with the utility values derived from the exploratory AveXis UK utilities elicitation study using the TTO results from the ‘parent vignettes’ as described in as described in Section 7.1.2: values for these states were [redacted] (B state), [redacted] (C state), [redacted] (D state) and [redacted] (E state);

- Utility outcomes are not counted i.e. results are ‘cost per life year gained’;

Alternative natural history sources

- The NeuroNext natural history cohort (5), which is used to inform overall survival and event-free survival in the D state in the base case is replaced with:

    - Data from the AveXis external control PNCR dataset (5)

    - Data from Finkel et al. 2017 (ENDEAR sham control) (57)

    - Data from De Sanctis et al. 2016 (PNCR, US and Italy study) (30)

Exploratory scenarios

Several exploratory analyses of scenarios are conducted – some optimistic and some pessimistic – within the model as follows:

- Improved survival for patients in the C state (sits unassisted):

    - Patients who achieve the C state (sits unassisted) have a life expectancy the same as the general population: applied to onasemnogene abeparvovec arm only

- Calculation of milestone attainment in the onasemnogene abeparvovec arm for different scenarios of milestone attainment in STR1VE-US patients, after 18 months of age (for which empirical data are currently lacking):

    - Use of the POOLED dataset, but with only one additional sitter compared with the empirical data in STR1VE-US after 18 months of age. The additional sitter sits between 24 and 30 months of age and therefore moves to sitting in cycle ending 36 months. This is more conservative than the base case

- Use of the POOLED dataset, but with only one additional walker compared with the empirical data in STR1VE-US after 18 months of age. The additional walker walks between 24 - 30 months of age and therefore moves to walking in cycle ending 36 months. This is more conservative than the base case
- Use of the POOLED dataset but use of the empirical data only from STR1VE-US. i.e. it assumes there are no additional patients who can sit or walk unassisted in STR1VE-US after 18 months of age. This exploratory scenario is considered highly pessimistic as:
    - STR1VE-US stopped when patients reached 18 months of age[32], which is only just past the upper limit of the WHO window for walking independently in normal childhood development (17.6 months is the 99th percentile for walking independently). This (18 months of age) is too strict a threshold at which to expect symptomatic SMA type 1 patients to have achieved all motor milestones
    - START data showed that patients continue to develop key gross motor milestones (sitting alone and walking alone) beyond 18 months of age. In START, 5 patients sat unassisted after 18 months of age and 2 patients walked unassisted after 18 months of age
    - START data showed that symptomatic SMA type 1 patients achieve gross motor milestones, but these are 'delayed' compared with WHO windows or normal childhood development: in START, the median age at sitting alone and walking alone was 17.1 months (range: 8.0–30.8 months) and 19.3 months (range: 18.9–19.6 months, respectively. As STR1VE-US stopped when patients reached 18 months of age, it is likely later or 'delayed' milestones will not be fully captured and hence underestimate the overall milestones attained by STR1VE-US patients once they reach 30 months of age
- Use of POOLED dataset, but with four new patients who can sit unassisted and four new patients who can walk unassisted in STR1VE-US after 18 months of age:
    - Two of the additional sitters sit, and two of the additional walkers walk between 18 and 24 months of age and therefore move to sitting and walking in cycle ending 30 months, respectively
    - Two of the additional sitters sit, and two of the additional walkers walk between 24 and 30 months of age and therefore move to sitting and walking in cycle ending 36 months, respectively
    - This scenario is based on the age of milestones attained by patients in the START trial, which followed patients up to 24 months post-dose (up to

[32] The End of Study visit must occur within 0 to 14 days after the date on which the patient reaches 18 months of age (or early termination).

approximately 30 months of age). In START, 5 patients sat unassisted after 18 months of age and 2 patients walked unassisted after 18 months of age

- Milestones, overall survival and event-free survival are based on those treated at ≤3.5 months of age in START and STR1VE-US (n=17):
    - Of those treated at or before 3.5 months of age across START and STR1VE-US, 14/17 (82.4%) sat independently of which 3/17 (17.6%) also walked independently
    - Of those treated at or before 3.5 months of age across START and STR1VE-US, one patient died (1/17) and no patients (0/17) went on to permanent assisted ventilation
    - The cut-off of 3.5 months of age was chosen, as this was the median age at which infants across START and STR1VE-US received onasemnogene abeparvovec.
- Milestones, overall survival and event-free survival are based on those treated in START only (n=12):
    - Of those treated in START, n=11/12 (91.7%) sat independently of which n=2/12 (16.7%) also walked independently
    - Of those treated in START, all were alive and event-free at the end of the study
- Use of the POOLED dataset, but the conservative 'offset' is not applied to milestone data in the model (milestones are not 'offset' by 6 months). This is less conservative than the base case:
    - Milestones are incorporated into the model, as they were observed in clinical trials. For example, if a patient sits at 9 months old, they would transition to the sitting health state in cycle 2 (between 6 and 12 months of age)
- E state overall survival is based on the 'pooled' Gregoretti cohort, i.e. patients with tracheostomy (n=42) or NIV (n=31) (defined as continuous non-invasive respiratory muscle aid [NRA], including non-invasive ventilation and mechanically assisted cough). Please note, in this scenario analysis amends to the cost calculator are made:
    - In the 'MedicalCostCalculator' sheet, HCRU costs in the E state are calculated assuming that 57.5% of patients in the E state receive a tracheostomy and 42.5% receive NIV >16 hours/day to match the ratio of tracheostomy use to NIV use reported in this pooled cohort
- Including caregiver disutility scores
    - This explorative scenario applies a disutility for caregivers that varies by the health state of the patient, drawing data from a proxy, but related, disease – spina bifida – see Section 7.1.2 for details. A study by Tilford et al. 2005 (70) compared QWB scale data from the primary caregivers of children aged 0–17 years (n=98) with spina bifida versus a control sample of parents of non-disabled/unaffected children (n=49). Spina

bifida children were categorised into three disability levels according to the location of the child's lesion: 1) sacral, 2) lower lumbar and 3) thoracic. When comparing caregivers of spina bifida patients to the control caregiver sample, the 'spill over' disutility of spina bifida caregivers are reported as: -0.03, -0.03 and -0.08 for the sacral, lower lumbar and thoracic lesion groups, respectively. Values were calculated using the method described by Wittenberg et al. 2013 (59). These caregiver disutilities are incorporated into the exploratory scenario analysis as follows: -0.08 for caregivers of a child in the E state (permanent assisted ventilation) or D state (not sitting) and -0.03 for a child in the C state (sits unassisted).

8.4.3.3 Values used in the multi-way sensitivity analyses

Multi-way sensitivity analysis

For the multi-way sensitivity analysis, the three variables with the largest impact on the results (excluding the cost of onasemnogene abeparvovec) were taken from the one-way sensitivity results for onasemnogene abeparvovec versus BSC (Table 70). These are: i) the cost of hospitalisations for C state patients, ii) the cost of social services for C state patients and, iii) the patient utility value of the C state. The two multi-way analyses, therefore used the following sets of values. The value of each variable was adjusted by +/- 20%.

Table 70 Variables used in multi-way scenario-based sensitivity analysis (onasemnogene abeparvovec versus BSC)

Variable	*Cost of hospitalisations for C state*	*Cost of social services for C state*	*Patient utility value for C state*
Base case value	£37,336	£18,598	0.6
Base case * 0.8	£29,869	£14,878	0.48
Base case * 1.2	£44,803	£22,318	0.72

Probabilistic Sensitivity Analysis

Variables included in the Probabilistic Sensitivity Analysis (PSA) are shown below in Table 71.

Table 71: Values used in the probabilistic sensitivity analysis

Category	Variable	Base case	Distribution
Annual SMA-care health state costs	E state: drug costs	£680	Gamma distribution with a standard error of 20%
	E state: medical tests	£645	
	E state: medical visits	£3,153	
	E state: hospitalisations	£200,247	
	E state: GP & emergency	£325	
	E state: health materials	£3,172	
	E state: social services	£49,994	
	D state: drug costs	£919	
	D state: medical tests	£873	
	D state: medical visits	£4,264	
	D state: hospitalisations	£63,516	
	D state: GP & emergency	£439	
	D state: health materials	£4,027	
	D state: social services	£27,896	
	C state: drug costs	£743	
	C state: medical tests	£651	
	C state: medical visits	£2,509	
	C state: hospitalisations	£37,336	
	C state: GP & emergency	£183	
	C state: health materials	£2,079	
	C state: social services	£18,598	

Category	Variable	Base case	Distribution
	B state: drug costs	£939	
	B state: medical tests	£533	
	B state: medical visits	£2,217	
	B state: hospitalisations	£452	
	B state: GP & emergency	£73	
	B state: health materials	£592	
	B state: social services	£2,952	
	A state: drug costs	£939	
	A state: medical tests	£533	
	A state: medical visits	£2,217	
	A state: hospitalisations	£452	
	A state: GP & emergency	£73	
	A state: health materials	£592	
	A state: social services	£2,952	
Onasemnogene abeparvovec costs	Onasemnogene abeparvovec drug acquisition cost: list price	£1,795,000	Fixed in PSA
	Onasemnogene abeparvovec administration cost	£2,803	Gamma distribution with SE of 20%
Nusinersen costs, administration costs and location[†]	Technology acquisition cost, per vial	£75,000	Value fixed in PSA
	Inpatient lumbar puncture: Aged ≤5 years	£1,545	Gamma distribution with SE of 20%
	Inpatient lumbar puncture: Aged 6–18 years	£1,327	
	Inpatient lumbar puncture: Aged ≥19 years	£815	
	Outpatient lumbar puncture: Aged ≤5 years	£224	
	Outpatient lumbar puncture: Aged 6–18 years	£220	

Category	Variable	Base case	Distribution
	Outpatient lumbar puncture: Aged ≥19 years	£315	
	Day case lumbar puncture: Aged ≤5 years	£1,224	
	Day case lumbar puncture: Aged 6–18 years	£891	
	Day case lumbar puncture: Aged ≥19 years	£565	
	% of patients having an elective inpatient procedure (all age groups)	40%	Dirichlet – gamma distribution
	% of patients having an outpatient procedure (all age groups)	30%	
	% of patients having a day case procedure (all age groups)	30%	
Discontinuation rate and milestone loss: nusinersen arm†	Rate of milestone loss for patients that discontinue nusinersen: C state	90.00%	Beta distribution with SE of 20%
	Rate of milestone loss for patients that discontinue nusinersen: D state	90.00%	
	Proportion of arm discontinuing nusinersen in C state	3.00%	
	Proportion of arm discontinuing nusinersen in D state	3.00%	
	Proportion of arm discontinuing nusinersen in E state	100%	Fixed in PSA
Utilities	Utility: E state	**0.000**	Fixed in PSA
	Utility: D state	0.190	Gamma distribution with SE of 5%
	Utility: C state	0.600	
	Utility B and A state: % male in Ara Brazier equation	0.417	Beta distribution with SE of 5%
	Utility B and A state: Ara Brazier equation intercept	0.9509	
	Utility B and A state: Ara Brazier sex coefficient	0.021	
	Utility: B and A state: Ara Brazier age coefficient	0.00026	
	Utility: B and A state: Ara Brazier age squared coefficient	0.00003	

Category	Variable	Base case	Distribution
	On-treatment utility increment: D state - onasemnogene abeparvovec and nusinersen†	0.100	
	On-treatment utility increment: C state - onasemnogene abeparvovec and nusinersen†	0.050	
Survival limits	Survival limit (years) for E state	16	Gamma distribution with SE of 20%
	Survival limit (proportion of remaining population) for D state – BSC	4	Gamma distribution with SE of 20%
	Survival limit (proportion of remaining population) for D state - onasemnogene abeparvovec	4	
	Survival limit (proportion of remaining population) for D state - nusinersen†	4	
Survival curve parameters	E state OS: Exponential distribution: lambda	0.0165	Cholesky decomposition.
	D state OS (disaggregated): Weibull: lambda	0.0131	
	D state OS (disaggregated): Weibull: gamma	1.4938	
	D state OS (aggregated): Weibull: lambda	0.0172	
	D state OS (aggregated): Weibull: gamma	1.3259	
	D state EFS: Weibull: lambda	0.0140	
	D state EFS: Weibull: gamma	1.5506	
	C state: generalised gamma: mu	6.35646	
	C state: generalised gamma: sigma	0.11002	
	C state: generalised gamma: q	5.35602	

Abbreviations: EFS, event-free survival; GP, general practitioner; OS, overall survival.

† Cost-effectiveness results of onasemnogene abeparvovec versus nusinersen are not presented in this revised submission, as nusinersen is no longer considered a valid comparator for this appraisal. As the revised economic model submitted to NICE still includes a nusinersen arm, for completion, the methods and inputs sections relating to the nusinersen arm of the economic model are described.

8.4.4 If any parameters or variables listed above were omitted from the sensitivity analysis, provide the rationale.

Not applicable. All relevant parameters were included in the one-way sensitivity analysis, multi-way sensitivity analysis, scenario sensitivity analysis, or probabilistic sensitivity analysis as described in Section 8.4.3.

8.5 *Results of economic analysis*

8.5.1 Base-case analysis

8.5.1.1 When presenting the results of the base case incremental cost effectiveness analysis in the table below, list the interventions and comparator(s) from least to most expensive. Present incremental cost-effectiveness ratios (ICERs) compared with baseline (usually standard care) and then incremental analysis ranking technologies in terms of dominance and extended dominance. If the company has formally agreed a patient access scheme with the Department of Health, present the results of the base-case incremental cost-effectiveness analysis with the patient access scheme. A suggested format is available in table D11.

In the base-case, the ICER for onasemnogene abeparvovec versus BSC is £230,568 per QALY gained. Total and incremental per patient costs, total and incremental life years gained and total and incremental QALYs gained are presented in Table 72. Costs and effects (QALYs and life years) are discounted at 3.5%.

Table 72: Base case results

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£) (versus BSC)	Incremental LYG (versus BSC)	Incremental QALYs (versus BSC)	ICER (£/QALY) (versus BSC)
BSC	381,131	2.15	0.210	N/A	N/A	N/A	N/A
Onasemnogene abeparvovec	2,640,022	15.39	10.007	2,258,891	13.24	9.80	230,568

Abbreviations: BSC, best supportive care; ICER, incremental cost-effectiveness ratio; LYG, life years gained; N/A, not applicable; QALYs, quality-adjusted life years.

8.5.1.2 For the outcomes highlighted in the decision problem, please provide the corresponding outcomes from the model and compare them with clinically important outcomes such as those reported in clinical trials. Discuss reasons for any differences between modelled and observed results (for example, adjustment for cross-over). Please use the following table format for each comparator with relevant outcomes included.

Not applicable. The economic model uses onasemnogene abeparvovec trial results until the end of their observation periods, although with one additional sitter and one additional walker assumed in STR1VE-US after 18 months of age. Both the additional sitter sits, and the additional walker walks between 24 - 30 months of age and therefore, transition to sitting and walking in cycle ending 36 months, respectively. After this period the model uses extrapolated results. Please see section 8.2.1.1 for full details and rationale supporting the base case assumption of applying one additional sitter and walker after 18 months of age.

8.5.1.3 Please provide (if appropriate) the proportion of the cohort in the health state over time (Markov trace) for each state, supplying one for each comparator.

Table 73 shows the probability of a patient being in one of the surviving health states or death over time.

Table 73: Probability of a patient being in surviving health states or death over the lifetime of the model by intervention arm

Patients who received onasemnogene abeparvovec						
Year after procedure	**Dead**	**E State (PAV)**	**D State**	**C State**	**B State**	**A State**
1	2.94%	2.94%	94.12%	0.00%	0.00%	0.00%
5	24.28%	1.93%	0.00%	62.04%	11.76%	0.00%
10	28.26%	0.71%	0.00%	59.27%	0.00%	11.75%
25	43.97%	0.00%	0.00%	44.32%	0.00%	11.71%
50	86.31%	0.00%	0.00%	2.31%	0.00%	11.38%
75	91.07%	0.00%	0.00%	0.00%	0.00%	8.93%
100	99.80%	0.00%	0.00%	0.00%	0.00%	0.20%
Patients who received BSC						
Year after procedure	**Dead**	**E State (PAV)**	**D State**	**C State**	**B State**	**A State**
1	46.69%	9.32%	43.99%	0.00%	0.00%	0.00%
5	86.76%	13.24%	0.00%	0.00%	0.00%	0.00%
10	95.09%	4.91%	0.00%	0.00%	0.00%	0.00%
25	100.00%	0.00%	0.00%	0.00%	0.00%	0.00%
50	100.00%	0.00%	0.00%	0.00%	0.00%	0.00%
75	100.00%	0.00%	0.00%	0.00%	0.00%	0.00%
100	100.00%	0.00%	0.00%	0.00%	0.00%	0.00%

Abbreviations: BSC, best supportive care; PAV, permanent assisted ventilation.

8.5.1.4 Please provide details of how the model assumes QALYs accrued over time. For example, Markov traces can be used to demonstrate QALYs accrued in each health state over time.

Table 74 shows QALYs accrued over time for a patient treated with onasemnogene abeparvovec or BSC. Note that this is based on the probability of the patient being in each of the health states in each time period. QALYs are discounted at 3.5%.

Table 74: QALYs accrued over time for a patient based on the probability of being in each health state in each time period (discounted at 3.5%)

Patients who received onasemnogene abeparvovec						
Year after procedure	**Total**	**E State (PAV)**	**D State**	**C State**	**B State**	**A State**
1	0.344	0.000	0.344	0.00	0.00	0.00
5	2.121	0.000	0.545	1.282	0.295	0.00
10	4.044	0.000	0.545	2.777	0.295	0.427
25	7.748	0.000	0.545	5.574	0.295	1.334
50	9.703	0.000	0.545	6.794	0.295	2.069
75	9.964	0.000	0.545	6.795	0.295	2.328
100	10.007	0.000	0.545	6.795	0.295	2.372
Patients who received BSC						
Year after procedure	**Total**	**E State (PAV)**	**D State**	**C State**	**B State**	**A State**
1	0.167	0.000	0.167	0.00	0.00	0.00
5	0.210	0.000	0.210	0.00	0.00	0.00
10	0.210	0.000	0.210	0.00	0.00	0.00
25	0.210	0.000	0.210	0.00	0.00	0.00
50	0.210	0.000	0.210	0.00	0.00	0.00
75	0.210	0.000	0.210	0.00	0.00	0.00
100	0.210	0.000	0.210	0.00	0.00	0.00

Abbreviations: BSC, best supportive care; PAV, permanent assisted ventilation.

8.5.1.5 Please indicate the life years (LY) and QALYs accrued for each clinical outcome listed for each comparator. For outcomes that are a combination of other states, please present disaggregated results.

The disaggregation of accrued LYs and QALYs is presented in Table 75. Note that results are discounted at 3.5% and with half cycle correction.

Table 75: Model outputs by clinical outcomes (discounted at 3.5%)

Patients who received onasemnogene abeparvovec		
Outcome	**Life years**	**QALYs**
E State (PAV)	0.154	0
D state	1.878	0.545
C State	10.454	6.795
B State	0.308	0.295
A State	2.590	2.372
TOTAL	15.385	10.007
Patients who received BSC		
Outcome	**Life years**	**QALYs**
E State (PAV)	1.040	0
D state	1.105	0.210
C State	0	0
B State	0	0
A State	0	0
TOTAL	2.145	0.210

Abbreviations: BSC, best supportive care; LYG, life years gained; PAV, permanent assisted ventilation; QALYs, quality-adjusted life years.

8.5.1.6 Please provide details of the disaggregated incremental QALYs by health state. Suggested formats are presented below.

The disaggregation of incremental QALYs by health state are presented in Table 76. Onasemnogene abeparvovec provides large incremental QALY gains: 9.797 QALYs when compared with BSC. Over 93% of the QALY gains for onasemnogene abeparvovec compared with BSC are due to gains in the C and A states.

Table 76: Summary of QALY gain differences by health state (onasemnogene abeparvovec versus BSC) – discounted

Outcome	QALYs onasemnogene abeparvovec	QALYs BSC	Increment	Absolute increment	% absolute increment
E State (PAV)	0	0	0	0	0
D state	0.545	0.210	0.335	0.335	3.42
C State	6.795	0	6.795	6.795	69.36
B State	0.295	0	0.295	0.295	3.01
A State	2.372	0	2.372	2.372	24.21
TOTAL	10.007	0.210	9.797	9.797	100

Abbreviations: BSC, best supportive care; PAV, permanent assisted ventilation; QALYs, quality-adjusted life years.

8.5.1.7 Please provide undiscounted incremental QALYs for the intervention compared with each comparator

Table 77 shows the undiscounted incremental QALYs for the intervention compared with each comparator.

Table 77: Undiscounted QALYs gained from onasemnogene abeparvovec and comparator and incremental QALYs gained from onasemnogene abeparvovec over comparator

Intervention	QALYs from intervention	Incremental QALYs (onasemnogene abeparvovec over comparator)
Onasemnogene abeparvovec	21.020	N/A
BSC	0.217	20.803

Abbreviations: BSC, best supportive care; N/A, not applicable; QALYs, quality-adjusted life years.

8.5.1.8 Provide details of the costs for the technology and its comparator by category of cost. A suggested format is presented in table D12.

Table 78 shows the costs of onasemnogene abeparvovec and BSC by category of costs. Of the total increase in costs, just under 77% are for the technology cost of onasemnogene abeparvovec with 23% for increased SMA treatment/care costs for patients (mainly due to increased survival).

Table 78: Costs of onasemnogene abeparvovec and comparator by category of cost (onasemnogene abeparvovec versus BSC) (discounted at 3.5%)†

Item	Cost onasemnogene abeparvovec	Cost BSC	Increment	Absolute increment	% absolute increment
Technology cost	£1,734,300	£0	£1,734,300	£1,734,300	76.78
Mean total SMA treatment cost (all care costs)	£903,015	£381,131	£521,884	£521,884	23.10
Administration cost of the technology	£2,708	£0	£2,708	£2,708	0.12
Total	£2,640,022	£381,131	£2,258,891	£2,258,891	100%

Abbreviations: BSC, best supportive care; SMA, spinal muscular atrophy. † Values are reported as per the economic model, discrepancies are due to rounding.

8.5.1.9 If appropriate, provide details of the costs for the technology and its comparator by health state. A suggested format is presented in table D13.

Table 79 shows the total costs for onasemnogene abeparvovec by health state versus BSC. Note that costs for the technology (onasemnogene abeparvovec) include the costs of the technology and SMA care costs incurred whilst in the health state.

Note also that since onasemnogene abeparvovec is a one-time, single IV treatment the discounted cost of onasemnogene abeparvovec and administration has been allocated between the health states by the proportion of the total (discounted) life years gained by health state. For example, since the ‘D’ state for onasemnogene abeparvovec produces 1.878 of the total (discounted) 15.385 life years gained, 12.207% (1.878/15.385) of the total onasemnogene abeparvovec and administration costs have been allocated to the ‘D’ state.

Table 79: Total costs of onasemnogene abeparvovec and BSC by health state (discounted at 3.5%)

Health state	Cost onasemnogene abeparvovec	Cost BSC	Increment	Absolute increment	% absolute increment
E state (PAV)	£57,256	£268,446	-£211,190	£211,190	7.88
D state	£403,487	£112,685	£290,802	£290,802	10.85
C state	£1,829,488	£0	£1,829,488	£1,829,488	68.23
B state	£37,164	£0	£37,164	£37,164	1.39
A state	£312,521	£0	£312,521	£312,521	11.66
Total	£2,639,916 (*)	£381,131	£2,258,785	£2,681,165	100%

Abbreviations: BSC, best supportive care; PAV, permanent assisted ventilation. Figures may not sum exactly due to rounding during onasemnogene abeparvovec apportioning between states.

8.5.1.10 If appropriate, provide details of the costs for the technology and its comparator by adverse event. A suggested format is provided in table D14.

Adverse events are not included in the model: see Section 8.3.5.1.

8.5.2 Sensitivity analysis results

8.5.2.1 Present results of deterministic one-way sensitivity analysis of the variables described in table D10.1.

Figure 45 shows the impact on the ICER from the one-way sensitivity analysis for onasemnogene abeparvovec versus BSC: results in table format are shown in Table 80. All variables were varied by +/- 20% or natural limits if these were within the +/- 20% range.

These results are discussed in Section 8.5.2.4.

Figure 45: Tornado diagram of impact of the one-way sensitivity analysis (+/- 20% or natural limit) on the ICER (onasemnogene abeparvovec versus BSC) – top 20 results only

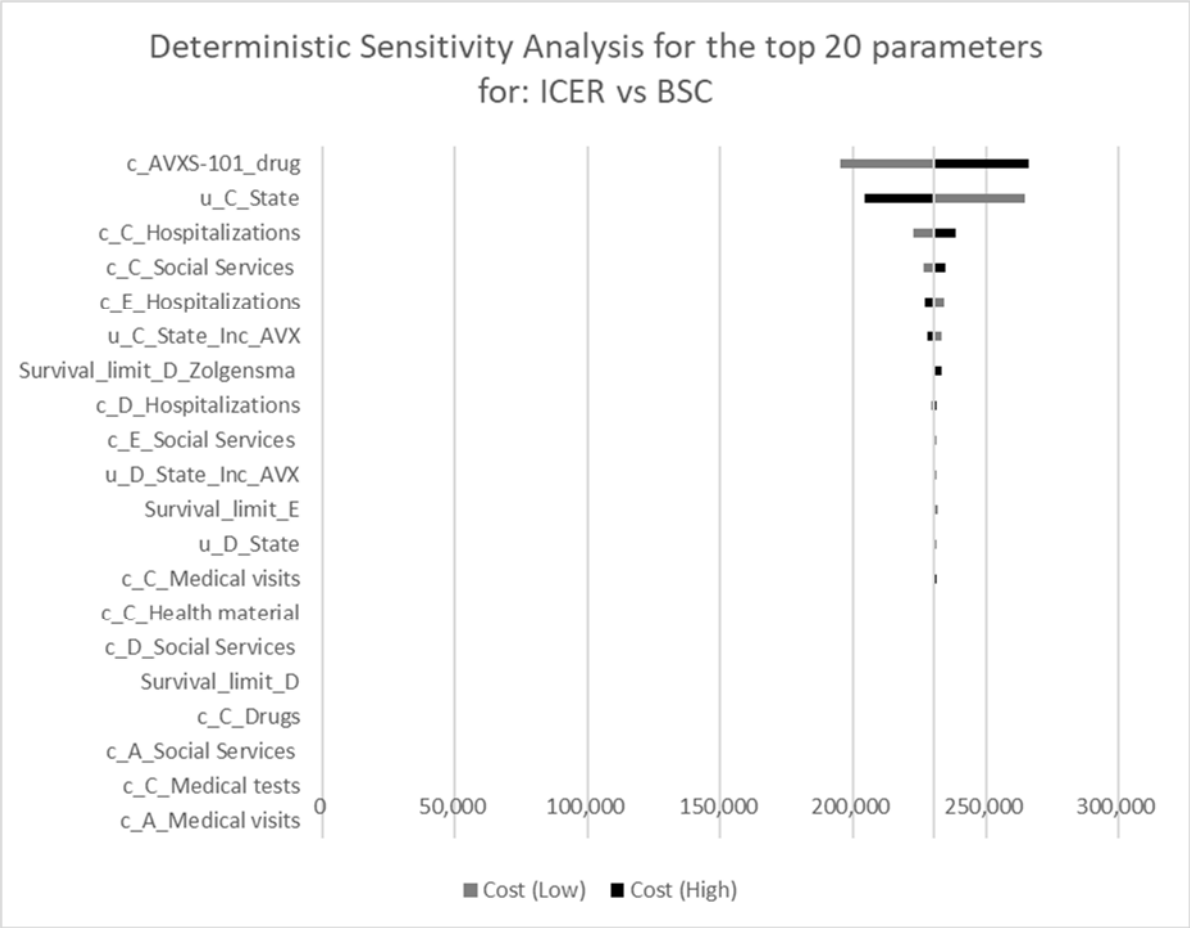


Table 80: Impact of the one-way sensitivity analysis (+/- 20% or natural limit) on the ICER (onasemnogene abeparvovec versus BSC) – top 20 results only

Parameter Description		Low	High	ICER using low value	ICER using high value	Range	Low % Change	High % Change
1	c_AVXS-101_drug	1,436,000.00	2,154,000.00	195,164	265,973	70,809	15%	15%
2	u_C_State	0.48	0.72	264,429	204,395	60,034	15%	11%
3	c_C_Hospitalizations	29,869.06	44,803.59	222,600	238,537	15,937	3%	3%
4	c_C_Social Services	14,878.08	22,317.12	226,599	234,537	7,938	2%	2%
5	c_E_Hospitalizations	160,197.95	24,0296.92	234,187	226,950	7,237	2%	2%
6	u_C_State_Inc_AVX	0.04	0.06	233,055	228,134	4,921	1%	1%
7	Survival_limit_D_Zolgensma	3.20	4.80	230,568	233,360	2,792	0%	1%
8	c_D_Hospitalizations	50,812.63	76,218.95	229,566	231,570	2,004	0%	0%
9	c_E_Social Services	39,994.88	59,992.32	231,472	229,665	1,807	0%	0%
10	u_D_State_Inc_AVX	0.08	0.12	231,456	229,688	1,768	0%	0%
11	Survival_limit_E	12.80	19.20	231,707	230,196	1,511	0%	0%
12	u_D_State	0.15	0.23	231,261	229,879	1,382	0%	0%
13	c_C_Medical visits	2007.50	3011.25	230,033	231,104	1,071	0%	0%
14	c_C_Health material	1663.53	2495.29	230,125	231,012	888	0%	0%
15	c_D_Social Services	22317.12	33475.68	230,128	231,008	880	0%	0%
16	Survival_limit_D	3.20	4.80	230,568	230,216	352	0%	0%
17	c_C_Drugs	594.25	891.38	230,410	230,727	317	0%	0%
18	c_A_Social Services	2361.60	3542.40	230,412	230,724	312	0%	0%
19	c_C_Medical tests	520.51	780.77	230,429	230,707	278	0%	0%
20	c_A_Medical visits	1773.25	2659.87	230,451	230,686	234	0%	0%

Abbreviations: ICER, incremental cost effectiveness ratio.

Table 81 presents further sensitivity analyses. Results show the impact of changing various assumptions on discount rates, cost assumptions, utility values, alternative natural history sources and exploratory scenarios.

These sensitivity analyses and scenarios are described in more detail in Section 8.4.3.2 and the results are discussed in Section 8.5.2.4.

Table 81: Further sensitivity analysis results and scenarios: impact on ICER for onasemnogene abeparvovec versus BSC

	Onasemnogene abeparvovec	BSC	ICER (£/QALY) ON-A vs BSC:
Base case results	Costs: £2,640,022 QALYs: 10.007	Costs: £381,131 QALYs: 0.210	230,568
DISCOUNT RATES			
Costs and effects at 0%	Costs: £3,301,464 QALYs: 21.020	Costs: £441,085 QALYs: 0.217	137,501
Costs and effects at 5%	Costs: £2,479,206 QALYs: 7.971	Costs: £360,121 QALYs: 0.207	272,931
Costs at 0%, effects at 5%	Costs: £3,301,464 QALYs: 7.971	Costs: £441,085 QALYs: 0.207	368,407
Costs at 5%, effects at 0%	Costs: £2,479,206 QALYs: 21.020	Costs: £360,121 QALYs: 0.217	101,866
Costs and effects at 1.5%	Costs: £2,948,256 QALYs: 14.599	Costs: £413,269 QALYs: 0.214	176,225
COST ASSUMPTIONS			
Use of RWE costs (scenario with SMA type 1 costs doubled) presented at the nusinersen NICE ACM3	Costs: £2,815,613 QALYs: 10.007	Costs: £317,933 QALYs: 0.210	254,942
SMA type 3 costs from RWE presented at nusinersen ACM3 applied to the A state and B state patients, other health state costs remain as base case	Costs: £2,680,614 QALYs: 10.007	Costs: £381,131 QALYs: 0.210	234,712
Cost of onasemnogene abeparvovec administration 10x higher than base case	Costs: £2,664,397 QALYs: 10.007	Costs: £381,131 QALYs: 0.210	233,056
UTILITY VALUES			
On-treatment utility using lower values than US ICER (0.05 for D state; 0.025 for C state)	Costs: £2,640,022 QALYs: 9.652	Costs:£381,131 QALYs: 0.210	239,244

	Onasemnogene abeparvovec	BSC	ICER (£/QALY) ON-A vs BSC:
On-treatment utility using higher values than US ICER (0.15 for D state; 0.075 for C state)	Costs: £2,640,022 QALYs: 10.362	Costs:£381,131 QALYs: 0.210	222,500
Using CHERISH values	Costs: £2,640,022 QALYs: 12.873	Costs: £381,131 QALYs: 1.595	200,293
Using Lloyd vignette study	Costs: £2,640,022 QALYs: 2.606	Costs: £381,131 QALYs: -0.476	732,879
Using exploratory AveXis UK utilities elicitation study using the TTO results from the 'parent' vignettes for states B to E	Costs: [redacted] QALYs: [redacted]	Costs: £381,131 QALYs: -0.536	[redacted]
No utility weights (cost per life year gained)	Costs: £2,640,022 Life years: 15.385	Costs: £381,131 Life years: 2.145	170,611
ALTERNATIVE NATURAL HISTORY SOURCE			
Use of AveXis external PNCR control dataset: fitted curve kept as Weibull, survival maximum equals 4 years	Costs: £2,663,332 QALYs: 10.016	Costs: £708,035 QALYs: 0.252	200,259
Use of Finkel et al. 2017a (ENDEAR sham control): fitted curve kept as Weibull, survival maximum equals 4 years	Costs: £2,649,192 QALYs: 10.113	Costs: £652,584 QALYs: 0.219	201,796
Use of De Sanctis et al. 2016 (PNCR, US and Italy study): fitted curve kept as Weibull, survival maximum equals 4 years	Costs: £2,655,619 QALYs: 10.104	Costs: £691,806 QALYs: 0.174	197,774
EXPLORATORY SCENARIOS			
Patients in the C state (sits unassisted) have a life expectancy the same as the general population: applied to onasemnogene abeparvovec arm only	Costs: £2,974,112 QALYs: 13.51	Costs: £381,131 QALYs: 0.210	195,030
One additional sitter in STR1VE-US after 18 months of age. The additional sitter sits between 24 - 30 months of age and therefore moves to sitting in cycle ending 36 months	Costs: £2,663,066 QALYs: 9.65	Costs: £381,131 QALYs: 0.210	241,653
One additional walker in STR1VE-US after 18 months of age. The additional walker walks between 24 - 30 months of age and therefore moves to walking in cycle ending 36 months	Costs: £2,618,401 QALYs: 9.77	Costs: £381,131 QALYs: 0.210	233,961
No additional sitters or walkers in STR1VE-US after 18 months of age	Costs: £2,641,445 QALYs: 9.42	Costs: £381,131 QALYs: 0.210	245,458

	Onasemnogene abeparvovec	BSC	ICER (£/QALY) ON-A vs BSC:
For new sitters and four new walkers in STR1VE-US after 18 months of age	Costs: £2,643,109 QALYs: 11.92	Costs: £381,131 QALYs: 0.210	193,236
E state overall survival based on the 'pooled' Gregoretti cohort, i.e. patients with tracheostomy (n=42) or NIV (n=31) with proportions adjusted accordingly in medical cost calculator; curve = exponential, survival limit = 16 years	Costs: £2,686,689 QALYs: 10.007	Costs: £694,197 QALYs: 0.210	203,377
Caregiver disutility scores included	Costs: £2,640,022 QALYs: 9.53	Costs: £381,131 QALYs: 0.04	237,968
Milestones, overall survival and event-free survival is based on those treated at ≤3.5 months of age in START and STR1VE-US (n=17)	Costs: £2,613,362 QALYs: 11.428	Costs: £381,131 QALYs: 0.210	198,990
Milestones, overall survival and event-free survival are based on those treated in START only (n=12)	Costs: £2,709,381 QALYs: 12.001	Costs: £381,131 QALYs: 0.210	197,464
Milestones are not 'offset' by a model cycle (i.e. not 'offset' by 6 months)	Costs: £2,637,501 QALYs: 10.339	Costs: £381,131 QALYs: 0.210	222,771

Abbreviations: ACM3, third appraisal committee meeting; BSC, best supportive care; EFS, event-free survival; ERG, evidence review group; ICER, incremental cost effectiveness ratio; Nus, nusinersen; ON-A, onasemnogene abeparvovec; OS, overall survival; PNCR, Pediatric Neuromuscular Clinical Research; QALY, quality-adjusted life-year; RWE, real-world evidence; UK, United Kingdom; US, United States; vs. versus.
† Values are reported per the economic model, discrepancies are due to rounding.

8.5.2.2 Present results of deterministic multi-way scenario sensitivity analysis described in table D10.2.

Table 82 below presents the results of a three-way sensitivity analysis.

From the one-way sensitivity results for onasemnogene abeparvovec versus BSC we took the three variables with the largest impact on the results (excluding the cost of onasemnogene abeparvovec). These are: i) the utility value of C state patients, ii) the cost of hospitalisations for C state patients and, iii) the cost of social services for C state patients. The tables show the results of varying these parameters in combination by the same percentage change as used in the one-way analysis.

These analyses are described in more detail in Section 8.4.3 and the results are discussed in Section 8.5.2.4.

Table 82: Multi-way analysis of three variables for onasemnogene abeparvovec versus BSC: ICER (£/QALY) results

	Hospitalisation cost in C state = base case	**Hospitalisation cost in C state = base case * 0.8**	**Hospitalisation cost in C state = base case * 1.2**
Social services cost in C state = base case	U1; 230,568 U2; 264,429 U3; 204,395	U1; 222,600 U2; 255,290 U3; 197,331	U1; 238,536 U2; 273,567 U3; 211,458
Social services cost in C state = base case * 0.8	U1; 226,599 U2; 259,877 U3; 200,876	U1; 218,631 U2; 250,738 U3; 193,813	U1; 234,567 U2; 269,015 U3; 207,940
Social services cost in C state = base case * 1.2	U1; 234,538 U2; 268,982 U3; 207,914	U1; 226,570 U2; 259,843 U3; 200,851	U1; 242,506 U2; 278,120 U3; 214,978

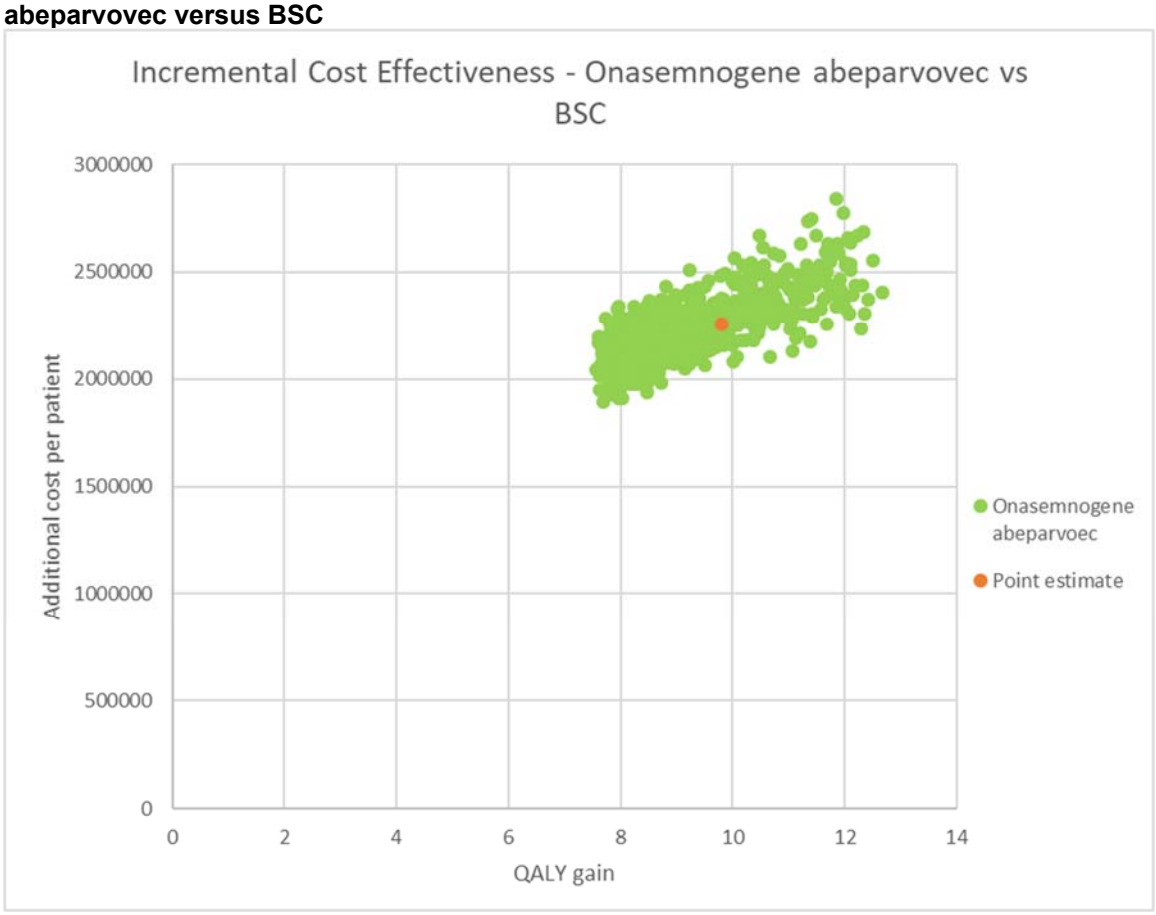
Abbreviations: BSC, best supportive care; ICER, incremental cost effectiveness ratio.
Note: U1 = base case utility value; U2 = base case utility value * 0.8; U3 = base case utility value * 1.2. Note: 'on treatment' C state utility addition (0.05) kept as per base case in all analyses.

8.5.2.3 Present results of the probabilistic sensitivity analysis described in table D10.3.

Figure 46 below shows the results from 1,000 simulations comparing the incremental cost effectiveness of onasemnogene abeparvovec over BSC.

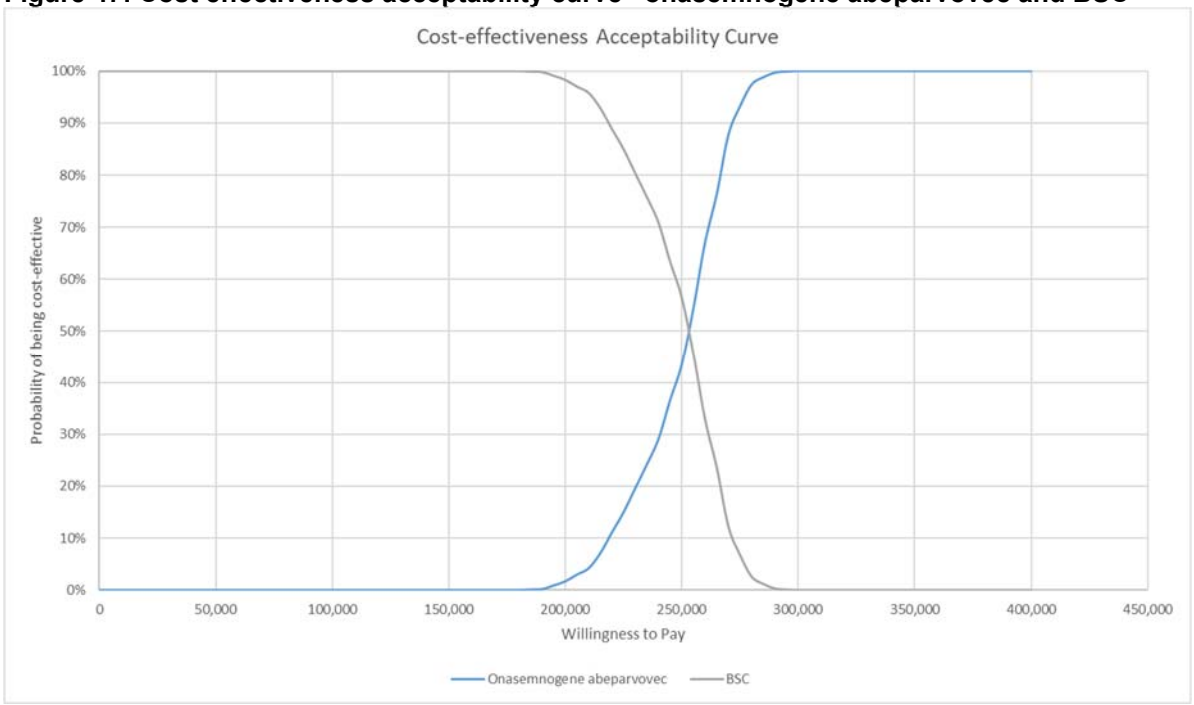
Figure 47 shows the Cost Effectiveness Acceptability Curve from 1,000 simulations comparing onasemnogene abeparvovec with BSC.

Figure 46: Incremental cost effectiveness results – 1,000 simulations of onasemnogene abeparvovec versus BSC



Abbreviations: BSC, best supportive care.

Figure 47: Cost effectiveness acceptability curve –onasemnogene abeparvovec and BSC



Abbreviations: BSC, best supportive care

Table 83 below shows the maximum and minimum results for costs, life years and QALYs.

Finally, Table 84 shows the ICER results (onasemnogene abeparvovec versus BSC) from the simulations.

These results of the probabilistic sensitivity analysis are discussed in answer to question 8.5.2.4.

Table 83: Results from 1,000 simulations of onasemnogene abeparvovec and BSC

	Max costs (£)	Min costs (£)	Max LYs	Min LYs	Max QALYs	Min QALYs
BSC	537,658	255,191	2.16	2.09	0.46	0.00
Onasemnogene abeparvovec	3,248,207	2,275,276	19.39	12.33	12.95	7.78

Abbreviations: BSC, best supportive care; LY, life-ears; QALY, quality-adjusted life-years.

Table 84: ICER (£/QALY) results from 1,000 simulations of onasemnogene abeparvovec and BSC

ICER ranges	Max ICER	Min ICER	Mean costs/ mean QALYs	Median	95% plausible interval - low	95% plausible interval - high
Onasemnogene abeparvovec versus BSC	295,099	182,044	246,713	252,984	203,330	280,686

Abbreviations: BSC, best supportive care; ICER, incremental cost effectiveness ratio; QALY, quality-adjusted life-years.

8.5.2.4 What were the main findings of each of the sensitivity analyses?

Onasemnogene abeparvovec versus BSC

One-way sensitivity analysis

All variables were varied by +/- 20% or natural limits if these were within the +/- 20% range.

The only variables that impacted on the ICER by 5% or greater in either direction were: i) the cost of onasemnogene abeparvovec (high ICER of £265,973; low ICER of £195,164) and; ii) the patient utility value attached to the C state (high ICER of £264,429; low ICER of £204,395).

We conducted further one-way analyses of the results. Only results that change the ICER by relatively large amounts or require further explanation are discussed. Full results are shown in Section 8.5.2.1.

- **Discount rates:** Discounting costs and effects at 0% decreases the ICER by 40% whilst discounting costs at 5% but applying no discounting to effects decreases the ICER by 56%. Discounting effects at 5% but not discounting costs increases the ICER by nearly 60%. Discounting both costs and effects at 1.5% decreases the ICER by over 23% to £176,225

- **Cost assumptions:** Of the cost assumptions tested in the model, most had minor effects on the ICER; i.e. SMA type 3 costs from RWE presented at nusinersen ACM3 (60) used for A state and B state patients and cost of onasemnogene abeparvovec administration 10x higher than baseline. The ICER increased by 10.6% (from £230,568 to £254,942) when the base case health state costs were replaced with the RWE costs (using SMA type 1 costs doubled) presented at the nusinersen ACM3.

- **Utility values:** The use of the utilities mapped from PedsQL in CHERISH (62) and the use of applying no utility weights (i.e. cost per LYG) both lead to the ICER decreasing from £230,568 to £200,293 and to £170,611, respectively. When the Lloyd et al. 2017 clinician-proxy vignette study (100) is used, the ICER increases to £732,879: note that the number of QALYs gained from BSC in this scenario is -0.476. The use of the exploratory AveXis UK utilities elicitation study (66) increases the ICER by [redacted]: note that the number of QALYs gained from BSC in this case is 0.536.

- **Alternative natural history source:** All of the alternative natural history sources decrease the ICER: by 12.5% when Finkel et al. 2017 (ENDEAR Sham control arm) (57) is used, by 14% when De Sanctis et al. 2016 (PNCR, US and Italian study) adjusted/disaggregated (30) dataset is used and by 13% when the AveXis external PNCR control (n=23) (5) adjusted/disaggregated dataset is used.

Multi-way sensitivity analysis

The multi-way sensitivity analysis compared the three variables (excluding the cost of onasemnogene abeparvovec) that had the largest impact on the ICER as shown by the one-

way analysis. These were the patient utility value attached to the C state (0.6 in the base case) the cost of hospitalisations in the C state (£37,336 in the base case) and the cost of social services in the C state (£18,598 in the base case). Values were varied by +/- 20%.

The results ranged from a low of £193,813 (20% reduction in C state hospitalisation costs, 20% reduction in C state social services costs and 20% increase in the C state utility value) to a high of £278,120 (20% increase in C state hospitalisation costs, 20% increase in C state social services costs and 20% reduction in C state utility value).

Further sensitivity analysis and exploratory scenarios

In the optimistic scenario that assumes there is improved survival for any patient that can sit unassisted (C state) in the onasemnogene abeparvovec arm, the ICER falls by 15% to £195,030.

Including caregiver disutility scores impacts on the ICER only slightly, increasing it to £237,968.

In scenarios that explored different milestone attainment in STR1VE-US patients after 18 months of age, in the POOLED dataset:

- The ICER increased by 4.8% to £241,653, for one additional sitter in STR1VE-US after 18 months of age
- The ICER increased by 1.5% to £233,961, for one additional walker in STR1VE-US after 18 months of age
- The ICER increased by 6.5% to £245,458, for no additional sitters or walkers in STR1VE-US after 18 months of age
- The ICER decreased by 16.2% to £193,236, for four new sitters and four new walkers in STR1VE-US after 18 months of age

In the scenario where milestones, overall survival and event-free survival are based on those treated at ≤3.5 months of age in START and STR1VE-US (n=17) the ICER decreased to £198,990.

In the scenario where milestones, overall survival and event-free survival are based on those treated in START only (n=12), the ICER decreases to £197,464.

In the scenario where the conservative model ‘offset’ is not applied to milestones in the POOLED dataset, the ICER decreases by 3.4% to £222,771.

In the scenario where the E state overall survival is based on the ‘pooled’ Gregoretti cohort, i.e. patients with tracheostomy (n=42) or NIV (n=31), the ICER decreases to £203,377.

Probabilistic sensitivity analysis

The minimum and maximum number of QALYs produced for BSC from the 1,000 simulations were 0.00 and 0.46; the minimum and maximum total costs were £255,191 and £537,658.

The minimum and maximum number of QALYs produced for onasemnogene abeparvovec from the 1,000 simulations were 7.78 and 12.95; the minimum and maximum total costs were £2,275,276 and £3,248,207.

The minimum and maximum ICERs produced from the simulations were £182,044 and £295,099 with a 95% credible range of between £203,330 and £280,686.

The mean and median ICERs produced from the simulations were £246,713 and £252,984, respectively. This simulation mean is 7% higher than the deterministic result of £230,568. Analysis of the results showed that this is due to the number of life years gained from the onasemnogene abeparvovec simulations were 78.5% of the runs produced total life years less than the onasemnogene abeparvovec deterministic value of 30.468 (undiscounted) life years (range 24.63 to 44.56). A total of 80.1% of the ICERs produced from the PSA simulations were above the deterministic ICER.

8.5.2.5 What are the key drivers of the cost results?

Table 85 shows the percentage of total lifetime costs for each cost category for each of the three interventions. A 3.5% discount rate has been used.

Table 85: Percentage of total costs by cost category

Cost Category	Intervention	
	Onasemnogene abeparvovec	**BSC**
Product cost	65.69%	0.00%
Product admin cost	0.10%	0.00%
Care costs		
Drugs	0.47%	0.45%
Medical tests	0.38%	0.43%
Medical visits	1.56%	2.10%
Hospitalisations	20.52%	73.04%
GP & emergency	0.11%	0.22%
Health materials	1.19%	2.03%
Social services	9.97%	21.73%
Total	**100.00%**	**100.00%**

Abbreviations: BSC, best supportive care; GP, general practitioner. Tables may not sum exactly to 100% due to rounding.

The cost of onasemnogene abeparvovec is the major cost component of total onasemnogene abeparvovec costs followed by the cost of hospitalisations and then the cost of social services support.

For BSC the major cost is the cost of hospitalisations followed by the cost of social services support.

8.5.3 Miscellaneous results

8.5.3.1 Describe any additional results that have not been specifically requested in this template. If none, please state.

None.

8.6 *Subgroup analysis*

8.6.1 Specify whether analysis of subgroups was undertaken and how these subgroups were identified. Cross-reference the response to the decision problem in table A1.

No subgroup analysis using pre-specified subgroups was undertaken. It is noted that, an exploratory scenario analysis is presented in Section 8.5.2 in which motor milestones, overall survival and event-free survival for the onasemnogene abeparvovec arm are based on those treated at ≤3.5 months of age in START and STR1VE-US (n=17). The cut-off of 3.5 months of age was chosen, as this was the median age at which infants across START and STR1VE-US received onasemnogene abeparvovec. This scenario is not presented as a formal subgroup analysis as this population was not a pre-specified group in the clinical trial protocols. However, this scenario has been presented to demonstrate the value of onasemnogene abeparvovec when used early in the course of the disease.

8.6.2 Define the characteristics of patients in the subgroup(s).

Not applicable.

8.6.3 Describe how the subgroups were included in the cost-effectiveness analysis.

Not applicable.

8.6.4 What were the results of the subgroup analysis/analyses, if conducted? The results should be presented in a table similar to that in section 12.5.6 (base-case analysis). Please also present the undiscounted incremental QALYs consistent with section 12.5.7

Not applicable.

8.6.5 Were any subgroups not included in the submission? If so, which ones, and why were they not considered?

Not applicable.

8.7 *Validation*

8.7.1 Describe the methods used to validate and cross-validate (for example with external evidence sources) and quality-assure the model. Provide references to the results produced and cross-reference to evidence identified in the clinical and resources sections.

Face validation of the appropriateness of the conceptual model (modelling technique, structure, health states, key sources for model input data, and model outcomes) was judged by clinical experts via clinical expert engagement during model conceptualisation and via a UK advisory board – see Section 8.2.5. The validity of the computerised models was assessed through derivation of Markov traces and by comparing modelled mortality and disease progression probabilities with the populated data. Extreme value and unit testing comprised setting model transition probabilities to 0 and 1, respectively and turning off specific costs and utility components as well as mortality.

8.8 *Interpretation of economic evidence*

8.8.1 Are the results from this cost-effectiveness analysis consistent with the published economic literature? If not, why do the results from this evaluation differ, and why should the results in the submission be given more credence than those in the published literature?

In our SLR of prior economic models, we found no models comparing onasemnogene abeparvovec to other treatment options in patients with SMA, however, we note that cost-effectiveness analyses of onasemnogene abeparvovec in SMA type 1 patients with a US perspective (74, 101) have subsequently been published after the date of our SLR search (11 March 2019); including:

- Final evidence report by US ICER (74), assessing onasemnogene abeparvovec versus BSC
- Publication by Malone et al. 2019 (101), assessing onasemnogene abeparvovec versus nusinersen

As both these assessments are conducted with a US-perspective, drawing upon the estimated incremental costs incurred is not considered completely relevant when making comparisons to our *de novo* cost-effectiveness analysis, due to the very different cost structures between the US and the UK. Both these published US assessments share very similar model frameworks when compared with the *de novo* model: 1) they employ a short-term model concordant with clinical study data followed by a long-term extrapolation model; 2) they adopt a model structure using four (US ICER (74)) or five (Malone et al. 2019 (101)) functional health states ranging from ‘permanent ventilation’ to either ‘walking’ (US ICER (74)) or within broad range of normal development (Malone et al. 2019 (101)). When

comparing the total QALYs reported in the US assessments to our *de novo* model, estimates are broadly aligned see Table 86.

Table 86: QALYs reported by region

Intervention	Discounted QALYs			Undiscounted QALYs		
	NICE model	US ICER	Malone et al. 2019	NICE model	US ICER	Malone et al. 2019
Onasemnogene abeparvovec	10.01	12.23	15.65	21.02	NR	29.86
BSC	0.21	0.46	NR	0.22	NR	NR

Abbreviations: BSC, best supportive care; NICE, National Institute of Health and Care Excellence; QALY, quality-adjusted life-year; US ICER, United States Institute of Clinical and Economic Review.
Sources: NICE model; executable file; US ICER (74); Malone et al. 2019 (101).

However, such comparisons are caveated by there being several key differences between these published assessments and our own, for example:

- Malone et al. 2019 (101) – uses different sources of data for: utilities (mapped from CHERISH); motor milestones for nusinersen arm (from ENDEAR only [not SHINE]); motor milestone for treatment arms in long-term model (employs extrapolation based on CHOP-INTEND); general population mortality in B state and A state (US data set); nusinersen stopping rules (no discontinuation applied for nusinersen)
- US ICER (74) – uses different sources of data for: BSC overall survival and event-free survival (ENDEAR sham control arm); long-term overall survival for treatment arms in non-sitting state (used death from non-invasive respiratory muscle aid survival curve only as reported in Gregoretti et al. 2013 (82) and non-sitting treatment arm patients could not explicitly transition to E state); general population mortality in walking state (US data set)

The *de novo* cost-effectiveness model for onasemnogene abeparvovec presented here, is deemed more applicable to the decision problem, as it has been parametrised and validated using an England-healthcare perspective, using more up to date and relevant clinical data sources, when compared with the aforementioned US assessments.

8.8.2 Is the cost- effectiveness analysis relevant to all groups of patients and specialised services in England that could potentially use the technology as identified in the scope?

AveXis considers the cost-effectiveness analysis relevant to all groups of patients that could potentially use onasemnogene abeparvovec as identified in the scope. However, it is recognised that the cost-effectiveness analysis does not include data for:

- Pre-symptomatic infants with a genetic phenotype predictive of SMA type 1 (i.e. up to three copies of the *SMN2* gene)
- Prevalent symptomatic SMA type 1 patients (e.g. those older than 6 months and/or those who have received another SMA-related therapy)

Only early, interim data from the ongoing pre-symptomatic trial (SPR1NT) were available at the time of this updated submission, precluding its incorporation into a cost-effectiveness analysis. Whilst the cost-effectiveness model only derives efficacy data from START and STR1VE-US, these trials showed that the substantial benefits in survival, motor function, and developmental milestone achievements relative to natural history cohorts were particularly striking for several patients treated at younger ages, as shown in the scenario analysis in Section 8.5.2.4: In this scenario analysis where milestones, overall survival and event-free survival are based on those treated at ≤3.5 months of age in START and STR1VE-US (n=17) the ICER decreased by 13.7% to £198,990, with 14/17 (82.4%) sitting independently and 3/17 (17.6%) walking independently at the end of the trial periods. Hence, this observation supports the one-time use of onasemnogene abeparvovec as early as possible, including pre-symptomatic patients, with the aim of intervening ahead of extensive neurodegeneration. Based on the milestone attainment seen in the ongoing SPR1NT study (please see Section 6.3.1.5) it can be expected that the ICER would improve when modelling is based on the outcomes of pre-symptomatic patients with a genetic phenotype predictive of SMA type 1 (i.e. up to three copies of the *SMN2* gene) treated with onasemnogene abeparvovec.

8.8.3 What are the main strengths and weaknesses of the analysis? How might these affect the interpretation of the results?

There are no head-to-head trials comparing onasemnogene abeparvovec to comparators, and sample sizes are limited to conduct robust matched, adjusted indirect comparisons or simulated treatment comparisons. Thus, the model makes no adjustment for differences in patient characteristics between the studies used for each treatment arm and relies on naïve, unanchored comparisons. However, with respect to the unanchored, naïve comparison to BSC, efforts have been made to source natural history data for overall survival and event-free survival in a SMA type 1 population that resembles START and STR1VE-US as close as possible, as described in section 8.2.1.3. For example, the natural history study chosen in the base case (NeuroNext) closely resembled the entry criteria for onasemnogene abeparvovec trials with respect to age and baseline function and the genetic profile of NeuroNext and onasemnogene abeparvovec cohorts were equivalent: all patients had bi-allelic deletions of SMN1 exon 7, *SMN2* copy x 2 and confirmation of exclusion of the *SMN2* modifier mutation c.859G>C. Furthermore, the model provides three alternative natural history sources informing outcomes for the BSC arm, all of which have been presented as scenario analyses.

It is noted that the sample sizes of the clinical studies used to inform the cost-effectiveness model are small, which is typical of trials in populations with ultra-rare paediatric diseases. The uncertainty associated with the small sample size for the onasemnogene abeparvovec arm has however been reduced in this updated submission by providing an updated POOLED model, which now draws on clinical effectiveness data from both START and STR1VE-US trials (n=34). In addition, the company has provided the interim data from ongoing trials, which provide clinical effectiveness data in an additional 62 patients, including the ongoing Phase III trial in SMA type 1 (STR1VE-EU, n=33) and Phase III trial in pre-symptomatic SMA (SPR1NT, n=29).

Another feature of the clinical trial data informing the cost-effectiveness model is that the follow-up time is relatively short, when compared with the lifetime time horizon of the model. As a result, observed data are only available for the first 6 model cycles for the onasemnogene abeparvovec arm, after which long-term extrapolation of overall survival and event-free survival are required. However, the NICE reference case and well-established methods have been adopted to ensure parametric curve fitting, best fit selection and incorporation into the PSA. We address the uncertainty in duration of effect of onasemnogene abeparvovec by providing clinical data from LT-001, in which prolonged and durable efficacy has been demonstrated in patients up to 5.6 years of age in Cohort 2 (as of 31 Dec 2019), with no loss of milestones reported during START or LT-001 and the attainment of additional milestones reported in LT-001.

The modelling approach used (Markov state-transition) was deemed the most appropriate to reflect the natural history of SMA type 1, for the data available. The model also accounts for the chronic nature of the condition by taking a lifetime perspective and accommodates a range of clearly differentiated motor milestone health states. A strength of this economic analysis is that the model framework was conceptualised with clinical experts, drawing on frameworks developed for nusinersen and models for similar rare genetic disorders. This enabled the model to adequately capture the patient experience in a reasonable number of health states, versus the data requirements of a more complex model.

A further challenge for the model was the need to source utility data from populations external to the clinical trials. However, the model adopts utility values that have been validated and accepted by independent assessment groups and clinical experts. Whilst it is well accepted that SMA has a substantial effect on the HRQoL of parents, caregivers and families, robust UK utility data for the SMA population and their caregivers are lacking. In addition, methods for performing economic evaluations including caregiver burden are still under development, and currently there are no formally accepted mechanisms of including caregiver disutilities due to bereavement and loss of a child. The uncertainty associated with health state utilities has been addressed by the provision of a number of sensitivity analyses, including using different sources of utility data, assessing caregiver disutility and applying an on-treatment utility benefit.

8.8.4 What further analyses could be undertaken to enhance the robustness/completeness of the results?

As described above, several of the limitations associated with the cost-effectiveness model related to the underpinning clinical data. Therefore, as more longer-term data become available for onasemnogene abeparvovec, cost-effectiveness analyses may be supplemented with longer-term clinical outcomes.

9 Cost to the NHS and Personal Social Services

The purpose of Section 13 is to allow the evaluation of the affordability of the technology.

9.1 *How many patients are eligible for treatment in England? Present results for the full marketing authorisation and for any subgroups considered. Also present results for the subsequent 5 years.*

The budget impact presented is based on the incident SMA type 1 population only as the budget impact model feeds directly from the cost-utility model, which contains clinical effectiveness data for incident SMA type 1 patients only, due to the eligibility criteria of the completed onasemnogene abeparvovec trials (START and STR1VE-US).

Whilst it is recognised there are other patient populations covered in the final scope that would be eligible for treatment with onasemnogene abeparvovec – pre-symptomatic infants with a genetic phenotype predictive of SMA type 1 (i.e. up to three copies of the *SMN2* gene) and in prevalent symptomatic SMA type 1 patients (e.g. those older than 6 months and/or those who have received another SMA-related therapy) – there is a paucity of clinical effectiveness data on which to develop a robust budget impact assessment. Furthermore, assessing the budget impact in the prevalent symptomatic SMA type 1 patients including those who have received nusinersen is challenging due to the lack of routine commissioning of nusinersen in England. Therefore, the company has presented a budget impact analysis for the incident SMA type 1 population for which the most robust data are available.

The following approach was taken to estimate the incident SMA type 1 population of England: SMA (all types) has an annual incidence of approximately 9.4:100,000 live births, as reported by Lally et al 2017 (19); this incidence rate is applied to the most recent live births data for England (reported as 625,651 live births in 2018 (22)), to estimate that there are 59 incident cases of SMA (all types) per year in England; applying that SMA type 1 accounts for 58% of all cases of SMA (20), this results in 34 incident cases of SMA type 1 per year in England. It is assumed this will be the case each year, for the next 5 years.

Real world evidence from the nusinersen UK early access programme (EAP) reported that in its last 12 months of operation, 32 babies were diagnosed with SMA type 1 and treated with nusinersen in England (personal communication; [redacted], Paediatric Neurologist). These 32 patients are considered to represent a “steady-state” of incident patients presenting for pharmacotherapy. Therefore, it is assumed that 2 of the expected 34 incident patients did not present for pharmacotherapy during this period and that this proportion, 5.9%, would not present for pharmacotherapy in any modelled treatment scenario. Potential reasons for this may include factors such as the poor condition of the baby or the beliefs/preferences of the family. Therefore, it is estimated that each year there are 32 incident cases of SMA type 1 per year in England who present for pharmacotherapy. The remaining criteria applied to assess eligibility depend on AAV9 antibody screening as shown in Figure 48.

Figure 48: Patient eligibility for pharmacotherapy

SMA type 1 incident cases (n=34, 100%)		
Present for pharmacotherapy (n=32, 94.1%)		Do not present for pharmacotherapy (n=2, 5.9%)
Eligible for onasemnogene abeparvovec (87.8%)	Not eligible for onasemnogene abeparvovec due to anti-AAV9 antibody titre (12.2%)	
100% treated with onasemnogene abeparvovec	100% treated with BSC	100% BSC

Abbreviations: AAV9, adeno-associated virus 9; BSC, best supportive care; SMA, spinal muscular atrophy.

Anti-AAV9 antibody screening

Some patients eligible for pharmacotherapy will not be eligible for onasemnogene abeparvovec due to a high anti-AAV9 antibody titre (all patients in the onasemnogene abeparvovec clinical trials had and an anti-AAV9 antibody titres at or below 1:50 before treatment). In the ongoing STR1VE-EU clinical trial, being conducted in Europe, the proportion of SMA type 1 incident cases ineligible for onasemnogene abeparvovec due to a high anti-AAV9 titre was 5 of 41 cases (12.2%) screened. STR1VE-EU screening data are the most generalisable to the English incident population given that newborn screening is not currently routinely available in the UK. Therefore, we assume of the patients who present for pharmacotherapy, 12.2% are not eligible for treatment with onasemnogene abeparvovec.

Treatment choice/availability

The budget impact model compares the ‘current situation’ to ‘onasemnogene abeparvovec becomes available’

a) ‘Current situation’ = BSC is the only treatment option for SMA type 1 patients

b) ‘Onasemnogene abeparvovec becomes available’ = Onasemnogene abeparvovec is introduced, and is the only pharmacotherapy treatment option available

9.2 *Describe the expected uptake of the technology and the changes in its demand over the next five years*

Expected market shares for onasemnogene abeparvovec are described below.

a) ‘Current situation’ (Table 87): 100% of cases would receive BSC

b) ‘Onasemnogene abeparvovec becomes available’ (Table 88): As described in Section 9.1, 12.2% of incident patients would be unsuitable for onasemnogene abeparvovec due to high anti-AAV9 antibody titres. Therefore, this 12.2% has been excluded from the patients who present for pharmacotherapy (i.e. 12.2% of the 94.1% presenting for pharmacotherapy [i.e. 11.5%] as discussed in Section 9.1). Based on the above, we have estimated that 82.6% of the patients would receive onasemnogene abeparvovec. For BSC, we have estimated that in addition to the 5.9% (who do not present for pharmacotherapy as discussed in Section 9.1), the

11.5% of the patients who would be unsuitable to receive onasemnogene abeparvovec (as discussed above) would also receive BSC. Therefore, it is estimated that in total 17.4% (11.5% + 5.9%) of the patients would receive BSC.

Table 87: Assumption of the distribution of SMA type 1 cases by treatment in the 'current situation' – only BSC is available

Intervention	Year 1	Year 2	Year 3	Year 4	Year 5
Onasemnogene abeparvovec	0%	0%	0%	0%	0%
BSC	100%	100%	100%	100%	100%

Abbreviations: BSC, best supportive care; SMA, spinal muscular atrophy.

Table 88: Assumption of the distribution of SMA type 1 cases by treatment in the 'onasemnogene abeparvovec becomes available'

Intervention	Year 1	Year 2	Year 3	Year 4	Year 5
Onasemnogene abeparvovec	82.6%	82.6%	82.6%	82.6%	82.6%
BSC	17.4%	17.4%	17.4%	17.4%	17.4%

Abbreviations: BSC, best supportive care; SMA, spinal muscular atrophy

9.3 *In addition to technology costs, please describe other significant costs associated with treatment that may be of interest to NHS England (for example, additional procedures etc)*

None expected; however, AveXis is committed to working with neuromuscular centres, including potential infusion centres and regional specialist centres, to scope and design a service delivery that includes onasemnogene abeparvovec.

Infants will require a test for the AAV9 antibody prior to treatment with onasemnogene abeparvovec. However, AAV9 antibody testing will be funded and coordinated by AveXis at a central European lab (Viroclinics, The Netherlands).

9.4 *Describe any estimates of resource savings associated with the use of the technology*

Because of the large increases in the quantity and quality of life that onasemnogene abeparvovec produces compared with BSC, the opportunities for absolute resource savings are limited. Patients who would otherwise have died still require some treatment related support. Section 8.5.1.8 shows that (discounted) mean total treatment costs (i.e. all SMA care costs) would be expected to rise from £381,131 for BSC patients to £903,015 for onasemnogene abeparvovec treated patients.

9.5 *Are there any other opportunities for resource savings or redirection of resources that it has not been possible to quantify?*

No opportunities for resource savings or redirection of resources are applicable for NHS/PSS/government funded programmes, apart from possible disability payments and education costs (see question10.2). If possible, changes to caregiver time/resources are considered to be applicable, see Section 10.4.

9.6 *Describe any costs or savings associated with the technology that are incurred outside of the NHS and PSS*

Possible costs for lost patient income are discussed in answer to question 10.1. Possible costs for lost caregiver income are discussed in answer to question 10.4.

9.7 *What is the estimated budget impact for the NHS and PSS over the first year of uptake of the technology, and over the next 5 years?*

The budget impact model is constructed as a module within the cost-effectiveness model. The numbers of patients who would be eligible for treatment within each year of a 5-year period and the current treatment options that onasemnogene abeparvovec would replace for each year are selected. All cost data for the analysis are drawn from the cost-effectiveness model. Discounting is not applied within the budget impact model. The model calculates the total cost of treatment for patients treated through Years 1 to 5 inclusive by reference to the model underlying the cost-effectiveness analysis. If a patient were to join in Year 2, then the model would begin calculation, again, from Year 1, but the Year 1 data for this patient are added to the Year 2 data for the first patient. Similarly, the Year 2 data for the second year patient are added to the Year 3 data for the patient who joined in Year 1.

We show i) the budget impact of onasemnogene abeparvovec replacing a single BSC patient over a 5 year period and ii) the budget impact using the estimated incident population treated with onasemnogene abeparvovec when this technology becomes available.

9.7.1 Budget impact of onasemnogene abeparvovec replacing a single BSC patient

Table 89 and Table 90 show the annual cost per year for up to 5 years of 1 patient treated with onasemnogene abeparvovec rather than BSC. The total budget impact (sum of years 1 to 5 of ‘total budget impact’ row in Table 90) is £1,864,902.

Table 89: Five year budget impact of treating 1 patient with onasemnogene abeparvovec ('onasemnogene abeparvovec becomes available') rather than BSC ('current situation')

Annual cost outcomes	Year 1	Year 2	Year 3	Year 4	Year 5
BSC only available					
Drug acquisition costs	0	0	0	0	0
Drug administration costs	0	0	0	0	0
Total drug costs	0	0	0	0	0
SMA medical costs	87,232	59,106	55,112	41,685	34,187
Total SMA care costs	87,232	59,106	55,112	41,685	34,187
Total costs	**87,232**	**59,106**	**55,112**	**41,685**	**34,187**
Onasemnogene abeparvovec becomes available'					
Onasemnogene abeparvovec: drug acquisition costs	1,795,000	0	0	0	0
Onasemnogene abeparvovec: drug administration costs	2,803	0	0	0	0
Onasemnogene abeparvovec: total drug costs	1,797,803	0	0	0	0
Nusinersen: drug acquisition costs	0	0	0	0	0
Nusinersen: drug administration costs	0	0	0	0	0
Nusinersen: total drug costs	0	0	0	0	0
Total drug costs	1,797,803	0	0	0	0
SMA medical costs	102,733	85,875	65,662	45,742	44,410
Total SMA care costs	102,733	85,875	65,662	45,742	44,410
Total costs	**1,900,535**	**85,875**	**65,662**	**45,742**	**44,410**

Abbreviations: BSC, best supportive care; SMA, spinal muscular atrophy.

Table 90: Five year budget impact of treating 1 patient with onasemnogene abeparvovec rather than BSC – net position

Budget impact	Year 1	Year 2	Year 3	Year 4	Year 5
Pharmacy budget impact	1,797,803	0	0	0	0
SMA care budget impact	15,501	26,769	10,550	4,057	10,223
Total budget impact	**1,813,304**	**26,769**	**10,550**	**4,057**	**10,223**

Abbreviations: BSC, best supportive care; SMA, spinal muscular atrophy.

9.7.2 Budget impact of onasemnogene abeparvovec on the estimated incident population of onasemnogene abeparvovec being introduced

Rationale and calculations underlying the expected market shares under this scenario are described in detail in Section 9.2, but are shown again below for completeness in Table 91 and Table 92.

Table 91: Assumption of the distribution of SMA type 1 cases by treatment in the 'current situation'

Intervention	Year 1	Year 2	Year 3	Year 4	Year 5
Onasemnogene abeparvovec	0%	0%	0%	0%	0%
BSC	100%	100%	100%	100%	100%

Abbreviations: BSC, best supportive care; SMA, spinal muscular atrophy.

Table 92: Assumption of the distribution of SMA type 1 cases by treatment in the 'onasemnogene abeparvovec becomes available' situation

Intervention	Year 1	Year 2	Year 3	Year 4	Year 5
Onasemnogene abeparvovec	82.6%	82.6%	82.6%	82.6%	82.6%
BSC	17.4%	17.4%	17.4%	17.4%	17.4%

Abbreviations: BSC, best supportive care; SMA, spinal muscular atrophy.

Table 93 and Table 94 show the annual cost per year for up to 5 years, assuming 34 incident SMA type 1 cases per year for each of the five years. The total budget impact (sum of years 1 to 5 in 'total budget impact' row in Table 94 is £259,035,498.

Table 93: Five year budget impact of 34 incident cases per year for each of the five years treated with onasemnogene abeparvovec (or BSC) ('onasemnogene abeparvovec becomes available') rather than BSC ('BSC only available')

Annual cost outcomes	Year 1	Year 2	Year 3	Year 4	Year 5
BSC only available					
Nusinersen: drug acquisition costs	0	0	0	0	0
Nusinersen: drug administration costs	0	0	0	0	0
Total drug costs	0	0	0	0	0
SMA medical costs	2,965,884	4,975,476	6,849,276	8,266,569	9,428,935
Total SMA care costs	2,965,884	4,975,476	6,849,276	8,266,569	9,428,935
Total costs	**2,965,884**	**4,975,476**	**6,849,276**	**8,266,569**	**9,428,935**
Onasemnogene abeparvovec becomes available					
Onasemnogene abeparvovec: drug acquisition costs	50,410,780	50,410,780	50,410,780	50,410,780	50,410,780
Onasemnogene abeparvovec: drug administration costs	78,707	78,707	78,707	78,707	78,707
Onasemnogene abeparvovec: total drug costs	50,489,487	50,489,487	50,489,487	50,489,487	50,489,487
Nusinersen: drug acquisition costs	0	0	0	0	0
Nusinersen: drug administration costs	0	0	0	0	0
Nusinersen: total drug costs	0	0	0	0	0
Total drug costs	50,489,487	50,489,487	50,489,487	50,489,487	50,489,487
SMA medical costs	3,401,214	6,162,590	8,332,683	9,863,905	11,313,810
Total SMA care costs	3,401,214	6,162,590	8,332,683	9,863,905	11,313,810
Total costs	**53,890,701**	**56,652,077**	**58,822,170**	**60,353,392**	**61,803,297**

Abbreviations: BSC, best supportive care; SMA, spinal muscular atrophy.

Table 94: Five year budget impact of treating of 34 incident cases per year for each of the five years treated with onasemnogene abeparvovec (or BSC) rather than BSC - net position

Budget impact	Year 1	Year 2	Year 3	Year 4	Year 5
Pharmacy budget impact	50,489,487	50,489,487	50,489,487	50,489,487	50,489,487
SMA care budget impact	435,330	1,187,115	1,483,407	1,597,336	1,884,875
Total budget impact	**50,924,817**	**51,676,602**	**51,972,894**	**52,086,823**	**52,374,362**

Abbreviations: BSC, best supportive care; SMA, spinal muscular atrophy.
Note: All values are taken from the economic model and are subject to rounding. Any discrepancies between results presented in the table and text are due to rounding.

9.8 *Describe the main limitations within the budget impact analysis (for example quality of data inputs and sources and analysis etc).*

Section 8.8.3 provides details of the limitations of the cost-effectiveness analysis. The limitations relating to the availability of the underlying data and any structural assumptions also apply to the budget impact analysis. In addition, small variations in the total number of patients treated per year may have a significant effect on the total budget impact. Finally, assumptions by AveXis on the number of patients who may be treated with onasemnogene abeparvovec in each of the first 5 years are planning assumptions and the true degree of the use of the technology relative to continued use of BSC is unknown.

Section E – Impact of the technology beyond direct health benefits

The purpose of Section 14 is to establish the impact of the technology beyond direct health benefits, that is, on costs and benefits outside of the NHS and PSS, and on the potential for research. Sponsors should refer to section 5.5.11 – 5.5.13 of the Guide to Methods for Technology Appraisal 2013 for more information.

It is also aimed at describing factors that are relevant to the provision of the (highly) specialised service by NHS England. Such factors might include issues relating to specialised service organisation and provision, resource allocation and equity, societal or ethical issues, plus any impact on patients or carers.

10 Impact of the technology beyond direct health benefits

10.1 *Describe whether a substantial proportion of the costs (savings) or benefits are incurred outside of the NHS and personal social services, or are associated with significant benefits other than health.*

Onasemnogene abeparvovec may have benefits beyond the outcomes assessed in trials. For example, if pharmacotherapy improves or retains children's mobility, children may attend school, reach educational achievement and participate in the workforce in the future. Greater independence for the child may also allow caregivers to return to work. An effective treatment also may reduce anxiety and stress among caregivers and wider communities, reduce other resources used (e.g. educational system), and promote more interaction between children with SMA and others in the community. Furthermore, even small improvements in motor abilities can allow patients greater ability for self-care and independence.

Patient educational achievement and workforce participation

Patients treated with onasemnogene abeparvovec could participate in the workforce in the future. Therefore, the possible educational achievement of patients and the impact on workforce participation was explored.

A comprehensive study of the educational achievement of patients with SMA was conducted by the Lewin Group for the Muscular Dystrophy Association in 2012 (102) to obtain US estimates.

Table 95 shows the highest level of education for SMA patients (which was attributed to the C state and B state) and the general US population (which was attributed to the A state). Of note, is that the SMA population from the Lewin Group study reported a higher percentage of SMA patients having a post-graduate degree than the general US population (19% vs. 11.4%).

Table 95: Potential educational achievement for patients who may live to working age

	Not available/ no attainment	Some high school	High School Graduate	Some college/ Associate Degree	College Degree	Post-graduate degree
C state†	4%	6%	13%	28%	30%	19%
B state†	4%	6%	13%	28%	30%	19%
A state	3.7%	7.3%	28.9%	28.6%	20.0%	11.4%

† Values from source have been rounded
Source: United States, Census Bureau: Educational Attainment in the United States, 2017 (103); Lewin Group for the Muscular Dystrophy Association in 2012 (102).

Information on UK median annual earnings (104), unemployment rates (105) and the percentage of people with disabilities that are employed by educational achievement level (106) was collated (Table 96).

Table 96: UK - General population income based on educational achievement

Educational achievement	Median annual earnings	Unemployment rate	People with disabilities - employed
Some high school	£17,868	5.6%	17.0%
High school graduate	£23,628	3.1%	45.6%
Some College/Associate Degree	£29,469	3.1%	45.6%
College Graduate	£34,909	2.3%	71.7%
Post-Graduate Degree	£40,527	2.3%	71.7%

For the A state patients the average expected income per patient per year by educational achievement was calculated as: percentage expected educational achievement from Lewin Group study * median annual UK income by educational achievement * the expected employment rate. The average income per patient from the sum of these weighted values was then calculated.

For C state patients, the same approach was used and the employment rate was that of people with disabilities. For patients in B state, the unemployment rate was assumed to be between the rate for the general population and for people with disabilities (note: set at 50% - user variable).

The resulting average income per patient (£19,141 for C state patients, £25,057 for B state patients and £28,427 for A state patients) was then input to the model between the ages of 25 and 68.

The consequences of introducing these lifetime potential earnings on total costs was that the total per patient costs for onasemnogene abeparvovec treated fell by £64,098 (from £2,640,022 to £2,575,924).

The impact of introducing these lifetime patient income benefits is that the ICER for onasemnogene abeparvovec versus BSC falls from £230,568 to £224,026.

10.2 *List the costs (or cost savings) to government bodies other than the NHS*

Patients treated with onasemnogene abeparvovec who would have otherwise died if treated with BSC may be entitled to disability payments. Similarly, since some of these patients may be unemployed, unemployment benefits may be required. Finally, some patients may have special education requirements during childhood and adolescence.

10.3 *List the costs borne by patients that are not reimbursed by the NHS*

Parents/caregivers may incur additional paid professional care costs over that provided by the NHS. In addition, modifications to housing and vehicles may not be provided by the NHS or related services. Survey B from the SMA UK Patient and Caregiver survey (March 2019) (69) found the mean annual out of pocket (OOP) costs incurred for health materials and travel and accommodation (associated appointment costs and hospital stays) per SMA person were on average £8,025 per year.

We applied these costs to all E, D and C state patients in the model. The ICER for onasemnogene abeparvovec versus BSC increased from £230,568 to £239,040. This increase are due to the extra life years gained from onasemnogene abeparvovec over BSC (mainly in the C state).

10.4 *Provide estimates of time spent by family members of providing care. Describe and justify the valuation methods used*

Information on the level of care required for patients with SMA by health state over time was collated from clinical experts (Table 97). These values derived from clinical experts are broadly in line with the average number of unpaid caregiving hours/week available from the SMA UK Patient and Caregiver survey (March 2019) (69): Walks unassisted (66 hours/week [9 hours/day]; Sits unassisted (100 hours/week [14 hours/day]); Not sitting (117 hours/week [17 hours/day]).

Table 97: Level of care required, by health state and age band

Cycle	Age band	SMA-specific care required (hours/day)				
		E	D	C	B	A
1–4	0<24 months	16–24	16–24	16–24	16–24	SMA-specific care not needed
5–8	24<60 months	16–24	16–24	16–24	16–24	SMA-specific care not needed
9–21	5–17 years	16–24	16–24	8–15	8–15	SMA-specific care not needed
22+	18+ years.	16–24	16–24	1–8	SMA-specific care not needed	SMA-specific care not needed

Source: Clinical expert advice
Abbreviations: SMA, spinal muscular atrophy.

We then used SMA results from the Lewin Group study for the Muscular Dystrophy Association in 2012 (102) and converted the estimated lost income by level of care required to UK £'s using a Purchasing Power Parity value of 0.69 from the Organisation for Economic Co-operation and Development (OECD) (107) (Table 98).

Table 98: Predicted lost family income (US$ converted to GBP)

Level of care required	Lost income
Lost family income - US$ (2018)	
16–24 hours/day	$21,598
8–15 hours/day	$7,323
1–8 hours/day	$4,170
SMA-specific care not needed	$0
Lost family income - GBP (2018)	
16–24 hours/day	£16,989
8–15 hours/day	£5,760
1–8 hours/day	£3,280
SMA-specific care not needed	£0

Abbreviations: GBP, Great British Pound; US, United States.

The resulting values were applied to the various health states dependent on the age of the patient (Table 99).

Table 99: Lost family income by health state and age band

Cycle	Age at end of cycle	E	D	C	B	A
1–4	0–<24 months	£8,494	£8,494	£8,494	£8,494	0
5–6	24–<36 months	£8,494	£8,494	£8,494	£8,494	0
7–8	36–<60 months	£16,989	£16,989	£16,989	£16,989	0
9–21	5–17 years	£16,989	£16,989	£5,760	£5,760	0
22+	18+ years	£16,989	£16,989	£3,280	£0	0

The consequences of introducing these lifetime potential earnings on total costs are that the total per patient costs for BSC treated patients increases by £36,444 (from £381,131 to £417,574) whilst the total per patient costs for onasemnogene abeparvovec treated patients increases by £112,152 (from £2,640,022 to £2,752,174).

The impact on the ICER of introducing these lifetime productivity estimates is that the ICER for onasemnogene abeparvovec versus BSC increases from £230,568 to £238,296.

When these results for lost family income are combined with the results from including potential income gains as discussed in Section 10.1, the baseline ICER (no inclusion for lost family income nor potential income gains) for onasemnogene abeparvovec versus BSC increases from £230,568 to £231,753.

We also used the results from the SMA UK Patient and Caregiver survey (March 2019) (69) to examine the impact on total costs. The survey found that the average annual cost for loss of productivity per unpaid caregiver at £14,350 based on reducing their hours by 25 hours per week. Using these costs in the model increased the total costs for BSC patients by £30,782 and by £177,555 for onasemnogene abeparvovec treated patients. We note, however, that the £14,350 figure is an average for all SMA patients and that these results probably underestimate the time inputs for non-sitting patients and overestimate the time inputs for walking patients. The ICER for onasemnogene abeparvovec versus BSC increased from £230,568 to £245,550.

It should be noted that these caregiver estimates are based only on a single carer. The SMA UK Patient and Caregiver survey (March 2019) (69) indicates that a wide range of carers provide support to patients with SMA ranging from immediate family friends and neighbours.

11 References

1. European Medicines Agency. Committee for Medicinal Products for Human Use. Summary of opinion (initial authorisation). Zolgensma onasemnogene abeparvovec. 2020.
2. European Medicines Agency. Press release: New gene therapy to treat spinal muscular atrophy. Available at: https://www.ema.europa.eu/en/documents/press-release/new-gene-therapy-treat-spinal-muscular-atrophy_en.pdf. 2020.
3. Finkel RS, McDermott MP, Kaufmann P, Darras BT, Chung WK, Sproule DM, et al. Observational study of spinal muscular atrophy type I and implications for clinical trials. Neurology. 2014a Aug 26;83(9):810-7.
4. Kolb SJ, Coffey CS, Yankey JW, Krosschell K, Arnold WD, Rutkove SB, et al. Natural history of infantile-onset spinal muscular atrophy. Ann Neurol. 2017 Dec;82(6):883-91.
5. AveXis. Data on file. PNCR and NeuroNext database report. 2018.
6. Wijnhoven TM, de Onis M, Onyango AW, Wang T, Bjoerneboe GE, Bhandari N, et al. Assessment of gross motor development in the WHO Multicentre Growth Reference Study. Food Nutr Bull. 2004 Mar;25(1 Suppl):S37-45.
7. National Institute for Health and Care Excellence. Highly Specialised Technologies Evaluation. Onasemnogene abeparvovec for treating spinal muscular atrophy type 1. Final scope. 2019.
8. 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. N Engl J Med. 2017 Nov 2;377(18):1713-22.
9. Al-Zaidy S, Pickard AS, Kotha K, Alfano LN, Lowes L, Paul G, et al. Health outcomes in spinal muscular atrophy type 1 following AVXS-101 gene replacement therapy. Pediatr Pulmonol. 2019 Feb;54(2):179-85.
10. Avexis. Data on file. Clinical Study Report (CSR). START (CL-101). 2018.
11. AveXis. Data on file. LT-001 Protocol. Version 5.0. 13 Jan 2020. 2020.
12. AveXis. Data on file. Clinical overview onasemnogene abeparvovec [data cut 31 December 2019]. 2020.
13. AveXis. Data on file. Efficacy Update onasemnogene abeparvovec [data cut 31 December 2019]. 2020.
14. AveXis. Data on file. Safety Update onasemnogene abeparvovec [data cut 31 December 2019]. 2020.
15. AveXis. Data on file. STR1VE-US (CL-303) Protocol. Version 4.0, 4 Oct 2018. 2018.
16. AveXis. Data on file. Clinical Study Report (CSR). STR1VE-US. 2020.
17. AveXis. Data on file. STR1VE-EU (CL-302) Protocol. Version 6.0, 26 November 2019. 2019.
18. AveXis. Data on file. SPR1NT (CL-304) Protocol. Version 5.0, 26 November 2019. 2019.
19. Lally C, Jones C, Farwell W, Reyna SP, Cook SF, Flanders WD. Indirect estimation of the prevalence of spinal muscular atrophy Type I, II, and III in the United States. Orphanet Journal of Rare Diseases. 2017 November 28;12(1):175.
20. Verhaart IEC, Robertson A, Wilson IJ, Aartsma-Rus A, Cameron S, Jones CC, et al. Prevalence, incidence and carrier frequency of 5q-linked spinal muscular atrophy - a literature review. Orphanet J Rare Dis. 2017 Jul 4;12(1):124.
21. National Congenital Anomaly and Rare Disease Registration Service. Spinal muscular atrophy type 1: NCARDRS data briefing. Availale at: https://www.gov.uk/government/publications/spinal-muscular-atrophy-type-1-ncardrs-data-briefing/spinal-muscular-atrophy-type-1-ncardrs-data-briefing. 2015.
22. Office for National Statistics. Birth Summary Tables, England and Wales 2018, August 2019. Available at:

https://www.ons.gov.uk/file?uri=%2fpeoplepopulationandcommunity%2fbirthsdeathsandmarriages%2flivebirths%2fdatasets%2fbirthsummarytables%2f2018/birthsummarytables2018.xls.
23. AveXis. Data on file. UK HES INCIDENCE data - 2013 - 2017. 2019.
24. World Health Organization. WHO Multicentre Growth Reference Study Group: WHO Child Growth Standards based on length/height, weight and age. Acta Paediatr Suppl. 2006b Apr;450:76-85.
25. Glanzman AM, McDermott MP, Montes J, Martens WB, Flickinger J, Riley S, et al. Validation of the Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders (CHOP INTEND). Pediatr Phys Ther. 2011 Winter;23(4):322-6.
26. Prior TW FE. Spinal muscular atrophy. Last updated: December 22, 2016. In: Pagon RA, Adam MP, Ardinger HH, et al, eds. GeneReviews® [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2017. 2016.
27. Farrar MA, Park SB, Vucic S, Carey KA, Turner BJ, Gillingwater TH, et al. Emerging therapies and challenges in spinal muscular atrophy. Ann Neurol. 2017 Mar;81(3):355-68.
28. World Health Organization. WHO Motor Development Study: windows of achievement for six gross motor development milestones. Acta Paediatr Suppl. 2006a Apr;450:86-95.
29. Wadman RI, Stam M, Gijzen M, Lemmink HH, Snoeck IN, Wijngaarde CA, et al. Association of motor milestones, SMN2 copy and outcome in spinal muscular atrophy types 0-4. J Neurol Neurosurg Psychiatry. 2017 Apr;88(4):365-7.
30. De Sanctis R, Coratti G, Pasternak A, Montes J, Pane M, S. Mazzone E, et al. Developmental milestones in type I spinal muscular atrophy. 2016.
31. Bayley N. Bayley scales of infant and toddler development: Bayley-III: Harcourt Assessment, Psych. Corporation. 2006.
32. Glanzman AM, Mazzone E, Main M, Pelliccioni M, Wood J, Swoboda KJ, et al. The Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders (CHOP INTEND): test development and reliability. Neuromuscul Disord. 2010 Mar;20(3):155-61.
33. D'Amico A, Mercuri E, Tiziano FD, Bertini E. Spinal muscular atrophy. Orphanet J Rare Dis. 2011 Nov 2;6:71.
34. Kolb SJ, Kissel JT. Spinal Muscular Atrophy. Neurol Clin. 2015 Nov;33(4):831-46.
35. Finkel R, Day, J., De Vivo, D., Kirschner, J., Mercuri, E., Muntoni, F., Shieh, P., Tizzano, E., Desguerre, I., Quijano-Roy, S., Saito, K., Droege, M., Dabbous, O., Shah, A., Menier, M., Chand, D., Anderson, F., Servais, L. Real-World Treatment Patterns and Outcomes in Patients With Spinal Muscular Atrophy Collected From the RESTORE Registry. Presented at the 2020 Muscular Dystrophy Association Clinical and Scientific Conference. 2020.
36. AveXis. Data on file. SPR1NT (CL-304) Protocol. Version 2.0, 27 September 2018. 2018.
37. Lowes LP, Al-Zaidy, S., Shell, R., Arnold, W.D., Rodino-Klapac, L., Prior, T.W., Alfano, L.N., Berry, K., Church, K., Kissel, J.T., Nagendran, S., L'Italien, J., Sproule, D.M., Wells, C., Burghes, A.H.M., Foust, K.D., Meyer, K., Likhite, S., Kaspar, B.K., Mendell, J.R. AVXS-101 Phase 1 Gene Replacement Therapy Clinical Trial in SMA Type 1: Patients Treated Early With the Proposed Therapeutic Dose Were Able to Sit Unassisted at a Younger Age. Data on file. 2018a.
38. AveXis. Data on file. Memorandum of video-documented speaking in START (CL-101). September 2017.
39. Lowes LPA, L.N.; Miller, N.f.; Iammarino, M.; Dugan, M.; Berry, K.; Al-Zaidy, S.; Mendell J.R. Gene replacement therapy study for spinal muscular atrophy type 1: patients demonstrate cognitive, fine motor and language abilities within the normal

range [poster]. Presented at the International Scientific Congress on Spinal Muscular Atrophy; January 25-27, 2018b; Krakow, Poland. 2018b.
40. Bromberg MB, Swoboda KJ. Motor unit number estimation in infants and children with spinal muscular atrophy. Muscle Nerve. 2002 Mar;25(3):445-7.
41. Mercuri E, Bertini E, Iannaccone ST. Childhood spinal muscular atrophy: controversies and challenges. Lancet Neurol. 2012 May;11(5):443-52.
42. Kolb SJ, Coffey CS, Yankey JW, Krosschell K, Arnold WD, Rutkove SB, et al. Baseline results of the NeuroNEXT spinal muscular atrophy infant biomarker study. Ann Clin Transl Neurol. 2016 Feb;3(2):132-45.
43. AveXis. Data on File: Draft SmPC onasemnogene abeparvovec. 2020.
44. Alanizi A, A., D'Argenzio, L,D., Hacohan, Y,H., Edel, L,E., Wallis, C,W., Chan, E,C., Abel, F,A., Munot, P,M., Robb, S,R., Craig, F,C., Muntoni, F,M., Manzur, A,M. Spinal Motor Atrophy Type 1: clinical outcome and evolution of care of SMA1 at a single neuromuscular centre in the decade 2007-2017. Abstract presented on the 4th January 2018 at the Developmental medicine and child neurology conference. 2018.
45. Sproule DM, Hasnain R, Koenigsberger D, Montgomery M, De Vivo DC, Kaufmann P. Age at Disease Onset Predicts Likelihood and Rapidity of Growth Failure Among Infants and Young Children With Spinal Muscular Atrophy Types 1 and 2. Journal of Child Neurology. 2012;27(7):845-51.
46. Sehara Y, Fujimoto KI, Ikeguchi K, Katakai Y, Ono F, Takino N, et al. Persistent Expression of Dopamine-Synthesizing Enzymes 15 Years After Gene Transfer in a Primate Model of Parkinson's Disease. Hum Gene Ther Clin Dev. 2017 Jun;28(2):74-9.
47. Foust KD, Wang X, McGovern VL, Braun L, Bevan AK, Haidet AM, et al. Rescue of the spinal muscular atrophy phenotype in a mouse model by early postnatal delivery of SMN. Nat Biotechnol. 2010 Mar;28(3):271-4.
48. Meyer K, Ferraiuolo L, Schmelzer L, Braun L, McGovern V, Likhite S, et al. Improving single injection CSF delivery of AAV9-mediated gene therapy for SMA: a dose-response study in mice and nonhuman primates. Mol Ther. 2015 Mar;23(3):477-87.
49. Ip S, Paulus JK, Balk EM, Dahabreh IJ, Avendano EE, Lau J. AHRQ Methods for Effective Health Care. Role of Single Group Studies in Agency for Healthcare Research and Quality Comparative Effectiveness Reviews. Rockville (MD): Agency for Healthcare Research and Quality (US); 2013.
50. De Sanctis R, Pane M, Coratti G, Palermo C, Leone D, Pera MC, et al. Clinical phenotypes and trajectories of disease progression in type 1 spinal muscular atrophy. Neuromuscul Disord. 2018 Jan;28(1):24-8.
51. Specht S, Eglon, G., Turner, M., Straub, V., Bettolo, C,M. Mortality in patients with spinal muscular atrophy over the last 10 years in the Northeast of the UK. Poster presented at the Twelfth UK Neuromuscular Translational Research Conference 4th –5th April 2019. 2019.
52. Borkowska J, Rudnik-Schoneborn S, Hausmanowa-Petrusewicz I, Zerres K. Early infantile form of spinal muscular atrophy (Werdnig-Hoffmann disease) with prolonged survival. Folia Neuropathol. 2002;40(1):19-26.
53. Ioos C, Leclair-Richard D, Mrad S, Barois A, Estournet-Mathiaud B. Respiratory capacity course in patients with infantile spinal muscular atrophy. Chest. 2004 Sep;126(3):831-7.
54. Bach JR, Baird JS, Plosky D, Navado J, Weaver B. Spinal muscular atrophy type 1: management and outcomes. Pediatr Pulmonol. 2002 Jul;34(1):16-22.
55. Chung BH, Wong VC, Ip P. Spinal muscular atrophy: survival pattern and functional status. Pediatrics. 2004 Nov;114(5):e548-53.
56. AveXis. Data on file: UK Clinical Advisory Board: Summary Report. 28 May 2019. 2019.

57. Finkel RS, Mercuri E, Darras BT, Connolly AM, Kuntz NL, Kirschner J, et al. Nusinersen versus Sham Control in Infantile-Onset Spinal Muscular Atrophy. N Engl J Med. 2017a Nov 2;377(18):1723-32.
58. AveXis. Data on file. Biodistribution of onasemnogene abeparvovec (AVXS-101) DNA, mRNA, and SMN protein in human tissue. Presented at MDA Clinical and Scientific Conference, April 13-17. 2019.
59. AveXis. Data on file. EMA Day 120 responses. 2019.
60. National Institute for Health and Care Excellence. Nusinersen for treating spinal muscular atrophy [GID-TA10281]. 3rd appraisal committee meeting public gallery slides. 6 March 2019. 2019.
61. Edwards S, J., Karner, C., Jhita, T., Kew, K., Marceniuk, G. . Onasemnogene abeparvovec for treating spinal muscular atrophy type 1: A Highly Specialised Technology Appraisal. BMJ Technology Assessment Group. 2020.
62. Thompson R, Vaidya S, Teynor M. The Utility of Different Approachs to Developing Health Utilities Data in Childhood Rare Diseases; A Case Study in Spinal Muscular Atrophy (SMA). Value in Health. 2017;20(9):A725-A6.
63. Tappenden P HJ, Kaltenthaler E, Hock E, Rawdin A, Mukuria C, Clowes M, Simonds A, Childs A. . Nusinersen for treating spinal muscular atrophy: A Single Technology Appraisal. School of Health and Related Research (ScHARR). . 2018.
64. Ara R, Brazier JE. Populating an economic model with health state utility values: moving toward better practice. Value Health. 2010 Aug;13(5):509-18.
65. Khan KA, Petrou S, Rivero-Arias O, Walters SJ, Boyle SE. Mapping EQ-5D utility scores from the PedsQL generic core scales. Pharmacoeconomics. 2014 Jul;32(7):693-706.
66. AveXis. Data on file. UK Health State Utilities Elicitation for Spinal Muscular Atrophy - Report. 01 August 2019. 2019. 2019.
67. Qian Y, McGraw S, Henne J, Jarecki J, Hobby K, Yeh WS. Understanding the experiences and needs of individuals with Spinal Muscular Atrophy and their parents: a qualitative study. BMC Neurol. 2015 Oct 24;15:217.
68. Klug C, Schreiber-Katz O, Thiele S, Schorling E, Zowe J, Reilich P, et al. Disease burden of spinal muscular atrophy in Germany. Orphanet J Rare Dis. 2016 May 4;11(1):58.
69. National Institute for Health and Care Excellence. SMA UK Patient and Caregiver Survey – Summary of results – 5 March 2019. 2019.
70. Tilford JM, Grosse SD, Robbins JM, Pyne JM, Cleves MA, Hobbs CA. Health state preference scores of children with spina bifida and their caregivers. Qual Life Res. 2005 May;14(4):1087-98.
71. Wittenberg E, Prosser LA. Disutility of illness for caregivers and families: a systematic review of the literature. Pharmacoeconomics. 2013 Jun;31(6):489-500.
72. Electronic Medicines Compendium (eMC), . Spinraza Summary of Product Characteristics. July 2019. Available at: https://www.medicines.org.uk/emc/product/2715/smpc. . 2019.
73. National Institute for Health and Care Excellence. Managed Access Agreement - Nusinersen for treating spinal muscular atrophy. Published date: 24 July 2019. 2019.
74. US Institute for Clinical and Economic Review. Spinraza® and Zolgensma® for Spinal Muscular Atrophy: Effectiveness and Value. Final Evidence Report. April 3, 2019. (Updated May 24, 2019). 2019.
75. AveXis. Date on file: UK Healthcare Resource Use Study Report. 14 June 2019. 2019.
76. National Institute for Health and Care Excellence. Single Technology Appraisal. Nusinersen for treating spinal muscular atrophy [ID1069], Appraisal Consultation Document Committee Papers. Published: 14 August 2018. 2018.

77. National Institute for Health Care Excellence. Guide to the methods of technology appraisal. 2013.
78. Castro D, Farrar, M,A., Finkel, R,S., Tulinius, M., Krosschell, K,J., Saito, K., Zhang, Y., Bhan, I., Farwell, W., Reyna, S,P,. Longer-term Assessment of the Safety and Efficacy of Nusinersen for the Treatment of Infantile-Onset Spinal Muscular Atrophy (SMA): An Interim Analysis of the SHINE Study. Poster presented at the American Academy of Neurology, April 21–27, 2018. Los Angeles, California, USA. . 2018.
79. Swoboda KJ, Prior TW, Scott CB, McNaught TP, Wride MC, Reyna SP, et al. Natural history of denervation in SMA: relation to age, SMN2 copy number, and function. Ann Neurol. 2005 May;57(5):704-12.
80. Finkel RS, Weiner DJ, Mayer OH, McDonough JM, Panitch HB. Respiratory muscle function in infants with spinal muscular atrophy type I. Pediatr Pulmonol. 2014b Dec;49(12):1234-42.
81. Feldkotter M, Schwarzer V, Wirth R, Wienker TF, Wirth B. Quantitative analyses of SMN1 and SMN2 based on real-time lightCycler PCR: fast and highly reliable carrier testing and prediction of severity of spinal muscular atrophy. Am J Hum Genet. 2002 Feb;70(2):358-68.
82. Gregoretti C, Ottonello G, Chiarini Testa MB, Mastella C, Rava L, Bignamini E, et al. Survival of patients with spinal muscular atrophy type 1. Pediatrics. 2013 May;131(5):e1509-14.
83. Zerres K, Rudnik-Schoneborn S, Forrest E, Lusakowska A, Borkowska J, Hausmanowa-Petrusewicz I. A collaborative study on the natural history of childhood and juvenile onset proximal spinal muscular atrophy (type II and III SMA): 569 patients. J Neurol Sci. 1997 Feb 27;146(1):67-72.
84. Office for national statistics. National Life Tables. United Kingdom. Based on data from the years 2014-2016. Published September 2018. Available at: https://www.ons.gov.uk/file?uri=/peoplepopulationandcommunity/birthsdeathsandmarriages/lifeexpectancies/datasets/nationallifetablesunitedkingdomreferencetables/current/nltuk1517reg.xls
85. Diaby V, Adunlin G, Montero AJ. Survival modeling for the estimation of transition probabilities in model-based economic evaluations in the absence of individual patient data: a tutorial. Pharmacoeconomics. 2014 Feb;32(2):101-8.
86. Hoyle MW, Henley W. Improved curve fits to summary survival data: application to economic evaluation of health technologies. BMC Med Res Methodol. 2011 Oct 10;11:139.
87. Tierney JF, Stewart LA, Ghersi D, Burdett S, Sydes MR. Practical methods for incorporating summary time-to-event data into meta-analysis. Trials. 2007 Jun 7;8:16.
88. National Institute for Health and Care Excellence Decision Support Unit (NICE DSU). TSD 14: Survival analysis for economic evaluations alongside clinical trials – extrapolation with patient-level data. Available at: http://nicedsu.org.uk/technical-support-documents/survival-analysis-tsd/.
89. Nusinersen EAP UK. Oral presentation. BPNA congress, January 2019.
90. Bladen CL, Thompson R, Jackson JM, Garland C, Wegel C, Ambrosini A, et al. Mapping the differences in care for 5,000 spinal muscular atrophy patients, a survey of 24 national registries in North America, Australasia and Europe. J Neurol. 2014 Jan;261(1):152-63.
91. Briggs AH, Claxton K, Sculpher MJ. Decision modelling for health economic evaluation. Oxford: Oxford University Press; 2006.
92. AveXis. Data on file: UK Clinical Advisory Board: Slide deck. 28 May 2019. 2019.
93. Department of Health and Social Care (NHS Improvement). NHS National Schedule of Reference Costs. National cost collection data 2018/2019. Available at https://improvement.nhs.uk/resources/national-cost-collection/.

94. British National Formulary. Spinraza 12mg/5ml solution for injection vials (Biogen Idec Ltd). Available at: https://bnf.nice.org.uk/medicinal-forms/nusinersen.html.
95. Curtis L, Burns, A. Unit Costs of Health and Social Care 2019. Project report. University of Kent. Available at: https://www.pssru.ac.uk/project-pages/unit-costs/unit-costs-2019/. 2019.
96. NHS Digital. Prescription Cost Analysis, England. 18 March 2018. https://data.gov.uk/dataset/3eecf351-fca5-4f00-87b8-6a2282fa0d13/prescription-cost-analysis-england.
97. NHS England. NHS Commissioning: Orthotic services; Local tariffs for direct access. Available at:, https://www.england.nhs.uk/wp-content/uploads/2015/11/orthcs-rep-attach-5.pdf.
98. National Institute for Health and Care Excellence. NICE, Motor neurone disease: assessment and management, 24 Feb 2016. Available at: https://www.nice.org.uk/guidance/ng42/resources/motor-neurone-disease-assessment-and-management-pdf-1837449470149. 2016.
99. Noyes J, Godfrey C, Beecham J. Resource use and service costs for ventilator-dependent children and young people in the UK. Health & Social Care in the Community. 2006;14(6):508-22.
100. Lloyd AJGK, Thompson, R., Vaidya, S., Teynor, M. . Estimation of the health-related quality of life benefits of treatment for spinal muscular atrophy (SMA). ISPOR 20th Annual European Congress; 2017; Glasgow, Scotland.
101. Malone DC, Dean R, Arjunji R, Jensen I, Cyr P, Miller B, et al. Cost-effectiveness analysis of using onasemnogene abeparvocec (AVXS-101) in spinal muscular atrophy type 1 patients. Journal of Market Access & Health Policy. 2019 2019/01/01;7(1):1601484.
102. The Lewin Group. Cost of Amyotrophic Lateral Sclerosis, Muscular Dystrophy, and Spinal Muscular Atrophy in the United States. . 2012.
103. United States CB. Educational Attainment in the United States, 2017. Available at: https://www.census.gov/data/tables/2017/demo/education-attainment/cps-detailed-tables.html.
104. Organisation for Economic Co-operation and Development. Education and earnings available at: https://stats.oecd.org/Index.aspx?DataSetCode=EAG_EARNINGS applied to Annual income for A level graduate from https://www.statista.com/statistics/281936/average-salary-by-education-level-in-the-united-kingdom-uk.
105. Organisation for Economic Co-operation and Development. Unemployment rates by education level. Available at: https://data.oecd.org/unemp/unemployment-rates-by-education-level.htm. .
106. Powell. People with disabilities in employment. House of Commons Library Briefing paper, Number 7540, 8 January 2018. 2018.
107. Organisation for Economic Co-operation and Development. Purchasing power aprities. Available at https://data.oecd.org/conversion/purchasing-power-parities-ppp.htm. .

Please note that a PDF for Briggs et al. 2006 is not provided in the reference pack accompanying this submission.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Highly Specialised Technologies

Patient Access Scheme submission template

May 2019

1. Introduction

In acknowledgment of the introduction of the 2019 Voluntary Scheme for Branded Medicines Pricing and Access (2019 VS) the transition arrangements as set out in paragraph 3.28 state that commercial flexibilities analogous to simple confidential and complex published Patient Access Schemes will continue to operate and be available for new products using existing processes and in accordance with existing criteria and terms as set out originally in the 2014 Pharmaceutical Price Regulation Scheme (PPRS), and guidance on the National Institute for Health and Care Excellence (NICE) website. Once NHS England establishes the approach in the commercial framework as referred to in paragraph 3.26 of the 2019 VS, any new commercial flexibilities analogous to simple confidential and complex published PAS will operate in accordance with the commercial framework.

The PPRS (2014) is a non-contractual scheme between the Department of Health and the Association of the British Pharmaceutical Industry. The purpose of the PPRS (2014) is to ensure that safe and cost-effective medicines are available on reasonable terms to the NHS in England and Wales. One of the functions of the PPRS (2014) is to improve patients' access to medicines at prices that better reflect their value through Patient Access Schemes.

Patient Access Schemes are arrangements which may be used on an exceptional basis for the acquisition of medicines for the NHS in England and Wales. Patient Access Schemes propose a discount, rebate or other variation from the list price of a medicine that may be linked to the number of patients estimated to receive the medicine, the clinical response of patients to the medicine or the collection of new evidence (outcomes) relating to the medicine. Proposed schemes should aim to improve the cost effectiveness of a medicine and therefore allow the National Institute for Health and Care Excellence (NICE) to recommend treatments which it would otherwise not have found to be cost effective. More information on the framework for Patient Access Schemes is provided in the PPRS (2014).

Patient Access Schemes are proposed by a pharmaceutical company and agreed with NHS England, with input from the Patient Access Schemes Liaison Unit (PASLU) within the Centre for Health Technology Evaluation at NICE.

The PPRS recognises the need to ensure that the cumulative burden on the NHS arising from Patient Access Schemes is manageable, and notes that these schemes should be the exception rather than the rule. Simple discount Patient Access Schemes are preferred to complex schemes because they create no significant implementation burden for the NHS. Where a more complex scheme is proposed, applicants should use the complex scheme proposal template rather than this simple discount scheme template, and will need to explain and justify their choice of scheme.

2. Instructions for companies and sponsors

This document is the Patient Access Scheme submission template for highly specialised technologies. If companies and sponsors want the National Institute for Health and Care Excellence (NICE) to consider a Patient Access Scheme as part of a highly specialised technologies evaluation, they should use this template. NICE can only consider a Patient Access Scheme after formal referral from NHS England.

The template contains the information NICE requires to assess the impact of a Patient Access Scheme on the clinical and cost effectiveness of a technology, in the context of a highly specialised technologies evaluation, and explains the way in which background information (evidence) should be presented. If you are unable to follow this format, you must state your reasons clearly. You should insert 'N/A' against sections that you do not consider relevant, and give a reason for this response.

Please refer to the following documents when completing the template:

- 'Highly Specialised Technologies Interim Evidence Submission Template' and
- Pharmaceutical Price Regulation Scheme 2014.

For further details on the highly specialised technologies evaluation process, please see NICE's 'Interim methods and process statement for highly specialised technologies'. The 'Highly Specialised Technologies Interim Evidence Submission Template' provides details on disclosure of information and equality issues.

Make the submission as brief and informative as possible. Only mark information as confidential when absolutely necessary. Sufficient information must be publicly available for stakeholders to comment on the full content of the highly specialised technologies evaluation, including details of the proposed Patient Access Scheme. Send submissions electronically via NICE docs: https://appraisals.nice.org.uk.

Appendices may be used to include additional information that is considered relevant to the submission. Do not include information in the appendices that has been requested in the template. Appendices should be clearly referenced in the main submission.

When making a Patient Access Scheme submission, include:

- an updated version of the checklist of confidential information, if necessary
- an economic model with the Patient Access Scheme incorporated.

If you are submitting the Patient Access Scheme at the end of the evaluation process, you should update the economic model to reflect the assumptions that the HST Evaluation Committee considered to be most plausible. No other changes should be made to the model.

3. Details of the Patient Access Scheme

3.1. Please give the name of the highly specialised technology and the disease area to which the Patient Access Scheme applies.

Onasemnogene abeparvovec for treating children with spinal muscular atrophy type 1 [ID1473].

3.2. Please outline the rationale for developing the Patient Access Scheme.

To enhance the value proposition of onasemnogene abeparvovec to the NHS.

3.3. Please describe the type of Patient Access Scheme, as defined by the PPRS (2014). If it is a Simple Discount scheme, please include details of the list price and the proposed percentage discount/fixed price

Confidential simple ([redacted]) discount on the published UK list price (£1,795,000), which means that the NHS will pay [redacted] per patient for this one-time treatment.

3.4. Please provide specific details of the patient population to which the Patient Access Scheme applies. Does the scheme apply to the whole licensed population or only to a specific subgroup? If so:

- How is the subgroup defined?
- If certain criteria have been used to select patients, why have these have been chosen?
- How are the criteria measured and why have the measures been chosen?

The confidential simple discount applies to the whole licensed indication.

3.5. Please provide details of when the scheme will apply to the population specified in 3.4. Is the scheme dependent on certain criteria, for example, degree of response, response by a certain time point, number of injections? If so:

- Why have the criteria been chosen?
- How are the criteria measured and why have the measures been chosen.

The confidential discount will be automatically applied to the invoice at the point of sale. It applies to all patients treated with onasemnogene abeparvovec.

3.6. What proportion of the patient population (specified in 3.4) is expected to meet the scheme criteria (specified in 3.5)?

All patients (100%).

3.7. Please explain in detail the financial aspects of the scheme. How will any rebates be calculated and paid?

The confidential discount will be automatically applied to the invoice at the point of sale. No additional calculations or payments will be required.

3.8. Please provide details of how the scheme will be administered. Please specify whether any additional information will need to be collected, explaining when this will be done and by whom.

The confidential discount will be automatically applied to the invoice at the point of sale. No additional information will need to be collected.

3.9. Please provide a flow diagram that clearly shows how the scheme will operate. Any funding flows must be clearly demonstrated.

The confidential discount will be automatically applied to the invoice at the point of sale. No additional funding flows are created.

3.10. Please provide details of the duration of the scheme.

The confidential discount will remain in place until NICE revisit their guidance for onasemnogene abeparvovec for this or any other future indication.

3.11. Are there any equity or equalities issues relating to the scheme, taking into account current legislation and, if applicable, any concerns identified during the course of the evaluation? If so, how have these been addressed?

There are no equity of equalities issues relating to this scheme.

3.12. In the exceptional case that you are submitting an outcome-based scheme, as defined by the PPRS, please also refer to appendix A.

4. Value for money

4.1. If the population to whom the scheme applies (as described in sections 3.4 and 3.5) has not been presented in the main company/sponsor submission of evidence for the highly specialised technologies evaluation (for example, the population is different as there has been a change in clinical outcomes or a new continuation rule), please re-submit the relevant sections from the 'Highly Specialised Technologies Interim Evidence Submission Template'. You should complete those sections both with and without the Patient Access Scheme. You must also complete the rest of this template.

The PAS applies to all patients treated with onasemnogene abeparvovec.

4.2. If you are submitting the Patient Access Scheme at the end of the highly specialised technologies evaluation process, you should update the economic model to reflect the assumptions that the HST Evaluation Committee considered to be most plausible. No other changes should be made to the model.

Not applicable. This Patient Access Scheme submission is at an interim step in the appraisal process. It should be noted though that the updated economic model base case submitted by the company adopts the six 'ERG-preferred base case' assumptions described in the interim ERG report (January 2020) and the latest ERG's clarification requests (June/July 2020) for this appraisal.

4.3. Please provide details of how the Patient Access Scheme has been incorporated into the economic model. If applicable, please also provide details of any changes made to the model to reflect the assumptions that the HST Evaluation Committee considered most plausible.

The confidential discount for onasemnogene abeparvovec is incorporated into the economic model by amending the 'cost per single dose' to [redacted] in cell K16 on tab 'AVXS-101Costs'

The updated economic model base case submitted by the company on the 2 July 2020 adopts the six 'ERG-preferred base case' assumptions described in the interim ERG report (January 2020) and the latest ERG's clarification requests (June/July 2020) for this appraisal. These changes are described in full in the company submission (May 2020, supplementary appendix) and the company's ERG clarification responses (July 2020), but briefly these include:

'ERG-preferred base case' from interim ERG report:

1. C and B state survival: Overall survival in the short-term model based on empirical data
2. E state survival: Exponential distribution for the extrapolation of the NRA OS KM from Gregoretti et al. 2013
3. D state survival: D state OS survival limit of 48 months and use of Weibull distribution, for both the onasemnogene abeparvovec and best supportive care (BSC) arms
4. Utility of zero for the E state
5. On-treatment utility for the D and C state
6. B health state costs applied to the A state

ERG clarification requests:

1. ERG question **B5:** Amendment of the empirical data period for OS and EFS in the D state from 0-30 months (cycle 1 to cycle 5, inclusive) to 0-36 months (cycle 1 to cycle 6, inclusive) for the onasemnogene abeparvovec arm
2. ERG question **B5:** Amendment of the empirical data period for OS in the C, B and A states from 0-30 months (cycle 1 to cycle 5, inclusive) to 0-36 months (cycle 1 to cycle 6, inclusive) for the onasemnogene abeparvovec arm
3. ERG question **B8:** Onasemnogene abeparvovec technology and administration costs have been assigned in cycle 0, where no discounting is applied. All other costs from cycle 1 onwards remain the same and are discounted.
4. ERG question **B10**: Amendment of the standard error for utilities from 5% to 20% for all PSA parameters specific to utilities: C, D and E health state utility values and their on-treatment utility increments and all the Ara and Brazier equation parameters used for estimating the A and B health state utility values

4.4. Please provide the clinical effectiveness data resulting from the evidence synthesis and used in the economic model which includes the Patient Access Scheme.

For a full description of the POOLED clinical data (n=34) for onasemnogene abeparvovec – i.e. data from the completed START and STR1VE-US trials – incorporated into the economic model, please see Section 7.2.1 of the company submission (May 2020, supplementary appendix). In brief, the POOLED data (n=34) incorporated into the economic model are:

- 97.1% overall survival at 30 months of age
    - STR1VE-US only followed patients up to 18 months of age, therefore, patients are censored from the overall survival curve at 18 months of age
- 94.1% event-free survival at 30 months of age
    - STR1VE-US only followed patients up to 18 months of age, therefore, patients are censored from the event-free survival curve at 18 months of age
- Following the latest ERG clarification requests (June/July 2020, question **B5)**, the base case model has been amended to use data for an extended empirical period of 36 months (up to cycle 6) for the onasemnogene abeparvovec arm. For cycle 6, it has been assumed that the same OS and EFS remains as in cycle 5 (last observation carried forward [LOCF] methodology]).
- 26/34 (76.5%) sit alone by 30 months of age, of which 4/34 (11.8%) patients also walk alone by 30 months of age. Please note, these milestone data include the assumptions that:
    - There is one additional independent sitter and one additional independent walker between 24 to 30 months of age, when compared to the empirical data available (see Table 1)
    - The motor milestones observed at the end of STR1VE-US at 18 months of age persist to 30 months of age

- In the model base case, all motor milestones attained in the START and STR1VE-US trial are 'offset' by a model cycle when incorporated into the model. This approach is conservative because milestone attainment is being modelled as occurring at a later age compared to the observed data from the trials.

- Full details and an explanation for these base case assumptions are provided in Section 7.2.1 of the company submission (May 2020, supplementary appendix)

For a full description of the clinical data incorporated into the economic model for BSC, please see Section 7.2.1 of the company submission (May 2020, supplementary appendix). In brief, the clinical outcomes in the best supportive care arm are derived from the NeuroNext natural history study (n=16):

- 50% overall survival at end of study (follow up to 24 months of age)
- 37.5% event-free survival at end of study (follow up to 24 months of age)
- No motor milestones were attained for any of the 16 SMA type 1 patients in this natural history study

Table 1: Milestone outcomes for onasemnogene abeparvovec incorporated into the economic model

	Empirical			Economic model: base case assumption‡‡ Inclusive of the base case assumption: one additional sitter and one additional walker in STR1VE-US		
	START, N=12¶ n (%)	STR1VE-US, N=22¶ n (%)	POOLED, N=34¶ n (%)	START, N=12¶ n (%)	STR1VE-US, N=22¶ n (%)	POOLED, N=34¶ n (%)
Non-sitters	1 (8.3%)	8 (36.4%)†	9 (26.5%)†	1 (8.3%)	7 (31.8%)†	8 (23.5%)†
Sits alone‡	11 (91.7%)	14 (63.6%)††	25 (73.5%)††	11 (91.7%)	15 (68.2%)††	26 (76.5%)††
Walks alone§	2 (16.7%)	1 (4.5%)	3 (8.8%)	2 (16.7%)	2 (9.1%)	4 (11.8%)

† Includes one patient who died aged 7.8 months and one patient who met the permanent-assisted ventilation event endpoint aged 11 months from STR1VE-US.
‡ Defined as Bayley Scales gross motor subtest item #26: Child sits alone without support for at least 30 seconds in STR1VE-US (centrally reviewed/video-confirmed); Defined as "Sits alone <10 seconds" for START (centrally reviewed/video-confirmed). All patients in the 'sitting < 10 seconds' category were able to sit for at least 5 seconds.
§ Bayley Scales gross motor subtest item #43: Child takes at least 5 steps independently, displaying coordination and balance (centrally reviewed/video-confirmed) used for STR1VE-US. Gross Motor Checklist: 'takes independent steps' or the Motor Milestone Development Survey: 'walks independently' used for START (centrally reviewed/video-confirmed).
¶ Percentages across the three rows are greater than 100% for each trial since patients can attain multiple milestones. For example, the patients who can walk alone can also sit alone.
†† For one patient in STR1VE-US the milestone of sits unassisted ≥30 seconds was not confirmed at the end of study 18 month visit, but was observed at the 16 month and 17 month visit. This patient did sit unassisted for ≥5 seconds at the 18 month visit (as recorded in the Bayley Scales assessment, gross motor item #22).
‡‡ The base case assumption assumes there is one additional independent sitter and one additional independent walker between 24 to 30 months of age, when compared to the empirical data available from STR1VE-US

4.5. Please list any costs associated with the implementation and operation of the Patient Access Scheme (for example, additional pharmacy time for stock management or rebate calculations). A suggested format is presented in table 1. Please give the reference source of these costs. .

The confidential discount will be automatically applied to the invoice at the point of sale. There are no costs associated with operating this Patient Access Scheme.

4.6. Please provide details of any additional treatment-related costs incurred by implementing the Patient Access Scheme. A suggested format is presented in table 2. The costs should be provided for the intervention both with and without the Patient Access Scheme. Please give the reference source of these costs.

The confidential discount will be automatically applied to the invoice at the point of sale. There are no costs associated with operating this Patient Access Scheme.

Summary results

Base-case analysis

4.7. Please present in separate tables the economic results as follows.[1]

- the results for the intervention without the Patient Access Scheme
- the results for the intervention with the Patient Access Scheme.

A suggested format is shown below

[1] For outcome-based schemes, please see section 5.7 in appendix A.

Results are shown below in Table 2 and Table 3.

All model costs and effects have been discounted at 3.5% (unless stated) and include half cycle correction. 'Other costs' are SMA-related care costs. Onasemnogene abeparvovec intervention costs include treatment administration costs.

Table 2: Base-case value for money results – List price

	Onasemnogene abeparvovec	Best supportive care
Intervention cost (£)	1,797,803	0
Other costs (£)	915,162	381,131
Total costs (£)	2,712,964	381,131
Difference in total costs (£)	2,331,833	-
LYG (or other outcome)	15.68	2.15
LYG difference	13.53	-
QALYs	10.213	0.210
QALY difference	10.003	-
QALYs (undiscounted)	21.406	0.217
QALY difference (undiscounted)	21.188	-
ICER vs BSC (£/QALY)	233,106	-

LYG: life-year gained; QALY: quality-adjusted life-year; ICER: incremental cost-effectiveness ratio.

Table 3: Base-case value for money results – PAS price

	Onasemnogene abeparvovec	Best supportive care
Intervention cost (£)	[redacted]	0
Other costs (£)	915,162	381,131
Total costs (£)	[redacted]	381,131
Difference in total costs (£)	[redacted]	-
LYG (or other outcome)	15.68	2.15
LYG difference	13.53	-
QALYs	10.213	0.210
QALY difference	10.003	-
QALYs (undiscounted)	21.406	0.217

	Onasemnogene abeparvovec	Best supportive care
QALY difference (undiscounted)	21.188	-
ICER vs BSC (£/QALY)	[redacted]	-

LYG: life-year gained; QALY: quality-adjusted life-year; ICER: incremental cost-effectiveness ratio.

4.8. Please present in separate tables the incremental results as follows.[2]

- the results for the intervention without the Patient Access Scheme
- the results for the intervention with the Patient Access Scheme.

Results are shown below in Table 4 and Table 5

As per the response to ERG question **B8,** onasemnogene abeparvovec technology and administration costs have been assigned in cycle 0, where no discounting is applied. All other costs from cycle 1 onwards remain the same and are discounted. All model costs and effects have been discounted at 3.5% and include half cycle correction.

[2] For outcome-based schemes, please see section 5.8 in appendix A.

Table 4: Base case results – List price

Technologies	Total			Incremental			ICER vs BSC (£/QALY)
	Costs (£)	LYG	QALYs	Costs (£)	LYG	QALYs	
BSC	381,131	2.15	0.210	-	-	-	-
Onasemnogene abeparvovec	2,712,964	15.68	10.213	2,331,833	13.53	10.003	233,106

Abbreviations: BSC, best supportive care; ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALY, quality adjusted life years.

Table 5: Base case results – PAS price

Technologies	Total			Incremental			ICER vs BSC (£/QALY)
	Costs (£)	LYG	QALYs	Costs (£)	LYG	QALYs	
BSC	381,131	2.15	0.210	-	-	-	-
Onasemnogene abeparvovec	[redacted]	15.68	10.213	[redacted]	13.53	10.003	[redacted]

Abbreviations: BSC, best supportive care; ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALY, quality adjusted life years.

Sensitivity analyses

4.9. Please present deterministic sensitivity analysis results as described for the main company/sponsor submission of evidence for the highly specialised technologies evaluation. Consider using tornado diagrams.

One-way and multi-way sensitivity analysis were conducted. The results shown below use the confidential PAS price.

Figure 1 shows the impact on the ICER from the one-way sensitivity analysis for onasemnogene abeparvovec versus BSC. Results in table format are shown in Table 6. All variables were varied by +/- 20% or natural limits if these were within the +/- 20% range.

Figure 1: Tornado diagram of impact of the one-way sensitivity analysis (+/- 20% or natural limit) on the ICER (onasemnogene abeparvovec versus BSC) – top 20 results only

Table 6: Impact of the one-way sensitivity analysis (+/- 20% or natural limit) on the ICER (onasemnogene abeparvovec versus BSC). Top 20 results.

Rank	Parameter Description	Low	High	ICER using Low value	ICER using High value	Range	Low % Change	High % Change
1	c_AVXS-101_drug	[redacted]	[redacted]	[redacted]	[redacted]	61,871	15%	15%
2	u_C_State	0.48	0.72	[redacted]	[redacted]	54,694	15%	11%
3	c_C_Hospitalizations	29869.06	44803.59	[redacted]	[redacted]	16,064	4%	4%
4	c_C_Social Services	14878.08	22317.12	[redacted]	[redacted]	8,002	2%	2%
5	c_E_Hospitalizations	160197.95	240296.92	[redacted]	[redacted]	7,352	2%	2%
6	u_C_State_Inc_AVX	0.04	0.06	[redacted]	[redacted]	4,482	1%	1%
7	Survival_limit_D_Zolgensma	3.20	4.80	[redacted]	[redacted]	2,354	0%	1%
8	c_D_Hospitalizations	50812.63	76218.95	[redacted]	[redacted]	2,004	0%	0%
9	c_E_Social Services	39994.88	59992.32	[redacted]	[redacted]	1,835	0%	0%
10	u_D_State_Inc_AVX	0.08	0.12	[redacted]	[redacted]	1,578	0%	0%
11	Survival_limit_E	12.80	19.20	[redacted]	[redacted]	1,558	1%	0%
12	u_D_State	0.15	0.23	[redacted]	[redacted]	1,249	0%	0%
13	c_C_Medical visits	2007.50	3011.25	[redacted]	[redacted]	1,080	0%	0%
14	c_C_Health material	1663.53	2495.29	[redacted]	[redacted]	895	0%	0%
15	c_D_Social Services	22317.12	33475.68	[redacted]	[redacted]	880	0%	0%
16	Survival_limit_D	3.20	4.80	[redacted]	[redacted]	345	0%	0%
17	c_C_Drugs	594.25	891.38	[redacted]	[redacted]	320	0%	0%
18	c_A_Social Services	2361.60	3542.40	[redacted]	[redacted]	306	0%	0%
19	c_C_Medical tests	520.51	780.77	[redacted]	[redacted]	280	0%	0%
20	c_A_Medical visits	1773.25	2659.87	[redacted]	[redacted]	230	0%	0%

Abbreviations: BSC, best supportive care; ICER, incremental cost effectiveness ratio.

The only variables that impacted on the ICER by 5% or greater in either direction were: i) the cost of onasemnogene abeparvovec (high ICER of [redacted]; low ICER of [redacted]) and; ii) the patient utility value attached to the C state (high ICER of [redacted]; low ICER of [redacted]).

Table 7 below present the results of a multi-way sensitivity analysis.

The multi-way sensitivity analysis compared the three variables (excluding the cost of onasemnogene abeparvovec) that had the largest impact on the ICER as shown by the one-way analysis. These were the patient utility value attached to the C state (0.6 in the base case) the cost of hospitalisations in the C state (£37,336 in the base case) and the cost of social services in the C state (£18,598 in the base case). Values were varied by +/- 20%.

Table 7: Multi-way analysis of three variables for onasemnogene abeparvovec versus BSC: ICER results (£/QALY)

	Hospitalisation cost in C state = base case	**Hospitalisation cost in C state = base case * 0.8**	**Hospitalisation cost in C state = base case * 1.2**
Social services cost in C state = base case	U1; [redacted] U2; [redacted] U3; [redacted]	U1; [redacted] U2; [redacted] U3; [redacted]	U1; [redacted] U2; [redacted] U3; [redacted]
Social services cost in C state = base case * 0.8	U1; [redacted] U2; [redacted] U3; [redacted]	U1; [redacted] U2; [redacted] U3; [redacted]	U1; [redacted] U2; [redacted] U3; [redacted]
Social services cost in C state = base case * 1.2	U1; [redacted] U2; [redacted] U3; [redacted]	U1; [redacted] U2; [redacted] U3; [redacted]	U1; [redacted] U2; [redacted] U3; [redacted]

Abbreviations: BSC, best supportive care; ICER, incremental cost effectiveness ratio.
Note: U1 = base case utility value; U2 = base case utility value * 0.8; U3 = base case utility value * 1.2.
Note: 'on treatment' C state utility addition (0.05) kept as per base case in all analyses.

The results ranged from a low ICER of [redacted] (20% reduction in C state hospitalisation costs, 20% reduction in C state social services costs and 20% increase in the C state utility value) to a high ICER of [redacted] (20% increase in C state hospitalisation costs, 20% increase in C state social services costs and 20% reduction in the C state utility value).

4.10. Please present scenario analysis results as described for the main company/sponsor submission of evidence for the highly specialised technologies evaluation.

Error! Reference source not found. presents further sensitivity analyses. All results use the confidential PAS price. Results show the impact of changing various assumptions on discount rates, cost assumptions, utility values, alternative natural history sources and exploratory scenarios.

Table 8: Further sensitivity analysis results and scenarios: impact on ICER for onasemnogene abeparvovec versus BSC†

#		Onasemnogene abeparvovec	BSC	ICER (£/QALY)
	Base case results	Costs: [redacted] QALYs: 10.213	Costs: £381,131 QALYs: 0.210	[redacted]
DISCOUNT RATES				
1	Costs and effects at 0%	Costs: [redacted] QALYs: 21.406	Costs: £441,085 QALYs: 0.217	[redacted]
2	Costs and effects at 5%	Costs: [redacted] QALYs: 8.137	Costs: £360,121 QALYs: 0.207	[redacted]
3	Costs at 0%, effects at 5%	Costs: [redacted] QALYs: 8.137	Costs: £441,085 QALYs: 0.207	[redacted]
4	Costs at 5%, effects at 0%	Costs: [redacted] QALYs: 21.406	Costs: £360,121 QALYs: 0.217	[redacted]
5	Costs and effects at 1.5%	Costs: [redacted] QALYs: 14.888	Costs: £413,269 QALYs: 0.214	[redacted]
COST ASSUMPTIONS				
6	Use of RWE costs (scenario with SMA type 1 costs doubled) presented at the nusinersen NICE ACM3	Costs: [redacted] QALYs: 10.213	Costs: £317,933 QALYs: 0.210	[redacted]
7	SMA type 3 costs from RWE presented at nusinersen ACM3 applied to the A state and B state patients, other health state costs remain as base case	Costs: [redacted] QALYs: 10.213	Costs: £381,131 QALYs: 0.210	[redacted]
8	Cost of onasemnogene abeparvovec administration 10x higher than base case	Costs: [redacted] QALYs: 10.213	Costs: £381,131 QALYs: 0.210	[redacted]
9	US ICER approach to the costing of ventilatory support (ERG question 2019, **B16**)	Costs: [redacted] QALYs: 10.213	Costs: £74,765 QALYs: 0.210	[redacted]

#		Onasemnogene abeparvovec	BSC	ICER (£/QALY)
10	Increase of total D state and E state costs explorative scenario 1 (ERG question 2019, **B20**)	Costs: [redacted] QALYs: 10.213	Costs: £506,221 QALYs:0.210	[redacted]
11	Increase of HCRU in the D state and E state costs explorative scenario 2 (ERG question 2019, **B20**)	Costs: [redacted] QALYs: 10.213	Costs: £394,557 QALYs: 0.210	[redacted]
12	Extreme scenario where all non-permanent ventilated patients (84% in state D, 56% in state C, 20% in state B/A) in whatever health state receive 100% of the Noyes social care/ social services costs (ERG question 2019, **B23**)	Costs: [redacted] QALYs: 10.213	Costs: £411,970 QALYs: 0.210	[redacted]
UTILITY VALUES				
13	On-treatment utility using lower values than US ICER (0.05 for D state; 0.025 for C state)	Costs: [redacted] QALYs: 9.850	Costs: £381,131 QALYs: 0.210	[redacted]
14	On-treatment utility using higher values than US ICER (0.15 for D state; 0.075 for C state)	Costs: [redacted] QALYs: 10.577	Costs: £381,131 QALYs: 0.210	[redacted]
15	Using CHERISH values	Costs: [redacted] QALYs: 13.114	Costs: £381,131 QALYs: 1.595	[redacted]
16	Using Lloyd vignette study	Costs: [redacted] QALYs: 2.623	Costs: £381,131 QALYs: -0.476	[redacted]
17	Using exploratory AveXis UK utilities elicitation study using the TTO results from the 'parent' vignettes for states B to E	Costs: [redacted] QALYs: [redacted]	Costs: £381,131 QALYs: -0.536	[redacted]
18	No utility weights (cost per life year gained)	Costs: [redacted] Life years: 15.676	Costs: £381,131 Life years: 2.145	[redacted]
ALTERNATIVE NATURAL HISTORY SOURCE				
19	Use of AveXis external PNCR control dataset: fitted curve kept as Weibull, survival maximum equals 4 years	Costs: [redacted] QALYs: 10.213	Costs: £708,035 QALYs: 0.252	[redacted]

#		Onasemnogene abeparvovec	BSC	ICER (£/QALY)
20	Use of Finkel et al. 2017a (ENDEAR sham control): fitted curve kept as Weibull, survival maximum equals 4 years	Costs: [redacted] QALYs: 10.213	Costs: £652,584 QALYs: 0.219	[redacted]
21	Use of De Sanctis et al. 2016 (PNCR, US and Italy study): fitted curve kept as Weibull, survival maximum equals 4 years	Costs: [redacted] QALYs: 10.213	Costs: £691,806 QALYs: 0.174	[redacted]
EXPLORATORY SCENARIOS				
22	Patients in the C state (sits unassisted) have a life expectancy the same as the general population: applied to onasemnogene abeparvovec arm only	Costs: [redacted] QALYs: 13.800	Costs: £381,131 QALYs: 0.210	[redacted]
23	Use of POOLED dataset, but with only one additional sitter compared to empirical data in STR1VE-US after 18 months of age. The additional sitter sits between 24–30 months of age and therefore moves to sitting in cycle ending 36 months	Costs: [redacted] QALYs: 9.858	Costs: £381,131 QALYs: 0.210	[redacted]
24	Use of POOLED dataset, but with only one additional walker compared to empirical data in STR1VE-US after 18 months of age. The additional walker walks between 24–30 months of age and therefore moves to walking in cycle ending 36 months	Costs: [redacted] QALYs: 9.918	Costs: £381,131 QALYs: 0.210	[redacted]
25	Use of POOLED dataset but use of the empirical data only from STR1VE-US. i.e. no additional patients who can sit or walk unassisted in STR1VE-US after 18 months of age.	Costs: [redacted] QALYs: 9.563	Costs: £381,131 QALYs: 0.210	[redacted]
26	Use of POOLED dataset but with four new sitters and four new walkers in STR1VE-US after 18 months of age. Half move in cycle ending 30 months and half move in cycle ending 36 months	Costs: [redacted] QALYs: 12.184	Costs: £381,131 QALYs: 0.210	[redacted]
27	E state overall survival based on the 'pooled' Gregoretti cohort, i.e. patients with tracheostomy (n=42) or NIV (n=31) with proportions adjusted accordingly in medical cost calculator; curve = exponential, survival limit = 16 years	Costs: [redacted] QALYs: 10.213	Costs: £694,197 QALYs: 0.210	[redacted]
28	Caregiver disutility scores included	Costs: [redacted] QALYs: 9.729	Costs: £381,131 QALYs: 0.038	[redacted]
29	Milestones, overall survival and event-free survival is based on those treated at ≤3.5 months of age in START and STR1VE-US (n=17)	Costs: [redacted] QALYs: 11.571	Costs: £381,131 QALYs: 0.210	[redacted]

#		Onasemnogene abeparvovec	BSC	ICER (£/QALY)
20	Milestones, overall survival and event-free survival are based on those treated in START only (n=12)	Costs: [redacted] QALYs: 12.370	Costs: £381,131 QALYs: 0.210	[redacted]
31	Milestones are not 'offset' by a model cycle (i.e. not 'offset' by 6 months)	Costs: [redacted] QALYs: 10.360	Costs: £381,131 QALYs: 0.210	[redacted]
32	Proxy pre-symptomatic scenario A: Assumes age-appropriate milestones (sitting and walking) are observed for all patients, but with conservative one cycle motor milestone offset still applied. Assumes overall survival and event-free survival is 100% in the D state for the short-term model for onasemnogene abeparvovec.	Costs: [redacted] QALYs: 23.796	Costs: £381,131 QALYs: 0.210	[redacted]
33	Proxy pre-symptomatic scenario B: Assumes sitting is observed in all patients, of which 50% attain age-appropriate sitting and 50% achieve delayed sitting. Assumes walking is observed for 82% of patients; of which 50% attain age-appropriate walking and 50% achieve delayed walking. The conservative one cycle motor milestone offset still applied to all milestones. Assumes overall survival and event-free survival is 100% in the D state for the short-term model for onasemnogene abeparvovec.	Costs: [redacted] QALYs: 21.414	Costs: £381,131 QALYs: 0.210	[redacted]
34	30 second threshold for sitting independently: Use of the POOLED dataset in which sitting independently is defined as 'sitting alone for ≥30 seconds' for both the START and STR1VE-US trials. All other base case assumptions regarding motor milestones (e.g. application of the conservative one model cycle offset and the assumption of one additional sitter and walker in STR1VE-US between 24 and 30 months of age) remain in place for this scenario. (ERG clarification questions 2020, **A3/B2**)	Costs: [redacted] QALYs: 9.612	Costs: £381,131 QALYs: 0.210	[redacted]

Abbreviations: ACM3, third appraisal committee meeting; BSC, best supportive care; EFS, event-free survival; ERG, evidence review group; ICER, incremental cost effectiveness ratio; Nus, nusinersen; ON-A, onasemnogene abeparvovec; OS, overall survival; PNCR, Pediatric Neuromuscular Clinical Research; QALY, quality-adjusted life-year; RWE, real-world evidence; UK, United Kingdom; US, United States; vs. versus.
† Values are reported per the economic model, discrepancies are due to rounding.

- **Discount rates:** Discounting costs and effects at 0% decreases the ICER by 40% whilst discounting costs at 5% but applying no discounting to effects decreases the ICER by over 56%. Discounting effects at 5% but not discounting costs increases the ICER by 60%. Discounting both costs and effects at 1.5% decreases the ICER by nearly 24% to [redacted]

- **Cost assumptions:** Of the cost assumptions tested in the model, most had minor effects on the ICER; i.e. SMA type 3 costs from RWE presented at nusinersen ACM3 (1) used for A state and B state patients, cost of onasemnogene abeparvovec administration 10x higher than baseline and both scenarios with increased D and E state costs. The ICER increased by approximately 12% (from [redacted] to [redacted] and [redacted], respectively) when the base case health state costs were replaced with the RWE costs (scenario with SMA type 1 costs doubled) presented at the nusinersen ACM3 (1) and when all non-permanent ventilated patients receive 100% of the social care costs obtained from Noyes et al 2006. The ICER was decreased most (by 22%) when the US ICER approach is applied to the costing of ventilatory support

- **Utility values:** The use of the utilities mapped from PedsQL in CHERISH and the use of applying no utility weights (i.e. cost per LYG) both lead to the ICER falling from [redacted] to [redacted] and to [redacted], respectively. When the Lloyd et al. 2017 (2) clinician-proxy vignette study is used, the ICER increases to [redacted]: note that the number of QALYs gained from BSC in this scenario is -0.476. The use of the exploratory AveXis UK utilities elicitation study increases the ICER by 61% to [redacted]: note that the number of QALYs gained from BSC in this case is -0.536

- **Alternative natural history source:** All of the alternative natural history sources decrease the ICER: by 13% when Finkel et al. 2017 (ENDEAR Sham control arm) (3) is used, by almost 15% when De Sanctis et al. 2016 (PNCR, US and Italy study) adjusted/disaggregated dataset (4) is used and by 15% when the AveXis external PNCR control (n=23) adjusted/disaggregated dataset is used

- Further sensitivity analysis and exploratory scenarios

In the optimistic scenario that assumes there is improved survival for any patient that can sit unassisted (C state) in the onasemnogene abeparvovec arm, the ICER falls by 14% to [redacted].

Including caregiver disutility scores impacts on the ICER only slightly, increasing by 3% to [redacted].

In scenarios that explored different milestone attainment in STR1VE-US patients after 18 months of age:

- The ICER increased by 4.8% to [redacted], for one additional sitter in STR1VE-US after 18 months of age
- The ICER increased by 1.7% to [redacted], for one additional walker in STR1VE-US after 18 months of age
- The ICER increased by 6.7% to [redacted] for no additional sitters or walkers in STR1VE-US after 18 months of age
- The ICER decreased by 16.1% to [redacted] for four new sitters and four new walkers in STR1VE-US after 18 months of age:

In the scenario where milestones, overall survival and event-free survival are based on those treated at ≤3.5 months of age in START and STR1VE-US (n=17) the ICER decreased to [redacted]. The cut-off of 3.5 months of age was chosen, as this was the median age at which infants across START and STR1VE-US received onasemnogene abeparvovec.

In the scenario where milestones, overall survival and event-free survival are based on those treated in START only (n=12), the ICER decreases to [redacted].

In the scenario that E state overall survival is based on the 'pooled' Gregoretti cohort, i.e. patients with tracheostomy (n=42) or NIV (n=31), the ICER decreases to [redacted].

In the scenario where milestones are not 'offset' by a model cycle (i.e. 6 months), the ICER decreases to [redacted].

In the two proxy pre-symptomatic scenarios, the ICER falls by 69% and 62%.

In the scenario where for sitting independently, the 30 seconds threshold used for both START and STR1VE-US, the ICER increased by almost 4%.

4.11. Please present any probabilistic sensitivity analysis results and include scatter plots and cost-effectiveness acceptability curves.

A typical run of the PSA using the PAS price is shown below.

Figure 2 shows the results from 1,000 simulations comparing the incremental cost effectiveness of onasemnogene abeparvovec ('OA') over BSC.

Abbreviations: BSC: best supportive care; QALY: quality-adjusted life-year; OA: onasemnogene abeparvovec

Figure 3 shows the Cost Effectiveness Acceptability Curve from 1,000 simulations comparing onasemnogene abeparvovec with BSC.

Figure 2: Incremental cost effectiveness results – 1,000 simulations of onasemnogene abeparvovec (OA) versus BSC

Abbreviations: BSC: best supportive care; QALY: quality-adjusted life-year; OA: onasemnogene abeparvovec

Figure 3: Cost effectiveness acceptability curve –onasemnogene abeparvovec (OA) and BSC

Abbreviations: BSC: best supportive care; OA: onasemnogene abeparvovec

Table 9 shows the maximum and minimum results for the two interventions for costs, life years and QALYs.

Finally, Table 10 shows the ICER results (onasemnogene abeparvovec versus BSC) from the simulations.

Table 9 Results from 1,000 simulations of onasemnogene abeparvovec and BSC

	Max costs	Min costs	Max LYs	Min LYs	Max QALYs	Min QALYs
BSC	552,283	245,454	2.16	2.09	1.03	-0.65
OA	[redacted]	[redacted]	19.59	12.77	15.26	5.78

Abbreviations: BSC, best supportive care; LY, life-years; OA, onasemnogene abeparvovec; QALY, quality-adjusted life-years.

Table 10: ICER (£/QALY) results from 1,000 simulations of onasemnogene abeparvovec and BSC

ICER ranges	Max ICER	Min ICER	Mean Costs/Mean QALYs	Median	95% Plausible interval - low	95% Plausible interval - high

OA vs BSC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: BSC, best supportive care; ICER, incremental cost effectiveness ratio; OA, onasemnogene abeparvovec; QALY, quality-adjusted life-years.

The minimum and maximum number of QALYs produced for BSC from the 1,000 simulations were –0.65 and 1.03; the minimum and maximum total costs were £245,454 and £552,283.

The minimum and maximum number of QALYs produced for onasemnogene abeparvovec from the 1,000 simulations were 5.78 and 15.26; the minimum and maximum total costs were [redacted] and [redacted].

The minimum and maximum ICERs produced from the simulations were [redacted] and [redacted] with a 95% credible range of between [redacted] and [redacted].

The mean and median ICERs produced from the simulations were [redacted] and [redacted], respectively. This simulation mean is 5.8% higher than the deterministic result of [redacted]. Analysis of the results showed that this is due to the number of life years gained from the onasemnogene abeparvovec simulations where 78.6% of the runs produced total life years less than the onasemnogene abeparvovec deterministic value of 31.02 (undiscounted) life years (range 25.49 to 45.22). A total of 74.1% of the ICERs produced from the PSA simulations were above the deterministic ICER.

4.12. If any of the criteria on which the Patient Access Scheme depends are clinically variable (for example, choice of response measure, level of response, duration of treatment), sensitivity analyses around the individual criteria should be provided, so that the HST Evaluation Committee can determine which criteria are the most appropriate to use.

Not applicable. The confidential discount will be automatically applied to the invoice at the point of sale.

Impact of Patient Access Scheme on ICERs

4.13. For financially based schemes, please present the results of the value for money analyses showing the impact of the Patient Access Scheme on the base-case and any scenario analyses. A suggested format is shown below (see table 4). If you are submitting the Patient Access Scheme at the end of the evaluation process, you must include the scenario with the assumptions that the HST Evaluation Committee considered to be most plausible.

See Table 11 below.

Table 11: Key scenarios for onasemnogene abeparvovec versus BSC, run at list and PAS price

#		ICER (£/QALY) versus BSC	
		Without PAS	**With PAS**
	Base case	233,106	[redacted]
1	Costs and effects at 0%	136,252	[redacted]
2	Costs and effects at 5%	279,168	[redacted]
3	Costs at 0%, effects at 5%	364,065	[redacted]
4	Costs at 5%, effects at 0%	104,480	[redacted]
5	Costs and effects at 1.5%	175,843	[redacted]
6	Use of RWE costs (scenario with SMA type 1 costs doubled) presented at the nusinersen NICE ACM3	257,607	[redacted]
7	SMA type 3 costs from RWE presented at nusinersen ACM3 applied to the A state and B state patients, other health state costs remain as base case	237,166	[redacted]
8	Cost of onasemnogene abeparvovec administration 10x higher than base case	235,627	[redacted]
9	US ICER approach to the costing of ventilatory support (ERG question 2019, **B16**)	187,425	[redacted]
10	Increase of total D state and E state costs explorative scenario 1 (ERG question 2019, **B20**)	227,966	[redacted]
11	Increase of HCRU in the D state and E state costs explorative scenario 2 (ERG question 2019, **B20**)	233,184	[redacted]
12	Extreme scenario where all non-permanent ventilated patients (84% in state D, 56% in state C, 20% in state B/A) in whatever health state receive 100% of the Noyes social care/ social services costs (ERG question 2019, **B23**)	258,733	[redacted]
13	On-treatment utility using lower values than US ICER (0.05 for D state; 0.025 for C state)	241,901	[redacted]
14	On-treatment utility using higher values than US ICER (0.15 for D state; 0.075 for C state)	224,927	[redacted]
15	Using CHERISH values	202,427	[redacted]

#		ICER (£/QALY) versus BSC	
		Without PAS	**With PAS**
16	Using Lloyd vignette study	752,527	[redacted]
17	Using exploratory AveXis UK utilities elicitation study using the TTO results from the 'parent' vignettes for states B to E	[redacted]	[redacted]
18	No utility weights (cost per life year gained)	172,337	[redacted]
19	Use of AveXis external PNCR control dataset: fitted curve kept as Weibull, survival maximum equals 4 years	201,269	[redacted]
20	Use of Finkel et al. 2017a (ENDEAR sham control): fitted curve kept as Weibull, survival maximum equals 4 years	206,144	[redacted]
21	Use of De Sanctis et al. 2016 (PNCR, US and Italy study): fitted curve kept as Weibull, survival maximum equals 4 years	201,329	[redacted]
22	Patients in the C state (sits unassisted) have a life expectancy the same as the general population: applied to onasemnogene abeparvovec arm only	196,802	[redacted]
23	Use of POOLED dataset, but with only one additional sitter compared to empirical data in STR1VE-US after 18 months of age. The additional sitter sits between 24–30 months of age and therefore moves to sitting in cycle ending 36 months	244,080	[redacted]
24	Use of POOLED dataset, but with only one additional walker compared to empirical data in STR1VE-US after 18 months of age. The additional walker walks between 24–30 months of age and therefore moves to walking in cycle ending 36 months	237,397	[redacted]
25	Use of POOLED dataset but use of the empirical data only from STR1VE-US. i.e. it assumes there are no additional patients who can sit or walk unassisted in STR1VE-US after 18 months of age.	248,881	[redacted]
26	Use of POOLED dataset but with four new sitters and four new walkers in STR1VE-US after 18 months of age. Half move in cycle ending 30 months and half move in cycle ending 36 months	195,584	[redacted]
27	E state overall survival based on the 'pooled' Gregoretti cohort, i.e. patients with tracheostomy (n=42) or NIV (n=31) with proportions adjusted accordingly in medical cost calculator; curve = exponential, survival limit = 16 years	205,544	[redacted]
28	Caregiver disutility scores included	240,622	[redacted]

#		ICER (£/QALY) versus BSC	
		Without PAS	**With PAS**
29	Milestones, overall survival and event-free survival is based on those treated at ≤3.5 months of age in START and STR1VE-US (n=17)	202,593	[redacted]
30	Milestones, overall survival and event-free survival are based on those treated in START only (n=12)	198,740	[redacted]
31	Milestones are not 'offset' by a model cycle (i.e. 6 months)	228,045	[redacted]
32	Proxy pre-symptomatic scenario A: Assumes age-appropriate milestones (sitting and walking) are observed for all patients, but with conservative one cycle motor milestone offset still applied. Assumes overall survival and event-free survival is 100% in the D state for the short-term model for onasemnogene abeparvovec.	74,810	[redacted]
33	Proxy pre-symptomatic scenario B: Assumes sitting is observed in all patients, of which 50% attain age-appropriate sitting and 50% achieve delayed sitting. Assumes walking is observed for 82% of patients; of which 50% attain age-appropriate walking and 50% achieve delayed walking. The conservative one cycle motor milestone offset still applied to all milestones. Assumes overall survival and event-free survival is 100% in the D state for the short-term model for onasemnogene abeparvovec.	91,571	[redacted]
34	30 second threshold for sitting independently: Use of the POOLED dataset in which sitting independently is defined as 'sitting alone for ≥30 seconds' for both the START and STR1VE-US trials. All other base case assumptions regarding motor milestones (e.g. application of the conservative one model cycle offset and the assumption of one additional sitter and walker in STR1VE-US between 24 and 30 months of age) remain in place for this scenario. (ERG clarification questions 2020, **A3/B2**)	242,322	[redacted]

Abbreviations: BSC, best supportive care; ICER, incremental cost-effectiveness ratio; PAS, patient access scheme

5. Appendix A: Details for outcome-based schemes only

5.1. If you are submitting an outcome based scheme which is expected to result in a price increase, please provide the following information:

- the current price of the intervention
- the proposed higher price of the intervention, which will be supported by the collection of new evidence
- a suggested date for when NICE should consider the additional evidence.

Not applicable.

5.2. If you are submitting an outcome based scheme which is expected to result in a price reduction or rebate, please provide the following details:

- the current price of the intervention (the price that will be supported by the collection of new evidence)
- the planned lower price of the intervention in the event that the additional evidence does not support the current price
- a suggested date for when NICE should consider the additional evidence.

Not applicable.

5.3. Provide the full details of the new information (evidence) planned to be collected, who will collect it and who will carry the cost associated with this planned data collection. Details of the new information (evidence) may include:

- design of the new study
- patient population of the new study
- outcomes of the new study
- expected duration of data collection
- planned statistical analysis, definition of study groups and reporting (including uncertainty)

- expected results of the new study
- planned evidence synthesis/pooling of data (if applicable)
- expected results of the evidence synthesis/pooling of data (if applicable).

Not applicable.

5.4. Please specify the period between the time points when the additional evidence will be considered.

Not applicable.

5.5. Please provide the clinical effectiveness data resulting from the evidence synthesis and used in the economic modelling of the scheme at the different time points when the additional evidence is to be considered.

Not applicable.

5.6. Please provide the other data used in the economic modelling of the scheme at the different time points when the additional evidence is to be considered. These data could include cost/resource use, health-related quality of life and utilities.

Not applicable.

5.7. Please present the cost-effectiveness results as follows.

- For a scheme that is expected to result in a price increase, please summarise in separate tables:
  - the results based on current evidence and current price
  - the anticipated results based on the expected new evidence and the proposed higher price.
- For a scheme that is expected to result in a price reduction or rebate, please summarise in separate tables:

- the results based on the expected new evidence and the current price (which will be supported by the additional evidence collection)
- the results based on the current evidence and the lower price (if the new evidence is not forthcoming).

A suggested format is shown in table 3, section 4.7.

Not applicable

5.8. Please present in separate tables the incremental results for the different scenarios as described above in section 5.2 for the type of outcome-based scheme being submitted.

Not applicable.

REFERENCES

1. National Institute for Health and Care Excellence. Nusinersen for treating spinal muscular atrophy [GID-TA10281]. 3rd appraisal committee meeting public gallery slides. 6 March 2019. 2019.
2. Lloyd AJGK, Thompson, R., Vaidya, S., Teynor, M. . Estimation of the health-related quality of life benefits of treatment for spinal muscular atrophy (SMA). ISPOR 20th Annual European Congress; 2017; Glasgow, Scotland.
3. Finkel RS, Mercuri E, Darras BT, Connolly AM, Kuntz NL, Kirschner J, et al. Nusinersen versus Sham Control in Infantile-Onset Spinal Muscular Atrophy. N Engl J Med. 2017a Nov 2;377(18):1723-32.
4. De Sanctis R, Coratti G, Pasternak A, Montes J, Pane M, S. Mazzone E, et al. Developmental milestones in type I spinal muscular atrophy. 2016.

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ZOLGENSMA® (onasemnogene abeparvovec) for treating spinal muscular atrophy type 1 [ID1473]

Response to ERG clarification questions

2 July 2020

Section A: Clarification on effectiveness data

- **A1. Priority question:** On page 14 of the company submission supplementary appendix the company states their position for onasemnogene abeparvovec as: “In England, onasemnogene abeparvovec is positioned for the treatment of children with SMA type 1 and pre-symptomatic infants with a genotype predictive of SMA type 1 (i.e. those with up to three copies of the *SMN2* gene).” Please detail how the population included in the license indication differs from the population included in the company submission. Please include details for both the incident and the prevalent populations and for SMA type 2 and 3.

The licensed indication for onasemnogene abeparvovec, as recommended by the European Medicines Agency (EMA) Committee for Medicinal Products for Human Use (CHMP) on 26 March 2020 and as per conditional marketing authorisation granted on 18 May 2020, is for the treatment of:

1. patients with 5q spinal muscular atrophy (SMA) with a bi-allelic mutation in the survival motor neuron (SMN) 1 gene and a clinical diagnosis of SMA type 1, or
2. patients with 5q SMA with a bi-allelic mutation in the *SMN1* gene and up to three copies of the *SMN2* gene

The population included in the company submission corresponds to the licensed indication as follows: In England, onasemnogene abeparvovec is positioned for the treatment of…:

- …children with SMA type 1
    - Aligned to bullet point ‘1.’ of the licensed indication
- …pre-symptomatic infants with a genotype predictive of SMA type 1 (i.e. those with up to three copies of the *SMN2* gene)
    - Aligned to bullet point ‘2.’ of the licensed indication

The company recognises that the wording of the licensed indication ‘patients with 5q SMA with a bi-allelic mutation in the *SMN1* gene and up to three copies of the *SMN2* gene’ for onasemnogene abeparvovec could be construed as including a broader population (for example, inclusive of symptomatic SMA type 2 and SMA type 3 populations) than that described in the company submission. However, it is essential to view the licensed indication in the context of the Summary of Product Characteristics (SPC) and European Public Assessment Report (EPAR). The recommendations in the SPC clearly indicate that the clinical evidence covers use in patients with a clinical diagnosis of SMA type 1 or a genotype predictive of SMA type 1 and identify the patient population who should be considered for treatment with onasemnogene abeparvovec. The SPC and EPAR provide clear guidance to treating clinicians on the evidence to support use including an assessment of the strength of that evidence. All data included in the SPC derives from the use of onasemnogene abeparvovec in SMA type 1 or in infants with pre-symptomatic SMA with up to three copies of *SMN2.* Therefore, the company’s submission and associated proposed positioning, reflects all the available evidence at this time.

SPC: Special warnings and precautions for use

As per the SPC, there are precautions associated with the use of onasemnogene abeparvovec that will need to be considered during decisions of patient eligibility.

There is limited experience in patients 2 years of age and older or with body weight above 13.5 kg, and therefore the safety and efficacy of onasemnogene abeparvovec in these patients have not been established. Although recommended dosing is provided for a weight range of 2.6–21.0 kg it is expected that the great majority of patients will weigh less than the upper end of this range.

The SPC also notes that anti-AAV9 antibody formation can take place after natural exposure. Patients should be tested for the presence of AAV9 antibodies prior to infusion with onasemnogene abeparvovec. It is not yet known whether or under what conditions onasemnogene abeparvovec can be safely and effectively administered in the presence of anti-AAV9 antibodies above 1:50. The frequency at which anti-AAV9 antibody titres above 1:50 appear in SMA populations not included in the onasemnogene abeparvovec existing clinical trial programme and evidence base are unknown.

It is the company's expectation that the above-mentioned precautions, and others, noted in the evidence package and SPC, will therefore inform clinical practice and decisions around patient eligibility. Please see the company's response to question **C1**.

The company emphasises that the population included in the company submission ('children with SMA type 1 and pre-symptomatic infants with a genotype predictive of SMA type 1' [interpreted as those with up to three copies of the SMN2 gene]) therefore corresponds to the available evidence base for onasemnogene abeparvovec. This positioning aligns with the final scope of this HST appraisal (i.e. children with SMA type 1). All clinical trial data available on which an HTA assessment can be based upon are for SMA type 1 patients (START, STR1VE-US, STR1VE-EU, LT-001 and LT-002) or for infants with pre-symptomatic SMA with up to three copies of the SMN2 gene (SPR1NT). The other populations (for example, symptomatic SMA type 2 and SMA type 3) are not detailed in the company's submission, due to a lack of clinical trial evidence.

- **A2. Priority question:** For the pooled analysis:
    - **a)** Please provide details of the methods used for pooling the studies.

The POOLED dataset (START [Cohort 2] and STR1VE-US) is calculated by summing up the number of patients attaining a motor milestone (sitting independently and/or walking independently) by each model cycle (6 monthly cycles up to 36 months of age [cycle 6]) from the START and STR1VE-US trials. For example, in START two patients sat independently by 12 months of age and in STR1VE-US six patients sat independently by 12 months of age. Therefore, in the POOLED dataset, it is calculated that eight patients sat independently by 12 months of age. The full population of STR1VE-US (N=22) and START Cohort 2 (N=12) were used. This approach is justified due to the similarity of the inclusion criteria across the two trials. The final proportions of patients in the POOLED dataset either sitting or walking per model cycle are adjusted by:

- Application of the conservative model 'offset' approach, in which the milestones attained in POOLED are 'offset' by a cycle when incorporated into the model: patients observed achieving a motor milestone during a model cycle are only transitioned in the next model cycle. For example, the eight patients who sat by 12 months of age only transition to the sitting health state (C state) in the next full model cycle, i.e. between 12 to 18 months of age. See Section 8.2.1.1 of the company submission (supplementary appendix, May 2020) for further details.

- The proportions attaining milestones described in the 'AVXS-milestones' worksheet in the model are calculated based on those patients who are alive and event-free. In other words, the modelled patients who have died or transitioned to the E state (permanent assisted ventilation) are removed from the denominator when calculating the proportions of patients who go on to sit and/or walk from the D state. This method is required as the health states are mutually exclusive.

A technical consideration when pooling the data from the START and STR1VE-US trials for the revised economic model is the difference in follow-up periods of each respective trial. START followed patients to 24 months post-dose (approximately 30 months of age), whereas STR1VE-US captured outcome data up to 18 months of age. Using an 18-month age timepoint would underestimate the likely maximum milestone attainment and potential benefit from treatment with onasemnogene abeparvovec (see Section 8.2.1.1 of the company submission, May 2020 for further details). Therefore, two assumptions were adopted when pooling the data:

- The base case assumption includes one additional independent sitter and one additional independent walker in STR1VE-US, over and above empirical data. These additional milestones are assumed to occur between 24 months and 30 months of age. Due to the milestone 'offset' approach, which is described above, these milestones are modelled between 30 to 36 months of age (model cycle 6).

- Except for the two additional milestones described above, for all other STR1VE-US patients contributing to the POOLED dataset the last observation carried forward (LOCF) methodology was used, between 18 months and 30 months of age, to bridge the gap between the follow up period available for STR1VE-US versus START. In other words, no further milestones were assumed to be gained so that the proportions observed sitting and walking at 18 months of age in STR1VE-US are assumed to remain the same up to 30 months of age.

The reasoning for these assumptions is described in Section 8.2.1.1 of the company submission (May 2020, supplementary appendix).

For overall survival and event-free survival, any event(s) (numerator) were converted into proportions using the POOLED sample size of 34 patients (START, Cohort 2: 12 patients; STR1VE-US: 22 patients) as the denominator. As STR1VE-US patients only provide survival data up to 18 months of age, they are censored from survival curves in the short-term model from 18 months to 36 months of age. Of the pooled patients from START and STR1VE-US (N=34), one patient died, and one patient met the permanent assisted ventilation event endpoint.

b) Please complete Table 1 to report results for all clinical outcomes for the pooled analysis of data from START and STR1VE-US, including those outcomes informing the economic evaluation. Please add rows for any additional outcomes as appropriate.

A completed Table 1 is shown below, with the following notes:

- Change from baseline to maximum post-baseline value in Bayley Scales raw scores is not provided for START or the POOLED analysis as the Bayley Scales were not a mandatory assessment in START and were only administered if a child reached or exceeded a score of 60 out of 64 on the CHOP-INTEND. Thus, Bayley Scales data for START are incomplete as they are only available for four patients. A baseline assessment for all patients was not collected as a result of the study protocol terms described.
- The results presented in Table 1 are the empirical data, thus they do not include the base case model assumption that there is one additional independent sitter and one additional independent walker in STR1VE-US, over and above the numbers observed during the trial period.
- Please refer to Table 49 in the company submission (May 2020, supplementary appendix), for further details of pooled motor milestones achieved by model cycle.

Table 1: Clinical outcomes for the START, STR1VE-US, and POOLED analysis

Outcome	Results		
	START (Cohort 2) **During trial period up to 24 months post-dose** **N=12**	**STR1VE-US** **During trial period up to 18 months of age** **N=22**	**POOLED (START & STR1VE-US)** **N=34**
Survived without permanent ventilation, n (%)	12/12 (100%)	20/22 (90.9%)[†]	32/34 (94.1%)
Proportion of patients who achieved CHOP-INTEND scores[‡], n (%)			
≥40	11/12 (91.7%)	21/22 (95.5%)	32/34 (94.1%)
≥50	11/12 (91.7%)	14/22 (63.6%)	25/34 (73.5%)
≥60	4/12 (33.3%)	5/22 (22.7%)	9/34 (26.5%)
Change from baseline to maximum post-baseline value in Bayley Scales raw scores, mean (SD)			
Gross motor subset	N/A	16.0 (9.19)	N/A
Fine motor subset	N/A	23.9 (6.60)	N/A
Developed significant motor milestones, n (%)			
Sits alone ≥5 seconds[§]	11/12 (91.7%)	14/22 (63.6%)[¶]	25/34 (73.5%)

Outcome	Results		
	START (Cohort 2) During trial period up to 24 months post-dose N=12	STR1VE-US During trial period up to 18 months of age N=22	POOLED (START & STR1VE-US) N=34
Sits alone ≥10 seconds††	10/12 (83.3%)	14/22 (63.6%)	24/34 (70.6%)
Sits alone ≥30 seconds‡‡	9/12 (75%)	14/22 (63.6%)	23/34 (67.6%)
Stands with assistance§§	2/12 (16.7%)	1/22 (4.5%)	3/34 (8.8%)
Stands alone¶¶	2/12 (16.7%)	1/22 (4.5%)	3/34 (8.8%)
Walks with assistance†††	2/12 (16.7%)	1/22 (4.5%)	3/34 (8.8%)
Walks alone‡‡‡	2/12 (16.7%)	1/22 (4.5%)	3/34 (8.8%)
Independent of ventilatory support, n (%)	6/12 (50%)	15/22 (68.2%)	21/34 (61.8%)
Maintained the ability to thrive, n (%)	5/7 (71.4%)	9/22 (40.9%)	14/34 (41.2%)
Proportion of patients in the SAS receiving non-oral feeding support, n (%)	6/12 (50%)	3/22 (13.6%)	9/34 (26.5%)

Abbreviations: CHOP-INTEND, Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders; CSR, clinical study report; SAS, safety analysis set; SD, standard deviation; WHO MGRS, World Health Organization Multicentre Growth Reference Trial.

† Reported at 14 months of age. Timepoint reported as it is the co-primary endpoint for STR1VE-US.

‡ Based on maximum post-baseline CHOP-INTEND score achieved.

§ Bayley Scales gross motor subtest item #22: Child sits alone without support for at least 5 seconds used for STR1VE-US (not centrally reviewed/video-confirmed). "Sits alone <10 seconds" for START (centrally reviewed/video-confirmed). All patients in the 'sitting < 10 seconds' category were able to sit for at least 5 seconds.

¶ [redacted]

†† WHO MGRS definition: Child sits up straight with head erect for at least 10 seconds. Child does not use arms or hands to balance body or support position (centrally reviewed/video-confirmed).

‡‡ Bayley Scales gross motor subtest item #26: Child sits alone without support for at least 30 seconds (centrally reviewed/video-confirmed).

§§ Bayley Scales gross motor subtest item #33: Child supports his or her own weight for at least 2 seconds, using your hands for balance only (centrally reviewed/video-confirmed).

¶¶ Bayley Scales gross motor subtest item #40: Child stands alone for at least 3 seconds after you release his or her hands (centrally reviewed/video-confirmed).

††† Bayley Scales gross motor subtest item #37: Child walks by making coordinated, alternated stepping movements (centrally reviewed/video-confirmed).

‡‡‡ Bayley Scales gross motor subtest item #43: Child takes at least 5 steps independently, displaying coordination and balance used for STR1VE-US (centrally reviewed/video-confirmed). Gross Motor Checklist: ‘takes independent steps’ or the Motor Milestone Development Survey: ‘walks independently’ used for START (centrally reviewed/video-confirmed).

c) Please provide a table of results for the post hoc exploratory analysis of effect of age at dosing on motor milestone development, based on the pooled data for START and STR1VE-US (akin to Table 24 of the company submission supplementary appendix) and based on the cut off of age of 3.5 months referred to as a scenario analysis in the economic section (Table 48; Exploratory scenarios of milestone achievements after treatment with onasemnogene abeparvovec). Please provide results for both age at treatment of <3.5 months and at ≥3.5 months based on baseline CHOP-INTEND score (high versus low score).

The exploratory analyses referred to by the ERG in the question as 'akin to Table 24', use a '3 month' age threshold and baseline CHOP INTEND score as stratification criterion; these are historical analyses conducted when only START data were available. The '3 month' threshold was selected as it was the median age at dosing in START (Cohort 2). The purpose of this stratified analysis was to explore the benefits of treating earlier versus later at a time when disease-modifying treatments for SMA has only recently been introduced. The selection of the stratifications was based upon descriptive statistics gathered from the START clinical trial and was not based upon thresholds relevant to outcomes in SMA.

The '3 month' age threshold does not correlate with any specific aspect of the natural history of SMA at which achievement (or otherwise) of a motor milestone or CHOP-INTEND score is prognostic of a particular outcome. The variability of timing of motor milestone development in healthy children is broad and, broader still, in children with SMA. As such, a single time-point assessment alone cannot be used to predict or refute a future motor milestone achievement.

The CHOP-INTEND assessment was designed as a tool to measure changes in motor function in SMA type 1 over time in the context of a clinical trial (1, 2). The use of CHOP-INTEND has allowed a better characterisation of motor function measurement in infants with severe neuromuscular disease. The CHOP-INTEND score has gained adoption in clinical practice, however, scores are only used to make descriptive and comparative assessments and are not solely relied upon to provide an overall assessment of SMA disease status. There is no clinically-accepted definition of what constitutes a 'high' versus a 'low' CHOP-INTEND score at baseline, hence, is it also not used in isolation for prognostic purposes.

As per the terms outlined in the SPC for onasemnogene abeparvovec (3), it is expected that treatment decision-making will be informed by a holistic assessment of each patient, including a consideration of the advancement of disease at the time of treatment across motor, respiratory and swallowing capacities (see question response **C1**). Furthermore, due to the size of the START and STR1VE-US trials, any post hoc exploratory subgroup analysis that splits the cohort into multiple categories (in this such request, four different categories) further limits the sample size in each group, which it is difficult to draw robust conclusions from.

It is for these reasons that post hoc exploratory analyses are presented stratified by age at dose only, and not further stratified using 'high' and 'low' CHOP-INTEND scores at baseline (Table 2). These post hoc exploratory analyses, and as per the economic exploratory scenario analysis submitted in the company submission (May 2020, supplementary appendix), use an age threshold of '3.5 months' defined from descriptive statistics of the

POOLED dataset: The median age at dose for the 34 patients treated in START (Cohort 2) and STR1VE-US is 3.5 months. These analyses are not intended to imply that age would reliably predict motor neuron preservation or final outcomes, or that it should be used as the sole basis for clinical decision-making. However, the results of this analysis appear to confirm the hypothesis that earlier treatment is associated with better outcomes. Such exploratory analyses are somewhat superseded by ongoing clinical trials exploring treatment in infants with pre-symptomatic SMA, which are demonstrating exceptional interim results. These findings have led to SMA being added to newborn screening panels in countries around the world, with similar efforts now underway in the UK.

The results presented in Table 2 are observed data, thus they do not include the base case model assumption that there is one additional independent sitter and one additional independent walker in STR1VE-US, over and above the numbers observed during the trial period.

Table 2: Motor milestones by age at dosing in Cohort 2 in START, STR1VE-US, and the POOLED dataset

	START, Cohort 2 (N=12)		STR1VE-US (N=22)		POOLED (N=34)	
	Dosing at ≤3.5 months of age (n=6)	**Dosing at >3.5 months of age (n=6)**	**Dosing at ≤3.5 months of age (n=11)**	**Dosing at >3.5 months of age (n=11)**	**Dosing at ≤3.5 months of age (n=17)**	**Dosing at >3.5 months of age (n=17)**
Age at dosing, months, mean	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Motor milestone achievements						
Sits unassisted for ≥5 seconds†, n	[redacted]	[redacted]	[redacted]	[redacted]	14/17 (82.4%)	[redacted]
Median age, months (range)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Sits unassisted for ≥30 seconds‡, n	[redacted]	[redacted]	[redacted]	[redacted]	14/17 (82.4%)	[redacted]
Median age, months (range)§	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Walking unassisted¶	[redacted]	[redacted]	[redacted]	[redacted]	3/17 (17.7%)	[redacted]
Median age, months (range)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

† Bayley Scales gross motor subtest item #22: "Child sits alone without support for at least 5 seconds" used for STR1VE-US (not centrally reviewed/confirmed). [redacted] "Sits alone <10 seconds" for START (centrally reviewed/video-confirmed). All patients in the 'sitting < 10 seconds' category were able to sit for at least 5 seconds

‡ Bayley Scales gross motor subtest item #26: "Child sits alone without support for at least 30 seconds" used for both STR1VE-US and START (centrally reviewed/confirmed for both).

§ [redacted]

¶ Bayley Scales gross motor subtest item #43: "Child takes at least 5 steps independently, displaying coordination and balance" used for STR1VE-US. Gross Motor Checklist: "takes independent steps" and the Motor Milestone Development Survey 'walks independently' used for START (centrally reviewed/video-confirmed for both).

d) Please provide definitions for each outcome and justify any differences in data included from the two studies.

The clinical outcomes as defined in START and STR1VE-US are summarised in Table 3. Differences in definitions are highlighted in bold.

As noted above, a technical consideration when pooling the data for the revised economic model is the difference in follow-up periods of each respective trial: START followed patients to 24 months post-dose (approximately 30 months of age), whereas STR1VE-US captured outcome data up to 18 months of age. As summarised in Section 8.2.1.1 of the company submission (May 2020), there is evidence to support that using an 18-month age timepoint as the basis for estimating maximum milestone attainment would result in an underestimate of the potential benefit from onasemnogene abeparvovec. Therefore, to account for the differences in follow-up period between START and STR1VE-US, two assumptions were adopted when pooling the data for inclusion into the economic model:

- The model base case assumption presented includes one additional independent sitter and one additional independent walker in STR1VE-US, over and above empirical data. These additional milestones are assumed to occur between 24 months and 30 months of age, which equates to between 30 to 36 months of age (model cycle 6) due to the milestone 'offset' approach, which is described above.
- Except for the two additional milestones described above, for all other STR1VE-US patients contributing to the POOLED dataset the last observation carried forward (LOCF) methodology was used, between 18 months and 30 months of age, to bridge the gap between the follow up period available for STR1VE-US versus START. In other words, no further milestones were assumed to be gained so that the proportions observed sitting and walking at 18 months of age in STR1VE-US are assumed to remain the same up to 30 months of age.

As requested, Table 3 highlights the differences in outcome definitions between START and STR1VE-US. The definitions of clinical outcomes used in START and STR1VE-US are very similar, and in most cases equivalent, and therefore consistent with the use of the pooling methodology described in response to question **A2a**.

Table 3: Definitions of clinical outcomes in START and STR1VE-US

Outcome	Definition	
	START (Cohort 2)	**STR1VE-US**
Survived without permanent ventilation	Patients alive and free of permanent ventilation (defined as tracheostomy or the requirement of ≥16 hours of respiratory assistance per day via non-invasive ventilatory support for ≥14 consecutive days in the absence of an acute reversible illness, excluding perioperative ventilation) **at 24 months post-dose (approximately 30 months of age)**	Patients alive and free of permanent ventilation (defined as tracheostomy or the requirement of ≥16 hours of respiratory assistance per day via non-invasive ventilatory support for ≥14 consecutive days in the absence of an acute reversible illness, excluding perioperative ventilation) **at 18 months of age**[†]
Proportion of patients who achieved CHOP-INTEND scores of:[‡] • ≥40 • ≥50 • ≥60	Proportion of patients who achieved scores of ≥40, ≥50, and ≥60 in the CHOP-INTEND motor function scale, administered by a qualified clinical evaluator **by 24 months post-dose (approximately 30 months of age)**[§]	Proportion of patients who achieved scores of ≥40, ≥50, and ≥60 in the CHOP-INTEND motor function scale, administered by a qualified clinical evaluator **by 18 months of age**[¶]
Change from baseline in Bayley Scales score: • Gross motor subtest • Fine motor subtest	Change from baseline score in the Bayley Scales of Infant and Toddler Development (Version 3), administered by a physical therapist. **Bayley Scales were not a mandatory assessment in START[††] and are not available for all patients**	Change from baseline score in the Bayley Scales of Infant and Toddler Development (Version 3), administered by a physical therapist. **The gross and fine motor subtests of the motor domain were administered at screening and at each monthly visit, up to 18 months of age**
Developed significant motor milestones[‡‡]	Attainment of the following centrally reviewed/video-confirmed motor milestones **by 24 months post-dose (approximately 30 months of age):**	Attainment of the following centrally reviewed/video-confirmed motor milestones, unless otherwise stated, **by 18 months of age:**

Outcome	Definition	
	START (Cohort 2)	**STR1VE-US**
Sits alone ≥5 seconds†	Attainment of Bayley Scales gross motor subtest item #22: Child sits alone without support for at least 5 seconds	Attainment of Bayley Scales gross motor subtest item #22: Child sits alone without support for at least 5 seconds **(*NB:* not centrally reviewed/video-confirmed – the source of this information is the Bayley individual item scores, as assessed during study visits)**
Sits alone ≥10 seconds‡	Child sits up straight with head erect for at least 10 seconds and does not use arms or hands to balance body or support position, as defined by WHO MGRS	Child sits up straight with head erect for at least 10 seconds and does not use arms or hands to balance body or support position, as defined by WHO MGRS
Sits alone ≥30 seconds§	Attainment of Bayley Scales gross motor subtest item #26: Child sits alone without support for at least 30 seconds	Attainment of Bayley Scales gross motor subtest item #26: Child sits alone without support for at least 30 seconds
Stands with assistance¶	Attainment of Bayley Scales gross motor subtest item #33: Child supports his or her own weight for at least 2 seconds, using your hands for balance only	Attainment of Bayley Scales gross motor subtest item #33: Child supports his or her own weight for at least 2 seconds, using your hands for balance only
Stands alone††	Attainment of Bayley Scales gross motor subtest item #40: Child stands alone for at least 3 seconds after you release his or her hands	Attainment of Bayley Scales gross motor subtest item #40: Child stands alone for at least 3 seconds after you release his or her hands
Walks with assistance‡‡	Attainment of Bayley Scales gross motor subtest item #37: Child walks by making coordinated, alternated stepping movements	Attainment of Bayley Scales gross motor subtest item #37: Child walks by making coordinated, alternated stepping movements

Outcome	Definition	
	START (Cohort 2)	**STR1VE-US**
Walks alone[§§]	**Attainment of Gross Motor Checklist: 'takes independent steps' or the Motor Milestone Development Survey: 'walks independently'**	**Attainment of Bayley Scales gross motor subtest item #43: Child takes at least 5 steps independently, displaying coordination and balance**
Independent of ventilatory support	Independent of ventilatory support **at 24 months post-dose (approximately 30 months of age)**	Independent of ventilatory support **at 18 months of age**
Maintained the ability to thrive	Patient met all of the following criteria **at 24 months post-dose (approximately 30 months of age)**:[§§] 1. The ability to tolerate thin liquids as demonstrated through a formal swallowing test 2. Not requiring nutrition through mechanical support such as a feeding tube 3. Maintained weight >3rd percentile based on WHO Child Growth Standards for age and gender	Patient met all of the following criteria **at 18 months of age**: 1. The ability to tolerate thin liquids as demonstrated through a formal swallowing test 2. Not requiring nutrition through mechanical support such as a feeding tube 3. Maintained weight >3rd percentile based on WHO Child Growth Standards for age and gender
Proportion of patients in the SAS receiving non-oral feeding support	The proportion of patients who used non-oral feeding at any time from baseline to **24 months post-dose (approximately 30 months of age)**	The proportion of patients who used non-oral feeding at any time from baseline to **18 months of age**

Abbreviations: CHOP-INTEND, Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders; SAS, safety analysis set; WHO, World Health Organization; MGRS, Multicentre Growth Reference Trial.

† It should be noted that the co-primary endpoint for STR1VE-US survival, was defined as avoidance of either (a) death or (b) permanent ventilation, at 14 months of age.

‡ Based on maximum post-Baseline CHOP-INTEND score achieved.

§ If a patient achieved 2 consecutive CHOP-INTEND scores of ≥62, a teleconference was conducted between the principal investigator, the physical therapist, and the sponsor to review the patient status and determine whether or not continued CHOP-INTEND assessments were necessary. If it was decided that no further assessments were necessary, the physical therapist ceased completion of the CHOP-INTEND assessment at subsequent visits; otherwise, CHOP-INTEND assessments continued monthly during Year 1 and quarterly during Year 2.

¶Patients who achieved three consecutive CHOP-INTEND scores ≥58 did not undergo any additional CHOP-INTEND examinations.

†† The Bayley gross and fine motor subtests were only to be administered if a patient reached or exceeded a score of 60 out of 64 on the CHOP-INTEND. If so, Bayley subtests were conducted monthly through the time point that the patient reached 15 months of age or 12 months post-dose, whichever was later, and then every 3 months except for subjects still being seen monthly for CHOP-INTEND assessments, up to 24 months post-dose (approximately 30 months of age).
‡‡ Physical therapy assessments and physical examinations conducted at each study visit will were video recorded in an effort to produce compelling, demonstrable, documented evidence of efficacy, as determined by changes in functional abilities. Videos were provided to an independent, centralized reviewer for unbiased assessment of developmental milestone achievement. Additionally, the Parent(s)/legal guardian(s) were able to submit additional videos demonstrating achievement of developmental milestones at any time during the study. These videos were handled in the same manner in which the study-derived videos are handled.
§§ Only 7 patients were able to be assessed for the maintenance of the ability to thrive as only 7 patients in Cohort 2 did not require non-oral nutrition at baseline.

e) Please provide a table to compare the baseline characteristics of the studies in the pooled analysis ensuring that all characteristics are reported for both studies, for example proportion of children swallowing thin liquids at baseline is not reported for STR1VE-US but is for START.

Please see Table 4.

Table 4: Baseline characteristics of START, STR1VE-US, and the POOLED dataset

Characteristics	START Cohort 2 (N=12)	STR1VE-US (N=22)	POOLED (N=34)
SMN2 copy number x 2, n	12/12 (100%)	22/22 (100%)	34/34 (100%)
Gestational age at birth, weeks			
n	10	22	32
Mean (SD)	38.5 (1.43)	39.045 (0.9501)	38.9 (1.13)
Mean age at diagnosis, days (range)	67.8 (1, 137)	79.2 (1, 163)	75.1 (1, 163)
Mean age at symptom onset, months (SD)	2.3 (1.47)	1.9 (1.24)	2.0 (1.31)
Age at treatment, months			
Mean (SD)	3.4 (2.06)	3.73 (1.6096)	3.64 (1.76)
Min, Max	0.93, 7.93	0.50, 5.90	0.50, 7.93
Sex, n (%)			
Female, %	7/12 (58.3%)	12/22 (54.5%)	19/34 (55.9%)
Male, %	5/12 (41.7%)	10/12 (45.5%)	15/34 (44.1%)
Race, n (%)			
White	11/12 (91.7%)	11/22 (50%)	22/34 (64.7%)
Other	1/12 (8.3%)	11/22 (50%)	12/34 (35.3%)
Ethnicity, n (%)			
Not Hispanic or Latino	10/12 (83.3%)	18/22 (81.8%)	28/34 (82.4%)
Hispanic or Latino	2/12 (16.7%)	4/22 (18.2%)	6/34 (17.6%)
Weight, mean (range), kg	5.69 (5.45, 8.4)	5.83 (3.9, 7.5)	5.78 (3.6, 8.4)
Mean CHOP-INTEND score (range)	28.2 (12, 50)	32.0 (18, 52)	30.6 (12, 52)
Swallowing thin liquid, n (%)			
Yes	4/12 (33.3%)	22/22 (100%)	26/34 (76.5%)
No	8/12 (66.7%)	0/22	8/34 (23.5%)

Characteristics	START Cohort 2 (N=12)	STR1VE-US (N=22)	POOLED (N=34)
Non-oral feeding support, n (%)			
Yes	5/12 (41.7%)	0/22	5/34 (14.7%)
No	7/12 (58.3%)	22/22 (100%)	29/34 (85.3%)
Ventilatory support (invasive/non-invasive), n (%)			
Yes	1/12 (8.3%)†	0/22	1/34 (2.9%)†
No	11/12 (91.7%)	22/22 (100%)	33/34 (97.1%)
Familial history of SMA including affected siblings or parent carriers, n (%)			
Yes	3/12 (25%)	7/22 (31.8%)	10/34 (29.4%)
No	8/12 (66.7%)	12/22 (54.5%)	20/34 (58.8%)
Unknown	1/12 (8.3%)	3/22 (13.6%)	4/34 (11.8%)
Total number of days of prednisolone administration, mean (SD)	73.8 (33.04)	73.7 (39.54)	73.7 (36.86)

Abbreviations: CHOP-INTEND, Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders; SD, standard deviation; SMA, spinal muscular atrophy; SMN, survival motor neuron.
Note: For age at diagnosis, patients who were diagnosed prior to birth have been assigned an age at diagnosis of 1 day.
† Does not include one additional patient in Cohort 2 who was receiving BiPAP at baseline but for whom data was mis-entered at the clinical site

- **A3. Priority question:** The ERG's clinical experts have fed back that unassisted sitting for 30 seconds is more clinically meaningful than unassisted sitting for 5 seconds. Please provide a revised pooled analysis for unassisted sitting for 30 seconds using the appropriate data from START and STR1VE-US: to our understanding, the supplied pooled analysis combines data for unassisted sitting for 5 seconds (START) with unassisted sitting for 30 seconds (STR1VE-US).

A threshold of 'independent sitting' when populating the economic model was originally defined as sitting alone for ≥5 seconds when only START data were available, for the following reasons:

- Infants with SMA type 1 managed with BSC never attain the ability to sit, therefore, selection of the ≥5 seconds threshold for sitting unassisted reflects a state never seen in the natural history of the disease and the earliest motor milestone that could be observed in clinical studies to indicate a treatment effect.
- The approach used in the base case to incorporate motor milestone attainment is already conservative as the motor milestones observed in the trials are 'offset' by a cycle when incorporated into the model. This approach is conservative because milestone attainment is being modelled as occurring at a later age compared to the observed data from the trials.
- The definition of independent sitting in clinical trials of other SMA active therapies lack any reference to a time threshold (e.g. HINE-2).
- The outcome of 'sits alone for ≥5 seconds' in START was centrally reviewed/video-confirmed

When pooling START data with STR1VE-US data, i.e. the POOLED dataset, a threshold of 'independent sitting' for patients treated in STR1VE-US was set as sitting alone for ≥30 seconds, for the following reasons:

- The outcome of 'sits alone for ≥30 seconds' in STR1VE-US was centrally reviewed/video-confirmed.
- The outcome of 'sits alone for ≥5 seconds' in STR1VE-US was not centrally reviewed/video-confirmed – the source of this information is the Bayley Scales individual item scores, as assessed during clinicians' assessments conducted at study visits only
- A co-primary efficacy endpoint in STR1VE-US was the proportion of patients who achieved functional independent sitting for at least 30 seconds at the 18 months of age study visit

Thus, the ERG's understanding is correct: The POOLED analysis used in the economic model provided in the company submission (May 2020) combines data whereby the proportion of patients who attain independent sitting is calculated using the definitions of:

- Sits alone for ≥5 seconds (item #22) in START– achieved by 11/12 patients

- Sits alone for ≥30 seconds (item #26) in STR1VE-US – achieved by 14/22 patients

Thus, when pooled, independent sitting is achieved by 25/34 patients. As described in the **A2** response, the model base case assumption includes one additional independent sitter and one additional independent walker in STR1VE-US, over and above empirical data, due to the different follow up periods of START and STR1VE-US. Therefore, the number of patients achieving independent sitting is 26/34 patients in the model base case. Please see Table 5 for details.

As previously described by the company, when using the ≥30 seconds definition as the clinical outcome for independent sitting in START, two patients ([redacted] and [redacted]) would no longer contribute to the modelled cohort who reside in the C state (sits unassisted) and hence remain in the D state (non-sitting). This is considered by the company to be an overly pessimistic scenario as:

- Patient [redacted] subsequently achieved [redacted]
- Patient [redacted] during START achieved the milestone of 'sits unassisted for ≥10 seconds' in accordance with the WHO Multicentre Growth Reference Study criterion: '*Child sits up straight with head erect for at least 10 seconds. Child does not use arms or hands to balance body or support position'*. In addition, patient [redacted] has subsequently achieved [redacted]

With this information, it is considered that excluding these two patients ([redacted]) from contributing to the cohort who achieves independent sitting in the model and thus transitions to the C state (sits unassisted) – which is the case in the scenario requested by the ERG – is overly pessimistic and therefore an inappropriate representation of the milestones attained by patients treated with onasemnogene abeparvovec. Furthermore, the approach used in the base case to incorporate motor milestone attainment is already conservative as the motor milestones observed in the trials are 'offset' by a cycle when incorporated into the model.

The company has provided a scenario analyses for the pooled data whereby the proportion of patients who attain independent sitting is calculated using the:

- Sits alone for ≥30 seconds (item #26) in START– achieved by 9/12 patients
- Sits alone for ≥30 seconds (item #26) in STR1VE-US – achieved by 14/22 patients

Thus, when data are pooled, independent sitting is achieved by 23/34 patients in this scenario. After application of the model base case assumption that includes one additional independent sitter and one additional independent walker in STR1VE-US, over and above

empirical data, independent sitting is achieved by 24/34 patients in this scenario. Please see Table 5 for details. This scenario analysis provided in the response to question **B2.**

Table 5: Milestone outcomes in START, STR1VE-US and POOLED: Empirical versus model base case assumption

	Empirical††			Base case assumption†† Inclusive of the base case assumption: one additional sitter and one additional walker in STR1VE-US		
	START, N=12 By 30 months of age	STR1VE-US, N=22 By 18 months of age	POOLED, N=34‡‡ By 30 months of age	START, N=12 By 30 months of age	STR1VE-US, N=22 By 30 months of age	POOLED, N=34‡‡ By 30 months of age
Non-sitters, n (%)†	1 (8.3%)	8 (36.4%)	9 (26.5%)	1 (8.3%)	7 (31.8%)	8 (23.5%)
Sits alone, n (%) base case definition‡	11 (91.7%)	14 (63.6%)§§	25 (73.5%)§§	11 (91.7%)	15 (68.2%)§§	26 (76.5%)§§
Sits alone, n (%) scenario definition§	9 (75%)	14 (63.6%)§§	23 (67.6%)§§	9 (75%)	15 (68.2%)§§	24 (70.6%)§§
Walks alone§	2 (16.7%)	1 (4.5%)	3 (8.8%)	2 (16.7%)	2 (9.1%)	4 (11.8%)

† Includes one patient who died aged 7.8 months and one patient who met the permanent-assisted ventilation event endpoint aged 11 months in STR1VE-US.
‡ Sits alone calculated using the ≥30 seconds (item #26) outcome in STR1VE-US and the ≥5 seconds (item #22) outcome in START.
§ Sits alone calculated using the ≥30 seconds (item #26) outcome in STR1VE-US and START
¶ Bayley Scales gross motor subtest item #43: Child takes at least 5 steps independently, displaying coordination and balance used for STR1VE-US. Gross Motor Checklist: 'takes independent steps' or the Motor Milestone Development Survey: 'walks independently' used for START.
†† Numbers and percentages across the rows are greater than 100%, respectively, since patients can attain multiple milestones. For example, the patients who can walk alone can also sit alone
‡‡ For STR1VE-US patients contributing to the POOLED dataset last observation carried forward (LOCF) methodology is used, between 18 months and 30 months of age, to bridge the gap between the follow up period available for STR1VE-US versus START. Except for the two additional milestones described as part of the base case assumptions, no further milestones were gained so that the proportions observed sitting and walking at 18 months of age in STR1VE-US are assumed to remain the same up to 30 months of age in the POOLED analysis.
§§ For one patient in STR1VE-US the milestone of sits unassisted ≥30 seconds was not confirmed at the end of study 18 month visit but was observed at the 16-month and 17-month visit. This patient did sit unassisted for ≥5 seconds at the 18-month visit (as recorded in the Bayley Scale assessment, gross motor item #22).

- **A4. Priority question:** Please provide results for clinical outcomes for STR1VE-US (equivalent table to Table 20 in the company submission supplementary appendix).

Please see Table 6.

Table 6: STR1VE-US efficacy results

Outcome	STR1VE-US N=22
Survived without permanent ventilation at 14 months of age, n (%)	20/22 95% CI: 0.39, 0.84 p<0.0001
Change from baseline in CHOP-INTEND score at 18 months of age, mean (SD)	19.3 (9.13)
Proportion of patients who achieved CHOP-INTEND scores n (%)	
≥40	21/22 (95.5%)
≥50	14/22 (63.6%)
≥60	5/22 (22.7%)
Change from baseline to maximum post-baseline value in Bayley Scales raw score, mean (SD)	
Gross motor subset	16.0 (9.19)
Fine motor subset	23.9 (6.60)
Developed significant motor function milestones after treatment, n (%)	
Rolling (back to side from both sides)†	13/22 (59.1%) 97.5% CI: 36.35, 100.00 p<0.0001
Hold head erect ≥3 seconds, unsupported‡	17/20 (85.0%) 97.5% CI: 62.11, 100.00 p<0.0001
Sits with support§	Not centrally reviewed/video-confirmed
Sits alone ≥10 seconds¶	14/22 (63.6%) 97.5% CI: 40.66, 100.00 p<0.0001
Sits alone ≥30 seconds††	14/22 (63.6%) 97.5% CI: 40.66, 100.00 p<0.0001
Crawls‡‡	1/22 (4.5%) 97.5% CI: 0.12, 100.00 p=0.0218
Pulls to stand§§	1/22 (4.5%) 97.5% CI: 0.12, 100.00 p=0.0218
Stands with assistance¶¶	1/22 (4.5%) 97.5% CI: 0.12, 100.00 p=0.0218
Stands alone†††	1/22 (4.5%) 97.5% CI: 0.12, 100.00 p=0.0218

Outcome	STR1VE-US N=22
Walks with assistance‡‡‡	1/22 (4.5%) 97.5% CI: 0.12, 100.00 p=0.0218
Walks alone§§§	1/22 (4.5%) 97.5% CI: 0.12, 100.00 p=0.0218
Independent of ventilatory support, n (%)	15/22 (68.2%) 97.5% CI: 45.1, 100.00 p<0.0001
Maintained the ability to thrive at 18 months of age, n (%)	9/22 (40.9%) 97.5% CI: 20.7, 100.0 p<0.0001
Proportion of patients in the SAS receiving non-oral feeding support, n (%)	
Gastrostomy with Nissen fundoplication	2/22 (9.1%)
Gastrostomy without Nissen fundoplication	0
Nasogastric	4/22 (18.2%)
Nasojejunal	2/22 (9.1%)
Gastrostomy with a jejunostomy tube threaded for feeds	0

Abbreviations: CHOP-INTEND, Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders; CI, confidence interval; SD, standard deviation.
† Bayley Scales gross motor subtest item #20: Child turns from back to both right and left sides.
‡ Bayley Scales gross motor subtest item #4: Child holds head erect for at least 3 seconds without support.
§ Bayley Scales gross motor subtest item #19: ability to sit with support
¶ WHO MGRS definition: Child sits up straight with head erect for at least 10 seconds. Child does not use arms or hands to balance body or support position.
†† Bayley Scales gross motor subtest item #26: Child sits alone without support for at least 30 seconds.
‡‡ Bayley Scales gross motor subtest item #34: Child makes forward progress of at least 5 feet by crawling on hands and knees.
§§ Bayley Scales gross motor subtest item #35: Child raises self to standing position using chair or other convenient object for support
††† Bayley Scales gross motor subtest item #33: Child supports his or her own weight for at least 2 seconds, using your hands for balance only.
§§ Bayley Scales gross motor subtest item #40: Child stands alone for at least 3 seconds after you release his or her hands.
‡‡‡ Bayley Scales gross motor subtest item #37: Child walks by making coordinated, alternated stepping movements.
§§§ Bayley Scales gross motor subtest item #43: Child takes at least 5 steps independently, displaying coordination and balance.
Note: Two-sided methodology used to calculate 95% CI; one-sided methodology used to calculate 97.5% CI. These analyses test the superiority of onasemnogene abeparvovec to the results from the natural history study PNCR (4)

- **A5. Priority question:** The company submission supplementary appendix indicates that updated efficacy data for STR1VE-EU will be available in [redacted].
  - **a)** Please provide results for clinical outcomes for STR1VE-EU (equivalent table to Table 20 in the company submission supplementary appendix) based on the latest cut off available and indicate the updated mean and median follow-up time (with accompanying measure of variance) for the cohort.

Data have been shared for STR1VE-EU as of the latest data cut (31 December 2019) (see Section 6.3.1.4 in the company submission, May 2020). Whilst another interim data cut is planned for [redacted], these data will not be available until [redacted]. Furthermore, this data cut is part of the conditional marketing authorisation terms and will only provide interim, incomplete data for STR1VE-EU. Final data for STR1VE-EU will not be available before [redacted].

Clinical outcomes for STR1VE-EU based on the latest cut off available (31 December 2019) are presented in Table 7. At the time of the 31 December data cut, enrolment for STR1VE-EU was complete with a total of 33 patients receiving onasemnogene abeparvovec. The study was ongoing and the median duration of follow-up at last visit was 11.9 months (range: 1.8–15.4); the median age of patients at last visit was 15.4 months (range: 6.9–18.6). One patient (3.0%) [redacted] was dosed at the age of 181 days and was therefore not included for the ITT population, and the data for this patient is therefore excluded from the results shown in Table 7.

Table 7: STR1VE-EU interim efficacy results – ITT population (31 December 2019 data cut)

Outcome	STR1VE-EU (N=32)
Survived without permanent ventilation at 14 months of age, n (%)	[redacted]
Change from baseline to maximum post-baseline value in CHOP-INTEND score, mean (SD)	[redacted]
Proportion of patients who achieved CHOP-INTEND scores, n (%)	
≥40	[redacted]
≥50	[redacted]
≥60	[redacted]
Change from baseline to maximum post-baseline value in Bayley Scales raw score, mean (SD)	
Gross motor subset	[redacted]
Fine motor subset	[redacted]
Functional independent sitting (≥30 seconds), n (%)	[redacted]
Developed significant motor function milestones, n (%)	
Holds head erect for ≥3 seconds without support†	[redacted]
Turns from back to both right and left sides‡	[redacted]
Sits alone without support for ≥30 seconds§	[redacted]
Sits independently for ≥10 seconds¶	[redacted]
Crawls at least 5 feet††	[redacted]
Crawls at least 3 movements‡‡	[redacted]
Stands with assistance – supports weight for at least 2 seconds§§	[redacted]
Stands with assistance – holding stable object¶¶	[redacted]
Walks with assistance†††	[redacted]
Independent of ventilatory support, n (%)	[redacted]
Maintained the ability to thrive at 18 months of age, n (%)	[redacted]

Outcome	STR1VE-EU (N=32)
Proportion of patients in the SAS receiving non-oral feeding support‡‡, n (%)	[redacted]
Gastrostomy with Nissen fundoplication	[redacted]
Gastrostomy without Nissen fundoplication	[redacted]
Nasogastric	[redacted]
Nasojejunal	[redacted]
Gastrostomy with a jejunostomy tube threaded for feeds	[redacted]
Percutaneous endoscopic gastrostomy (PEG)	[redacted]

Abbreviations: CHOP-INTEND, Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders.
† Bayley Scales gross motor subtest Item #4: Child holds head erect for at least 3 seconds without support.
‡ Bayley Scales gross motor subtest Item #20: Child turns from back to both right and left sides.
§ Bayley Scales gross motor subtest Item #26: Child sits alone without support for at least 30 seconds.
¶ WHO MGRS definition: Child sits up straight with head erect for at least 10 seconds. Child does not use arms or hands to balance body or support position.
†† Bayley Scales gross motor subtest Item #34: Child makes forward progress of at least 5 feet by crawling on hands and knees.
‡‡ WHO MGRS definition: Child alternately moves forward or backward on hands and knees. The stomach does not touch the supporting surface. There are continuous and consecutive movements, at least 3 in a row.
§§ Bayley Scales gross motor subtest Item #33: Supports weight. Child supports his or her own weight for at least 2 seconds, using your hands for balance only.
¶¶ WHO MGRS definition: Child stands in upright position on both feet, holding onto a stable object (e.g., furniture) with both hands without leaning on it. The body does not touch the stable object, and the legs support most of the body weight. Child thus stands with assistance for at least 10 seconds.
††† Bayley Scales gross motor subtest item #37: Child walks by making coordinated, alternated stepping movements.

b) If appropriate, please include STR1VE-EU in the pooled analysis with START and STR1VE-US and provide a table of results for all clinical outcomes as requested in Q1 and ensure that all baseline characteristics are reported as for START and STR1VE-US.

It is not possible to provide a pooled analysis that includes STR1VE-EU at this time, as this trial is currently ongoing, and the data are not sufficiently mature for inclusion in any analyses as several patients have not reached the age when even a normal healthy child would be expected to sit, stand or walk.

c) If a pooled analysis with STR1VE-EU is not possible, please indicate when data suitable for pooling would be expected to be available.

Final data for STR1VE-EU will become available in [redacted]. Given that the duration of the STR1VE-EU study is 18 months of age, which is a relatively short period of follow up in which to assess clinical outcomes, a completed trial is required before the feasibility of pooling for incorporation into the model can be considered.

- **A6. Priority question:** The company submission supplementary appendix reports that scoliosis was captured as a treatment-emergent adverse effect, with 40.9% of children in STR1VE-US developing scoliosis during follow-up. Please clarify how many children enrolled in all of the other onasemnogene studies (where it has been administered intravenously and at the recommended dose) have developed scoliosis (e.g. Cohort 2 in START).

The number of patients with scoliosis at baseline, and the number of patients experiencing a treatment-emergent adverse event (TEAE) of scoliosis in completed and ongoing trials where onasemnogene abeparvovec has been administered intravenously and at the recommended dose are described in Table 8. Data are reported for the safety populations.

Table 8: Aggregated data of scoliosis in infants treated with IV onasemnogene abeparvovec

	START Cohort 2 (N=12)	STR1VE-US (N=22)	STR1VE-EU (N=33) (interim)	SPR1NT (N=30) (interim)
Scoliosis at baseline, n (%)	2/12 (16.7%)†	0/22	0/33	0/30
Patients with scoliosis TEAE, n (%)	1/12 (8.3%)	9/22 (40.9%)	1/33 (3.0%)	0/30
Total scoliosis TEAE events	1	12	1	0

Abbreviations: TEAE, treatment-emergent adverse event.
†For one of the two patients who had scoliosis at baseline, while no TEAE of scoliosis is reported for this patient, scoliosis surgery is presumed due to the record a TEAE of 'wound infection secondary to scoliosis surgery'.

The company notes that there is also a separate MedDRA code for 'kyphoscoliosis'. The number of patients with kyphoscoliosis at baseline, and the number of patients experiencing a TEAE of kyphoscoliosis in completed and ongoing trials where onasemnogene

abeparvovec has been administered intravenously and at the recommended dose are described in Table 9. Data are reported for the safety populations.

Table 9: Aggregated data of kyphoscoliosis in infants treated with IV onasemnogene abeparvovec

	START Cohort 2 (N=12)	STR1VE-US (N=22)	STR1VE-EU (N=33) (interim)	SPR1NT (N=30) (interim)
Kyphoscoliosis at baseline, n (%)	0/12	0/22	0/33	0/30
Patients with kyphoscoliosis TEAE, n (%)	0/12	1/22 (4.5%)	0/33	0/30
Total kyphoscoliosis TEAE events	0	1	0	0

Abbreviations: TEAE, treatment emergent adverse event.

- **A7. Priority question:** For the patient that died in STR1VE-US ([redacted]), what milestones did they achieve (if any)?

Patient [redacted] in STR1VE-US died at age 7.8 months due to respiratory failure that was not considered related to onasemnogene abeparvovec. The patient was dosed at age 2.1 months. The patient did not attain any centrally reviewed/video-confirmed motor milestones.

- **A8.** Please clarify how many children, if any, went on to receive subsequent treatment with an SMA-targeted therapy (e.g., nusinersen) in STR1VE-US and STR1VE-EU and provide an equivalent table to that reported in Table 27 of the company submission supplementary appendix (to include the start date of nusinersen and highest development milestone).

Onasemnogene abeparvovec is a one-time gene therapy, administered via a single-dose intravenous infusion only. [redacted]. Further details of study LT-002 are reported in Section 6.1 of the company submission (May 2020).

- **A9.** Please provide the results by baseline CHOP-INTEND score (high or low) for START for the patients aged over 3 months in Table 24 of the company submission supplementary appendix.

Please see our response to question **A2c.**

- **A10.** Please provide the equivalent of Table 24 in the company submission supplementary appendix with results by baseline CHOP-INTEND score (high or low) for:

a) STR1VE-US;

b) STR1VE-EU;

c) Pooled analysis including STR1VE-EU if available.

For part a) please see our response to question **A2c.**

For parts b) and c) the company considers the requests for analyses that include STR1VE-EU as not feasible at this time, as this trial is currently ongoing, and the data are not sufficiently mature for inclusion in any analyses as several patients have not reached the age when even a normal healthy child would be expected to sit, stand or walk.

Section B: Clarification on cost-effectiveness data

For any scenarios requested in Section B, please ensure these are implemented as user selectable options in the economic model. Furthermore, if the company chooses to update its base case results, please ensure that cost-effectiveness results, sensitivity and scenario analyses incorporating the revised base case assumptions are provided with the response.

An updated set of cost-effectiveness results are provided at list price (Appendix A) and PAS price (Appendix B). A full list of amends to base case parameters and assumptions are also included in a summary table at the start of Appendix A.

Model structure

- **B1. Priority question:** The indication for onasemnogene now includes patients with 5q SMA with a bi-allelic mutation in the *SMN1* gene and up to three copies of the *SMN2* gene, which is reflective of the patient population is SPR1NT (pre-symptomatic patients). Clinical results for cohort 1 and cohort 2 of SPR1NT have been presented in the supplementary appendix to the company submission.
  - **a)** Please clarify why supporting cost-effectiveness evidence has not been submitted for the pre-symptomatic population based on the results from SPR1NT, in line with the proposed indication?

Currently, only early, interim data are available from the ongoing SPR1NT trial in infants with pre-symptomatic SMA. These results are not sufficiently mature for incorporation into full cost-effectiveness analysis.

The cost-effectiveness model submitted derives efficacy data from START and STR1VE-US in symptomatic SMA type 1 patients; these trials showed that the substantial benefits in survival, event-free survival and motor milestones relative to natural history cohorts were particularly striking for several patients treated at younger ages. This was evidenced by the exploratory economic scenario analysis provided in which milestones, overall survival and event-free survival are based on those patients treated at ≤3.5 months of age in START and STR1VE-US (n=17). The age threshold of '3.5 months' is defined from descriptive statistics of the POOLED dataset: The median age at dose for the 34 patients treated in START (Cohort 2) and STR1VE-US is 3.5 months. In this scenario, the ICER decreased by 13.1% from the base case to £202,593/QALY, with 14 of 17 patients (82.4%) sitting independently and 3 of 17 patients (17.6%) walking independently at the end of the trial periods. This observation supports the one-time use of onasemnogene abeparvovec as early as possible, including pre-symptomatic patients, with the aim of intervening ahead of extensive neurodegeneration. Based on the interim results of SPR1NT, in which age-appropriate motor milestones have been observed, it is expected that the ICER would improve when modelling is based on the outcomes of infants with pre-symptomatic SMA with a genetic phenotype predictive of SMA type 1 (i.e. up to three copies of the *SMN2* gene) treated with onasemnogene abeparvovec. Please see the question response to **B1b**.

We also note that newborn screening (NBS) is not currently part of established care in England, and very few patients are currently being diagnosed pre-symptomatically as a result of newborn genetic testing referral, initiated due to a sibling history of SMA.

b) In order for the appraisal committee to consider the pre-symptomatic population in its recommendation, please provide supporting cost-effectiveness evidence, economic model and results.

Although the current economic model was not developed to consider infants with pre-symptomatic SMA specifically, an attempt to explore scenarios for this population has been made in the confines of the current economic model (which is designed for symptomatic SMA type 1). As mentioned above, the interim data available from the ongoing SPR1NT trial are not considered sufficiently mature to be used in a cost-effectiveness analysis, and thus exploratory scenarios for this population have been generated based on the following assumptions:

1) Proxy pre-symptomatic scenario A

    - Assumes age-appropriate milestones (sitting and walking) are observed for all (100%) pre-symptomatic SMA infants treated with onasemnogene abeparvovec, but with the conservative one model cycle motor milestone offset applied:
        - All patients are assumed to sit by 9.2 months of age (which is the 99th percentile of the WHO window for sitting independently in normal childhood), and therefore transition to sitting in the 12 to 18 months age cycle, due to the conservative one model cycle offset
        - All patients are assumed to walk by 17.6 months of age (which is the 99th percentile of the WHO window for walking independently in normal childhood), and therefore transition to walking in the 18 to 24 months age cycle, due to the conservative one model cycle offset
    - Assumes overall survival and event-free survival is 100% in the D state for the short-term model (up to 36 months of age) for onasemnogene abeparvovec.

2) Proxy pre-symptomatic scenario B

    - Assumes sitting is observed in all (100%) pre-symptomatic SMA infants treated with onasemnogene abeparvovec, of which 50% attain age-appropriate sitting and 50% achieve delayed sitting relative to WHO windows:
        - Although all patients with pre-symptomatic SMA treated with onasemnogene abeparvovec are expected to sit independently, in this scenario 50% of patients are assumed to sit by 9.2 months of age (which is the 99th percentile of the WHO window for sitting independently in normal childhood) and 50% are assumed to sit between 12 and 18 months of age, i.e. at a delayed age relative to WHO windows. Therefore, 50% of patients transition to sitting in the 12 to 18 months age cycle (age-appropriate) and 50% of patients transition to sitting in the 18 to 24 months age cycle (delayed relative

to WHO) due to the application of the conservative one model cycle offset to all milestones

- Assumes walking is observed in 82% of pre-symptomatic SMA infants treated with onasemnogene abeparvovec, of which 50% attain age-appropriate walking and 50% achieve delayed walking relative to WHO windows:
    - Of the 82% who can walk independently, 50% are assumed to walk by 17.6 months of age (which is the 99th percentile of the WHO window for walking independently in normal childhood), and 50% are assumed to walk between 24 to 30 months of age, i.e. at a delayed age relative to WHO windows. Therefore, 50% of patients who go on to walk transition to walking in the 18 to 24 months age cycle (age-appropriate) and 50% of patients transition to walking in the 30 to 36 months age cycle (delayed relative to WHO) due to the conservative one model cycle offset.
- Assumes overall survival and event-free survival is 100% in the D state for the short-term model for onasemnogene abeparvovec.

Results of these two exploratory scenarios are presented in Section 1.1.2.4 of the updated cost effectiveness results (Appendix A).

As mentioned above, the current economic model is developed to reflect the treatment pathway of symptomatic SMA type 1 patients treated with onasemnogene abeparvovec, which is likely to differ from the treatment pathway of pre-symptomatic SMA infants. It is expected that infants treated pre-symptomatically with onasemnogene abeparvovec would require less healthcare resource utilisation (HCRU) at different motor milestones health states, as they will have fewer symptoms and complications of SMA. For example, interim results from SPR1NT show that no patients in the study required feeding support and no patients required ventilatory support of any kind, including no non-invasive ventilatory support, invasive ventilatory support, cough assist, or BiPAP. Thus, the health state specific SMA-care related costs (current defined by proxies of SMA type 1–3) are overestimated in the current model and do not reflect the true resource use and costs of infants with pre-symptomatic SMA treated with onasemnogene abeparvovec.

As further supporting economic evidence, AveXis has conducted a cost-effectiveness analysis of NBS for SMA in the United States, which supports the case for why NBS and therefore pre-symptomatic treatment is cost-effective (5). When comparing no NBS screening and symptomatic treatment for SMA (Arm 1) versus NBS screening and pre-symptomatic treatment with onasemnogene abeparvovec (Arm 2) the incremental cost per QALY gained was $57,969/QALY. When comparing no NBS screening and symptomatic treatment for SMA (Arm 1) versus NBS screening and pre-symptomatic treatment with onasemnogene abeparvovec only in infants with ≤3 *SMN2* copies (Arm 3), the strategy was dominant, producing more incremental QALYs (8.42) at a lower cost (-$142,303). Therefore, at a willingness-to-pay threshold of $150,000 per QALY, the adoption of NBS and allowing infants with pre-symptomatic SMA to receive onasemnogene abeparvovec is a cost-effective option for US payers.

- **B2. Priority question:** Please provide a scenario analysis based on the analysis requested in question A3.

The company has provided a scenario analyses for the pooled data whereby the proportion of patients who attain independent sitting is calculated using the:

- Sits alone for ≥30 seconds (item #26) in START– achieved by 9/12 patients
- Sits alone for ≥30 seconds (item #26) in STR1VE-US – achieved by 14/22 patients

When pooled, independent sitting is achieved by 23/34 patients. In this scenario, all other base case assumptions regarding motor milestones are kept the same. Thus, after application of the model base case assumption that includes one additional independent sitter and one additional independent walker in STR1VE-US, over and above empirical data, independent sitting is achieved by 24/34 patients in this scenario in the model. Results are presented in Section 1.1.2.4 of the updated cost effectiveness results (Appendix A).

- **B3. Priority question:** Based on the response to question A5, please provide a scenario where the pooled analysis includes data from STR1VE-EU (if available).

Not applicable. Please see response to **A5.**

- **B4. Priority question:** Based on the data requested in question A6, please provide a scenario analysis where costs of scoliosis are included for patients in the onasemnogene arm of the model.

Costs for scoliosis are already adequately captured as part of the healthcare resource utilisation (HCRU) study, used to calculate health state costs. Scoliosis surgery rates of 56.67%, 19.62, and 3.75% were applied for the D, C, and B states, respectively, according to rates reported in the HCRU study. The company considers an additional scenario to add these costs for patients in the onasemnogene arm would not be appropriate as that would result in double counting of the costs of scoliosis in the model and thus this scenario was not completed. It is important to note that scoliosis is a broad term that describes a range of spinal developmental issues, not all of which require surgery, many of which can be managed with non-surgical orthotics. The company considers that it is unlikely that scoliosis surgery would be required in all patients reporting a TEAE of scoliosis as described in **A6**, given the young age of these patients. Furthermore, the company notes that the impact of scoliosis on treatment administration is not applicable for this technology, given that onasemnogene abeparvovec is delivered via a single-dose intravenous infusion only.

- **B5. Priority question:** D to E transitions in the short-term model for the onasemnogene arm are based on NeuroNext OS and EFS. Please clarify the rationale for this approach instead of using the pooled data set as with the other heath state transitions for the short-term model.
  - **a)** Please provide a scenario using the pooled data set for D to E transitions in the short-term model.

The company notes that in the economic model submitted in May 2020, the OS and EFS data from the onasemnogene abeparvovec POOLED dataset were applied to cycles 1-5 (i.e. up to 30 months of age) in line with the START trial follow up period, after which BSC (using data from NeuroNext) OS and EFS data are applied.

However, to align with the model cycle offset applied for the motor milestone achievements from the same POOLED dataset (resulting in final motor milestone transitions in cycle 6), the POOLED OS and EFS data used for the D state have been extended by one cycle to cycle 6 (from 30 months to 36 months of age). For cycle 6, it has been assumed that the same OS and EFS remains as in cycle 5 (last observation carried forward [LOCF] methodology]). Therefore, in the revised economic model presented with these ERG question responses, empirical OS/EFS data for the onasemnogene abeparvovec arm are used up to and including cycle 6, after which BSC (using data from NeuroNext) OS and EFS data are applied in the long-term model until the set survival cut-off of 4 years (please see D_Survival_AVXS worksheet in the model). Following this amended approach, the OS assumptions for the onasemnogene abeparvovec arm in the C, B and A states have also been amended and 100% survival has also been applied up to and including cycle 6 in the revised economic model base case. As the economic base case has been amended in response to this question, a separate scenario is not generated.

- **B6.** Please clarify if the Weibull distribution was used for both the aggregated and disaggregated D-state overall survival (OS) based on NeuroNext data.
  - **a)** Please provide a comparison of the assessed distributions against the disaggregated OS KM data and the AIC/BIC statistics.

In the base case, Weibull distribution was used for both the aggregated and disaggregated OS (based on NeuroNext data) in the D state.

Please find the assessed distributions and their AIC/BIC statistics for all the D-state OS (aggregated and disaggregated) and EFS curves in the model worksheets outlined in Table 10 below.

Table 10: Location of AIC/BIC values and KM and fitted OS and EFS curves for the D state in the model

Data source	Curve type	Location of AIC/BIC values	Location of graphs with KM and fitted curves
NeuroNext (Kolb)	OS (disaggregated)	Sheet: D_Survival_BSC Cells: I103:N104 when Q12=1 And: Sheet: D_Death_Kolb Cells: R11:S21	Sheet: D_Survival_BSC Chart under option 1 (LHS)
	OS (aggregated)	Sheet: D_Death_Ag_Kolb Cells: R11:S21	Sheet: D_Death_Ag_Kolb
	EFS	Sheet: D_E_Kolb Cells: R11:S21	Sheet: D_Survival_BSC Chart under option 1 (RHS)
Sham control (Finkel)	OS	Sheet: D_Survival_BSC Cells: I103:N104 when Q12=2 And: Sheet: D_Death_ENDEAR_SHAM Cells: R11:S21	Sheet: D_Survival_BSC Chart under option 2 (LHS)
	EFS	Sheet: D_E_SHAM Cells: R11:S21	Sheet: D_Survival_BSC Chart under option 2 (RHS)
Internal PNCR data (AveXis)	OS (disaggregated)	Sheet: D_Survival_BSC Cells: I103:N104 when Q12=4 And: Sheet: D_Death_PNCR_Int Cells: R11:S21	Sheet: D_Death_PNCR_Int
	OS (aggregated)	Sheet: D_Death_Ag_PNCR_Int Cells: R11:S21	Sheet: D_Death_Ag_PNCR_Int
	EFS	Sheet: D_E_PNCR_Int Cells: R11:S21	Sheet: D_E_PNCR_Int

Published PNCR data (De Sanctis)	OS (disaggregated)	Sheet: D_Survival_BSC Cells: I103:N104 when Q12=3 And: Sheet: D_Death_DeSanctis Cells: R11:S21	Sheet: D_Survival_BSC Chart under option 3 (LHS)
	OS (aggregated)	Sheet: D_Death_Ag_DeSanctis Cells: R11:S21	Sheet: D_Death_Ag_DeSanctis
	EFS	Sheet: D_E_DeSanctis Cells: R11:S21	Sheet: D_Survival_BSC Chart under option 3 (RHS)

Abbreviations: EFS: Event-free survival; LHS: Left hand side; OS: Overall survival; RHS: Right hand side.

- **B7. Priority question:** Please clarify the follow-up assessment timepoints in STR1VE-US and if these align to the model cycles (6-monthly) used for the short-term model?

Follow-up assessments in STR1VE-US were performed on a monthly basis and these align with the 6-monthly model cycles in the short-term model. Motor milestones observed in trials were offset by 6 months when incorporated into the model.

- **B8.** Please clarify why the cost of onasemnogene is applied in cycle 1 rather than cycle 0.

The company acknowledges the ERG's feedback on this point, therefore, the economic model base case has been updated accordingly. In the revised model submitted with this ERG clarification response, onasemnogene abeparvovec technology and administration costs have been assigned in cycle 0, where no discounting is applied. Although not considered a comparator, similar amends have been made in the nusinersen arm, whereby the cost of the first injection of nusinersen (both drug acquisition and administration costs) is now assigned in cycle 0 (i.e. no discounting applied). All other costs from cycle 1 onwards remain the same and are discounted.

- **B9.** For onasemnogene versus best supportive care (BSC), please provide one-way sensitivity results for each hospitalisation variable included in health states E, D and C.

One-way sensitivity analyses have been performed for each hospitalisation variable used for estimating SMA-care related costs in the E, D and C states. Variables have been varied by +/-20%. Please see results in Table 11 below. These analyses can also be found in the model's 'MedicalCostCalculator' worksheet in the economic model file (between rows 76 and 110) and can be rerun if any parameter is changed.

Table 11: One-way sensitivity results for hospitalisation variable used for estimating SMA-care related costs in the E, D and C states

Variable	Default value	Low variation	High variation	Results with low value			Results with high value		
				Cost-AVXS	Cost-BSC	ICER vs BSC (£/QALY)	Cost-AVXS	Cost-BSC	ICER vs BSC (£/QALY)
ITU_trach	10%	8%	12%	£2,712,561	£377,676	233,411	£2,713,368	£384,586	232,800
ITU_NIV>16hpd	15%	12%	18%	£2,710,888	£363,360	234,674	£2,715,041	£398,902	231,537
ITU_NIV<16hpd_D	5%	4%	6%	£2,700,664	£373,954	232,593	£2,725,265	£388,308	233,618
ITU_NIV<16hpd_C	5%	4%	6%	£2,665,537	£381,131	228,364	£2,760,392	£381,131	237,847
high_dep_trach	30%	24%	36%	£2,712,441	£376,650	233,501	£2,713,488	£385,613	232,710
high_dep_NIV>16hpd	15%	12%	18%	£2,712,067	£373,448	233,784	£2,713,862	£388,814	232,427
high_dep_NIV<16hpd_D	5%	4%	6%	£2,707,313	£377,834	232,870	£2,718,616	£384,428	233,341
high_dep_NIV<16hpd_C	5%	4%	6%	£2,690,711	£381,131	230,881	£2,735,218	£381,131	235,330
Noyes_cost_high_dep	£415,808	£332,646	£498,970	£2,679,435	£361,373	231,729	£2,746,494	£400,889	234,482
Noyes_cost_ITU	£833,592	£666,874	£1,000,310	£2,646,661	£349,349	229,655	£2,779,268	£412,914	236,557
c_NIV>16hpd_high_dep	£48,288	£38,630	£57,945	£2,711,791	£371,091	233,992	£2,714,138	£391,171	232,219
c_NIV>16hpd_ITU	£96,805	£77,444	£116,166	£2,710,613	£361,003	234,883	£2,715,316	£401,259	231,329
c_trach_high_dep	£28,167	£22,533	£33,800	£2,712,280	£375,275	233,623	£2,713,649	£386,988	232,588
c_trach_ITU	£18,823	£15,058	£22,587	£2,712,507	£377,217	233,451	£2,713,422	£385,045	232,760
c_NIV<16hpd_high_dep_D	£17,464	£13,971	£20,957	£2,706,347	£377,270	232,830	£2,719,582	£384,992	233,381
c_NIV<16hpd_ITU_D	£35,011	£28,009	£42,013	£2,699,698	£373,390	232,553	£2,726,231	£388,872	233,658
c_NIV<16hpd_high_dep_C	£11,643	£9,314	£13,971	£2,687,910	£381,131	230,601	£2,738,019	£381,131	235,610
c_NIV<16hpd_ITU_C	£23,341	£18,672	£28,009	£2,662,737	£381,131	228,084	£2,763,192	£381,131	238,127

- **B10.** Please clarify why the standard error for utilities was assumed to be 5% of the mean value and not 20% of the mean value to align with the standard error for costs and survival limits

The standard error for utilities was assumed to be 5% of the mean due to the small variation in these values published in previous studies. This assumption has been amended to 20% in the revised economic model for all parameters specific to utilities: C, D and E health state utility values and their on-treatment utility increments and all the Ara and Brazier equation parameters used for estimating the A and B health state utility values. Please see the 'Parameters' tab in the revised economic model file.

Section C: Textual clarifications and additional points

- **C1. Priority question:** On page 31 of the company submission supplementary appendix, there is the statement that, “For both incident and prevalent SMA type 1 populations, further eligibility criteria need to be considered such as antibody AAV9 titre levels, advancement of disease and patient/caregiver treatment choice, as in some cases BSC alone may be chosen even in the presence of available treatments.” Please clarify when eligibility criteria will be further defined, and what impact, if any, you consider this could have on the number of children likely to be eligible for treatment. Please provide an answer for the full population covered by the license indication and not only for SMA type 1 populations.

It is the role of treating clinicians to interpret the evidence and terms outlined in the SPC to determine patient eligibility. The company understands that treatment decisions will be based on a holistic assessment of each patient, taking into account possible benefits and risks of treatment options and caregiver preferences. Results from a UK SMA early access programme indicated that a minority of patients chose to receive best supportive care even when an active therapy was available (6).

As per the company submission to NICE on 1 May 2020, in England onasemnogene abeparvovec is positioned for the treatment of children with SMA type 1 and in pre-symptomatic infants with a genotype predictive of SMA type 1 (i.e. those with up to three copies of the *SMN2* gene). The following terms, noted in the SPC, are expected to inform clinicians’ assessments of patient eligibility in these two patient populations:

- **Children with SMA type 1:**
    - 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 (Section 4.2, SPC (3)).
    - Recommended dosing is provided for a weight range of 2.6 to 21.0 kg (Section 4.2, SPC (3)).
    - Anti-AAV9 antibody formation can take place after natural exposure, patients should be tested for the presence of AAV9 antibodies prior to infusion with onasemnogene abeparvovec. It is not yet known whether or under what conditions onasemnogene abeparvovec can be safely and effectively administered in the presence of anti-AAV9 antibodies above 1:50 (Section 4.4, SPC (3)). According to the screening conducted as part of the ongoing Phase III trial in SMA type 1 (STR1VE-EU), it is estimated that up to 12% of infants in the European population may have anti-AAV9 antibody titres above this (1:50) level and may not be eligible for onasemnogene abeparvovec (see Section 6.1.6 of company submission supplementary appendix, May 2020).
    - Since SMA results in progressive and non-reversible damage to motor neurons, the benefit of onasemnogene abeparvovec in symptomatic patients depends on the degree of disease burden at the time of treatment (3), with earlier treatment resulting in potential higher benefit. The treating physician

should consider that the benefit is seriously reduced in patients with profound muscle weakness and respiratory failure, patients on permanent ventilation, and patients not able to swallow (Section 4.4, SPC (3)).

- **Pre-symptomatic infants with a genotype predictive of SMA type 1 (i.e. those with up to three copies of the *SMN2* gene):**
    - In England there is currently no national newborn screening programme, and therefore cases of pre-symptomatic SMA are only identified through genetic testing referrals due to a sibling history of SMA. It is therefore anticipated that only a very small number (current estimates are 1-3 infants per year) of pre-symptomatic infants with up to three copies of the *SMN2* gene will be identified each year as being eligible for treatment with onasemnogene abeparvovec.
    - The eligibility of infants with pre-symptomatic SMA will be informed by anti-AAV9 antibody titres, as per the SPC special warnings and precautions for use (Section 4.4, SPC (3)). According to the screening conducted as part of the ongoing Phase III trial in pre-symptomatic SMA (SPR1NT), two patients (4.5%) were excluded on the grounds of high (>1:50) anti-AAV9 antibodies (see Section 6.1.6 of company submission supplementary appendix, May 2020).

As per our response to question **A1**, the company recognises that the wording of the licensed indication for onasemnogene abeparvovec, without the context of the SPC and EPAR, could be interpreted as potentially covering a more inclusive population than that described in the company submission. The SPC and EPAR provide clear guidance to treating clinicians on the availability, or not, of evidence to support use including an assessment of the strength of that evidence. The company expects that the above mentioned precautions, noted in the evidence package and SPC, will therefore inform clinical practice and decisions around patient eligibility.

The impact of patient eligibility criteria on expected patient numbers in the populations covered in the company submission (i.e. in children with SMA type 1 and pre-symptomatic infants with a genotype predictive of SMA type 1) have already been shared with NICE in the company submission (Section 5.1, May 2020, supplementary appendix) and via the budget impact test.

For the patient populations that could be construed as being covered by the licensed indication, but that are not included in the company submission (e.g. patients with symptomatic SMA type 2 and 3), it is expected that implementation of the terms of the SPC, and acknowledgement by treating clinicians of the current lack of formal clinical trial evidence in these populations, will limit the number of patients deemed suitable for treatment in this more inclusive patient group.

- **C2.** The scenarios included in the submission (Table 81) are not all included in the model (Results5!). Please update the model to include all scenarios in the submission.

All scenarios presented in the updated submission submitted in May 2020 (Table 81) have been incorporated in the revised model's 'Result5' worksheet. These scenarios can be run all at once by using the 'Run All Scenarios' button (in cells K33:L35) and individually by using each scenario's button (in rows 32-36). When scenarios are run individually, the model will be set up with the specific scenario. To restore to the base case, the 'Restore' button specific to the run scenario should be used.

- **C3.** For the exploratory scenarios presented in Table 81 of the company submission, please advise how these can be run individually rather than altogether in the "Results5" tab of the economic model. Please provide user selectable options for these scenarios, if not already available.

In the revised economic model submitted with this ERG clarification response, the exploratory scenarios can be run individually in the 'Results5' worksheet. Please see the response to **C2** on how to run scenarios individually

- **C4.** Please provide a version of Table 50 in the company submission for data from STR1VE-US.

The requested data are provided in Table 12. Please note, the company considers it more appropriate for the economic model to incorporate clinical data from the POOLED dataset (i.e. START and STR1VE-US), rather than STR1VE-US alone. Not only does the POOLED dataset have a larger sample size, but it also accommodates the longer-term follow period of the patients treated in START (24 months post dose; to approximately 30 months of age). As described previously, STR1VE-US followed up patients to 18 months of age which would likely underestimate the likely maximum milestone attainment and potential benefit from onasemnogene abeparvovec (see Section 8.2.1.1 of the company submission, May 2020 for further details). Therefore, if an economic analysis were to be conducted using STR1VE-US data alone, the assumptions regarding milestone attainment between 18 months and 30 months of age would need to be revised, as the dataset would no longer include the longer-term data available from START.

Table 12: Proportions of patients achieving motor milestones in STR1VE-US versus 'offset' data for those that are alive and event-free†

Cycle	Age at end of cycle (mo.)	Observed‡ Inclusive of the base case assumption: one additional sitter and one additional walker in STR1VE-US						'Offset' modelled§ Inclusive of the base case assumption: one additional sitter and one additional walker in STR1VE-US					
		Not sitting		Sitting but not walking¶††		Walking		Not sitting		Sitting but not walking¶††		Walking	
		n	%	n	%	n	%	n	%	n	%	n	%
1	6	22	100.0%	0	0.0%	0	0.0%	22	100.0%	0	0.0%	0	0.0%
2	12	14	70.0%	6	30.0%	0	0.0%	20	100.0%	0	0.0%	0	0.0%
3	18	7	35.0%	12	60.0%	1	5.0%	14	70.0%	6	30.0%	0	0.0%
4	24	6	30.0%	13	65.0%	1	5.0%	7	35.0%	12	60.0%	1	5.0%
5	30	5	25.0%	13	65.0%	2	10.0%	6	30.0%	13	65.0%	1	5.0%
6	36	N/A‡‡	N/A‡‡	N/A‡‡	N/A‡‡	N/A‡‡	N/A‡‡	5	25.0%	13	65.0%	2	10.0%

Abbreviations: mo., month; N/A, not applicable.

† Proportions achieving milestones are calculated based on those who are alive and event-free.

‡ Age at milestone attainment is taken from 'Listing 16.2.6.1 Listing of Age at which Central Confirmed Developmental Milestones first achieved'. 'Observed' data also includes the base case assumption of one additional sitter and one additional walker in the STR1VE-US cohort between 24–30 months of age, as per the described base case assumption of the revised model

§ The motor milestones attained in STR1VE-US have been 'offset' by a model cycle in the modelled data. For example, if a patient was observed to sit unassisted at 9 months of age (i.e. during cycle 2 [6 to 12 months of age]), they would not contribute to the transition probability of moving from the D state (not sitting) to the C state (sits unassisted) until cycle 3 (12 to 18 months of age). Different green shading in the table has been used to show how the milestones in STR1VE-US are 'offset' by a model cycle in the modelled data.

¶ Sitting unassisted for ≥30 seconds is in accordance with the criteria of item 26 on the Bayley-III assessment tool gross motor subtest for STR1VE-US.

†† For one patient in STR1VE-US the milestone of sits unassisted ≥30 seconds was not confirmed at the end of study 18 month visit but was observed at the 16-month and 17-month visit. This patient did sit unassisted for ≥5 seconds at the 18-month visit (as recorded in the Bayley Scale assessment, gross motor item #22).

‡‡ Data are described as not available since the maximum follow-up period for the STR1VE-US data was 18 months (+ 14 days) of age. Last observation carried forward is used for model cycle 5 and cycle 6, including the base case assumption of one additional sitter and one additional walker in the STR1VE-US cohort between 24–30 months of age, as per the described base case assumption of the revised model

- **C5.** Please outline the rationale for the decision not to update any of the SLR searches originally conducted in March 2019 that is those covering clinical and cost-effectiveness.

The company has performed an update to the previous March 2019 report originally submitted in August 2019. The updated SLR report was not finalised until late May 2020, and hence not available at the time of the 1 May 2020 company submission.

The database search of the updated SLR was performed in March 2020 to identify studies reporting on the efficacy and safety of onasemnogene abeparvovec and competing interventions for the treatment of SMA, and to gather evidence of the HRQoL, economic burden, and natural history of SMA. The SLR report, including full methods and results, is provided as a reference (7). The updated SLR was expanded from the previous version to include SMA types 1–3, as opposed to SMA type 1 only, for the search of natural history studies. This expansion of the natural history search was to potentially inform the C state and B state of the economic model, as SMA type 2 and SMA type 3 proxies are used to model the outcomes of SMA type 1 treated patients that go on to sit unassisted and walk unassisted. The US ICER report, which was included in the previous SLR but was identified by hand searching after the SLR was performed, was formally incorporated into the updated SLR. The additional publications included in the updated SLR for HRQoL, economic burden, and natural history of SMA are presented in Table 13, Table 14 and Table 15. The additional studies identified in the updated clinical SLR relevant to the decision problem, i.e. clinical trials assessing onasemnogene abeparvovec, have already been shared with NICE as part of the latest data cut (31 Dec 19) for the ongoing trials (STR1VE-EU and SPR1NT), as well as the final data for the completed trials (START and STR1VE-US) submitted as part of the company submission (May 2020).

Note that, although new studies reporting on the natural history of SMA and the utilities of infants with SMA were identified in this SLR update, these were not used to update the onasemnogene abeparvovec economic model as insufficient detail regarding the methods and outcomes reported were provided. For some studies, the outcomes reported were not applicable to the economic model, for example, the use of the Pediatric Quality of Life Inventory (PedsQL) tool for which a robust mapping algorithm is currently lacking. Only two of the new publications reporting utilities used EQ-5D (8, 9), which is the preferred measure of HRQoL in the NICE reference case; however, these publications are secondary publications for the same study identified in the previous SLR (10), which has already been considered as part of an economic exploratory scenario analysis in the company submission. A further study Love 2019 (11) reported on utilities in SMA using the Health Utilities Index; however, only an abstract is available and details regarding key characteristics of the study population (e.g. motor milestone status, treatment status, age etc) are lacking, preventing further use of these data. In addition, the sources currently used in the economic model submitted have been validated from a UK healthcare perspective.

Table 13: Study characteristics from the SMA natural history 2020 SLR update

Study ID	Title	Study type	Reference type
Alvarez 2019 (12)	Observations from a nationwide vigilance program in medical care for spinal muscular atrophy patients in Chile	Prospective cohort	Full text
Exposito 2019 (13)	Longitudinal study of the natural history of spinal muscular atrophy type 2 and 3	Longitudinal cohort	Abstract
Pera 2019 (14)	Revised upper limb module for spinal muscular atrophy: 12 month changes	Longitudinal cohort	Full text
Mercuri 2019 (15)	Trajectories of disease progression in ambulant and non ambulant SMA: 12 month follow-up	Prospective cohort	Abstract
NatHis-SMA (16)	Prospective and longitudinal natural history study of patients with type 2 and 3 spinal muscular atrophy: Baseline data nathis-sma study	Prospective cohort	Full text
Kaufmann 2012 (17)	Prospective cohort study of spinal muscular atrophy types 2 and 3	Prospective cohort	Full text
Mazzone 2014 (18)	Hammersmith functional motor scale and motor function measure-20 in non ambulant SMA patients	Prospective cohort	Full text
Mazzone 2013 (19)	Six minute walk test in type III spinal muscular atrophy: A 12month longitudinal study	Prospective, longitudinal cohort	Full text
ULENAP (20)	Upper limb evaluation and one-year follow up of non-ambulant patients with spinal muscular atrophy: An observational multicenter trial	Longitudinal cohort	Full text
Sivo 2015 (21)	Upper limb module in non-ambulant patients with spinal muscular atrophy: 12 month changes	Longitudinal cohort	Full text
Montes 2018 (22)	Ambulatory function in spinal muscular atrophy: Age-related patterns of progression	Prospective, longitudinal cohort	Full text

Table 14: Study characteristics from the HRQoL and utilities 2020 SLR update

Study ID	Title	Study type	Reference type
CHERISH (23)	Impact of caregiver experience and HRQoL in later-onset spinal muscular atrophy (SMA): Results from the phase 3 cherish trial	RCT	Poster
Landfeldt 2019 (24)	Quality of life of patients with spinal muscular atrophy: A systematic review	Systematic review	Full text
Lloyd 2019 (8)	Estimation Of The Quality Of Life Benefits Associated With Treatment For Spinal Muscular Atrophy	Clinician survey	Full text
Love 2019 (11)	Utility based health related quality of life in children and adolescents with spinal muscular atrophy	Patient/caregiver survey	Abstract

Malone 2019 (25),(26)	Nd2 cost-utility analysis of single dose gene-replacement therapy for spinal muscular atrophy type 1 compared to chronic nusinersen treatment	Cost-effectiveness analysis	Full text
Wadman 2020 (27)	Drug treatment for spinal muscular atrophy types II and III	Systematic review	Full text
Weaver 2020 (28)	A Prospective, Crossover Survey Study of Child- and Proxy-Reported Quality of Life According to Spinal Muscular Atrophy Type and Medical Interventions	Randomized survey	Full text
Zuluaga-Sanchez 2019 (9)	Cost effectiveness of nusinersen in the treatment of patients with infantile-onset and later-onset spinal muscular atrophy in Sweden	Infantile-onset, later-onset	Full text

Table 15: Study characteristics from the economic 2020 SLR update

Study ID	Title	Study type	Reference type
Cost analyses			
Ali et al 2019 (29)	Healthcare utilisation in children with SMA type 1 treated with nusinersen: A single centre retrospective review	Cost analysis	Full text
Cardenas et al 2019 (30)	High healthcare resource use in hospitalized patients with a diagnosis of spinal muscular atrophy type 1 (SMA1): Retrospective analysis of the kids' inpatient database (KID)	Cost analysis	Full text
Droege et al 2020 (31)	Economic burden of spinal muscular atrophy in the united states: A contemporary assessment	Cost analysis	Full text
Kockaya et al 2019 (32)	Annual cost of treatment of spinal muscular atrophy patients in turkey	Cost analysis	Abstract
Lopez Bastida et al 2019 (33)	The economic impact and health-related quality of life of spinal muscular atrophy (SMA). An analysis across three European countries	Cost analysis	Abstract
Starner and Gleason 2019 (34)	Spinal muscular atrophy: An integrated medical and pharmacy claims analysis of nusinersen uptake and gene therapy forecast among 15 million commercially insured	Cost analysis	Abstract
Economic evaluations			

Dabbous et al 2019 (35)	Cost-effectiveness and budget impact of onasemnogene abeparvovec for spinal muscular atrophy type 1: Post-hoc analysis of a model developed by ICER	Cost-effectiveness analysis	Abstract
Malone et al 2019 (25)	Cost-utility analysis of single dose gene-replacement therapy for spinal muscular atrophy type 1 compared to chronic nusinersen treatment	Cost-effectiveness analysis	Abstract
Malone et al 2019 (26)	Cost-effectiveness analysis of using onasemnogene abeparvocec (avxs-101) in spinal muscular atrophy type 1 patients	Cost-effectiveness analysis	Full text
Thokala et al 2019 (36)	Cost-effectiveness of nusinersen and onasemnogene abeparvovec for infantile-onset spinal muscular atrophy (type I SMA) in the US	Cost-effectiveness analysis	Abstract
Zuluaga Sanchez et al 2019 (37)	Improved quality of life and life-years in patients with infantile-onset sma following treatment with nusinersen	Cost-effectiveness analysis	Abstract
Zuluaga Sanchez et al 2019 (38)	Improved quality of life for patients and caregivers among patients with later-onset sma following treatment with nusinersen	Cost-effectiveness analysis	Abstract
US ICER 2019 (39)	Spinraza® and Zolgensma® for Spinal Muscular Atrophy: Effectiveness and Value	HTA Agency Recommendation	Full text

- **C6.** A study by Lopez-Bastia et al. 2017 assessed the HRQoL of SMA caregivers in Spain, using the EQ-5D. Please explain why this source was not considered appropriate to inform the exploratory scenario that included a disutility for caregivers.

This study enrolled only a very small number of patients with SMA type 1 (8/81 patients). Furthermore, due to the small overall sample size, the authors did not provide HRQoL data for each health state included in the company's economic model, and only provides values for SMA type 2 patients (60/81 patients). The inclusion of average disutility scores as reported gives net (patient plus caregiver) utility scores of –0.5 for state E, –0.31 for state D and 0.1 for state C. The study also did not provide a control population (i.e. caregiver utility for a child of the same age without SMA). Given these limitations, it was not considered appropriate to use this study to inform the exploratory scenario.

- **C7.** The ERG has identified discrepancies in "other costs" reported in Table 3 of the PAS submission ([redacted] for onasemnogene and [redacted] for BSC) and the list model and PAS model ([redacted] for onasemnogene and [redacted] for BSC). Please clarify if the values in the models or submission are correct.

The company believes this is not an error, but instead due to a different meaning of the term 'other costs' used in the HST and PAS templates versus the economic model file. The term 'other costs' in the HST and PAS templates refers to 'SMA-related costs', whereas 'other costs' in the economic model file relates to societal/personal costs.

- **C8.** The ERG has identified discrepancies between the total costs in the five-year budget impact for onasemnogene between the submission (Table 93) and model (BIMModel2!I42:M42) (Table 16). Please clarify if the values in the submission or model are correct.

Table 16: Total costs in the five-year budget impact for onasemnogene in submission Table 93 and the model (BIMModel2!I42:M42)

	Year 1	Year 2	Year 3	Year 4	Year 5
Submission Table 93	53,890,701	56,652,077	58,822,170	60,353,392	61,803,297
Model BIMModel2!I42:M42	64,618,205	67,537,948	69,770,455	71,325,677	72,836,153

The company believes this is not an error. Please note the sheet referred to (BIMModel2!I42:M42) is an intermediate sheet that calculates on the basis that all patients receive onasemnogene abeparvovec. Table 93 in submission is calculated on the basis that some patients still receive BSC.

References

1. Glanzman AM, McDermott MP, Montes J, Martens WB, Flickinger J, Riley S, et al. Validation of the Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders (CHOP INTEND). Pediatr Phys Ther. 2011 Winter;23(4):322-6.

2. Glanzman AM, Mazzone E, Main M, Pelliccioni M, Wood J, Swoboda KJ, et al. The Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders (CHOP INTEND): test development and reliability. Neuromuscul Disord. 2010 Mar;20(3):155-61.

3. AveXis. SmPC onasemnogene abeparvovec.

4. Finkel RS, McDermott MP, Kaufmann P, Darras BT, Chung WK, Sproule DM, et al. Observational study of spinal muscular atrophy type I and implications for clinical trials. Neurology. 2014a Aug 26;83(9):810-7.

5. Arjunji R, Zhou J, Patel A, Edwards ML, Harvey M, Wu E, et al. Cost-effectiveness Analysis of Newborn Screening for Spinal Muscular Atrophy (SMA) in the United States. Poster presented at ECRD2020. Data on file. 2020.

6. Nusinersen EAP UK. Oral presentation. BPNA congress, January 2019.

7. AveXis. Data on file. Systematic literature review of clinical and economic evidence for interventions for spinal muscular atrophy. Technical Report. 11 May 2020.

8. Lloyd AJ, Thompson R, Gallop K, Teynor M. Estimation Of The Quality Of Life Benefits Associated With Treatment For Spinal Muscular Atrophy. Clinicoecon Outcomes Res. 2019;11:615-22.

9. Zuluaga-Sanchez S, Teynor M, Knight C, Thompson R, Lundqvist T, Ekelund M, et al. Cost Effectiveness of Nusinersen in the Treatment of Patients with Infantile-Onset and Later-Onset Spinal Muscular Atrophy in Sweden. PharmacoEconomics. 2019 Feb 4.

10. Lloyd A, Gallop K, Thompson R, Vaidya S, Teynor M. Estimation Of The Health-Related Quality Of Life Benefits Of Treatment For Spinal Muscular Atropy (SMA). Value in Health. 2017;20(9):A559.

11. Love D, Hicks R, Wei Y, Aldana EZ, Almobarak S, Campbell C. P. 218Utility based health related quality of life in children and adolescents with spinal muscular atrophy. Neuromuscular Disorders. 2019;29:S130.

12. Alvarez K, Suarez B, Palomino MA, Hervias C, Calcagno G, Martinez-Jalilie M, et al. Observations from a nationwide vigilance program in medical care for spinal muscular atrophy patients in Chile. Arquivos de Neuro Psiquiatria. 2019;77(7):470-7.

13. Exposito J, Natera-de Benito D, Carrera L, Frongia A, Alarcon M, Borras A, et al. P.226Longitudinal study of the natural history of spinal muscular atrophy type 2 and 3. Neuromuscular Disorders. Conference: 24th International Congress of the World Muscle Society. Tivoli Gardens, Denmark. 2019;29(Supplement 1).

14. Pera MC, Coratti G, Mazzone ES, Montes J, Scoto M, De Sanctis R, et al. Revised upper limb module for spinal muscular atrophy: 12 month changes. Muscle and Nerve. 2019;59(4):426-30.

15. Mercuri E, Coratti G, Pera M, Scoto M, Goemans N, Pane M, et al. P.221Trajectories of disease progression in ambulant and non ambulant SMA: 12 month follow-up. Neuromuscular Disorders. Conference: 24th International Congress of the World Muscle Society. Tivoli Gardens, Denmark. 2019;29(Supplement 1).

16. Chabanon A, Seferian AM, Daron A, Pereon Y, Cances C, Vuillerot C, et al. Prospective and longitudinal natural history study of patients with Type 2 and 3 spinal muscular atrophy: Baseline data NatHis-SMA study. PLoS One. 2018;13(7):e0201004.

17. Kaufmann P, McDermott MP, Darras BT, Finkel RS, Sproule DM, Kang PB, et al. Prospective cohort study of spinal muscular atrophy types 2 and 3. Neurology. 2012 Oct 30;79(18):1889-97.

18. Mazzone E, De Sanctis R, Fanelli L, Bianco F, Main M, Van den Hauwe M, et al. Hammersmith functional motor scale and motor function measure-20 in non ambulant SMA patients. Neuromuscular Disorders. 2014;24(4):347-52.

19. Mazzone E, Bianco F, Main M, Van den Hauwe M, Ash M, De Vries R, et al. Six minute walk test in type III spinal muscular atrophy: a 12 month longitudinal study. Neuromuscular Disorders. 2013;23(8):624-8.

20. Seferian AM, Moraux A, Canal A, Decostre V, Diebate O, Le Moing AG, et al. Upper limb evaluation and one-year follow up of non-ambulant patients with spinal muscular atrophy: an observational multicenter trial. PLoS One. 2015;10(4):e0121799.

21. Sivo S, Mazzone E, Antonaci L, De Sanctis R, Fanelli L, Palermo C, et al. Upper limb module in non-ambulant patients with spinal muscular atrophy: 12 month changes. Neuromuscular Disorders. 2015;25(3):212-5.

22. Montes J, McDermott MP, Mirek E, Mazzone ES, Main M, Glanzman AM, et al. Ambulatory function in spinal muscular atrophy: Age-related patterns of progression. PLoS ONE. 2018;13(6).

23. Johnson N, Paradis A, Naoshy S, Montes J, Krasinski D. PRO13 Impact of caregiver experience and HRQoL in later-onset spinal muscular atrophy (SMA): Results from the phase 3 Cherish trial. Value in Health Regional Issues. 2019;19:S76.

24. Landfeldt E, Edström J, Sejersen T, Tulinius M, Lochmüller H, Kirschner J. Quality of life of patients with spinal muscular atrophy: A systematic review. European journal of paediatric neurology : EJPN : official journal of the European Paediatric Neurology Society. 2019 May;23(3):347-56.

25. Malone D, Dean R, Miller B, Arjunji R, Feltner DE, Sproule DM, et al. Nd2 Cost-Utility Analysis of Single Dose Gene-Replacement Therapy for Spinal Muscular Atrophy Type 1 Compared to Chronic Nusinersen Treatment. Value in Health. 2019 May;22 (Supplement 2):S42-S3.

26. Malone DC, Dean R, Arjunji R, Jensen I, Cyr P, Miller B, et al. Cost-effectiveness analysis of using onasemnogene abeparvocec (AVXS-101) in spinal muscular atrophy type 1 patients. Journal of Market Access & Health Policy. 2019 2019/01/01;7(1):1601484.

27. Wadman RI, van der Pol WL, Bosboom WM, Asselman FL, van den Berg LH, Iannaccone ST, et al. Drug treatment for spinal muscular atrophy types II and III. Cochrane Database of Systematic Reviews. 2020(1).

28. Weaver MS, Hanna R, Hetzel S, Patterson K, Yuroff A, Sund S, et al. A Prospective, Crossover Survey Study of Child-and Proxy-Reported Quality of Life According to Spinal Muscular Atrophy Type and Medical Interventions. Journal of Child Neurology. 2020;35(5):322-30.

29. Strauss KA, Swoboda KJ, Farrar MA, McMillan HJ, Parsons J, Krueger JM, et al. Onasemnogene abeparvovec gene-replacement therapy (GRT) in presymptomatic spinal muscular atrophy (SMA): SPR1NT study update. Journal of the Neurological Sciences. 2019 15 October;405 (Supplement):268-9.

30. Cardenas J, Menier M, Heitzer MD, Sproule DM. High Healthcare Resource Use in Hospitalized Patients with a Diagnosis of Spinal Muscular Atrophy Type 1 (SMA1): Retrospective Analysis of the Kids' Inpatient Database (KID). PharmacoEconomics - Open. 2019 01 Jun;3(2):205-13.

31. Droege M, Sproule D, Arjunji R, Gauthier-Loiselle M, Cloutier M, Dabbous O. Economic burden of spinal muscular atrophy in the United States: a contemporary assessment. Journal of Medical Economics. 2020 02 Jan;23(1):70-9.

32. Kockaya G, Oguzhan Ergin G, Caliskan Z. Pro49 Annual Cost of Treatment of Spinal Muscular Atrophu Patients in Turkey. Value in Health. 2019 November;22 (Supplement 3):S849-S50.

33. Lopez Bastida J, Pena-Longobardo LM, Aranda-Reneo I, Oliva-Moreno J, Litzkendorf S, Durand-Zaleski I, et al. Pro44 the Economic Impact and Health-Related Quality of Life of Spinal Muscular Atrophy (Sma). An Analysis across Three European Countries. Value in Health. 2019 November;22 (Supplement 3):S848-S9.

34. Starner C, Gleason P. Spinal muscular atrophy: An integrated medical and pharmacy claims analysis of nusinersen uptake and gene therapy forecast among 15 million commercially insured. Journal of Managed Care and Specialty Pharmacy. 2019 March;25 (3-A SUPPL.):S54.

35. Dabbous O, Dean R, Arjunji R, Sproule DM, Feltner DE, Malone DC. Pro51 Cost-Effectiveness and Budget Impact of Onasemnogene Abeparvovec for Spinal Muscular Atrophy Type 1: Post-Hoc Analysis of a Model Developed by Icer. Value in Health. 2019 November;22 (Supplement 3):S850.

36. Thokala P, Stevenson M, Kumar VM, Ren S, Chapman R, Ellis A, et al. Pro15 Cost-Effectiveness of Nusinersen and Onasemnogene Abeparvovec for Infantile-Onset Spinal Muscular Atrophy (Type I SMA) in the Us. Value in Health. 2019 May;22 (Supplement 2):S337-S8.

37. Zuluaga Sanchez S, Purser M, Mader G, Gould IG, Knight C, Johnson NB, et al. Pro14 Improved Quality of Life and Life-Years in Patients with Infantile-Onset SMA Following Treatment with Nusinersen. Value in Health. 2019 May;22 (Supplement 2):S337.

38. Zuluaga Sanchez S, Purser M, Mader G, Gould IG, Knight C, Patel M, et al. Pro16 Improved Quality of Life for Patients and Caregivers among Patients with Later-Onset SMA Following Treatment with Nusinersen. Value in Health. 2019 May;22 (Supplement 2):S338.

39. ICER. Spinraza® and Zolgensma® for Spinal Muscular Atrophy: Effectiveness and Value. 2019.

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Highly Specialised Technologies Evaluation Programme

INTERIM

ZOLGENSMA® (onasemnogene abeparvovec) for treating spinal muscular atrophy type 1 [ID1473]

ERG question response

Appendix A

2 July 2020

The Appendix provides a revised set of cost-effectiveness results at the list price.

Amendments to the base case since the company submission submitted in May 2020 are provided in the '**List of amendments implemented'** on pages 6-7 of this Appendix.

An updated list of the scenarios included since the company submission submitted in May 2020 are provided in the '**List of scenarios'** on page 8-14 of this Appendix.

Contents

List of tables and figures

Abbreviations

AAV9	Adeno-associated virus subtype 9
ACM	Appraisal committee meeting
AE	Adverse event
AIC	Akaike information criterion
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
BIC	Bayesian information criterion
BIM	Budget impact model
BiPAP	Bi-level positive airway pressure
BSC	Best supportive care
CHMP	Committee for Medicinal Products for Human Use
CHOP-INTEND	Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders
CI	Confidence interval
CMAP	Compound motor action potential
CPAP	Continuous positive airway pressure
CSF	Cerebrospinal fluid
CSR	Clinical study report
DILI	Drug-induced liver injury
DSU	Decision support unit
EAP	Early access programme
ECG	Electrocardiogram
EFS	Event-free survival
EMA	European Medicines Agency
EQ-5D	EuroQol-5 Dimensions
ERG	Evidence review group
EU	Europe
FAS	Full analysis set
FDA	Food and Drug Administration
GBP	Great British Pound
GGT	Gamma-glutamyl transferase
GMS	Gross motor skills
GOSH	Great Ormond Street Hospital
GP	General Practitioner
HCRU	Health care resource utilisation

HFMSE	Hammersmith Functional Motor Scale - Expanded
HIV	Human immunodeficiency virus
HRQoL	Health-related quality of life
HST	Highly specialised technology
ICER	Incremental cost effectiveness ratio
IMP	Investigational medicinal product
IT	Intrathecal
ITC	indirect treatment comparison
ITT	Intention to treat
IV	Intravenous
KM	Kaplan-Meier
KOL	Key opinion leader
LYG	Life-years gained
MAA	Managed access agreement
MDT	Multidisciplinary team
mITT	Modified intention to treat
mo.	Month
MUNE	Motor unit number estimation
N/A	Not applicable
NA	Not available
NCH	Nationwide Children's Hospital
ND	Nasoduodenal;
NeuroNext	Network for Excellence in Neuroscience Clinical Trials
NG	Nasogastric
NHS	National Health Service
NHSE	National Health Service England
NICE	National Institute for Health and Care Excellence
NIV	Non-invasive ventilation
NJ	Nasojejunal
NR	Not reported
NRA	Non-invasive respiratory muscle aid
OECD	Organisation for Economic Co-operation and Development
OOP	Out of pocket
OS	Overall survival

PAS	Patient access scheme
PAV	Permanent assisted ventilation
PCA	Prescription Cost Analysis
PCR	Polymerase chain reaction
PedsQL	Pediatric Quality of Life Inventory
PEG	Percutaneous endoscopic gastrostomy
PNCR	Pediatric Neuromuscular Clinical Research database
PSSRU	Personal Social Services Research Unit
QALY	Quality-adjusted life-year
QoL	Quality of life
qPCR	Quantitative polymerase chain reaction
QWB	Quality of Well-Being
RWE	Real World Evidence
SAE	Serious adverse event
SAS	Safety analysis set
SD	Standard deviation
SE	Standard error
SLR	Systematic literature review
SMA	Spinal muscular atrophy
SMN	Survival motor neurone
SmPC	Summary of product characteristics
STA	Single technology appraisal
TEAE	Treatment emergent adverse event
TTO	Time-Trade-Off
UCL	University College London
ULN	Upper limit of normal
UK	United Kingdom
US	United States
US ICER	United States Institute of Clinical and Economic Review
WBC	White blood cell
WHO	World Health Organization
WHO MGRS	World Health Organization Multicentre Growth Reference Trial

List of amendments implemented

The below table lists the updates to the economic model since the company submission submitted in May 2020, to reflect the amendments made to the base case and scenarios in response to the Evidence Review Group (ERG) clarification questions received in June 2020.

Economic model updates:

#	Updates	In response to
1	• Amendment of the empirical data period for OS and EFS in the D state from 0-30 months (cycle 1 to cycle 5, inclusive) to 0-36 months (cycle 1 to cycle 6, inclusive) for the onasemnogene abeparvovec arm in the base case: o In the economic model submitted in May 2020, the OS and EFS data from the onasemnogene abeparvovec POOLED dataset were applied to cycles 1-5 (i.e. up to 30 months of age) in line with the START trial follow up period, after which BSC (using data from NeuroNext) OS and EFS data are applied. o However, to align with the model cycle offset applied for the motor milestone achievements from the same POOLED dataset (resulting in final motor milestone transitions in cycle 6), the POOLED OS and EFS data used for the D state have been extended by one cycle to cycle 6 (from 30 months to 36 months of age). o For cycle 6, it has been assumed that the same OS and EFS remains as in cycle 5 (last observation carried forward [LOCF] methodology]).	ERG question **B5**
2	• Amendment of the empirical data period for OS in the C, B and A states from 0-30 months (cycle 1 to cycle 5, inclusive) to 0-36 months (cycle 1 to cycle 6, inclusive) for the onasemnogene abeparvovec arm in the base case: o As per the approach described in model amend #1, the OS assumptions for the onasemnogene abeparvovec arm in the C, B and A states have also been extended to cycle 6 using LOCF methodology, and hence 100% survival is applied up to and including cycle 6 in the revised economic model base case in these health states	ERG question **B5**

#	Updates	In response to
3	• Approach to discounting: o Onasemnogene abeparvovec technology and administration costs have been assigned in cycle 0, where no discounting is applied. o All other costs from cycle 1 onwards remain the same and are discounted.	ERG question **B8**
4	• Amendment of the standard error for utilities in the PSA o Standard error for utilities in the PSA is updated from 5% to 20% for all PSA parameters specific to utilities: C, D and E health state utility values and their on-treatment utility increments and all the Ara and Brazier equation parameters used for estimating the A and B health state utility values	ERG question **B10**
5	• Expansion of the in-built scenarios to 'Results5' o All scenarios presented in the company submission submitted in May 2020 (Table 81) have been incorporated in the revised model's 'Result5' worksheet. Additonal scenarios in response to ERG questions (received in 2020) **B1** and **B2**, and ERG questions (received in 2019) **B16, B20** and **B23** have also been added. The equivalent table of scenario in this appendix is Table 11 o These scenarios can be run all at once by using the 'Run All Scenarios' button (in cells K33:L35) and individually by using each scenario's button (in rows 32-36). When scenarios are run individually, the model will be set up with the specific scenario. To restore to the base case, the 'Restore' button specific to the run scenario should be used.	ERG questions **B1, B2, C2** and **C3**
6	• One-way sensitivity analysis macro o A one-way sensitivity analyses macro for each hospitalisation variable used for estimating SMA-care related costs in the E, D and C states has been added. Variables have been varied by +/-20%. o These analyses can also be found in the model's 'MedicalCostCalculator' worksheet in the economic model file (between rows 76 and 110) and can be rerun if any parameter is changed.	ERG question **B9**

Abbreviations: BSC, best supportive care; EFS, event-free survival; ERG, Evidence Review Group; OS, overall survival

List of scenarios

AveXis examined the impact of varying the underlying data and assumptions in the model on the onasemnogene abeparvovec versus BSC ICER; the data values and sources explored included:

Discount rates:

- Costs and effects at 0%;
- Costs and effects at 5%;
- Costs at 0%, effects at 5%;
- Costs at 5%, effects at 0%;
- Costs and effects at 1.5%.

Cost assumptions:

- Replacing the base case health state costs with the 'Real World Evidence (RWE)' costs presented at the nusinersen NICE third appraisal committee meeting (ACM3) (1). Values used were:
    - 'SMA type 1' costs of £148,214 for the E state and D state (i.e. using the doubled SMA type 1 costs)
    - 'SMA type 2' costs of £68,322 used as a proxy for the C state
    - 'SMA type 3' costs of £21,765 used as a proxy for the B state (and A state)
- SMA type 3 costs from RWE presented at nusinersen ACM3 applied to the A state and B state patients, other health state costs remain as base case
- Pessimistic scenario that the costs of onasemnogene abeparvovec administration are 10× greater than the base case of £2,803 (i.e. £28,030);
- Using the US ICER approach to the costing of ventilatory support, in which the Noyes et al 2006 costs are removed from health state costs (added on the request of the ERG [ERG question 2019, **B16**]). Briefly, under this scenario, the following amends are made:
    i. set the percentage of ventilated patients in states D, C and B to zero (this means that for these states the only costs are those from the HCRU study);
    ii. set the Noyes social services cost to zero (not strictly necessary since i) above removes them from the analysis but conducted for clarity);
    iii. set Noyes hospital costs to zero
    iv. set the E state costs to equal the D state patients plus £26,140 (the ICER cost of $32,413 in sterling at an exchange rate of $1.24 = £1).

- Increase to the total D state and E state costs (explorative scenario 1, added on the request of the ERG [ERG question 2019, **B20**]). In this scenario, total health state costs are increased from £101,934 (base case) to £135,389 in the D state and from £258,216 (base case) to £342,965 in the E state.

- Increase to the costs derived from the HCRU study for the D state and E state (explorative scenario 2, added on the request of the ERG [ERG question 2019, **B20**]). In this scenario, total health state costs are increased from £101,934 (base case) to £109,097 in the D state and from £258,216 (base case) to £263,514 in the E state

- Extreme scenario where all non-permanent ventilated patients (84% in state D, 56% in state C, 20% in state B/A) receive 100% of the Noyes social care/social services costs (added on the request of the ERG [ERG question 2019, **B23**]).

Utility values:

- On-treatment utilities (i.e. an additional utility of 0.1 compared with BSC in the D state and an additional utility of 0.05 compared with BSC in the C state) are applied in the base case, to accommodate the 'ERG-preferred base case' assumptions: *Interim milestones that maybe achieved with the use of onasemnogene abeparvovec are considered by the ERG's clinical experts to have an impact on a patient's quality of life. Consequently, the ERG considers the inclusion of on-treatment utility values based on values reported in the US ICER report should be included to account for these benefits of treatment.* Scenarios applied to the on-treatment utilities included:

    - Analysis as above but with lower "on-treatment" utilities than used by US ICER. A value of 0.05 was added to the D state (not sitting) and a value of 0.025 was added to the C state (sits unassisted)

    - Analysis as above but with higher "on treatment" utilities than used by US ICER. A value of 0.15 was added to the D state (not sitting) and a value of 0.075 was added to the C state (sits unassisted)

- The base case values for the C, D and E states were substituted with the utility values derived from the mapping of the PedsQL score in the CHERISH nusinersen study to EQ-5D-Y: values for these states were 0.878 (B state), 0.764 (C state), 0.756 (D state) and 0.730 (E state);

- The base case values for the C, D and E states were substituted with the utility values derived from the Lloyd et al 2017 Clinician-proxy Case Vignette study: values for these states were 0.710 (B state), -0.04 (C state), -0.12 (D state) and -0.33 (E state);

- The base case values for the B, C, D and E states were substituted with the utility values derived from the exploratory AveXis UK utilities elicitation study using the TTO results from the 'parent vignettes': values for these states were [redacted] (B state), [redacted] (C state), [redacted] (D state) and [redacted] (E state);

- Utility outcomes are not counted i.e. results are 'cost per life year gained';

Alternative natural history sources

- The NeuroNext natural history cohort (2), which is used to inform overall survival and event-free survival in the D state in the base case is replaced with:
    - Data from the AveXis external control PNCR dataset (2)
    - Data from Finkel et al. 2017 (ENDEAR sham control) (3)
    - Data from De Sanctis et al. 2016 (PNCR, US and Italy study) (4)

Exploratory scenarios

Several exploratory analyses of scenarios are conducted – some optimistic and some pessimistic – within the model as follows:

- Improved survival for patients in the C state (sits unassisted):
    - Patients who achieve the C state (sits unassisted) have a life expectancy the same as the general population: applied to onasemnogene abeparvovec arm only
- Calculation of milestone attainment in the onasemnogene abeparvovec arm for different scenarios of milestone attainment in STR1VE-US patients, after 18 months of age (for which empirical data are currently lacking):
    - Use of the POOLED dataset, but with only one additional sitter compared with the empirical data in STR1VE-US after 18 months of age. The additional sitter sits between 24 and 30 months of age and therefore moves to sitting in cycle ending 36 months. This is more conservative than the base case
    - Use of the POOLED dataset, but with only one additional walker compared with the empirical data in STR1VE-US after 18 months of age. The additional walker walks between 24–30 months of age and therefore moves to walking in cycle ending 36 months. This is more conservative than the base case
    - Use of the POOLED dataset but use of the empirical data only from STR1VE-US. i.e. it assumes there are no additional patients who can sit or walk unassisted in STR1VE-US after 18 months of age. This exploratory scenario is considered highly pessimistic as:
        - STR1VE-US stopped when patients reached 18 months of age[1], which is only just past the upper limit of the WHO window for walking independently in normal childhood development (17.6 months is the 99th percentile for walking independently). This (18 months of age) is too strict a threshold at which to expect symptomatic SMA type 1 patients to have achieved all motor milestones

[1] The End of Study visit must occur within 0 to 14 days after the date on which the patient reaches 18 months of age (or early termination).

        - START data showed that patients continue to develop key gross motor milestones (sitting alone and walking alone) beyond 18 months of age. In START, five patients sat unassisted after 18 months of age and two patients walked unassisted after 18 months of age
        - START data showed that symptomatic SMA type 1 patients achieve gross motor milestones, but these are 'delayed' compared with WHO windows or normal childhood development: in START, the median age at sitting alone and walking alone was 17.1 months (range: 8.0–30.8 months) and 19.3 months (range: 18.9–19.6 months), respectively. As STR1VE-US stopped when patients reached 18 months of age, it is likely later or 'delayed' milestones will not be fully captured and hence the overall milestones attained by STR1VE-US patients once they reach 30 months of age will be underestimated
    - Use of POOLED dataset, but with four new patients who can sit unassisted and four new patients who can walk unassisted in STR1VE-US after 18 months of age:
        - Two of the additional sitters sit, and two of the additional walkers walk between 18 and 24 months of age and therefore move to sitting and walking in cycle ending 30 months, respectively
        - Two of the additional sitters sit, and two of the additional walkers walk between 24 and 30 months of age and therefore move to sitting and walking in cycle ending 36 months, respectively
        - This scenario is based on the age of milestones attained by patients in the START trial, which followed patients up to 24 months post-dose (up to approximately 30 months of age). In START, five patients sat unassisted after 18 months of age and two patients walked unassisted after 18 months of age
- Milestones, overall survival and event-free survival are based on those treated at ≤3.5 months of age in START and STR1VE-US (n=17):
    - Of those treated at or before 3.5 months of age across START and STR1VE-US, 14/17 (82.4%) sat independently, of which 3/17 (17.6%) also walked independently
    - Of those treated at or before 3.5 months of age across START and STR1VE-US, one patient died (1/17) and no patients (0/17) went on to permanent assisted ventilation
    - The cut-off of 3.5 months of age was chosen, as this was the median age at which infants across START and STR1VE-US received onasemnogene abeparvovec.
- Milestones, overall survival and event-free survival are based on those treated in START only (n=12):

    - Of those treated in START, 11/12 (91.7%) sat independently of which 2/12 (16.7%) also walked independently
    - Of those treated in START, all were alive and event-free at the end of the study
- Use of the POOLED dataset, but the conservative 'offset' is not applied to milestone data in the model (milestones are not 'offset' by 6 months). This is less conservative than the base case:
    - Milestones are incorporated into the model, as they were observed in clinical trials. For example, if a patient sits at 9 months of age, they would transition to the sitting health state in cycle 2 (between 6 and 12 months of age)
- E state overall survival is based on the 'pooled' Gregoretti cohort, i.e. patients with tracheostomy (n=42) or NIV (n=31) (defined as continuous non-invasive respiratory muscle aid [NRA], including non-invasive ventilation and mechanically assisted cough). Please note, in this scenario analysis amends to the cost calculator are made:
    - In the 'MedicalCostCalculator' sheet, HCRU costs in the E state are calculated assuming that 57.5% of patients in the E state receive a tracheostomy and 42.5% receive NIV >16 hours/day to match the ratio of tracheostomy use to NIV use reported in this pooled cohort
- Including caregiver disutility scores:
    - This explorative scenario applies a disutility for caregivers that varies by the health state of the patient, drawing data from a proxy, but related, disease – spina bifida. A study by Tilford et al. 2005 (5) compared QWB scale data from the primary caregivers of children aged 0–17 years (n=98) with spina bifida versus a control sample of parents of non-disabled/unaffected children (n=49). Spina bifida children were categorised into three disability levels according to the location of the child's lesion: 1) sacral, 2) lower lumbar and 3) thoracic. When comparing caregivers of spina bifida patients to the control caregiver sample, the 'spill over' disutility of spina bifida caregivers are reported as: -0.03, -0.03 and -0.08 for the sacral, lower lumbar and thoracic lesion groups, respectively. Values were calculated using the method described by Wittenberg et al. 2013 (6). These caregiver disutilities are incorporated into the exploratory scenario analysis as follows: -0.08 for caregivers of a child in the E state (permanent assisted ventilation) or D state (not sitting) and -0.03 for a child in the C state (sits unassisted).
- Proxy pre-symptomatic scenario A:
    - Assumes age-appropriate milestones (sitting and walking) are observed for all (100%) pre-symptomatic SMA infants treated with onasemnogene abeparvovec, but with the conservative one model cycle motor milestone offset still applied:
        - All patients are assumed to sit by 9.2 months of age (which is the 99th percentile of the WHO window for sitting independently in normal childhood (7)), and therefore transition to sitting in the 12 to 18 months age cycle, due to the conservative one model cycle offset

        - All patients are assumed to walk by 17.6 months of age (which is the 99th percentile of the WHO window for walking independently in normal childhood (7)), and therefore transition to walking in the 18 to 24 months age cycle, due to the conservative one model cycle offset
    - Assumes overall survival and event-free survival is 100% in the D state for the short-term model (up to 36 months of age) for onasemnogene abeparvovec.
- Proxy pre-symptomatic scenario B:
    - Assumes sitting is observed in all (100%) pre-symptomatic SMA infants treated with onasemnogene abeparvovec, of which 50% attain age-appropriate sitting and 50% achieve delayed sitting relative to WHO windows:
        - Although all patients with pre-symptomatic SMA treated with onasemnogene abeparvovec are expected to sit independently, in this scenario 50% of patients are assumed to sit by 9.2 months of age (which is the 99th percentile of the WHO window for sitting independently in normal childhood (7)) and 50% are assumed to sit between 12 and 18 months of age, i.e. at a delayed age relative to WHO windows. Therefore, 50% of patients transition to sitting in the 12 to 18 months age cycle (age-appropriate) and 50% of patients transition to sitting in the 18 to 24 months age cycle (delayed relative to WHO) due to the application of the conservative one model cycle offset to all milestones
    - Assumes walking is observed in 82% of pre-symptomatic SMA infants treated with onasemnogene abeparvovec, of which 50% attain age-appropriate walking and 50% achieve delayed walking relative to WHO windows:
        - Of the 82% who can walk independently, 50% are assumed to walk by 17.6 months of age (which is the 99th percentile of the WHO window for walking independently in normal childhood (7)), and 50% are assumed to walk between 24 to 30 months of age, i.e. at a 'delayed' age relative to WHO windows. Therefore, 50% of patients who go on to walk transition to walking in the 18 to 24 months age cycle (age-appropriate) and 50% of patients transition to walking in the 30 to 36 months age cycle (delayed relative to WHO) due to the conservative one model cycle offset.
    - Assumes overall survival and event-free survival is 100% in the D state for the short-term model for onasemnogene abeparvovec.
- Use of the 30 second threshold for sitting independently:
    - On request of the ERG (ERG clarification questions 2020, **A3/B2**) a scenario analysis is presented using the POOLED dataset in which sitting unassisted is defined as 'sitting alone for ≥30 seconds' for both the START and STR1VE-US trials. All other base case assumptions regarding motor milestones (e.g. application of the conservative one model cycle offset and the assumption of one additional sitter and walker in STR1VE-US between 24 and 30 months of age) remain in place for this scenario.
    - As previously described in Section 8.2.1.1 of the company submission submitted in May 2020, the company considers this scenario analysis to be overly pessimistic.

Values used in the multi-way sensitivity analyses

For the multi-way sensitivity analysis, the three variables with the largest impact on the results (excluding the cost of onasemnogene abeparvovec) were taken/combined from the one-way sensitivity results for onasemnogene abeparvovec versus BSC (Table 1). From the onasemnogene abeparvovec versus BSC analysis these are: i) the cost of hospitalisations for C state patients, ii) the cost of social services for C state patients and, iii) the patient utility value of the C state. The multi-way analysis therefore used the following sets of values. For each variable we varied the value by +/- 20%.

Table 1: Variables used in multi-way scenario-based sensitivity analysis (onasemnogene abeparvovec versus BSC)

Variable	*Cost of hospitalisations for C state*	*Cost of social services for C state*	*Patient utility value for C state*
Base case value	£37,336	£18,598	0.6
Base case * 0.8	£29,869	£14,878	0.48
Base case * 1.2	£44,804	£22,317	0.72

1 Economic analysis

1.1 *Results of economic analysis*

1.1.1 Base-case analysis

1.1.1.1 When presenting the results of the base case incremental cost effectiveness analysis in the table below, list the interventions and comparator(s) from least to most expensive. Present incremental cost-effectiveness ratios (ICERs) compared with baseline (usually standard care) and then incremental analysis ranking technologies in terms of dominance and extended dominance. If the company has formally agreed a patient access scheme with the Department of Health, present the results of the base-case incremental cost-effectiveness analysis with the patient access scheme. A suggested format is available in table D11.

In the base case, the ICER for onasemnogene abeparvovec versus BSC is £233,106 per QALY gained. Total and incremental per patient costs, total and incremental life years gained and total and incremental QALYs gained are presented in Table 2. As per the response to ERG question **B8**, onasemnogene abeparvovec technology and administration costs have been assigned in cycle 0, where no discounting is applied. All other costs from cycle 1 onwards remain the same and are discounted. All model costs and effects have been discounted at 3.5% and include half cycle correction.

Table 2: Base case results

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£) (versus BSC)	Incremental LYG (versus BSC)	Incremental QALYs (versus BSC)	ICER (£/QALY) (versus BSC)
BSC	381,131	2.15	0.210	N/A	N/A	N/A	N/A
Onasemnogene abeparvovec	2,712,964	15.68	10.213	2,331,833	13.53	10.003	233,106

Abbreviations: BSC, best supportive care; ICER, incremental cost-effectiveness ratio; LYG, life years gained; N/A, not applicable; QALYs, quality-adjusted life years.

1.1.1.2 For the outcomes highlighted in the decision problem, please provide the corresponding outcomes from the model and compare them with clinically important outcomes such as those reported in clinical trials. Discuss reasons for any differences between modelled and observed results (for example, adjustment for cross-over). Please use the following table format for each comparator with relevant outcomes included.

Not applicable. The economic model uses onasemnogene abeparvovec trial results until the end of their observation periods, although with one additional sitter and one additional walker assumed in STR1VE-US after 18 months of age. Both the additional sitter sits, and the additional walker walks between 24–30 months of age and therefore, transition to sitting and walking in cycle ending 36 months, respectively. After this period the model uses extrapolated results. Please see Section 8.2.1.1 of the company submission submitted in May 2020 for full details and rationale supporting the base case assumption of applying one additional sitter and walker after 18 months of age.

1.1.1.3 Please provide (if appropriate) the proportion of the cohort in the health state over time (Markov trace) for each state, supplying one for each comparator.

Table 3 shows the probability of a patient being in one of the surviving health states or death over time.

Table 3: Probability of a patient being in surviving health states or death over the lifetime of the model by intervention arm

Patients who received onasemnogene abeparvovec						
Year after procedure	**Dead**	**E State (PAV)**	**D State**	**C State**	**B State**	**A State**
1	2.94%	2.94%	94.12%	0.00%	0.00%	0.00%
5	22.94%	1.33%	0.00%	63.97%	11.76%	0.00%
10	26.63%	0.49%	0.00%	61.11%	0.00%	11.76%
25	42.58%	0.00%	0.00%	45.70%	0.00%	11.72%
50	86.23%	0.00%	0.00%	2.38%	0.00%	11.39%
75	91.07%	0.00%	0.00%	0.00%	0.00%	8.93%
100	99.80%	0.00%	0.00%	0.00%	0.00%	0.20%
Patients who received BSC						
Year after procedure	**Dead**	**E State (PAV)**	**D State**	**C State**	**B State**	**A State**
1	46.69%	9.32%	43.99%	0.00%	0.00%	0.00%
5	86.76%	13.24%	0.00%	0.00%	0.00%	0.00%
10	95.09%	4.91%	0.00%	0.00%	0.00%	0.00%
25	100.00%	0.00%	0.00%	0.00%	0.00%	0.00%
50	100.00%	0.00%	0.00%	0.00%	0.00%	0.00%
75	100.00%	0.00%	0.00%	0.00%	0.00%	0.00%
100	100.00%	0.00%	0.00%	0.00%	0.00%	0.00%

Abbreviations: BSC, best supportive care; PAV, permanent assisted ventilation.
Values are reported per the economic model, discrepancies are due to rounding.

1.1.1.4 Please provide details of how the model assumes QALYs accrued over time. For example, Markov traces can be used to demonstrate QALYs accrued in each health state over time.

Table 4 shows QALYs accrued over time for a patient treated with onasemnogene abeparvovec or BSC. Note that this is based on the probability of the patient being in each of the health states in each time period. QALYs are discounted at 3.5%.

Table 4: QALYs accrued over time for a patient based on the probability of being in each health state in each time period (discounted at 3.5% and with half cycle correction)

Patients who received onasemnogene abeparvovec						
Year after procedure	**Total**	**E State (PAV)**	**D State**	**C State**	**B State**	**A State**
1	0.344	0.000	0.344	0.00	0.00	0.00
5	2.154	0.000	0.549	1.309	0.296	0.00
10	4.124	0.000	0.549	2.851	0.296	0.428
25	7.915	0.000	0.549	5.735	0.296	1.335
50	9.909	0.000	0.549	6.993	0.296	2.071
75	10.170	0.000	0.549	6.994	0.296	2.331
100	10.213	0.000	0.549	6.994	0.296	2.375
Patients who received BSC						
Year after procedure	**Total**	**E State (PAV)**	**D State**	**C State**	**B State**	**A State**
1	0.167	0.000	0.167	0.00	0.00	0.00
5	0.210	0.000	0.210	0.00	0.00	0.00
10	0.210	0.000	0.210	0.00	0.00	0.00
25	0.210	0.000	0.210	0.00	0.00	0.00
50	0.210	0.000	0.210	0.00	0.00	0.00
75	0.210	0.000	0.210	0.00	0.00	0.00
100	0.210	0.000	0.210	0.00	0.00	0.00

Abbreviations: BSC, best supportive care; PAV, permanent assisted ventilation.

1.1.1.5 Please indicate the life years (LY) and QALYs accrued for each clinical outcome listed for each comparator. For outcomes that are a combination of other states, please present disaggregated results.

The disaggregation of accrued LYs and QALYs is presented in Table 5. Note that results are discounted at 3.5% and with half cycle correction.

Table 5: Model outputs by clinical outcomes (discounted at 3.5% and with half-cycle correction)

Patients who received onasemnogene abeparvovec		
Outcome	**Life years**	**QALYs**
E State (PAV)	0.095	0
D state	1.615	0.549
C State	9.599	6.994
B State	0.219	0.296
A State	4.148	2.375
TOTAL	15.676	10.213
Patients who received BSC		
Outcome	**Life years**	**QALYs**
E State (PAV)	1.040	0
D state	1.105	0.210
C State	0	0
B State	0	0
A State	0	0
TOTAL	2.145	0.210

Abbreviations: BSC, best supportive care; LYG, life years gained; PAV, permanent assisted ventilation; QALYs, quality-adjusted life years.

1.1.1.6 Please provide details of the disaggregated incremental QALYs by health state. Suggested formats are presented below.

The disaggregation of incremental QALYs by health state are presented in Table 6. Onasemnogene abeparvovec provides large incremental QALY gains: 9.797 QALYs when compared with BSC. Over 93% of the QALY gains for onasemnogene abeparvovec compared with BSC are due to gains in the C and A states.

Table 6: Summary of QALY gain differences by health state (onasemnogene abeparvovec versus BSC) – discounted

Outcome	QALYs onasemnogene abeparvovec	QALYs BSC	Increment	Absolute increment	% absolute increment
E State (PAV)	0	0	0	0	0
D state	0.549	0.210	0.339	0.339	3.39
C State	6.994	0	6.994	6.994	69.92
B State	0.296	0	0.296	0.296	2.95
A State	2.375	0	2.375	2.375	23.74
TOTAL	10.213	0.210	10.003	10.003	100

Abbreviations: BSC, best supportive care; PAV, permanent assisted ventilation; QALYs, quality-adjusted life years.
Values are reported per the economic model, discrepancies are due to rounding.

1.1.1.7 Please provide undiscounted incremental QALYs for the intervention compared with each comparator

Table 7 shows the undiscounted incremental QALYs for the intervention compared with each comparator.

Table 7: Undiscounted QALYs gained from onasemnogene abeparvovec and comparator and incremental QALYs gained from onasemnogene abeparvovec over comparator

Intervention	QALYs from intervention	Incremental QALYs (onasemnogene abeparvovec over comparator)
Onasemnogene abeparvovec	21.406	N/A
BSC	0.217	21.189

Abbreviations: BSC, best supportive care; N/A, not applicable; QALYs, quality-adjusted life years.

1.1.1.8 Provide details of the costs for the technology and its comparator by category of cost. A suggested format is presented in table D12.

Table 8 shows the costs of onasemnogene abeparvovec and BSC by category of costs. Of the total increase in costs, just under 77% are for the technology cost of onasemnogene abeparvovec with 23% for increased SMA treatment/care costs for patients due to increased survival.

Table 8: Costs of onasemnogene abeparvovec and comparator by category of cost (onasemnogene abeparvovec versus BSC) (discounted at 3.5%)†

Item	Cost onasemnogene abeparvovec	Cost BSC	Increment	Absolute increment	% absolute increment
Technology cost	£1,795,000	£0	£1,795,000	£1,795,000	76.98
Mean total SMA treatment cost (all care costs)	£915,162	£381,131	£534,031	£534,031	22.90
Administration cost of the technology	£2,803	£0	£2,803	£2,803	0.12
Total	£2,712,964	£381,131	£2,331,833	£2,331,833	100%

Abbreviations: BSC, best supportive care; SMA, spinal muscular atrophy. † Values are reported as per the economic model (i.e. includes half-cycle correction).

1.1.1.9 If appropriate, provide details of the costs for the technology and its comparator by health state. A suggested format is presented in table D13.

Table 9 shows the total costs for onasemnogene abeparvovec by health state versus BSC. Note that costs for the technology (onasemnogene abeparvovec) include the costs of the technology and SMA care costs incurred whilst in the health state.

Note also that since onasemnogene abeparvovec is a one-time, single IV treatment the cost of onasemnogene abeparvovec and administration has been allocated between the health states by the proportion of the total (discounted) life years gained by health state. For example, since the 'D' state for onasemnogene abeparvovec produces 1.615 of the total (discounted) 15.676 life years gained we have allocated 10.30% (1.615/15.676) of the total onasemnogene abeparvovec and administration costs to the 'D' state.

Table 9: Total costs of onasemnogene abeparvovec and BSC by health state (discounted at 3.5% and with half-cycle correction)

Health state	Cost onasemnogene abeparvovec	Cost BSC	Increment	Absolute increment	% absolute increment
E state (PAV)	£42,314	£268,446	-£226,132	£226,132	8.12
D state	£378,361	£112,685	£265,676	£265,676	9.54
C state	£1,769,003	£0	£1,769,003	£1,769,003	63.54
B state	£27,505	£0	£27,505	£27,505	0.99

A state	£495,781	£0	£495,781	£495,781	17.81
Total	£2,712,965	£381,131	£2,331,834	£2,784,097	100%

Abbreviations: BSC, best supportive care; PAV, permanent assisted ventilation.
Figures may not sum exactly due to rounding during onasemnogene abeparvovec apportioning between states.

1.1.1.10 If appropriate, provide details of the costs for the technology and its comparator by adverse event. A suggested format is provided in table D14.

Adverse events are not included in the model: see Section 8.3.5 of the company submission submitted in May 2020.

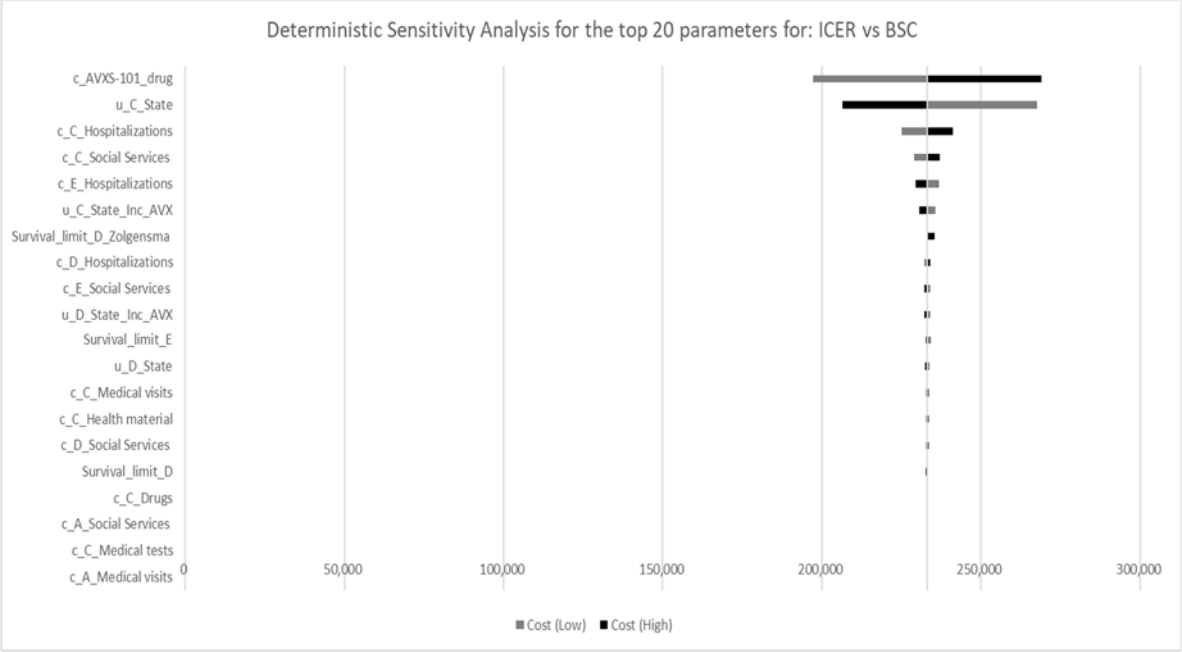
1.1.2 Sensitivity analysis results

1.1.2.1 Present results of deterministic one-way sensitivity analysis of the variables described in table D10.1.

Figure 1 shows the impact on the ICER from the one-way sensitivity analysis for onasemnogene abeparvovec versus BSC: results in table format are shown in Table 10. All variables were varied by +/- 20% or natural limits if these were within the +/- 20% range.

These results are discussed in Section 1.1.2.4.

Figure 1: Tornado diagram of impact of the one-way sensitivity analysis (+/- 20% or natural limit) on the ICER (onasemnogene abeparvovec versus BSC) – top 20 results only



Abbreviations: BSC, best supportive care; ICER, incremental cost effectiveness ratio.

Table 10: Impact of the one-way sensitivity analysis (+/- 20% or natural limit) on the ICER (onasemnogene abeparvovec versus BSC) – top 20 results only

Parameter Description		Low	High	ICER using low value	ICER using high value	Range	Low % Change	High % Change
1	c_AVXS-101_drug	1,436,000.00	2,154,000.00	197,218	268,994	71,776	15%	15%
2	u_C_State	0.48	0.72	267,653	206,457	61,195	15%	11%
3	c_C_Hospitalizations	29,869.06	44,803.59	225,074	241,137	16,064	3%	3%
4	c_C_Social Services	14,878.08	22,317.12	229,105	237,106	8,002	2%	2%
5	c_E_Hospitalizations	160,197.95	240,296.92	236,781	229,430	7,352	2%	2%
6	u_C_State_Inc_AVX	0.04	0.06	235,640	230,625	5,015	1%	1%
7	Survival_limit_D_Zolgensma	3.20	4.80	233,106	235,407	2,302	0%	1%
8	c_D_Hospitalizations	50,812.63	76,218.95	232,103	234,108	2,004	0%	0%
9	c_E_Social Services	39,994.88	59,992.32	234,023	232,188	1,835	0%	0%
10	u_D_State_Inc_AVX	0.08	0.12	233,992	232,226	1,766	0%	0%
11	Survival_limit_E	12.80	19.20	234,279	232,722	1,558	1%	0%
12	u_D_State	0.15	0.23	233,806	232,409	1,398	0%	0%
13	c_C_Medical visits	2,007.50	3,011.25	232,566	233,645	1,080	0%	0%
14	c_C_Health material	1,663.53	2,495.29	232,658	233,553	895	0%	0%
15	c_D_Social Services	22,317.12	33,475.68	232,665	233,546	880	0%	0%
16	Survival_limit_D	3.20	4.80	233,106	232,760	345	0%	0%
17	c_C_Drugs	594.25	891.38	232,946	233,265	320	0%	0%
18	c_A_Social Services	2,361.60	3,542.40	232,953	233,259	306	0%	0%
19	c_C_Medical tests	520.51	780.77	232,966	233,246	280	0%	0%
20	c_A_Medical visits	1,773.25	2,659.87	232,991	233,220	230	0%	0%

Abbreviations: ICER, incremental cost effectiveness ratio.

Table 11 presents further sensitivity analyses. Results show the impact of changing various assumptions on discount rates, cost assumptions, utility values, alternative natural history sources and exploratory scenarios.

These sensitivity analyses and scenarios are described in more detail in the list of scenarios and the results are discussed in Section 1.1.2.4.

Table 11: Further sensitivity analysis results and scenarios: impact on ICER for onasemnogene abeparvovec versus BSC

#		Onasemnogene abeparvovec	BSC	ICER (£/QALY) ON-A vs BSC:
Base case results		Costs: £2,712,964 QALYs: 10.21	Costs: £381,131 QALYs: 0.21	233,106
DISCOUNT RATES				
1	Costs and effects at 0%	Costs: £3,328,051 QALYs: 21.41	Costs: £441,085 QALYs: 0.22	136,252
2	Costs and effects at 5%	Costs: £2,573,873 QALYs: 8.14	Costs: £360,121 QALYs: 0.21	279,168
3	Costs at 0%, effects at 5%	Costs: £3,328,051 QALYs: 8.14	Costs: £441,085 QALYs: 0.21	364,065
4	Costs at 5%, effects at 0%	Costs: £2,573,873 QALYs: 21.41	Costs: £360,121 QALYs: 0.22	104,480
5	Costs and effects at 1.5%	Costs: £2,993,488 QALYs: 14.89	Costs: £413,269 QALYs: 0.21	175,843
COST ASSUMPTIONS				
6	Use of RWE costs (scenario with SMA type 1 costs doubled) presented at the nusinersen NICE ACM3	Costs: £2,894,865 QALYs: 10.21	Costs: £317,933 QALYs: 0.21	257,607
7	SMA type 3 costs from RWE presented at nusinersen ACM3 applied to the A state and B state patients, other health state costs remain as base case	Costs: £2,753,580 QALYs: 10.21	Costs: £381,131 QALYs: 0.21	237,166
8	Cost of onasemnogene abeparvovec administration 10× higher than base case	Costs: £2,738,192 QALYs: 10.21	Costs: £381,131 QALYs: 0.21	235,627
9	US ICER approach to the costing of ventilatory support (ERG question 2019, **B16**)	Costs: £1,949,638 QALYs: 10.21	Costs: £74,765 QALYs: 0.21	187,425
10	Increase of total D state and E state costs explorative scenario 1 (ERG question 2019, **B20**)	Costs: £2,786,646 QALYs: 10.21	Costs: £506,221 QALYs: 0.21	227,966

#		Onasemnogene abeparvovec	BSC	ICER (£/QALY) ON-A vs BSC:
11	Increase of HCRU in the D state and E state costs explorative scenario 2 (ERG question 2019, **B20**)	Costs: £2,727,180 QALYs: 10.21	Costs: £394,557 QALYs: 0.21	233,184
12	Extreme scenario where all non-permanent ventilated patients (84% in state D, 56% in state C, 20% in state B/A) in whatever health state receive 100% of the Noyes social care/social services costs (ERG question 2019, **B23**)	Costs: £3,000,166 QALYs: 10.21	Costs: £411,970 QALYs: 0.21	258,733
UTILITY VALUES				
13	On-treatment utility using lower values than US ICER (0.05 for D state; 0.025 for C state)	Costs: £2,712,964 QALYs: 9.85	Costs: £381,131 QALYs: 0.21	241,901
14	On-treatment utility using higher values than US ICER (0.15 for D state; 0.075 for C state)	Costs: £2,712,964 QALYs: 10.58	Costs: £381,131 QALYs: 0.21	224,927
15	Using CHERISH values	Costs: £2,712,964 QALYs: 13.11	Costs: £381,131 QALYs: 1.59	202,427
16	Using Lloyd vignette study	Costs: £2,712,964 QALYs: 2.62	Costs: £381,131 QALYs: -0.48	752,527
17	Using exploratory AveXis UK utilities elicitation study using the TTO results from the 'parent' vignettes for states B to E	Costs: [redacted] QALYs: [redacted]	Costs: £381,131 QALYs: -0.54	[redacted]
18	No utility weights (cost per life year gained)	Costs: £2,712,964 Life years: 15.68	Costs: £381,131 Life years: 2.15	172,337
ALTERNATIVE NATURAL HISTORY SOURCE				
19	Use of AveXis external PNCR control dataset: fitted curve kept as Weibull, survival maximum equals 4 years	Costs: £2,712,964 QALYs: 10.21	Costs: £708,035 QALYs: 0.25	201,269
20	Use of Finkel et al. 2017a (ENDEAR sham control): fitted curve kept as Weibull, survival maximum equals 4 years	Costs: £2,712,964 QALYs: 10.21	Costs: £652,584 QALYs: 0.22	206,144
21	Use of De Sanctis et al. 2016 (PNCR, US and Italy study): fitted curve kept as Weibull, survival maximum equals 4 years	Costs: £2,712,964 QALYs: 10.21	Costs: £691,806 QALYs: 0.17	201,329
EXPLORATORY SCENARIOS				

#		Onasemnogene abeparvovec	BSC	ICER (£/QALY) ON-A vs BSC:
22	Patients in the C state (sits unassisted) have a life expectancy the same as the general population: applied to onasemnogene abeparvovec arm only	Costs: £3,055,580 QALYs: 13.80	Costs: £381,131 QALYs: 0.21	196,802
23	One additional sitter in STR1VE-US after 18 months of age. The additional sitter sits between 24 - 30 months of age and therefore moves to sitting in cycle ending 36 months	Costs: £2,736,058 QALYs: 9.86	Costs: £381,131 QALYs: 0.21	244,080
24	One additional walker in STR1VE-US after 18 months of age. The additional walker walks between 24 - 30 months of age and therefore moves to walking in cycle ending 36 months	Costs: £2,685,702 QALYs: 9.92	Costs: £381,131 QALYs: 0.21	237,397
25	No additional sitters or walkers in STR1VE-US after 18 months of age	Costs: £2,708,796 QALYs: 9.56	Costs: £381,131 QALYs: 0.21	248,881
26	Four new sitters and four new walkers in STR1VE-US after 18 months of age	Costs: £2,722,973 QALYs: 12.18	Costs: £381,131 QALYs: 0.21	195,584
27	E state overall survival based on the 'pooled' Gregoretti cohort, i.e. patients with tracheostomy (n=42) or NIV (n=31) with proportions adjusted accordingly in medical cost calculator; curve = exponential, survival limit = 16 years	Costs: £2,750,319 QALYs: 10.21	Costs: £694,197 QALYs: 0.21	205,544
28	Caregiver disutility scores included	Costs: £2,712,964 QALYs: 9.73	Costs: £381,131 QALYs: 0.04	240,622
29	Milestones, overall survival and event-free survival is based on those treated at ≤3.5 months of age in START and STR1VE-US (n=17)	Costs: £2,682,709 QALYs: 11.57	Costs: £381,131 QALYs: 0.21	202,593
30	Milestones, overall survival and event-free survival are based on those treated in START only (n=12)	Costs: £2,797,742 QALYs: 12.37	Costs: £381,131 QALYs: 0.21	198,740
31	Milestones are not 'offset' by a model cycle (i.e. not 'offset' by 6 months)	Costs: £2,695,690 QALYs: 10.36	Costs: £381,131 QALYs: 0.21	228,045
32	Proxy pre-symptomatic scenario A: Assumes age-appropriate milestones (sitting and walking) are observed for all patients, but with conservative one cycle motor milestone offset still applied. Assumes overall survival and event-free survival is 100% in the D state for the short-term model for onasemnogene abeparvovec.	Costs: £2,145,592 QALYs: 23.80	Costs: £381,131 QALYs: 0.21	74,810
33	Proxy pre-symptomatic scenario B: Assumes sitting is observed in all patients, of which 50% attain age-appropriate sitting and 50% achieve delayed sitting. Assumes walking is observed for 82% of patients; of which 50% attain age-appropriate walking and 50% achieve delayed walking. The conservative one cycle motor milestone offset	Costs: £2,322,787 QALYs: 21.41	Costs: £381,131 QALYs: 0.21	91,571

#		Onasemnogene abeparvovec	BSC	ICER (£/QALY) ON-A vs BSC:
	still applied to all milestones. Assumes overall survival and event-free survival is 100% in the D state for the short-term model for onasemnogene abeparvovec.			
34	30 second threshold for sitting independently: Use of the POOLED dataset in which sitting independently is defined as 'sitting alone for ≥30 seconds' for both the START and STR1VE-US trials. All other base case assumptions regarding motor milestones (e.g. application of the conservative one model cycle offset and the assumption of one additional sitter and walker in STR1VE-US between 24 and 30 months of age) remain in place for this scenario. (ERG clarification questions 2020, **A3/B2**)	Costs: £2,659,514 QALYs: 9.61	Costs: £381,131 QALYs: 0.21	242,322

Abbreviations: ACM3, third appraisal committee meeting; BSC, best supportive care; EFS, event-free survival; ERG, evidence review group; ICER, incremental cost effectiveness ratio; Nus, nusinersen; ON-A, onasemnogene abeparvovec; OS, overall survival; PNCR, Pediatric Neuromuscular Clinical Research; QALY, quality-adjusted life-year; RWE, real-world evidence; TTO, time trade off; UK, United Kingdom; US, United States; vs. versus.
† Values are reported per the economic model, discrepancies are due to rounding.

1.1.2.2 Present results of deterministic multi-way scenario sensitivity analysis described in table D10.2.

Table 12 below presents the results of a three-way sensitivity analysis.

From the one-way sensitivity results for onasemnogene abeparvovec versus BSC we took the three variables with the largest impact on the results (excluding the cost of onasemnogene abeparvovec). These are: i) the utility value of C state patients, ii) the cost of hospitalisations for C state patients and, iii) the cost of social services for C state patients. The tables show the results of varying these parameters in combination by the same percentage change as used in the one-way analysis.

These analyses are described in more detail in the list of scenarios and the results are discussed in Section 1.1.2.4.

Table 12: Multi-way analysis of three variables for onasemnogene abeparvovec versus BSC: ICER (£/QALY) results

	Hospitalisation cost in C state = base case	**Hospitalisation cost in C state = base case * 0.8**	**Hospitalisation cost in C state = base case * 1.2**
Social services cost in C state = base case	U1; £233,106 U2; £267,653 U3; £206,457	U1; £225,074 U2; £258,430 U3; £199,344	U1; £241,137 U2; £276,875 U3; £213,571
Social services cost in C state = base case * 0.8	U1; £229,105 U2; £263,059 U3; £202,914	U1; £221,073 U2; £253,837 U3; £195,800	U1; £237,137 U2; £272,281 U3; £210,028
Social services cost in C state = base case * 1.2	U1; £237,106 U2; £272,246U3; £210,001	U1; £229,074 U2; £263,024 U3; £202,887	U1; £245,138 U2; £281,468 U3; £217,114

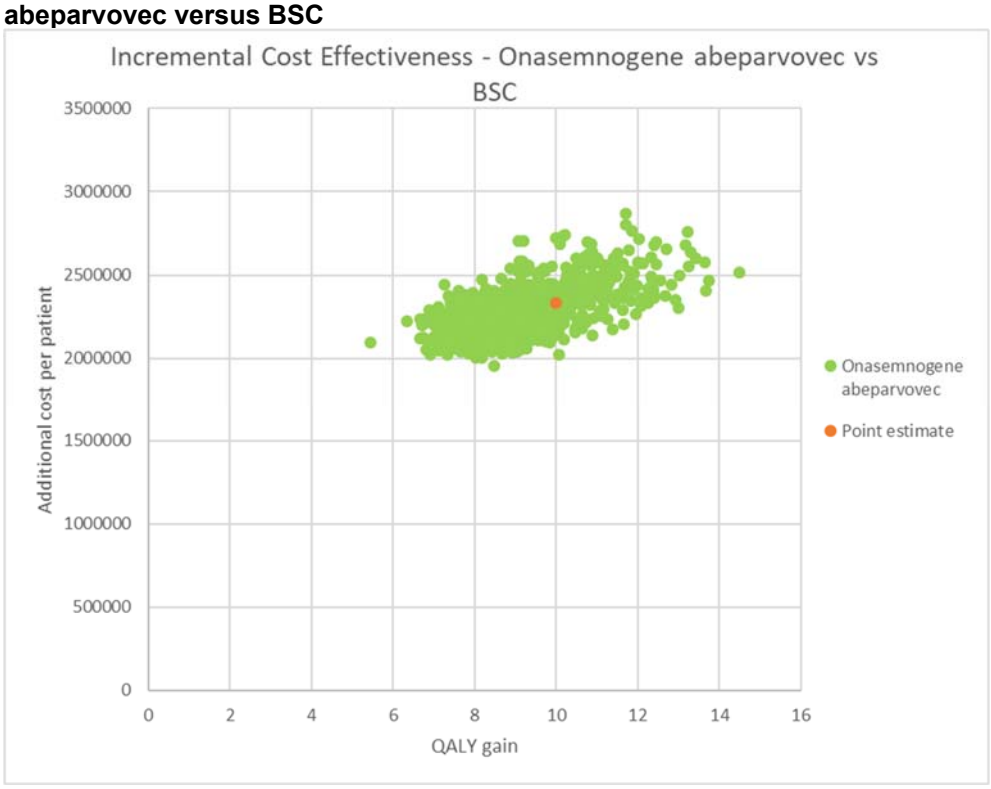
Abbreviations: BSC, best supportive care; ICER, incremental cost effectiveness ratio.
Note: U1 = base case utility value; U2 = base case utility value * 0.8; U3 = base case utility value * 1.2. Note: 'on treatment' C state utility addition (0.05) kept as per base case in all analyses.

1.1.2.3 Present results of the probabilistic sensitivity analysis described in table D10.3.

Figure 2 below shows the results from 1,000 simulations comparing the incremental cost effectiveness of onasemnogene abeparvovec over BSC.

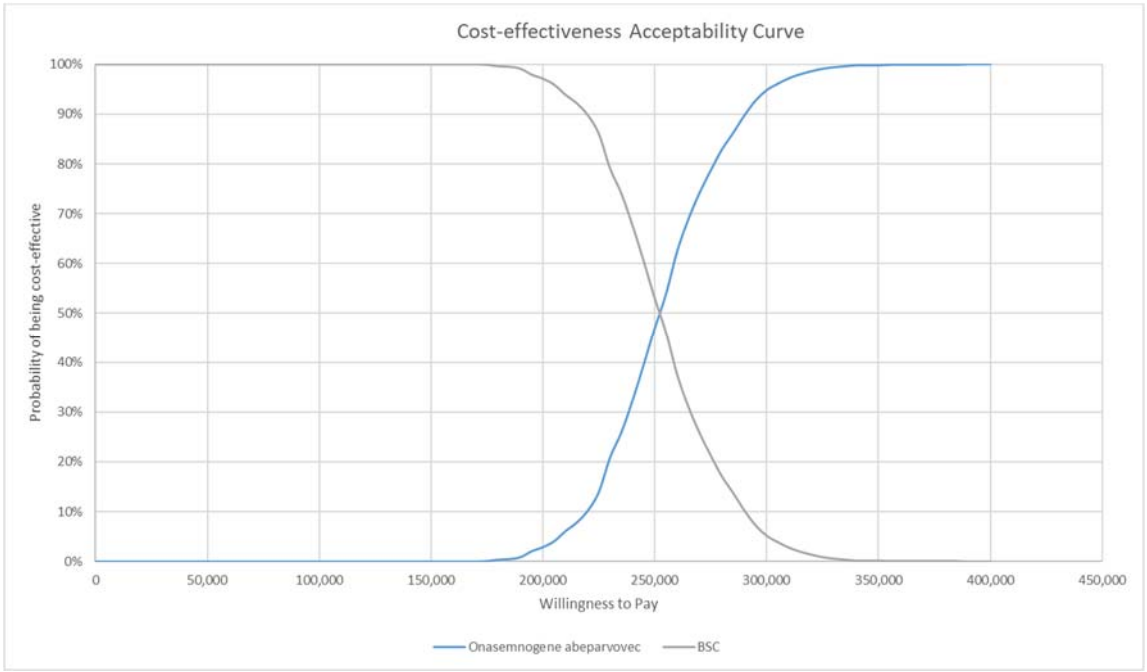
Figure 3 shows the Cost Effectiveness Acceptability Curve from 1,000 simulations comparing onasemnogene abeparvovec with BSC.

Figure 2: Incremental cost effectiveness results – 1,000 simulations of onasemnogene abeparvovec versus BSC



Abbreviations: BSC, best supportive care.

Figure 3: Cost effectiveness acceptability curve –onasemnogene abeparvovec and BSC



Abbreviations: BSC, best supportive care

Table 13 below shows the maximum and minimum results for the two interventions for costs, life years and QALYs.

Finally, Table 14 shows the ICER results (onasemnogene abeparvovec versus BSC) from the simulations.

The results of the probabilistic sensitivity analysis are discussed in answer to question 1.1.2.4.

Table 13: Results from 1,000 simulations of onasemnogene abeparvovec and BSC

	Max costs (£)	Min costs (£)	Max LYs	Min LYs	Max QALYs	Min QALYs
BSC	520,503	248,661	2.16	2.09	0.94	-0.73
Onasemnogene abeparvovec	3,189,601	2,375,849	19.59	12.77	14.61	5.34

Abbreviations: BSC, best supportive care; LY, life-ears; QALY, quality-adjusted life-years.

Table 14: ICER (£/QALY) results from 1,000 simulations of onasemnogene abeparvovec and BSC

ICER ranges	Max ICER	Min ICER	Mean costs/ mean QALYs	Median	95% plausible interval - low	95% plausible interval - high
Onasemnogene abeparvovec versus BSC	385,444	173,915	249,547	251,969	198,085	312,012

Abbreviations: BSC, best supportive care; ICER, incremental cost effectiveness ratio; QALY, quality-adjusted life-years.

1.1.2.4 What were the main findings of each of the sensitivity analyses?

Onasemnogene abeparvovec versus BSC

One-way sensitivity analysis

All variables were varied by +/- 20% or natural limits if these were within the +/- 20% range.

The only variables that impacted on the ICER by 5% or greater in either direction were: i) the cost of onasemnogene abeparvovec (high ICER of £268,994; low ICER of £197,218) and; ii) the patient utility value attached to the C state (high ICER of £206,457; low ICER of £267,653).

We conducted further one-way analyses of the results. Only results that change the ICER by relatively large amounts or require further explanation are discussed. Full results are shown in Section 1.1.2.1.

- **Discount rates:** Discounting costs and effects at 0% decreases the ICER by over 41% whilst discounting costs at 5% but applying no discounting to effects decreases the ICER by 55%. Discounting effects at 5% but not discounting costs increases the ICER by 56%. Discounting both costs and effects at 1.5% decreases the ICER by over 24% to £175,843

- **Cost assumptions:** Of the cost assumptions tested in the model, most had minor effects on the ICER; i.e. SMA type 3 costs from RWE presented at nusinersen ACM3 (1) used for A state and B state patients and cost of onasemnogene abeparvovec administration 10× higher than baseline. The ICER increased by 10.5% (from £233,106 to £257,607) when the base case health state costs were replaced with the RWE costs (using SMA type 1 costs doubled) presented at the nusinersen ACM3. Results from applying ERG exploratory assumptions on total D and E state costs (ERG question 2019, **B20**) decreased the ICER by 2% to £227,966 when scenario 1 was employed whilst the ICER was essentially unchanged when scenario 2 was used at £233,184. Using the extreme scenario where all non-permanent ventilated patients in whatever health state receive 100% of the Noyes et al 2006 social care/social services costs (ERG question 2019, **B23**) increased the ICER by £25,628 (11%). Using the US ICER approach to the cost of ventilatory support (ERG question 2019, **B16**) reduced the ICER by £45,681 (19.6%) to £187,425.

- **Utility values:** The use of the utilities mapped from PedsQL in CHERISH (8) and the use of applying no utility weights (i.e. cost per LYG) both lead to the ICER decreasing from £233,106 to £202,427 and to £172,337, respectively. When the Lloyd et al. 2017 clinician-proxy vignette study (9) is used, the ICER increases to £752,527: note that the number of QALYs gained from BSC in this scenario is -0.48. The use of the exploratory AveXis UK utilities elicitation study (10) increases the ICER by [redacted] to [redacted]: note that the number of QALYs gained from BSC in this case is -0.54.

- **Alternative natural history source:** All of the alternative natural history sources decrease the ICER: by 11.6% when Finkel et al. 2017 (ENDEAR Sham control arm) (3) is used, by 13.6% when De Sanctis et al. 2016 (PNCR, US and Italian study)

adjusted/disaggregated (4) dataset is used and by 13.7% when the AveXis external PNCR control (n=23) (2) adjusted/disaggregated dataset is used.

Multi-way sensitivity analysis

The multi-way sensitivity analysis compared the three variables (excluding the cost of onasemnogene abeparvovec) that had the largest impact on the ICER as shown by the one-way analysis. These were the patient utility value attached to the C state (0.6 in the base case) the cost of hospitalisations in the C state (£37,336 in the base case) and the cost of social services in the C state (£18,598 in the base case). Values were varied by +/- 20%.

The results ranged from a low of £195,800 (20% reduction in C state hospitalisation costs, 20% reduction in C state social services costs and 20% increase in the C state utility value) to a high of £281,468 (20% increase in C state hospitalisation costs, 20% increase in C state social services costs and 20% reduction in C state utility value).

Further sensitivity analysis and exploratory scenarios

In the optimistic scenario that assumes there is improved survival for any patient that can sit unassisted (C state) in the onasemnogene abeparvovec arm, the ICER falls by £36,304 (16%) to £196,802.

Including caregiver disutility scores impacts on the ICER only slightly, increasing it by £7,516 to £240,622.

In scenarios that explored different milestone attainment in STR1VE-US patients after 18 months of age, in the POOLED dataset:

- The ICER increased by 4.7% to £244,080, for one additional sitter in STR1VE-US after 18 months of age
- The ICER increased by 1.8% to £237,397, for one additional walker in STR1VE-US after 18 months of age
- The ICER increased by 6.8% to £248,881, for no additional sitters or walkers in STR1VE-US after 18 months of age
- The ICER decreased by 16.1% to £195,584, for four new sitters and four new walkers in STR1VE-US after 18 months of age

In the scenario where milestones, overall survival and event-free survival are based on those treated at ≤3.5 months of age in START and STR1VE-US (n=17) the ICER decreased by £30,513 (13.1%) to £202,593.

In the scenario where milestones, overall survival and event-free survival are based on those treated in START only (n=12), the ICER decreases by £34,366 (14.7%) to £198,740.

In the scenario where the conservative model ‘offset’ is not applied to milestones in the POOLED dataset, the ICER decreases by 2.2% to £228,045.

In the scenario where the E state overall survival is based on the 'pooled' Gregoretti cohort, i.e. patients with tracheostomy (n=42) or NIV (n=31), the ICER decreases by £27,562 (11.8%) to £205,544.

In the proxy pre-symptomatic SMA scenario A, in which all (100%) pre-symptomatic SMA infants treated with onasemnogene abeparvovec are assumed to attain age-appropriate milestones (sitting and walking), but with the conservative one model cycle motor milestone offset still applied the ICER decreased by £158,296 (68%) to £74,810.

In the proxy pre-symptomatic SMA scenario B, in which all (100%) pre-symptomatic SMA infants treated with onasemnogene abeparvovec are assumed to attain sitting, of which 50% do so at an age-appropriate age and of which 50% do so at a delayed age relative to WHO windows the ICER decreased by £141,534 (60.7%) to £91,571. This scenario assumed walking is attained in 82% of pre-symptomatic SMA infants treated with onasemnogene abeparvovec, of which 50% attain age-appropriate walking and 50% achieve delayed walking relative to WHO windows.

In the scenario where milestones are based on using the POOLED dataset but in which sitting unassisted is defined as 'sitting alone for ≥30 seconds' for both the START and STR1VE-US trials, the ICER increased by £9,217 (4%) to £242,322.

Probabilistic sensitivity analysis

The minimum and maximum number of QALYs produced for BSC from the 1,000 simulations were -0.73 and 0.94; the minimum and maximum total costs were £248,661 and £520,503.

The minimum and maximum number of QALYs produced for onasemnogene abeparvovec from the 1,000 simulations were 5.34 and 14.61; the minimum and maximum total costs were £2,375,849 and £3,189,601.

The minimum and maximum ICERs produced from the simulations were £173,915 and £385,444 with a 95% credible range of between £198,085 and £312,012.

The mean and median ICERs produced from the simulations were £249,547 and £251,969, respectively. This simulation mean is 7% higher than the deterministic result of £233,106 . Analysis of the results showed that this is due to the number of life years gained from the onasemnogene abeparvovec simulations were 78.7% of the runs produced total life years less than the onasemnogene abeparvovec deterministic value of 31.02 (undiscounted) life years (range 25.49 to 45.23). A total of 76.2% of the ICERs produced from the PSA simulations were above the deterministic ICER.

1.1.2.5 What are the key drivers of the cost results?

Table 15 shows the percentage of total lifetime costs for each cost category for each of the two interventions. A 3.5% discount rate has been used.

Table 15: Percentage of total costs by cost category

Cost Category	Intervention	
	Onasemnogene abeparvovec	BSC

Product cost	66.16%	0.00%
Product admin cost	0.10%	0.00%
Care costs		
Drugs	0.46%	0.45%
Medical tests	0.38%	0.43%
Medical visits	1.54%	2.10%
Hospitalisations	20.19%	73.04%
GP & emergency	0.11%	0.22%
Health materials	1.18%	2.03%
Social services	9.86%	21.73%
Total	**100.00%**	**100.00%**

Abbreviations: BSC, best supportive care; GP, general practitioner. Tables may not sum exactly to 100% due to rounding.

The cost of onasemnogene abeparvovec is the major cost component of total onasemnogene abeparvovec costs followed by the cost of hospitalisations and then the cost of social services support.

For BSC the major cost is the cost of hospitalisations followed by the cost of social services support.

1.1.3 Miscellaneous results

None.

1.1.4 Describe any additional results that have not been specifically requested in this template. If none, please state.

None.

1.2 *Subgroup analysis*

1.2.1 Specify whether analysis of subgroups was undertaken and how these subgroups were identified. Cross-reference the response to the decision problem in table A1.

No subgroup analysis using pre-specified subgroups was undertaken. It is noted that, an exploratory scenario analysis is presented in Section 1.1.2 in which motor milestones, overall survival and event-free survival for the onasemnogene abeparvovec arm are based on those treated at ≤3.5 months of age in START and STR1VE-US (n=17). The cut-off of 3.5 months of age was chosen, as this was the median age at which infants across START and STR1VE-US received onasemnogene abeparvovec. This scenario is not presented as a

formal subgroup analysis as this population was not a pre-specified group in the clinical trial protocols. However, this scenario has been presented to demonstrate the value of onasemnogene abeparvovec when used early in the course of the disease.

1.2.2 Define the characteristics of patients in the subgroup(s).

Not applicable.

1.2.3 Describe how the subgroups were included in the cost-effectiveness analysis.

Not applicable.

1.2.4 What were the results of the subgroup analysis/analyses, if conducted? The results should be presented in a table similar to that in section 12.5.6 (base-case analysis). Please also present the undiscounted incremental QALYs consistent with section 12.5.7

Not applicable.

1.2.5 Were any subgroups not included in the submission? If so, which ones, and why were they not considered?

Not applicable.

2 Cost to the NHS and Personal Social Services

The purpose of Section 13 is to allow the evaluation of the affordability of the technology.

2.1 *How many patients are eligible for treatment in England? Present results for the full marketing authorisation and for any subgroups considered. Also present results for the subsequent 5 years.*

The budget impact presented is based on the incident SMA type 1 population only as the budget impact model feeds directly from the cost-utility model, which contains clinical effectiveness data for incident SMA type 1 patients only, due to the eligibility criteria of the completed onasemnogene abeparvovec trials (START and STR1VE-US).

Whilst it is recognised there are other patient populations covered in the final scope that would be eligible for treatment with onasemnogene abeparvovec – pre-symptomatic infants with a genetic phenotype predictive of SMA type 1 (i.e. up to three copies of the *SMN2* gene) and in prevalent symptomatic SMA type 1 patients (e.g. those older than 6 months and/or those who have received another SMA-related therapy) – there is a paucity of clinical effectiveness data on which to develop a robust budget impact assessment. Furthermore, assessing the budget impact in the prevalent symptomatic SMA type 1 patients including those who have received nusinersen is challenging due to the lack of routine commissioning of nusinersen in England. Therefore, the company has presented a budget impact analysis for the incident SMA type 1 population for which the most robust data are available.

The following approach was taken to estimate the incident SMA type 1 population of England: SMA (all types) has an annual incidence of approximately 9.4:100,000 live births, as reported by Lally et al 2017 (11); this incidence rate is applied to the most recent live births data for England (reported as 625,651 live births in 2018 (12)), to estimate that there are 59 incident cases of SMA (all types) per year in England; applying that SMA type 1 accounts for 58% of all cases of SMA (13), this results in 34 incident cases of SMA type 1 per year in England. It is assumed this will be the case each year, for the next 5 years.

Real world evidence from the nusinersen UK early access programme (EAP) reported that in its last 12 months of operation, 32 babies were diagnosed with SMA type 1 and treated with nusinersen in England (personal communication; [redacted], Paediatric Neurologist). These 32 patients are considered to represent a “steady-state” of incident patients presenting for pharmacotherapy. Therefore, it is assumed that 2 of the expected 34 incident patients did not present for pharmacotherapy during this period and that this proportion, 5.9%, would not present for pharmacotherapy in any modelled treatment scenario. Potential reasons for this may include factors such as the poor condition of the baby or the beliefs/preferences of the family. Therefore, it is estimated that each year there are 32 incident cases of SMA type 1 per year in England who present for pharmacotherapy. The remaining criteria applied to assess eligibility depend on AAV9 antibody screening as shown in Figure 4.

Figure 4: Patient eligibility for pharmacotherapy

SMA type 1 incident cases (n=34, 100%)		
Present for pharmacotherapy (n=32, 94.1%)		Do not present for pharmacotherapy (n=2, 5.9%)
Eligible for onasemnogene abeparvovec (87.8%)	Not eligible for onasemnogene abeparvovec due to anti-AAV9 antibody titre (12.2%)	
100% treated with onasemnogene abeparvovec	100% treated with BSC	100% BSC

Abbreviations: AAV9, adeno-associated virus 9; BSC, best supportive care; SMA, spinal muscular atrophy.

Anti-AAV9 antibody screening

Some patients eligible for pharmacotherapy will not be eligible for onasemnogene abeparvovec due to a high anti-AAV9 antibody titre (all patients in the onasemnogene abeparvovec clinical trials had and an anti-AAV9 antibody titres at or below 1:50 before treatment). In the ongoing STR1VE-EU clinical trial, being conducted in Europe, the proportion of SMA type 1 incident cases ineligible for onasemnogene abeparvovec due to a high anti-AAV9 titre was 5 of 41 cases (12.2%) screened. STR1VE-EU screening data are the most generalisable to the English incident population given that newborn screening is not currently routinely available in the UK. Therefore, we assume of the patients who present for pharmacotherapy, 12.2% are not eligible for treatment with onasemnogene abeparvovec.

Treatment choice/availability

The budget impact model compares the 'current situation' to 'onasemnogene abeparvovec becomes available'

a) 'Current situation' = BSC is the only treatment option for SMA type 1 patients

b) 'Onasemnogene abeparvovec becomes available' = Onasemnogene abeparvovec is introduced, and is the only pharmacotherapy treatment option available

2.2 *Describe the expected uptake of the technology and the changes in its demand over the next five years*

Expected market shares for onasemnogene abeparvovec are described below.

a) 'Current situation' (Table 16): 100% of cases would receive BSC

b) 'Onasemnogene abeparvovec becomes available' (Table 17): As described in Section 2.1, 12.2% of incident patients would be unsuitable for onasemnogene abeparvovec due to high anti-AAV9 antibody titres. Therefore, this 12.2% has been excluded from the patients who present for pharmacotherapy (i.e. 12.2% of the 94.1% presenting for pharmacotherapy [i.e. 11.5%] as discussed in Section 2.1). Based on the above, we have estimated that 82.6% of the patients would receive onasemnogene abeparvovec. For BSC, we have estimated that in addition to the 5.9% (who do not present for pharmacotherapy as discussed in Section 2.1), the

11.5% of the patients who would be unsuitable to receive onasemnogene abeparvovec (as discussed above) would also receive BSC. Therefore, it is estimated that in total 17.4% (11.5% + 5.9%) of the patients would receive BSC.

Table 16: Assumption of the distribution of SMA type 1 cases by treatment in the 'current situation' – only BSC is available

Intervention	Year 1	Year 2	Year 3	Year 4	Year 5
Onasemnogene abeparvovec	0%	0%	0%	0%	0%
BSC	100%	100%	100%	100%	100%

Abbreviations: BSC, best supportive care; SMA, spinal muscular atrophy.

Table 17: Assumption of the distribution of SMA type 1 cases by treatment in the 'onasemnogene abeparvovec becomes available'

Intervention	Year 1	Year 2	Year 3	Year 4	Year 5
Onasemnogene abeparvovec	82.6%	82.6%	82.6%	82.6%	82.6%
BSC	17.4%	17.4%	17.4%	17.4%	17.4%

Abbreviations: BSC, best supportive care; SMA, spinal muscular atrophy

2.3 *In addition to technology costs, please describe other significant costs associated with treatment that may be of interest to NHS England (for example, additional procedures etc)*

None expected; however, AveXis is committed to working with neuromuscular centres, including potential infusion centres and regional specialist centres, to scope and design a service delivery that includes onasemnogene abeparvovec.

Infants will require a test for the AAV9 antibody prior to treatment with onasemnogene abeparvovec. However, AAV9 antibody testing will be funded and coordinated by AveXis at a central European lab (Viroclinics, The Netherlands).

2.4 *Describe any estimates of resource savings associated with the use of the technology*

Because of the large increases in the quantity and quality of life that onasemnogene abeparvovec produces compared with BSC, the opportunities for absolute resource savings are limited. Patients who would otherwise have died still require some treatment related support. Section 1.1.1.8 shows that (discounted) mean total treatment costs (i.e. all SMA care costs) would be expected to rise from £381,131 for BSC patients to £915,162 for onasemnogene abeparvovec treated patients.

2.5 *Are there any other opportunities for resource savings or redirection of resources that it has not been possible to quantify?*

No opportunities for resource savings or redirection of resources are applicable for NHS/PSS/government funded programmes, apart from possible disability payments and education costs (see question 3.2). If possible, changes to caregiver time/resources are considered to be applicable, see Section 3.4.

2.6 *Describe any costs or savings associated with the technology that are incurred outside of the NHS and PSS*

Possible costs for lost patient income are discussed in answer to question 3.1. Possible costs for lost caregiver income are discussed in answer to question 3.4.

2.7 *What is the estimated budget impact for the NHS and PSS over the first year of uptake of the technology, and over the next 5 years?*

The budget impact model is constructed as a module within the cost-effectiveness model. The numbers of patients who would be eligible for treatment within each year of a 5-year period and the current treatment options that onasemnogene abeparvovec would replace for each year are selected. All cost data for the analysis are drawn from the cost-effectiveness model. Discounting is not applied within the budget impact model. The model calculates the total cost of treatment for patients treated through Years 1 to 5 inclusive by reference to the model underlying the cost-effectiveness analysis. If a patient were to join in Year 2, then the model would begin calculation, again, from Year 1, but the Year 1 data for this patient are added to the Year 2 data for the first patient. Similarly, the Year 2 data for the second year patient are added to the Year 3 data for the patient who joined in Year 1.

We show i) the budget impact of onasemnogene abeparvovec replacing a single BSC patient over a 5 year period and ii) the budget impact using the estimated incident population treated with onasemnogene abeparvovec when this technology becomes available.

2.7.1 Budget impact of onasemnogene abeparvovec replacing a single BSC patient

Table 18 and Table 19 show the annual cost per year for up to 5 years of one patient treated with onasemnogene abeparvovec rather than BSC. The total budget impact (sum of years 1 to 5 of ‘total budget impact’ row in Table 19) is £1,865,249.

Table 18: Five year budget impact of treating one patient with onasemnogene abeparvovec ('onasemnogene abeparvovec becomes available') rather than BSC ('current situation')

Annual cost outcomes	Year 1	Year 2	Year 3	Year 4	Year 5
BSC only available					
Drug acquisition costs	0	0	0	0	0
Drug administration costs	0	0	0	0	0
Total drug costs	0	0	0	0	0
SMA medical costs	87,232	59,106	55,112	41,685	34,187
Total SMA care costs	87,232	59,106	55,112	41,685	34,187
Total costs	**87,232**	**59,106**	**55,112**	**41,685**	**34,187**
Onasemnogene abeparvovec becomes available'					
Onasemnogene abeparvovec: drug acquisition costs	1,795,000	0	0	0	0
Onasemnogene abeparvovec: drug administration costs	2,803	0	0	0	0
Onasemnogene abeparvovec: total drug costs	1,797,803	0	0	0	0
Total drug costs	1,797,803	0	0	0	0
SMA medical costs	102,733	85,875	67,014	45,075	44,072
Total SMA care costs	102,733	85,875	67,014	45,075	44,072
Total costs	**1,900,535**	**85,875**	**67,014**	**45,075**	**44,072**

Abbreviations: BSC, best supportive care; SMA, spinal muscular atrophy.

Table 19: Five year budget impact of treating one patient with onasemnogene abeparvovec rather than BSC – net position

Budget impact	Year 1	Year 2	Year 3	Year 4	Year 5
Pharmacy budget impact	1,797,803	0	0	0	0
SMA care budget impact	15,501	26,769	11,902	3,390	9,885
Total budget impact	**1,813,304**	**26,769**	**11,902**	**3,390**	**9,885**

Abbreviations: BSC, best supportive care; SMA, spinal muscular atrophy.

2.7.2 Budget impact of onasemnogene abeparvovec on the estimated incident population of onasemnogene abeparvovec being introduced

Rationale and calculations underlying the expected market shares under this scenario are described in detail in Section 2.2, but are shown again below for completeness in Table 20 and Table 21.

Table 20: Assumption of the distribution of SMA type 1 cases by treatment in the 'current situation'

Intervention	Year 1	Year 2	Year 3	Year 4	Year 5
Onasemnogene abeparvovec	0%	0%	0%	0%	0%
BSC	100%	100%	100%	100%	100%

Abbreviations: BSC, best supportive care; SMA, spinal muscular atrophy.

Table 21: Assumption of the distribution of SMA type 1 cases by treatment in the 'onasemnogene abeparvovec becomes available' situation

Intervention	Year 1	Year 2	Year 3	Year 4	Year 5
Onasemnogene abeparvovec	82.6%	82.6%	82.6%	82.6%	82.6%
BSC	17.4%	17.4%	17.4%	17.4%	17.4%

Abbreviations: BSC, best supportive care; SMA, spinal muscular atrophy.

Table 22 and Table 23 show the annual cost per year for up to 5 years, assuming 34 incident SMA type 1 cases per year for each of the five years. The total budget impact (sum of years 1 to 5 in 'total budget impact' row in Table 23 is £259,101,959.

Table 22: Five year budget impact of 34 incident cases per year for each of the five years treated with onasemnogene abeparvovec (or BSC) ('onasemnogene abeparvovec becomes available') rather than BSC ('BSC only available')

Annual cost outcomes	Year 1	Year 2	Year 3	Year 4	Year 5
BSC only available					
Nusinersen: drug acquisition costs	0	0	0	0	0
Nusinersen: drug administration costs	0	0	0	0	0
Total drug costs	0	0	0	0	0
SMA medical costs	2,965,884	4,975,476	6,849,276	8,266,569	9,428,935
Total SMA care costs	2,965,884	4,975,476	6,849,276	8,266,569	9,428,935
Total costs	**2,965,884**	**4,975,476**	**6,849,276**	**8,266,569**	**9,428,935**
Onasemnogene abeparvovec becomes available					
Onasemnogene abeparvovec: drug acquisition costs	50,410,780	50,410,780	50,410,780	50,410,780	50,410,780
Onasemnogene abeparvovec: drug administration costs	78,707	78,707	78,707	78,707	78,707
Onasemnogene abeparvovec: total drug costs	50,489,487	50,489,487	50,489,487	50,489,487	50,489,487
Total drug costs	50,489,487	50,489,487	50,489,487	50,489,487	50,489,487
SMA medical costs	3,401,214	6,162,590	8,370,642	9,883,126	11,323,091
Total SMA care costs	3,401,214	6,162,590	8,370,642	9,883,126	11,323,091
Total costs	**53,890,701**	**56,652,077**	**58,860,129**	**60,372,614**	**61,812,578**

Abbreviations: BSC, best supportive care; SMA, spinal muscular atrophy.

Table 23: Five year budget impact of treating of 34 incident cases per year for each of the five years treated with onasemnogene abeparvovec (or BSC) rather than BSC - net position

Budget impact	Year 1	Year 2	Year 3	Year 4	Year 5
Pharmacy budget impact	50,489,487	50,489,487	50,489,487	50,489,487	50,489,487
SMA care budget impact	435,330	1,187,115	1,521,366	1,616,557	1,894,155
Total budget impact	**50,924,817**	**51,676,602**	**52,010,853**	**52,106,044**	**52,383,643**

Abbreviations: BSC, best supportive care; SMA, spinal muscular atrophy.
Note: All values are taken from the economic model and are subject to rounding. Any discrepancies between results presented in the table and text are due to rounding.

3 Impact of the technology beyond direct health benefits

3.1 *Describe whether a substantial proportion of the costs (savings) or benefits are incurred outside of the NHS and personal social services, or are associated with significant benefits other than health.*

Onasemnogene abeparvovec may have benefits beyond the outcomes assessed in trials. For example, if pharmacotherapy improves or retains children's mobility, children may attend school, reach educational achievement and participate in the workforce in the future. Greater independence for the child may also allow caregivers to return to work. An effective treatment also may reduce anxiety and stress among caregivers and wider communities, reduce other resources used (e.g. educational system), and promote more interaction between children with SMA and others in the community. Furthermore, even small improvements in motor abilities can allow patients greater ability for self-care and independence.

Patient educational achievement and workforce participation

Patients treated with onasemnogene abeparvovec could participate in the workforce in the future. Therefore, the possible educational achievement of patients and the impact on workforce participation was explored.

A comprehensive study of the educational achievement of patients with SMA was conducted by the Lewin Group for the Muscular Dystrophy Association in 2012 (14) to obtain US estimates.

Table 24 shows the highest level of education for SMA patients (which was attributed to the C state and B state) and the general US population (which was attributed to the A state). Of note, is that the SMA population from the Lewin Group study reported a higher percentage of SMA patients having a post-graduate degree than the general US population (19% vs. 11.4%).

Table 24: Potential educational achievement for patients who may live to working age

	Not available/ no attainment	Some high school	High School Graduate	Some college/ Associate Degree	College Degree	Post-graduate degree
C state†	4%	6%	13%	28%	30%	19%
B state†	4%	6%	13%	28%	30%	19%
A state	3.7%	7.3%	28.9%	28.6%	20.0%	11.4%

† Values from source have been rounded
Source: United States, Census Bureau: Educational Attainment in the United States, 2017 (15); Lewin Group for the Muscular Dystrophy Association in 2012 (14).

Information on UK median annual earnings (16), unemployment rates (17) and the percentage of people with disabilities that are employed by educational achievement level (18) was collated (Table 25).

Table 25: UK - General population income based on educational achievement

Educational achievement	Median annual earnings	Unemployment rate	People with disabilities - employed
Some high school	£17,868	5.6%	17.0%
High school graduate	£23,628	3.1%	45.6%
Some College/Associate Degree	£29,469	3.1%	45.6%
College Graduate	£34,909	2.3%	71.7%
Post-Graduate Degree	£40,527	2.3%	71.7%

For the A state patients the average expected income per patient per year by educational achievement was calculated as: percentage expected educational achievement from Lewin Group study * median annual UK income by educational achievement * the expected employment rate. The average income per patient from the sum of these weighted values was then calculated.

For C state patients, the same approach was used and the employment rate was that of people with disabilities. For patients in B state, the unemployment rate was assumed to be between the rate for the general population and for people with disabilities (note: set at 50% - user variable).

The resulting average income per patient (£19,141 for C state patients, £25,057 for B state patients and £28,427 for A state patients) was then input to the model from the age of 25.

The consequences of introducing these lifetime potential earnings on total costs was that the total per patient costs for onasemnogene abeparvovec treated fell by £65,232 (from £2,712,964 to £2,647,733).

The impact of introducing these lifetime patient income benefits is that the ICER for onasemnogene abeparvovec versus BSC falls from £233,106 to £226,585.

3.2 *List the costs (or cost savings) to government bodies other than the NHS*

Patients treated with onasemnogene abeparvovec who would have otherwise died if treated with BSC may be entitled to disability payments. Similarly, since some of these patients may be unemployed, unemployment benefits may be required. Finally, some patients may have special education requirements during childhood and adolescence.

3.3 *List the costs borne by patients that are not reimbursed by the NHS*

Parents/caregivers may incur additional paid professional care costs over that provided by the NHS. In addition, modifications to housing and vehicles may not be provided by the NHS or related services. Survey B from the SMA UK Patient and Caregiver survey (March 2019) (19) found the mean annual out of pocket (OOP) costs incurred for health materials and travel and accommodation (associated appointment costs and hospital stays) per SMA person were on average £8,025 per year.

We applied these costs to all E, D and C state patients in the model. The ICER for onasemnogene abeparvovec versus BSC increased from £233,106 to £241,634. This increase is due to the extra life years gained from onasemnogene abeparvovec over BSC (mainly in the C state).

3.4 *Provide estimates of time spent by family members of providing care. Describe and justify the valuation methods used*

Information on the level of care required for patients with SMA by health state over time was collated from clinical experts (Table 26). These values derived from clinical experts are broadly in line with the average number of unpaid caregiving hours/week available from the SMA UK Patient and Caregiver survey (March 2019) (19): Walks unassisted (66 hours/week [9 hours/day]; Sits unassisted (100 hours/week [14 hours/day]); Not sitting (117 hours/week [17 hours/day]).

Table 26: Level of care required, by health state and age band

Cycle	Age band	SMA-specific care required (hours/day)				
		E	D	C	B	A
1–4	0<24 months	16–24	16–24	16–24	16–24	SMA-specific care not needed
5–8	24<60 months	16–24	16–24	16–24	16–24	SMA-specific care not needed
9–21	5–17 years	16–24	16–24	8–15	8–15	SMA-specific care not needed
22+	18+ years.	16–24	16–24	1–8	SMA-specific care not needed	SMA-specific care not needed

Source: Clinical expert advice
Abbreviations: SMA, spinal muscular atrophy.

We then used SMA results from the Lewin Group study for the Muscular Dystrophy Association in 2012 (14) and converted the estimated lost income by level of care required to GBP using a Purchasing Power Parity value of 0.69 from the Organisation for Economic Co-operation and Development (OECD) (20) (Table 27).

Table 27: Predicted lost family income (US$ converted to GBP)

Level of care required	Lost income
Lost family income - US$ (2018)	
16–24 hours/day	$21,598
8–15 hours/day	$7,323
1–8 hours/day	$4,170
SMA-specific care not needed	$0
Lost family income - GBP (2018)	
16–24 hours/day	£16,989
8–15 hours/day	£5,760
1–8 hours/day	£3,280
SMA-specific care not needed	£0

Abbreviations: GBP, Great British Pound; US, United States.

The resulting values were applied to the various health states dependent on the age of the patient (Table 28).

Table 28: Lost family income by health state and age band

Cycle	Age at end of cycle	E	D	C	B	A
1–4	0–<24 months	£8,494	£8,494	£8,494	£8,494	0
5–6	24–<36 months	£8,494	£8,494	£8,494	£8,494	0
7–8	36–<60 months	£16,989	£16,989	£16,989	£16,989	0
9–21	5–17 years	£16,989	£16,989	£5,760	£5,760	0
22+	18+ years	£16,989	£16,989	£3,280	£0	0

The consequences of introducing these lifetime potential earnings on total costs are that the total per patient costs for BSC treated patients increases by £36,444 (from £381,131 to £417,574) whilst the total per patient costs for onasemnogene abeparvovec treated patients increases by £113,794 (from £2,712,964 to £2,826,759).

The impact on the ICER of introducing these lifetime productivity estimates is that the ICER for onasemnogene abeparvovec versus BSC increases from £233,106 to £240,838.

When these results for lost family income are combined with the results from including potential income gains as discussed in Section 3.1, the baseline ICER (no inclusion for lost family income nor potential income gains) for onasemnogene abeparvovec versus BSC increases from £233,106 to £234,317.

We also used the results from the SMA UK Patient and Caregiver survey (March 2019) (19) to examine the impact on total costs. The survey found that the average annual cost for loss of productivity per unpaid caregiver at £14,350 based on reducing their hours by 25 hours per week. Using these costs in the model for patients who require any level of SMA related care (and assuming that caregivers are 28 years old at baseline and may give care until their age is 65 years if the patient is still alive) increased the total costs for BSC patients by £30,782 and by £181,514 for onasemnogene abeparvovec treated patients. We note, however, that the £14,350 figure is an average for all SMA patients and that these results probably underestimate the time inputs for non-sitting patients and overestimate the time inputs for walking patients. The ICER for onasemnogene abeparvovec versus BSC increased from £233,106 to £248,174.

It should be noted that these caregiver estimates are based only on a single carer. The SMA UK Patient and Caregiver survey (March 2019) (19) indicates that a wide range of carers provide support to patients with SMA ranging from immediate family friends and neighbours.

4 References

Please note that a PDF for Briggs et al. 2006 is not provided in the reference pack accompanying this submission.

1. National Institute for Health and Care Excellence. Nusinersen for treating spinal muscular atrophy [GID-TA10281]. 3rd appraisal committee meeting public gallery slides. 6 March 2019. 2019.
2. AveXis. Data on file. PNCR and NeuroNext database report. 2018.
3. Finkel RS, Mercuri E, Darras BT, Connolly AM, Kuntz NL, Kirschner J, et al. Nusinersen versus Sham Control in Infantile-Onset Spinal Muscular Atrophy. N Engl J Med. 2017a Nov 2;377(18):1723-32.
4. De Sanctis R, Coratti G, Pasternak A, Montes J, Pane M, S. Mazzone E, et al. Developmental milestones in type I spinal muscular atrophy. 2016.
5. Tilford JM, Grosse SD, Robbins JM, Pyne JM, Cleves MA, Hobbs CA. Health state preference scores of children with spina bifida and their caregivers. Qual Life Res. 2005 May;14(4):1087-98.
6. Wittenberg E, Prosser LA. Disutility of illness for caregivers and families: a systematic review of the literature. PharmacoEconomics. 2013 Jun;31(6):489-500.
7. World Health Organization. WHO Multicentre Growth Reference Study Group: WHO Child Growth Standards based on length/height, weight and age. Acta Paediatr Suppl. 2006b Apr;450:76-85.
8. Thompson R, Vaidya S, Teynor M. The Utility of Different Approachs to Developing Health Utilities Data in Childhood Rare Diseases; A Case Study in Spinal Muscular Atrophy (SMA). Value in Health. 2017;20(9):A725-A6.
9. Lloyd AJGK, Thompson, R., Vaidya, S., Teynor, M. . Estimation of the health-related quality of life benefits of treatment for spinal muscular atrophy (SMA). ISPOR 20th Annual European Congress; 2017; Glasgow, Scotland.
10. AveXis. Data on file. UK Health State Utilities Elicitation for Spinal Muscular Atrophy - Report. 01 August 2019. 2019. 2019.
11. Lally C, Jones C, Farwell W, Reyna SP, Cook SF, Flanders WD. Indirect estimation of the prevalence of spinal muscular atrophy Type I, II, and III in the United States. Orphanet Journal of Rare Diseases. 2017 November 28;12(1):175.
12. Office for National Statistics. Birth Summary Tables, England and Wales 2018, August 2019. Available at: https://www.ons.gov.uk/file?uri=%2fpeoplepopulationandcommunity%2fbirthsdeathsandmarriages%2flivebirths%2fdatasets%2fbirthsummarytables%2f2018/birthsummarytables2018.xls.
13. Verhaart IEC, Robertson A, Wilson IJ, Aartsma-Rus A, Cameron S, Jones CC, et al. Prevalence, incidence and carrier frequency of 5q-linked spinal muscular atrophy - a literature review. Orphanet J Rare Dis. 2017 Jul 4;12(1):124.
14. The Lewin Group. Cost of Amyotrophic Lateral Sclerosis, Muscular Dystrophy, and Spinal Muscular Atrophy in the United States. . 2012.
15. United States CB. Educational Attainment in the United States, 2017. Available at: https://www.census.gov/data/tables/2017/demo/education-attainment/cps-detailed-tables.html.
16. Organisation for Economic Co-operation and Development. Education and earnings available at: https://stats.oecd.org/Index.aspx?DataSetCode=EAG_EARNINGS applied to Annual income for A level graduate from https://www.statista.com/statistics/281936/average-salary-by-education-level-in-the-united-kingdom-uk.

17. Organisation for Economic Co-operation and Development. Unemployment rates by education level. Available at: https://data.oecd.org/unemp/unemployment-rates-by-education-level.htm. .
18. Powell. People with disabilities in employment. House of Commons Library Briefing paper, Number 7540, 8 January 2018. 2018.
19. National Institute for Health and Care Excellence. SMA UK Patient and Caregiver Survey – Summary of results – 5 March 2019. 2019.
20. Organisation for Economic Co-operation and Development. Purchasing power aprities. Available at https://data.oecd.org/conversion/purchasing-power-parities-ppp.htm. .

NICE National Institute for Health and Care Excellence

Patient organisation submission

Onasemnogene abeparvovec for treating type 1 spinal muscular atrophy [ID1473]

Thank you for agreeing to give us your organisation's views on this technology and its possible use in the NHS.

You can provide a unique perspective on conditions and their treatment that is not typically available from other sources.

To help you give your views, please use this questionnaire with our guide for patient submissions.

You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type.

Information on completing this submission

- Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable
- We are committed to meeting the requirements of copyright legislation. If you intend to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Your response should not be longer than 10 pages.

About you	
1.	**Your name**
	[redacted]

2.	**Name of organisation**
	Spinal Muscular Atrophy UK (SMA UK) and Muscular Dystrophy UK (MDUK)
3.	**Job title or position**
	[redacted]
4a.	**Brief description of the organisation (including who funds it). How many members does it have?**
	Spinal Muscular Atrophy UK (SMA UK) In September 2018, the charities SMA Support UK and The SMA Trust merged to form **SMA UK**. **SMA Support UK** (previously the Jennifer Trust) had, since 1985 had as its prime focus the provision of free information and support to anyone affected by any form of SMA in the UK. **The SMA Trust** had been funding research since 2003. We are in touch with some 700 households in the UK with a child, young person or adult living with SMA. We estimate this to be over 60% of the total UK population. We are also in contact with more than 350 families who have been bereaved by SMA – the majority by SMA Type 1. SMA UK is accredited to the Information Standard. Our SMA-related information sheets are signposted by the NHS website. In 2018, SMA UK's SMA Type 1 information pages had 17,840 views. That year in the UK, we supported 257 children, young people and adults with SMA and their families via phone, email and home visits. 32 of these were families in England newly affected by SMA Type 1; 3 were families with a child in England with SMA Type 1 whom we had supported previously. Including these 35, we were in touch with a total of 67 families with a child living with SMA Type 1 – via our monthly enews communications (total 2,530 signed up) which keep people abreast of what's happening with services, access to treatments and research related topics.

	Our Research Correspondents (a clinical and a research doctor) report to the SMA community on the development of all drug treatments and clinical trials. We have regular contact with the SMA REACH UK clinical network – which includes clinicians who administer the nusinersen treatment programme and the clinical trials for onasemnogene abeparvovec. Our funding comes predominantly from Trusts, the SMA Community and some corporates. Last financial year, 2018/19, we received funds from four pharmaceutical companies, including the manufacturer of onasemnogene abeparvovec. This was for our core 'outreach' services (4.22% of overall income) We don't receive any government funding. **Muscular Dystrophy UK** Muscular Dystrophy UK (previously known as the Muscular Dystrophy Campaign) was founded in 1959 and has been leading the fight against muscle-wasting conditions ever since. We bring together individuals, families and professionals from more than 60 rare and very rare progressive muscle-weakening and wasting conditions, affecting around 70,000 children and adults in the UK, including SMA. We have 450 individuals on our database with a personal interest in SMA. We provide information, advice and practical and emotional support along with a network of local groups and an online community so that people living with a muscle-wasting condition can find someone to talk to. Every day counts for people with neuromuscular conditions which is why Muscular Dystrophy UK funds pioneering research for better treatments to improve lives today and transform those of future generations. We also press for better recognition of neuromuscular conditions so that people get the best care and support and access to potential drugs much sooner. Our funding comes from donations, gifts, grants and trusts. We have received funds from 11 pharmaceutical companies, including the manufacturers of nusinersen. These were educational grants and one grant for mitochondrial disease research. The funds equate to 0.1% of our overall income. We don't receive any government funding. We received £7,000 from the manufacturers of onasemnogene abeparvovec for our Translational research conference, which other companies also sponsor.
4b.	**Do you have any direct or indirect links with, or funding from, the tobacco industry?**
	No

5.	**How did you gather information about the experiences of patients and carers to include in your submission?**
	In early 2018, in preparation for our submissions to NICE re: the appraisal of nusinersen treatment, SMA UK invited people in the SMA community to complete our on-line surveys. There were: • 128 returns describing **the health-related impacts of SMA** for 128 people living with SMA Types 1-3. Only two of these were from those whose children were affected by SMA Type 1 • 29 returns describing **the experiences of parents whose children had been treated with nusinersen**. The survey responses were integral to the patient group submissions as part of the evaluation of nusinersen. In July 2019 SMA UK and MDUK jointly conducted a survey asking people within the SMA community for their views on the possibility of the NHS funding onasemnogene abeparvovec (for ease referred to as Zolgensma™ in the survey and from now on in this submission). This was disseminated via the charities' (SMA UK, MDUK and TreatSMA) social media channels and SMA UK's monthly e-news. The questionnaire, information sheet and collation of all the 14 responses are in Appendices 1 – 3. This submission draws on: these surveys; the experience and knowledge of SMA UK Support Services Team as a result of its contact over many years with many families affected by SMA Type 1 and MDUK's Information and Support Team's experience.
Living with the condition	
6.	**What is it like to live with the condition? What do carers experience when caring for someone with the condition?**
	SMA Type 1 is the most severe form of SMA with symptoms usually beginning between 0 and 6 months. Generally speaking, the earlier the onset of symptoms the more severe the condition. Babies are unable to sit without support and may be described as **'non-sitters'**. It's not possible to predict life expectancy accurately but for most children, without intervention for breathing difficulties, this has previously been estimated as less than two years[1]. Evidence suggests that since the International Standards of Care for SMA introduced more proactive management in 2007, children have been living longer[2].

Each child is affected differently, but in general, babies with SMA Type 1 are:

- bright, alert and responsive; their intelligence isn't affected
- able to smile and frown as their facial muscles aren't severely affected
- often described as 'floppy' babies due to their low muscle tone (hypotonia) and severe muscle weakness
- unable to support or lift their head due to their weak neck muscles
- unable to sit unsupported and have difficulty rolling over
- able to move their hands and fingers but have difficulty lifting their arms and legs

They have:

- breathing muscle weakness, which can cause a weak cry and difficulties with breathing and coughing
- an increased chance of chest infections, which can be life-threatening
- difficulty swallowing their saliva and other secretions, which may make them sound chesty or make them cough
- difficulties feeding and gaining weight
- an increased risk of fluids or food passing into their lungs (aspiration), which can cause choking and, potentially, chest infections or pneumonia which can quickly become life-threatening.

Children receive care and support from a multidisciplinary healthcare team including specialists in:

- hospital or community paediatric
- respiratory care
- physiotherapy
- occupational therapy
- dietetics
- speech and language therapy
- palliative care
- general practice and community health care.

This can feel overwhelming.

Positioning is very important. If an infant is too upright or lies on anything that sags or is curved, their chest may concertina or 'hunch up' which makes it more difficult for them to take deeper breaths. During the day they need to have their position changed every hour or so. This helps to relieve pressure to ensure that their joints don't become stiff and gives them a change of

view. Often their neck muscles are weak, and they may need a small neck roll to steady their neck in a more comfortable position and help with breathing. They may be provided with a collar to help and, if they're experiencing tightening of their muscles (contractures) and discomfort, they may have foot and hand splints. As children have a limited range of comfortable positions, they are at risk of developing pressure sores.

Spine, hips and bones

60-90% of children with SMA Type 1 or 2 develop a scoliosis[2]. Children are monitored for this and if there are signs, they may be provided with a spinal brace to wear during the day to help them to sit and breathe more comfortably. It's common for children to have unstable hips which may affect one hip or both and will need monitoring.

Breathing

Weak breathing muscles are common resulting in 'insufficient' breathing which is a leading cause of health problems. To help their child, parents may have to manage:

- Chest physiotherapy to help with comfort and clearing secretions from their child's chest.
- A suction machine to help remove their child's excess secretions.
- Medications that can break down the secretions (such as glycopyrrolate). These have to be used carefully as too high a dose can dry out the secretions too much, which then makes them harder to remove.
- Pain relief if their child is in pain or distress because of breathlessness
- Antibiotics which need to be prescribed quickly when their child is at risk of, or to treat, a chest infection.
- A mechanical insufflator – exsufflator machine (Cough assist) to help clear the secretions from their child's the lungs.
- Oxygen sometimes
- Non-invasive ventilation (NIV) (BiPAP) to help make their child's breathing easier. The SoC guidelines recommend really proactive use of NIV for all infants with symptoms of 'insufficient' breathing and that they start using it early before signs of breathing problems start.
- Short term invasive ventilation if their child has a medical emergency.
- A small number of children may have a tracheostomy

Feeding, nutrition and swallowing

Due to their muscle weakness, a child with SMA Type 1 may have difficulties with feeding and swallowing. Safe swallowing is one of the most important aspects of their care as children with a weak swallow are at risk of inhaling (aspirating) their feed

	which can cause choking and respiratory infections. Children often have a weak suck, and mealtimes take longer. Food may get stuck in their cheeks (pocketing) or they may find it hard to open their mouth due to muscle weakness. Infants will need a Video Fluoroscopic Swallow Study and to be monitored for the common problems of gastroesophageal reflux, constipation and vomiting. If swallowing becomes unsafe, or if a child isn't gaining enough weight, short-term options may include feeding through a nasogastric (NG) or nasojejunal (NJ) tube. A Gastrostomy (PEG) tube is a longer-term option. A Nissen Fundoplication**,** which helps to reduce any reflux, may be done at the same time. Diet has to be very carefully monitored and managed. **Day and Night Care** SMA can make children very sweaty with flushed faces and hot or cold hands. This can make it difficult to judge if their temperature is safe, creating anxiety for their parents. Thin, loose layers of clothing help maintain a comfortable temperature but changing clothing isn't easy, especially if their child is tired or uncomfortable. Parents need to avoid having to lie their child on their tummy due to breathing difficulties. Care is 24 hour 7 days a week. **Impact on Families** The impact of a diagnosis of early onset SMA Type 1 on families is enormous. It often comes as a shock with parents expressing feelings of disbelief, confusion, anger and sadness. The 24 hour-a-day responsibility of caring for a child with complex medical needs that follows is physically, emotionally and psychologically exhausting: constant re-positioning and care, large amounts of medical equipment – many families having to adjust bedroom and living arrangements, the need for specialist car seats and buggies that aren't funded by the NHS, frequent hospital appointments and planned and emergency admissions, involvement of palliative and hospice care, caring for other children, the chronic grief and potential looming loss of their child. Parents describe sleep deprivation, often one will give up or cut back their paid work, social lives disappear. Those that have other children and caring responsibilities can struggle to keep up. The impact ripples out to siblings, grandparents and other relatives and friends, many of whom will try to help in some way, all of whom are also emotionally impacted. Caring for a child with SMA Type 1 also comes with significant financial implications due to the additional costs of living with a disability but also because family members may need to reduce their hours or stop working in order to meet the care needs of the child. Parents whose children had, in early 2018, begun treatment with nusinersen and responded to our survey that year reflected:

	Before treatment; **"**he could not even grasp …. he was in intensive care on life support for every cold he got." "We were told to enjoy our time left with our child at point of diagnosis which was simply heart-breaking. Life as we knew it stopped. Numb with pain and filled with fear we were unable to work/sleep/deal with normal day to day life."
Current treatment of the condition in the NHS	
7.	**What do patients or carers think of current treatments and care available on the NHS?**
	The November 2017 international Standards of Care for SMA (SoC)[2,3,4] outline the minimum care, assessments and interventions families and adults should expect to find in any neuromuscular centre anywhere. This is the current core standard for the management and care of those with SMA Type 1 in England. They include the interventions outlined above. Parents aim for their child to have the best health and quality of life as possible and agree with clinicians that this proactive management and care is essential and should go hand in hand with any potential treatment. Nusinersen is the only currently possible treatment for SMA Type 1. It seeks to increase the amount of SMN protein needed for someone to have healthy lower motor neurons[5]. Without this, these specialist nerve cells in the spinal cord deteriorate restricting the delivery of signals from the brain to the muscles, making movement difficult. The muscles then waste due to lack of use - muscular atrophy. To maintain the necessary levels, nusinersen needs to be delivered regularly over a person's lifetime by intrathecal injection into the cerebro-spinal fluid. It cannot cross the blood-brain barrier. The Nusinersen Expanded Access Programme (EAP) for infants with SMA Type 1 slowly started to roll out in 2017, closing to new patients in November 2018. During this time the vast majority of those with SMA Type 1 were treated – over 80 across the UK. The treatment will now be provided via the Managed Access Programme (MAA). There will be very few if any children with SMA Type 1 who will not be eligible for this treatment. This combined with the SoC is therefore likely to be the current NHS treatment for children with SMA Type 1. When we conducted our survey in early 2018, children had not been on the EAP for long. Of the 29 parents who responded, nine parents didn't provide any commentary about their views of the impact of the treatment on their child or their family. In their open comments, the other twenty reported already seeing the following advantages for their child:

Total of 20 respondents making 'open' comments	Nos.	%
Physical / muscle improvements	19	95
Much happier	8	40
Respiratory gains	7	35
General improvement in health	4	20
Increased vocalisation	2	10
Tolerates procedure well	2	10
No physical / muscle improvement	1	5
No respiratory gain	1	5
Improved swallow	1	5
Improved quality of life	1	5

"Before treatment he could not even grasp - now he can use both hands to play with toys… he is beginning to hold his head up and can move his legs a little. He has been managing colds all through winter at home whereas before he was in intensive care on life support for every cold he got. He is a happy boy who can now start to explore his surroundings, he is also beginning to talk … and can sing and clap." **Treatment started < 7 months, 5-7 injections**

"She has gained skills whereas before treatment she was just losing skills. She has gained head control, more movement in arms and legs. She is able to roll forward which was something she could never do. It has given us all hope. She has stayed off respiratory support and feeding support." **Treatment started age 13 - 24 months, 0-4 injections**

In their open comments, the following advantages were reported for the parents/family:

Total of 20 respondents made comments	**Nos.**	**%**
Given hope	13	65
Emotionally positive / happier	8	40
Decrease in care needed	4	20
More inclusive family time	1	5
More relaxed	1	5

“This has completely turned our lives around… now I'm witnessing first-hand the benefits of nusinersen I’m simply filled with hope for my child's future. This has had such a positive turnaround for our family, myself, my husband, siblings, grandparents. I feel like I'm no longer waiting on a ticking time bomb, but now look forward to my child's future.” **Treatment started age 13-24 months, 5-7 injections**

Our recent survey required respondents to read accurate information about the administration and clinical trial outcomes of nusinersen and Zolgensma™ **and** then, score aspects of each one separately on a scale of 1 (strong disadvantage) to 5 (strong advantage). Results for nusinersen were as follows, showing quite a range of opinion:

	Strong Disadvantage 1		2		3		4		Strong Advantage 5		Total
	%	No.	%	No.	%	No.	%	No.	%	No.	
How it is delivered	21.4	3	21.4	3	35.7	5	14.3	2	7.1	1	14
How often it is delivered	35.7	5	28.6	4	14.3	2	7.1	1	14.3	2	14
The range of cells and tissues it reaches in the body	14.3	2	14.3	2	35.7	5	14.3	2	21.4	3	14
The long-term effects on the patient's genetic make-up	14.3	2	14.3	2	28.6	4	14.3	2	28.6	4	14
The potential risks and how these are managed	0.0	0	7.1	1	50.0	7	35.7	5	7.1	1	14
Based on clinical trial results, possible effect on survival / life expectancy	7.1	1	7.1	1	14.3	2	35.7	5	35.7	5	14
Based on clinical trial results, possible effect on breathing	7.1	1	0.0	0	21.4	3	35.7	5	35.7	5	14
Based on clinical trial results, possible effect on motor milestones	0.0	0	21.4	3	21.4	3	28.6	4	28.6	4	14
What is known about this technology	0.0	0	0.0	0	28.6	4	57.1	8	14.3	2	14

8. **Is there an unmet need for patients with this condition?**

Taken at face value, just 14 respondents interested in giving their views on the potential provision of Zolgensma™ by the NHS doesn't show a great unmet need. However, our survey took place at a time when many in the SMA community were completely focused on campaigning and advocacy for the provision of nusinersen for **all** with SMA, which is perhaps why the response rate was so low. In addition, some people may have been overwhelmed by the complexity of the questions being asked and not felt confident responding, despite our best efforts to provide the necessary information to aid their response.

	The scope for Zolgensma™ is for SMA Type 1 only. It would be fair to say as well that any parent with a child with SMA Type 1 awaiting access to nusinersen, and most parents caring for children on the programme already, would be unlikely to have the time, energy or wish to complete a survey that may cause them to question the treatment that had /would imminently be available to them and the road on which they were embarked. Even with the MAA making nusinersen available for those with SMA Type 1, if this new 'one off' treatment offers equal or better potential for quality of life, parents and clinicians need to have the choice to access it. The unmet need is for parents, in consultation with clinicians, to choose what they jointly consider will offer the best potential outcomes for their child.
Advantages of the Technology	
9.	**What do patients or carers think are the advantages of the technology?**
	The Science SMN protein is not just found in the spinal cord, it's also present in all cells as soon as an egg is first fertilised. This means that other organs and parts of the body may be affected by a lack of the protein. Scientists investigating animal models of SMA have suggested that reduced SMN protein may have an impact on the brain, nerves, heart and pancreas. However, only a minority of people with SMA have clearly had challenges with other organs and in those who have, it has not been demonstrated that the cause is the SMA. Research is ongoing[3]. This science does suggest that a treatment that can cross the blood-brain barrier and reach more cells may have an advantage. Our survey required respondents to read accurate information about the administration and clinical trial outcomes of nusinersen and zolgensma and then score aspects of Zolgensma™ on a scale of 1 (strong disadvantage) to 5 (strong advantage). Results were that the Zolgensma™ treatment was seen by the majority to have strong advantages. The views expressed seem to be a reasonable reflection of the comments we hear anecdotally from people and are not unexpected:

	Strong Disadvantage 1		2		3		4		Strong Advantage 5		Total
	%	No.	%	No.	%	No.	%	No.	%	No.	
How often it is delivered									100	14	14
Based on clinical trial results, possible effect on breathing							7.14	1	92.9	13	14
The range of cells and tissues it reaches in the body					7.1	1	7.14	1	85.7	12	14
Based on clinical trial results, possible effect on survival / life expectancy							14.3	2	85.7	12	14
Based on clinical trial results, possible effect on motor milestones							21.4	3	78.6	11	14
How it is delivered					7.1	1	21.4	3	71.4	10	14
The long-term effects on the patient's genetic make-up			7.1	1	21.4	3	14.3	2	57.1	8	14
What is known about this technology			7.1	1	28.6	4	35.7	5	28.6	4	14
The potential risks and how these are managed					57.1	8	21.4	3	21.4	3	14

When asked on a scale of 1 (totally unacceptable) to 5 (totally acceptable) for their view of as a treatment for an infant newly diagnosed with SMA Type 1: 13 (93%) said it was totally acceptable; 1 (7%) considered it acceptable.

When asked to choose one treatment only for an infant newly diagnosed with SMA Type 1 who is well enough to receive nusinersen and who is well enough to receive, and has been screened as suitable for, Zolgensma™ treatment, 13 (93%) chose Zolgensma™ – including two parents whose children are currently receiving nusinersen treatment; 1 (7%) chose nusinersen but stated: 'Only because there is more evidence to show it works. If Zolgensma™ had more case studies to relate to I would chose Zolgensma' (**Parent of child with SMA Type 2 age 0 - 4 yrs. never had drug treatment**); no one chose neither and to only opt for management as outlined in the international Standards of Care for SMA and palliative care.

It's possible that people electing to respond to this survey could be more favourably disposed to Zolgensma™ but the summary information they were required to read was neutrally written (Appendix 2).

	It's also important to note that a small number of parents have elected **not** to have nusinersen treatment and a small number may elect **not** to have Zolgensma™ treatment. Neither treatment is a cure and there is no guarantee of the outcome for an individual child. It's vitally important that, though the earlier the treatment the better, parents have as much time as possible during this very distressing time of receiving a diagnosis to have a fully informed confidential discussion with their clinician about the choices open to them, and that this takes into account emotional, spiritual, cultural and personal circumstances. Parents who choose not to have treatment for their child often express that they support the choice for others.
Disadvantages of the technology	
10.	**What do patients or carers think are the disadvantages of the technology?**
	Our survey required respondents to read accurate information about the administration and clinical trial outcomes of nusinersen and Zolgensma™ and then on a scale of 1 – 5 score aspects of Zolgensma™ on a scale of 1 (strong disadvantage) to 5 (strong advantage). Results were that no one felt there were any strong disadvantages. Potential risks and how they are managed was seen by 8 (57%) as neither an advantage nor disadvantage. These results are a reasonable reflection of the comments we hear anecdotally from people and are not unexpected.

	Strong Disadvantage 1		2		3		4		Strong Advantage 5		Total
	%	No.	%	No.	%	No.	%	No.	%	No.	
How often it is delivered									100	14	14
Based on clinical trial results, possible effect on breathing							7.14	1	92.9	13	14
The range of cells and tissues it reaches in the body					7.1	1	7.14	1	85.7	12	14
Based on clinical trial results, possible effect on survival / life expectancy							14.3	2	85.7	12	14
Based on clinical trial results, possible effect on motor milestones							21.4	3	78.6	11	14
How it is delivered					7.1	1	21.4	3	71.4	10	14
The long-term effects on the patient's genetic make-up			7.1	1	21.4	3	14.3	2	57.1	8	14
What is known about this technology			7.1	1	28.6	4	35.7	5	28.6	4	14
The potential risks and how these are managed					57.1	8	21.4	3	21.4	3	14

Not possible for all children with SMA Type 1

The virus that is packaged with the SMN gene to create Zolgensma™ can be found in the environment; so, some people, including people with SMA, will have a natural immunity to the virus which means the Zolgensma™ therapy as currently delivered will not work for them. Any child being considered for treatment with Zolgensma™ always has a screening blood test to see if they have this immunity and would therefore not be eligible for the treatment.

There may be age, weight and health criteria for treatment which would exclude some infants.

Patient population	
11	**Are there any groups of patients who might benefit more or less from the technology than others? If so, please describe them and explain why.**
	We understand from clinical evidence that, as with all the treatments being developed, the earlier the treatment the better the potential outcome, including for those who are pre-symptomatic. As such, there is a need to reconsider newborn screening for SMA.
Equality	
12.	**Are there any potential equality issues that should be taken into account when considering this condition and the technology?**
	This treatment is for children who are disabled with a condition that impacts severely on them, any siblings and family members.
Other issues	
13.	**Are there any other issues that you would like the committee to consider?**
	Access to this 'one-off' intravenous treatment leading to improvements in the outcomes listed in the NICE scoping document would be a step-change in the treatment and management of the condition. It was approved for use in the USA in May 2019. It is important to highlight the one-off aspect of this treatment when conducting the appraisal and considering the budget impact. With clinical guidance, families living with SMA Type 1 should be able to choose the treatment that they consider has the most advantages and the best potential health outcomes for their child.

	We urge the NICE appraisal committee to recommend that newborn screening for SMA in the UK is reviewed by the National Screening Committee as a matter of urgency given the advent of both this treatment and nusinersen, both of which can evidence that the earlier the treatment the better the potential outcome.
	References 1. Wang CH, Finkel RS, Bertini ES, Schroth M, Simonds A, Wong B, Aloysius A, Morrison L, Main M, Crawford TO, Trela A; Participants of the International Conference on SMA Standard of Care (2007) Consensus statement for standard of care in spinal muscular atrophy. J Child Neurol 22: 1027-1049. 2. Mercuri E, Finkel RS, Muntoni F, Wirth B, Montes J, Main M, Mazzone ES, Vitale M, Snyder B, Quijano-Roy S, Bertini E, Davis RH, Meyer OH, Simonds AK, Schroth MK, Graham RJ, Kirschner J, Iannaccone ST, Crawford TO, Woods S, Qian Y, Sejersen T; SMA Care Group. Diagnosis and management of spinal muscular atrophy: Part 1: recommendations for diagnosis, rehabilitation, orthopedic and nutritional care. Neuromuscul Disord. 2018 Feb;28(2):103-115. doi:10.1016/j.nmd.2017.11.005. Epub 2017 Nov 23. 3. Finkel RS, Mercuri E, Meyer OH, Simonds AK, Schroth MK, Graham RJ, Kirschner J, Iannaccone ST, Crawford TO, Woods S, Muntoni F, Wirth B, Montes J, Main M, Mazzone ES, Vitale M, Snyder B, Quijano-Roy S, Bertini E, Davis RH, Qian Y,Sejersen T; SMA Care group. Diagnosis and management of spinal muscular atrophy: Part 2: Pulmonary and acute care; medications, supplements and immunizations; other organ systems; and ethics. Neuromuscul Disord. 2018 Mar;28(3):197-207. doi: 10.1016/j.nmd.2017.11.004. Epub 2017 Nov 23. **4.** The Guide to the 2017 International Standards of Care for SMA www.treat-nmd.org/care-overview/2017-standards-of-care-for-spinal-muscular-atrophy-sma/the-guide-to-the-2017-international-standards-of-care-for-sma/ 5. 'More detail on how nusinersen works in SMA.' www.smauk.org.uk/more-detail-on-how-nusinersen-works-in-sma

Key Messages	
15. In up to 5 bullet points, please summarise the key messages of your submission	
	• SMA Type 1 is a complex and severely disabling condition. Zolgensma™ treatment seeks to address the recent evidence that SMN protein is not just found in the spinal cord, it's also present in all cells as soon as an egg is first fertilised. This means that other organs and parts of the body may be affected by a lack of the protein. • Current treatment will be management as outlined in the international Standards of Care for SMA along with nusinersen. Treatment has to be regular over a child's lifetime with delivery into the cerebro-spinal fluid via lumber puncture. The treatment does not cross the blood-brain barrier • Zolgensma™ is a 'one off' treatment. Delivered via intravenous injection, it can cross the blood-brain barrier • A child with immunity to the virus used in the therapy would not be eligible for the treatment, there may also be criteria of weight, age and health status limiting eligibility • The NHS should fund this ground-breaking treatment which has so much potential. Neither nusinersen nor Zolgensma™ treatment is a cure and there is no guarantee of the outcome for an individual child. It's vitally important that, though the earlier the treatment the better, parents have as much time as possible during this very distressing time of receiving a diagnosis to have a fully informed confidential discussion with their clinician about the choices open to them, and that this takes into account emotional, spiritual, cultural and personal circumstances. Some parents may elect for their child not to have either treatment.

Thank you for your time.

Please log in to your NICE Docs account to upload your completed submission.

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NICE National Institute for Health and Care Excellence

Patient organisation submission

Onasemnogene abeparvovec for treating type 1 spinal muscular atrophy [ID1473]

Thank you for agreeing to give us your organisation's views on this technology and its possible use in the NHS.

You can provide a unique perspective on conditions and their treatment that is not typically available from other sources.

To help you give your views, please use this questionnaire with our guide for patient submissions.

You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type.

Information on completing this submission

- Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable
- We are committed to meeting the requirements of copyright legislation. If you intend to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Your response should not be longer than 10 pages.

About you	
1.Your name	[redacted]

2. Name of organisation	The Annabelle Rose Foundation for spinal Muscular atrophy
3. Job title or position	[redacted]
4a. Brief description of the organisation (including who funds it). How many members does it have?	The Annabelle Rose Foundation for spinal Muscular atrophy is a registered charity made up of 10 volunteers,all are trustees. he Annabelle Rose Foundation aim to support sufferers of sma and their families however we can, in line with our objectives: e.g. funding for car/home adaptations, funding specialist medical equipment and toys, providing families with the opportunity of short holidays for those with a short prognosis (as we know first-hand the value of such things) and provide help support with funeral costs/arrangements, as well as providing emotional support for the families affected by the condition & donating to fund research. Our funding stream comes from voluntary donations from public and through fundraising events.
4b. Do you have any direct or indirect links with, or funding from, the tobacco industry?	NO

5. How did you gather information about the experiences of patients and carers to include in your submission?	**Personal experience. Discussions through support groups. Surveys. Social media platforms.**
Living with the condition	
6. What is it like to live with the condition? What do carers experience when caring for someone with the condition?	Caring for a person with SMA is challenging and affects all members of the family. The condition is progressive and unless the treatment is available, the condition is fatal. As SMA progresses most of physical abilities are lost and the person becomes completely dependant on carers. An SMA patient will lose ability to swallow and breath and will require intensive support. The carer will have to become a medical expert and the life you have dreamed for you child and yourself is becomes a permanent loss. Physically and mentally the family is drained. Financially exhausted.
Current treatment of the condition in the NHS	
7. What do patients or carers think of current treatments and care available on the NHS?	At the moment the only treatment for SMA is palliative care. We envisage that this will be changed with completion of Managed Access Agreement for Spinraza in the near future. Palliative care is very much lacking, and a shortfall of proper physiotherapy support means that people with SMA have very poor prognosis. Access to Spinraza will be beneficial to many patients, but it will be an ongoing treatment with associated costs.
8. Is there an unmet need for patients with this condition?	Should Spinraza be is approved, it would be a treatment, but not a cure… Whilst Spinraza is an excellent treatment and a beneficial one, The administration and on-going dosing means that there are associated costs, trips to the hospital and potential complications that may arise.

Advantages of the technology	
9. What do patients or carers think are the advantages of the technology?	This is a potential cure and the results coming out from the clinical trials show significant improvement on current results with Spinraza. the possibility of one-off treatment is very appealing and exciting.
Disadvantages of the technology	
10. What do patients or carers think are the disadvantages of the technology?	Patients or patient cares do not see any disadvantages of this technology.
Patient population	
11. Are there any groups of patients who might benefit more or less from the technology than others? If so, please describe them and explain why.	We expect that all children with SMA (regardless of classification by type) but under certain weight will benefit immediately from this curative treatment. Gene therapy restores the missing gene and ensure normal production of the protein required to prevent necrosis of motorneurons. The younger the patient the more functional motorneurons are still available and the faster the results could be seen. The only limiting factor at the moment is body weight as this influences the required viral dose. Guidance received from a working partnership with TREATSMA

Equality	
12. Are there any potential equality issues that should be taken into account when considering this condition and the technology?	**Yes. The clinical classification of SMA by Type potentially means that children who are diagnosed with borderline type 1/2 can miss out in clinics where they are diagnosed as weak type 2 by clinicians. We think that this could be a postcode lottery based on consultant experience.** **Further more the point of diagnosis often denotes the type, we believe SMA is SMA and in fact it has a vast spectrum of severity**.
Other issues	
13. Are there any other issues that you would like the committee to consider?	This is an exceptional chance for children with SMA to grow up without symptoms present and have a life without influence of this debilitating condition!
14. To be added by technical team at scope sign off. Note that topic-specific questions will be added only if the treatment pathway or likely use of the technology remains uncertain after scoping consultation, for example if there were differences in opinion; this is not expected to be required for every appraisal.]	

if there are none delete highlighted rows and renumber below	

Key messages
15. In up to 5 bullet points, please summarise the key messages of your submission: • • • • •

Thank you for your time.

Please log in to your NICE Docs account to upload your completed submission.

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Appendix D - professional organisation statement template

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Highly Specialised Technology Evaluation

Onasemnogene abeparvovec for treating type 1 spinal muscular atrophy [ID1473]

Thank you for agreeing to give us a statement on your organisation's view of the technology and the way it should be used in the NHS.

Healthcare professionals can provide a unique perspective on the technology within the context of current clinical practice which is not typically available from the published literature.

To help you in making your statement, we have provided a template. The questions are there as prompts to guide you. It is not essential that you answer all of them.

Please do not exceed 12 pages.

About you

Your name: [redacted] representing British Society of Childrens Orthopaedic Surgeons(BSCOS)

Name of your organisation:
Are you (tick all that apply):

- a specialist in the treatment of people with the condition for which NICE is considering this technology?
    - o YES

- a specialist in the clinical evidence base that is to support the technology (e.g. involved in clinical trials for the technology)?

- an employee of a healthcare professional organisation that represents clinicians treating the condition for which NICE is considering the technology? If so, what is your position in the organisation where appropriate (e.g. policy officer, trustee, member etc)?

    - o YES I am member of BSCOS and an elected member of the Board.

- other? (please specify)

Links with, or funding from the tobacco industry - please declare any direct or indirect links to, and receipt of funding from the tobacco industry:

No links

Appendix D - professional organisation statement template

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Highly Specialised Technology Evaluation

Onasemnogene abeparvovec for treating type 1 spinal muscular atrophy [ID1473]

What is the expected place of the technology in current practice?

Please provide information on the number of patients in England with the condition. How many of them would be expected to receive treatment with the technology?

How is the condition currently treated in the NHS? Is there a specialised or highly specialised service provision? Is there significant geographical variation in current practice? Are there differences of opinion between professionals as to what current practice should be? What are the current alternatives (if any) to the technology, and what are their respective advantages and disadvantages?

Are there any subgroups of patients with the condition who have a different prognosis from the typical patient? Are there differences in the capacity of different subgroups to benefit from or to be put at risk by the technology?

What is the likely impact of the technology on the delivery of the specialised service? Would there be any requirements for additional staffing and infrastructure, or professional input (for example, community care, specialist nursing, home care provision, other healthcare professionals)?

If the technology is already available, is there variation in how it is being used in the NHS? Is it always used within its licensed indications? If not, under what circumstances does this occur?

Please tell us about any relevant **clinical guidelines** and comment on the appropriateness of the methodology used in developing the guideline and the specific evidence that underpinned the various recommendations.

These are rare conditions and tend to be managed in tertiary paediatric centres by a multidisciplinary team often led by a paediatric neurologist.

With regard to the musculoskeletal system, in general ,orthopaedic surgery is rarely indicated in this group of patients. This is in part due to limited their survival and the high potential for respiratory complications associated with major surgery such as scoliosis correction. There is also almost never an indication to stabilise dislocated hips for pain or function as muscle weakness which causes these problems had been irremediable to treatment. Practice is therefore fairly consistent across the UK at present.
However should the introduction of these drugs either improve survival or indeed reverse muscle weakness partially it may necessitate a review of the present clinical opinion.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Highly Specialised Technology Evaluation

Onasemnogene abeparvovec for treating type 1 spinal muscular atrophy [ID1473]

The advantages and disadvantages of the technology

NICE is particularly interested in your views on how the technology, when it becomes available, will compare with current alternatives used in the UK. Will the technology be easier or more difficult to use, and are there any practical implications (for example, concomitant treatments, other additional clinical requirements, patient acceptability/ease of use or the need for additional tests) surrounding its future use?

If appropriate, please give your view on the nature of any rules, informal or formal, for starting and stopping the use of the technology; this might include any requirements for additional testing to identify appropriate subgroups for treatment or to assess response and the potential for discontinuation.

If you are familiar with the evidence base for the technology, please comment on whether the use of the technology under clinical trial conditions reflects that observed in clinical practice. Do the circumstances in which the trials were conducted reflect current UK practice, and if not, how could the results be extrapolated to a UK setting? What, in your view, are the most important outcomes, and were they measured in the trials? If surrogate measures of outcome were used, do they adequately predict long-term outcomes?

What is the relative significance of any side effects or adverse reactions? In what ways do these affect the management of the condition and the patient's quality of life? Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently during routine clinical practice?

Not applicable to orthopaedic surgery directly.

Any additional sources of evidence

Can you provide information about any relevant evidence that might not be found by a technology-focused systematic review of the available trial evidence? This could be information on recent and informal unpublished evidence, or information from registries and other nationally coordinated clinical audits. Any such information must include sufficient detail to allow a judgement to be made as to the quality of the evidence and to allow potential sources of bias to be determined.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Highly Specialised Technology Evaluation

Onasemnogene abeparvovec for treating type 1 spinal muscular atrophy [ID1473]

Implementation issues

Following a positive recommendation, NICE will recommend that NHS England provide funding for the technology within a specified period of time.

If the technology is unlikely to be available in sufficient quantity or the staff and facilities to fulfil the general nature of the guidance cannot be put in place within the specified period of time, NICE may advise NHS England to vary this direction.

Please note that NICE cannot suggest such a variation on the basis of budgetary constraints alone.

How would possible NICE guidance on this technology affect the delivery of care for patients with this condition? Would staff need extra education and training? Would any additional resources be required (for example, facilities or equipment)?

If surgery to spine and wider lower limb musculoskeletal system is required this may necessitate resources to tertiary centres to match this demand.The surgical technology involved is already available on the NHS and is well established.

Equality

NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Please let us know if you think that this evaluation:

- could exclude from full consideration any people protected by the equality legislation who fall within the patient population for which the treatment will be licensed;
- could lead to recommendations that have a different impact on people protected by the equality legislation than on the wider population, e.g. by making it more difficult in practice for a specific group to access the technology;
- could lead to recommendations that have any adverse impact on people with a particular disability or disabilities.

Please tell us what evidence should be obtained to enable the Evaluation Committee to identify and consider such impacts.

None that I aware of.

Thank you for your time.

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NICE National Institute for Health and Care Excellence

NHS organisation submission (CCG and NHS England)

Onasemnogene abeparvovec for treating type 1 spinal muscular atrophy [ID1473]

Thank you for agreeing to give us your organisation's views on this technology and its possible use in the NHS.

You can provide a unique perspective on the technology in the context of current clinical practice that is not typically available from the published literature.

To help you give your views, please use this questionnaire. You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type.

Information on completing this submission

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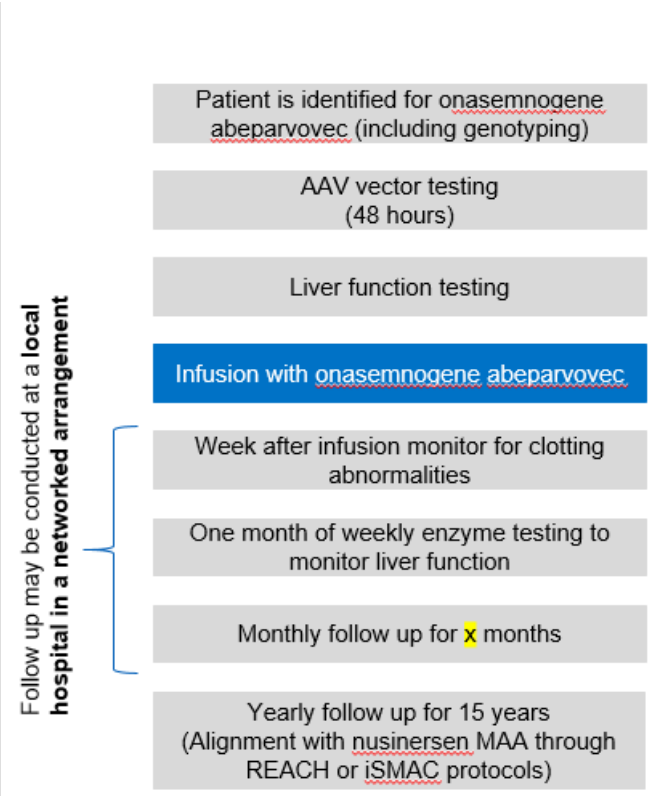
- We are committed to meeting the requirements of copyright legislation. If you intend to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Your response should not be longer than 10 pages.

About you	
1. Your name	**Fiona Marley**
2. Name of organisation	**NHS England and NHS Improvement**

3. Job title or position	**Head Highly Specialised Commissioning**
4. Are you (please tick all that apply):	☒ commissioning services for a CCG or NHS England in general? ☒ commissioning services for a CCG or NHS England for the condition for which NICE is considering this technology? ☐ responsible for quality of service delivery in a CCG (for example, medical director, public health director, director of nursing)? ☐ an expert in treating the condition for which NICE is considering this technology? ☐ an expert in the clinical evidence base supporting the technology (for example, an investigator in clinical trials for the technology)? ☐ other (please specify):
5a. Brief description of the organisation (including who funds it).	**NHS England and NHS Improvement** NHS England and NHS Improvement leads the National Health Service (NHS) in England. We set the priorities and direction of the NHS and encourage and inform the national debate to improve health and care. NHS England shares out more than £100 billion in funds and holds organisations to account for spending this money effectively for patients and efficiently for the tax payer
5b. Do you have any direct or indirect links with, or funding from, the tobacco industry?	**No**
Current treatment of the condition in the NHS	

6. Are any clinical guidelines used in the treatment of the condition, and if so, which?	There are published international standards of care set out in Mercuri et al (2018) and Finkel et al (2018).
7. Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please state if your experience is from outside England.)	The pathway of care for the current diagnosis is well defined, with standard genetic testing widely available. Patients are cared for as set out in the international standards of care. NHS England and NHS Improvement has recently developed a pathway of care for another therapy for this disease, nusinersen, for which NICE published positive guidance in July 2019. The proposed intervention, a type of advanced therapy medicinal product (ATMP), and its place in therapy is not well defined because it is a new treatment with a novel mode of administration. This includes the logistics of providing the intervention and the services required to provide the treatment should the product receive positive NICE guidance.
8. What impact would the technology have on the current pathway of care?	This technology has the potential to revolutionise current treatment strategies for patients and offers the potential for a cure. The extent of the impact on outcomes and the time taken to achieve its potential is unknown. The technology is expected to require new pathways for the preparation of patients, the transfer of the medicine from the manufacturer, clinical delivery of the medicine and long-term monitoring of the patient. Consideration should be given to the role of this therapy in relation to the existing licensed product; nusinersen and whether or not these two therapies could and should be given sequentially. A further product, risdiplam, is now available via the EAMS for individuals with type 1 and type 2 Spinal Muscular Atrophy (SMA) aged 2 months and older and who are not suitable for treatment with nusinersen.

The use of the technology	
9. To what extent and in which population(s) is the technology being used in your local health economy?	This product has been available through research trials only. If the technology receives a positive NICE guidance, it will be used in accordance with its MA in those patients who are eligible for treatment and who want to undertake the treatment. However, the infrastructure to support the implementation of a safe treatment environment will need to be in place before access can be allowed, this may require a variation to the funding requirement. The eligible incident population is relatively small (circa 40 per year). This means the right balance of geographical spread and concentration of expertise will be challenging and required from the start. Further consideration will need to be given, depending on the MA, as to whether the therapy will be available for the prevalent population most of whom are currently receiving treatment with nusinersen.
10. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice?	It is not currently available within the NHS except as part of ongoing trials. The technology is different to current care and NHS England and NHS Improvement expect to identify providers through an 'expression of interest' process against which dedicated providers will be designated and established. It is likely that a subset of the 13 paediatric providers that are currently administering nusinersen will be able to offer onasemnogene abeparvovec, should it be recommended.
• How does healthcare resource use differ between the technology and current care?	Currently patients are treated in line with the international standards of care, this is mostly in regard to supportive therapies. NHS England and NHS Improvement has developed a pathway to treat patients with

	nusinersen. See below for an indicative patient pathway for this therapy – this will need to be ratified following marketing authorisation. 
• In what clinical setting should the technology be used? (For example, primary or secondary care, specialist clinics.)	The service may be delivered in tertiary paediatric settings that have been selected through an expression of interest process. Ongoing monitoring could be conducted in secondary, in a networked model.

• What investment is needed to introduce the technology? (For example, for facilities, equipment, or training.)	Staff on site will need to be trained on the handling and provision of the product and we understand this should be provided by the company as part of regulatory requirements. Specialist equipment may also be required. This will include training for pharmacy staff who will be handling and storing the final product before administration to the patient, in accordance with the regulation of medicines.
• If there are any rules (informal or formal) for starting and stopping treatment with the technology, does this include any additional testing?	This product is a one-off treatment. Starting criteria will depend on any MA received and any further access considerations in the NICE Guidance. Consideration should be given around the requirement of a national MDT should there be a ramping up period and patients require prioritisation in terms of urgency.
11. What is the outcome of any evaluations or audits of the use of the technology?	No audits have been undertaken.
Equality	
12a. Are there any potential equality issues that should be taken into account when considering this treatment?	NHS England and NHS Improvement do not anticipate there are any issues for the incident population. Further consideration will need to be given should the MA include the prevalent population and whether a phased introduction (varying the funding requirement) to manage the implementation of the treatment is required.

12b. Consider whether these issues are different from issues with current care and why.	The introduction of nusinersen has also required a phased approach. The relationship between these medicines and their introduction will require further consideration.

Thank you for your time.

Please log in to your NICE Docs account to upload your completed submission.

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NICE National Institute for Health and Care Excellence

Clinical expert statement

Onasemnogene abeparvovec for treating type 1 spinal muscular atrophy [ID1473]

Thank you for agreeing to give us your views on this technology and its possible use in the NHS.

You can provide a unique perspective on the technology in the context of current clinical practice that is not typically available from the published literature.

To help you give your views, please use this questionnaire. You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type.

Information on completing this expert statement

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- We are committed to meeting the requirements of copyright legislation. If you intend to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Your response should not be longer than 13 pages.

About you	
1. Your name	**Adnan Manzur**
2. Name of organisation	**Great Ormond Street Hospital**

3. Job title or position	**Consultant Neuromuscular, Dubowitz Neuromuscular team, GOSH**
4. Are you (please tick all that apply):	☐ **yes** an employee or representative of a healthcare professional organisation that represents clinicians? ☐ **yes** a specialist in the treatment of people with this condition? ☐ **yes** a specialist in the clinical evidence base for this condition or technology? ☐ **yes** other (please specify): clinical lead for the North Star clinical network for Duchenne muscular dystrophy, past key clinician role for SmartNet work establishment and data collection
5. Do you wish to agree with your nominating organisation's submission? (We would encourage you to complete this form even if you agree with your nominating organisation's submission)	☐ yes, I agree with it ☐ no, I disagree with it ☐ I agree with some of it, but disagree with some of it ☐ **X** other (they didn't submit one, I don't know if they submitted one etc.) - I was unable to locate this on the NICE website
6. If you wrote the organisation submission and/ or do not have anything to add, tick here. (If you tick this box, the	☐ yes

rest of this form will be deleted after submission.)	
The aim of treatment for this condition	
7. What is the main aim of treatment? (For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability.)	To improve all aspects of muscle function including mobility, respiratory function, truncal strength, swallowing.
8. What do you consider a clinically significant treatment response? (For example, a reduction in tumour size by x cm, or a reduction in disease activity by a certain amount.)	Achievement of motor milestones not usually seen in the natural history of SMA1, for example sitting, standing, walking. In the longer term, prevention of scoliosis. Prevention of respiratory failure, reduction of hours of ventilatory support required. Improvement in cough strength. Achievement of swallowing of food with decreased use of gastrostomy or nasogastric feeds. Development of voice speech and communication
9. In your view, is there an unmet need for patients and	Yes, there are unmet needs of patients with SMA1, both with regards to standards of care and implementation, the recent limited availability of novel medication/genetic treatments.

healthcare professionals in this condition?	
What is the expected place of the technology in current practice?	
10. How is the condition currently treated in the NHS?	Standards of care management (aiming to comply with Mercuri et al. 2018, Finkel et al. 2018, reference is quoted in the section below) with regards to Nutritional - nasogastric tube feeding/gastrostomy/Nissens fundoplication, Respiratory - chest physiotherapy, cough machine, non-invasive ventilation, prophylactic antibiotics, prophylactic vaccinations Physiotherapy - assessment and management is aimed at promoting sitting, posture, reduction of contractures, seating, psychosocial support for the family. Recent availability of nusinersen intrathecal treatment program under the managed access agreement but this is limited to patients with SMA1 who have less than 16 hours per day of ventilatory support.
• Are any clinical guidelines used in the treatment of the condition, and if so, which?	Diagnosis and management of spinal muscular atrophy: Part 1: Recommendations for diagnosis, rehabilitation, orthopedic and nutritional **care**. **Mercuri** E, Finkel RS, Muntoni F, Wirth B, Montes J, Main M, Mazzone ES, Vitale M, Snyder B, Quijano-Roy S, Bertini E, Davis RH, Meyer OH, Simonds AK, Schroth MK, Graham RJ, Kirschner J, Iannaccone ST, Crawford TO, Woods S, Qian Y, Sejersen T; **SMA Care** Group. Neuromuscul Disord. 2018 Feb;28(2):103-115. doi: 10.1016/j.nmd.2017.11.005. Epub 2017 Nov 23. Diagnosis and management of spinal muscular atrophy: Part 2: Pulmonary and acute **care**; medications, supplements and immunizations; other organ systems; and ethics. Finkel RS, **Mercuri** E, Meyer OH, Simonds AK, Schroth MK, Graham RJ, Kirschner J, Iannaccone ST, Crawford TO, Woods S, Muntoni F, Wirth B, Montes J, Main M, Mazzone ES, Vitale M, Snyder B, Quijano-Roy S, Bertini E, Davis RH, Qian Y, Sejersen T; **SMA Care** group. Neuromuscul Disord. 2018 Mar;28(3):197-207. doi: 10.1016/j.nmd.2017.11.004. Epub 2017 Nov 23.

• Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please state if your experience is from outside England.)	Within England, the pathway of care in different hospitals is the local adaptation of Standards of care management, aiming to comply with Mercuri et al. 2018, Finkel et al. 2018. There appears to be a wide variation in the availability of respiratory expertise in particular, especially with regards to the availability and timing of intervention with cough insufflator excavator machines and non-invasive ventilation. The prophylactic vaccination schedules and their implementation may vary. The nutritional management especially with regards to amino acid diets is variable.
• What impact would the technology have on the current pathway of care?	Firstly referral and treatment pathways will need to be established for treatment with Onasemnogene in centres with gene therapy can be undertaken. The pathways of collaboration between these and local centres will need to be identified. If early treatment is instituted, and is beneficial in reducing complications, this will have a beneficial effect on hospitalisations and burden of care required on NHS services.
11. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice?	SMN1 gene therapy with Onasemnogene is currently not available on the NHS. The Onasemnogene treatment program implementation will be a novel change in the treatment and will require new pathways, re-emphasising early and rapid diagnosis. The gene therapy administration expertise is likely to be restricted to certain centres and hub and spoke models will need to be developed, with clear referral patterns, responsibilities and sharing of care. New guidelines will need to be developed as to any subgroups of children with SMA1 who will not be offered this treatment.

• How does healthcare resource use differ between the technology and current care?	The Onasemnogene has an entirely different basis for treatment, preparation and mode of administration requires distinctly separate post treatment administration care with immunosuppression and its monitoring. New guidance will need to be developed with regards to offer of the choice of SMA gene therapy versus nusinersen which is currently available on managed access agreement.
• In what clinical setting should the technology be used? (For example, primary or secondary care, specialist clinics.)	The Onasemnogene SMA gene therapy should be implemented in specialist centres, because the special conditions required for handling and administration of the drug and the Peri-procedure care and immunosuppression required. The overall implementation of standards of care and the follow-up of the patients can be negotiated between the specialist centres and the local centres. Even the local centres care should be at the SmartNet / SMA reach network recognise centres
• What investment is needed to introduce the technology? (For example, for facilities, equipment, or training.)	This is a specialist subject. The requirements for Onasemnogene handling should be outlined by the pharmaceutical company. The facilities for training staff will need to be provided through courses and workshops. Special attention will need to be paid for developing the network for individual patient data acquisition , data and collation and entered into a database. I understand that there are already be specific discussions in place to re-use the existing Smart net SMA reach network and database arrangements
12. Do you expect the technology to provide clinically meaningful benefits compared with current care?	The key comparison that needs to be made in this context is to compare Onasemnogene with nusinersen, their pros and cons, especially with regards to Efficacy risks and adverse effect profile the risk of immunosuppression around Onasemnogene administration versus the risk and inconvenience of long-term lumbar punctures for intrathecal nusinersen administration long-term costs to health service, and to the families I may have some initial review, but this requires evidence-based exploration and comparisons, which to my knowledge has not been published

• Do you expect the technology to increase length of life more than current care?	In comparison to the basic standards of care, Onasemnogene will increase length of life. In comparison to antisense oligonucleotide treatments especially nusinersen which is available on the managed access agreement, this is an open question that needs to be answered with evidence base
• Do you expect the technology to increase health-related quality of life more than current care?	Yes, quite likely
13. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	Individuals with SMA1 who are older especially older than 2 years of age are likely to have less benefit as compared to SMA1 infants who are given the medication soon after early diagnosis
The use of the technology	
14. Will the technology be easier or more difficult to use for patients or healthcare professionals than current care? Are there any practical	Once the expertise for assessment, administration and management of immunosuppression around Onasemnogene administration has been developed, the Onasemnogene treatment is less difficult to use as compared to nusinersen intrathecal administration which has to be repeated on a regular basis through lumbar punctures.

implications for its use (for example, any concomitant treatments needed, additional clinical requirements, factors affecting patient acceptability or ease of use or additional tests or monitoring needed.)	
15. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	Yes, guidance will need to be provided for inclusion and exclusion criteria for use of Onasemnogene. Apart from viral vector antibody testing, most of the other assessments are the same as for the management of SMA1
16. Do you consider that the use of the technology will result in any substantial health-related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation?	Yes, this technology is anticipated to cause substantial health-related benefits, but experience from recent NICE appraisal of novel genetically based treatments of SMA1 should be referred to with regards to the difficulty in having these benefits being weighted in the QALY calculations. The long-term outcome from Onasemnogene clinical trials is not yet available because of the recent completion of clinical trials and this will result in the difficulty of QALY calculations.

17. Do you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits and how might it improve the way that current need is met?	The Onasemnogene technology is innovative and has huge potential to radically change the natural history as far as atrophy type I in a most positive manner. The current need in this regard is partly met by the use of nusinersen treatment which is for a limited availability under the managed access agreement.
• Is the technology a 'step-change' in the management of the condition?	Yes
• Does the use of the technology address any particular unmet need of the patient population?	Yes
18. How do any side effects or adverse effects of the technology affect the management of the condition and the patient's quality of life?	The main difficulty is the liver involvement after the viral vector gene therapy and immunosuppression required to control this. The risk is pituitary adrenal axis suppression and the increased risk for infection while under treatment with steroid immunosuppression. This however can be managed effectively with good endocrine care

Sources of evidence	
19. Do the clinical trials on the technology reflect current UK clinical practice?	Yes
• If not, how could the results be extrapolated to the UK setting?	The results can be extrapolated to the newly diagnosed SMA1 patients. The results cannot be extrapolated to children with SMA1 who are older than 2 years of age
• What, in your view, are the most important outcomes, and were they measured in the trials?	The clinical trials for short-term, but focused on the important clinical outcomes of : motor developments,both with regards to the motor milestones, and functional motor assessments, respiratory outcomes with regards to ventilator use recording of outcome of oral feeding
• If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes?	The surrogate measure of CHOP scores are appropriate surrogate, but long-term outcome prediction from CHOP scores is not yet available

• Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	The risks of immunosuppression and pituitary adrenal axis suppression, have not been highlighted in the published clinical trial
20. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	The relevant evidence that is not published should be available to the pharmaceutical licence holder because it was the obligation from the clinical trial to collect the data. Additional data may be available through the FDA which has given approval for use in SMA under 2 years of age
21. How do data on real-world experience compare with the trial data?	The real world experience is limited as compared to the published clinical trial data. There is one publication of the use of Onasemnogene into patient with previously been treated with nusinersen with limited benefit
Equality	
22a. Are there any potential equality issues that should be taken into account when considering this treatment?	If the inclusion criteria for use of medication is for a selected subgroup of SMA1 patients for medical reasons, the equality issues will still have to be addressed

22b. Consider whether these issues are different from issues with current care and why.	These issues are similar to the current care for example the lack of availability of nusinersen MAA to SMA1 infants requiring ventilation for more than 16 hours per day
Topic-specific questions	
23a. Please describe the progression over time of SMA Type 1 (including key milestones, main characteristics) without treatment. 23b. Please describe the progression over time of other types of SMA (including key milestones, main characteristics) without treatment.	The huge majority of SMA1 infants do not develop head control, except for the borderline SMA 1C/SMA2 patients. These patients lose has control at the few years of age. Unfortunately death is a key milestone in SMA1, and abundant data on this is available for natural history and with basic standards of care with NIV support. Untreated, the mean age of death in SMA1 infants is 8 months, and survival beyond 2 years is exceptional. We standards of care application and provision of non-invasive ventilatory support, the survival may be prolonged to a few years or longer.

Key messages	
24. In up to 5 bullet points, please summarise the key messages of your statement. • Onasemnogene represents a most major development in genetic treatment of SMA and offers a step change in treatment with achievement of motor milestones and prolongation of survival • a comparison of Onasemnogene with the managed access agreement available nusinersen will need to be made • the overall framework of specialist centres delivering Onasemnogene treatment, and local neuromuscular centres providing standards of care SMA1 treatment will need to be established • training of personnel including medical, physiotherapy, MDT care including endocrine, respiratory, intensive care, will need to be formally put in place. This can be built on top of the existing arrangements and standards of care application • arrangements for efficacy and safety data collection and resource allocation will need to be made, and this could utilise some of the existing SmartNet/SMA reach networks	

Thank you for your time.

Please log in to your NICE Docs account to upload your completed statement, declaration of interest form and consent form.

Dr Adnan manzur

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NICE National Institute for Health and Care Excellence

Clinical expert statement

Onasemnogene abeparvovec for treating type 1 spinal muscular atrophy [ID1473]

Thank you for agreeing to give us your views on this technology and its possible use in the NHS.

You can provide a unique perspective on the technology in the context of current clinical practice that is not typically available from the published literature.

To help you give your views, please use this questionnaire. You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type.

Information on completing this expert statement

- Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable
- We are committed to meeting the requirements of copyright legislation. If you intend to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Your response should not be longer than 13 pages.

About you	
1. Your name	**Volker Straub**
2. Name of organisation	**Newcastle University and Newcastle Hospitals NHS Foundation Trust**

3. Job title or position	**Harold Macmillan Professor of Medicine, consultant clinical geneticist.**
4. Are you (please tick all that apply):	☐ an employee or representative of a healthcare professional organisation that represents clinicians? ☒ a specialist in the treatment of people with this condition? ☐ a specialist in the clinical evidence base for this condition or technology? ☐ other (please specify):
5. Do you wish to agree with your nominating organisation's submission? (We would encourage you to complete this form even if you agree with your nominating organisation's submission)	☐ yes, I agree with it ☐ no, I disagree with it ☐ I agree with some of it, but disagree with some of it ☒ other (they didn't submit one, I don't know if they submitted one etc.) I agree in principal with AveXis' submission to get NICE approval for onasemnogene to treat patients with spinal muscular atrophy type 1 (SMA1), but haven't seen the submission documents.
6. If you wrote the organisation submission and/ or do not have anything to add, tick here. (If you tick this box, the rest of this form will be deleted after submission.)	☐ yes

The aim of treatment for this condition	
7. What is the main aim of treatment? (For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability.)	Simplistically one could say that the main aim of the treatment is to improve motor development and survival of patients with SMA1. Improved motor function due to improved motor unit activity does also mean improved respiratory function. The more complex and realistic view is that the aim of the treatment and the outcome will depend on the timing of the treatment. Treating patients early, ideally even pre-symptomatically, will have the best outcome and therefore one could state that in pre-symptomatic patients the aim of the treatment is to cure the condition. This aim will change for patients that have already developed clear symptoms. The more severely patients are affected and the older patients are the less likely it is to see an improvement of the condition and the aim will only be to prevent further progression. Realistically, if patients are diagnosed with SMA1, which is within the first few months of life, and get access to treatment without delay, the aim of the treatment is to improve the condition and the life expectancy and quality of life of patients. Just one additional comment: the outcome will also depend on the number of *SMN2* gene copies. Patients with 3 copies will show a better response than patients with 2 copies.
8. What do you consider a clinically significant treatment response? (For example, a reduction in tumour size by x cm, or a reduction in disease activity by a certain amount.)	Keeping the comments about the onset of treatment in mind and that the outcome will depend on the severity of the disease when the treatment is started, I would consider an improvement in motor and respiratory function a clinically significant treatment response. By definition untreated patients with SMA1 will never manage to sit independently. Achieving independent sitting would be considered a clinically significant treatment response. All untreated patients with SMA1 would need to be ventilated at some point of their disease, unless they die before then. I would consider an increase in ventilator-free survival of patients with SMA1 a clinically significant treatment response. For treated patients that are already ventilated, a reduction in time on the ventilator would also be considered by me as a clinically significant treatment response.
9. In your view, is there an unmet need for patients and	Untreated, SMA1 is one of the leading genetic causes of infant death. Up until recently no drug treatment for SMA1 was available, but this has changed with the approval for nusinersen (Spinraza™). Despite the fact that nusinersen is now available for patients with SMA1, there are still challenges with the repeated

healthcare professionals in this condition?	intrathecal administration and the efficacy of the medication. In my view there is still a lot of space for improvement for treating patients with SMA1
What is the expected place of the technology in current practice?	
10. How is the condition currently treated in the NHS?	The international SMA stakeholder community has developed standards of care guidelines for patients with SMA (https://treat-nmd.org/care-overview/2017-standards-of-care-for-spinal-muscular-atrophy-sma/). The centres in the UK that see patients with SMA1 apply the international care guidelines. Since NHS/NICE approval for nusinersen (Spinraza™), patients with SMA1 are also treated with the intrathecally administered antisense oligonucleotide.
• Are any clinical guidelines used in the treatment of the condition, and if so, which?	See above
• Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please state if your experience is from outside England.)	Neuromuscular centres in the UK that see patients with SMA1 are very well connected and will all aim to apply the internationally developed standards of care guidelines (see above) for patients with SMA.

• What impact would the technology have on the current pathway of care?	Based on the published outcome of the clinical trials and published data for the treatment of SMA1 patients with onasemnogene, it appears that treatment with this AAV based systemic gene replacement therapy would become part of the standards of care if approved. The FDA has already approved the treatment and I would expect approval by the EMA and other regulatory agencies will follow in the near future.
11. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice?	I would expect that the iv administration of onasemnogene will not be widely available, but would be restricted to a few treatment centres that have experience with AAV based gene therapy delivery. Newly diagnosed patients may need to be referred for gene therapy to dedicated treatment centres. There will need to be an agreement between treatment and care centres about the monitoring of safety and efficacy outcomes of the treatment. Patients may need to stay at treatment centres for a defined time period directly after the administration of the gene therapy, while patients are also immunosuppressed.
• How does healthcare resource use differ between the technology and current care?	As mentioned above, the delivery of viral vector based systemic gene replacement therapy requires a health care infrastructure and experience that won't be available in many hospitals in the NHS. For now the treatment won't be delivered through GP surgeries or through General District Hospitals, but through designated treatment centres that have experience in the care of patients with SMA1 and in the delivery of systemic gene therapy. This is similar to the delivery of nusinersen (Spinraza^{TM}), but will most likely be even more restricted.
• In what clinical setting should the technology be used? (For example, primary or secondary care, specialist clinics.)	The treatment should only be administered in specialist clinics/hospitals due to the infrastructure (e.g. pharmacy) and expertise that is required for viral vector based systemic gene replacement therapy. For now there is still fairly little information about acute side effects in this vulnerable patient population.
• What investment is needed to introduce the technology? (For example, for facilities, equipment, or training.)	In my view it will be critical to have sufficient pharmacy capacity for the preparation of the viral vector based systemic gene replacement therapy in place and to have hospital beds available, as for now the treatment should not be delivered in an outpatient setting. Sites that would meet the criteria of treatment centres are still limited and it would be important to have enough trained staff at those sites.

12. Do you expect the technology to provide clinically meaningful benefits compared with current care?	Yes. Based on published data I have seen it looks as if the treatment response is clinically meaningful when the treatment is administered within the first few months of life. There is still insufficient experience and knowledge about the long-term effect of the compound and it will also be important to learn more about safety and efficacy in older, more severely affected patients.
• Do you expect the technology to increase length of life more than current care?	Yes. The treatment has a clear effect on survival.
• Do you expect the technology to increase health-related quality of life more than current care?	Yes. Compared to current care standards I would expect the treatment to further increase health-related quality of life of patients with SMA1, when administered in the first few months of life.
13. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	I understand that the approval would be for patients with SMA1, also defined by their number of *SMN2* gene copies (patients with 2 or 3 *SMN2* copies). Patients with only 1 *SMN2* copy would most likely not benefit from the treatment and patients with SMA2 and SMA3 have so far not been tested in clinical trials. I expect that we will see more publications about the treatment response to onasemnogene in patients with more advanced stages of SMA1. The technology would be most effective for pre-symptomatic patients, but this would almost require a national neonatal screening programme. Based on the published data one can definitely say: the earlier you treat the better the outcome.
The use of the technology	

14. Will the technology be easier or more difficult to use for patients or healthcare professionals than current care? Are there any practical implications for its use (for example, any concomitant treatments needed, additional clinical requirements, factors affecting patient acceptability or ease of use or additional tests or monitoring needed.)	Access to onasemnogene will be a great opportunity for patients with SMA1, but will also add a level of complexity for patients, families and for healthcare professionals. First of all there need to be clear eligibility criteria for SMA1 patients, one of which will be the lack of anti-AAV antibodies. Testing for anti-AAV antibodies is currently not routinely available, but test results need to be provided in a timely manner. The patients will also need to be treated with steroids for immunosuppression before receiving the gene replacement therapy. I anticipate that the immunosuppressive treatment will change in the future and may become more sophisticated than just using oral glucocorticoids. During the period of immunosuppression patients are more vulnerable to infections, which is also a challenge for the family. Clear instructions need to be provided how to reduce the risk of infections. Viral shedding may also be a problem in case there is any contact to other patients/families. As mentioned above, the treatment should only be administered in specialist centres that have experience in the care of patients with SMA1 and in the delivery of gene therapy. Close monitoring of side effects will be especially important during the first couple of weeks after gene therapy treatment, which may require that patients stay in close vicinity to the treatment centre. Blood tests will need to be carried out on a regular basis to monitor the immune response of the patient to the viral vector. It will be important that costs are covered and that there is sufficient capacity at the treatment centres to monitor patients closely.
15. Will any rules (informal or formal) be used to start or stop treatment with the technology?	There will need to be clear eligibility criteria for getting the treatment, including genetic testing, antibody status, health status, vaccination status. This implies that additional testing is required and that a clinical diagnosis of SMA1 isn’t sufficient to get the treatment. As delivery of the treatment is only anticipated as a single delivery, there won’t be any rules in place to stop the treatment. It will be important though that there

Do these include any additional testing?	are clear rules in place how the patients are monitored for both safety and efficacy after administration of the treatment.
16. Do you consider that the use of the technology will result in any substantial health-related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation?	It is still a bit early to speculate about the long-term effects of the treatment and I think in terms of health related benefits one always needs to come back to the question of when the treatment has been started and what the *SMN2* copy number is. With early treatment (within the first few months of life) I would expect an increase in QALYs. I am not certain which health-related benefits are included in the QALY calculation to answer the question.
17. Do you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits and how might it improve the way that current need is met?	From published data showing the effect of the treatment in SMA1 patients that were treated very early, there is no doubt that the treatment (technology) has indeed a significant and substantial impact on health-related benefits. The fact that some patient learned to walk independently is beyond what anyone would have expected could be achieved. The fact that a single administration of a medicinal product can have such a profound effect is fantastic. The treatment meets the need to improve the quality of life and the life expectancy of patients that are treated early. Even for patients that are treated after 6 months of age there may still be a significant and substantial impact on health-related benefits, but there is still a lack of data to support this.
• Is the technology a 'step-change' in the	Without a doubt this technology is a 'step-change' in the treatment of newly diagnosed patients with SMA1.

management of the condition?	
• Does the use of the technology address any particular unmet need of the patient population?	Up until the approval of nusinersen (Spinraza™) there hasn't been any drug treatment with clear efficacy for patients with SMA1. Even with the availability of nusinersen (Spinraza™) there was still an unmet need to provide patients with SMA1 with an effective treatment that doesn't require repetitive intrathecal administration, which onasemnogene addresses. Beside the improved route of administration, onasemnogene also shows efficacy and a good safety profile.
18. How do any side effects or adverse effects of the technology affect the management of the condition and the patient's quality of life?	The high viral vector load can trigger an immune response that is currently mitigated by treating patients with oral glucocorticoids. Despite the steroid treatment there is still a risk that antibody-negative patients may develop an immune response that could affect the quality of life and even life expectancy. Overall the data that have been collected so far support a very good safety profile of the technology. Potential side effects or adverse effects in response to the high viral load seem to be controlled quite well with the steroid administration.
Sources of evidence	
19. Do the clinical trials on the technology reflect current UK clinical practice?	Yes.

• If not, how could the results be extrapolated to the UK setting?	
• What, in your view, are the most important outcomes, and were they measured in the trials?	The most important outcomes are the improved motor development, the time off the ventilator and the increase in life expectancy. All outcomes were measured in the trials and were improved.
• If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes?	The clinical outcomes were striking.
• Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	Not that I'm aware of.
20. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	Not that I'm aware of.

21. How do data on real-world experience compare with the trial data?	So far we don't have any real-world experience with the technology/treatment in Europe, but experience in the US confirms the positive outcomes from the trials.
Equality	
22a. Are there any potential equality issues that should be taken into account when considering this treatment?	No.
22b. Consider whether these issues are different from issues with current care and why.	No.
Topic-specific questions	
23a. Please describe the progression over time of SMA Type 1 (including key milestones, main	The majority of patients with SMA1 will die within the first year of life due to chest infections, respiratory failure or sudden death. More than 90% of SMA1 patients will have died by 20 months of age. Patients with SMA1 will present with muscle hypotonia (floppiness), muscle weakness and paradoxical breathing (predominant use of the diaphragm) within the first few months of life. Patients will never be able to sit without support. Without treatment the weakness will progress and patients will also start to develop bulbar signs with difficulty to swallow. Patients will require ventilator support (respirator) and feeding support. The

characteristics) without treatment.	progressive weakness will lead to general paralysis ultimately affecting all skeletal muscles, including the facial muscles, which means that patients will be unable to smile or even cry.
23b. Please describe the progression over time of other types of SMA (including key milestones, main characteristics) without treatment.	In contrast to patients with SMA1, patients with SMA2 will at some point achieve the ability to sit without support, but will never manage to stand or walk independently. Patients with SMA3 will at some point achieve the ability to stand and walk independently. As SMA is a progressive disease all patients will lose motor function over time, which means that patients with SMA2 may at some point not be able to sit independently and patients with SMA3 may become wheelchair bound. SMA is a disease with a continuous spectrum of severity and the classification into SMA1, 2 and 3 patients, although helpful, is artificial. Patients with SMA2 have a reduced life expectancy because of progressive respiratory weakness and even patients with SMA3 may require ventilator support at some stage of their disease. While patients with SMA1 normally die before they develop a scoliosis, patients with SMA2 and young patients with SMA3 will in most cases develop a scoliosis.
Key messages	

24. In up to 5 bullet points, please summarise the key messages of your statement.

- Without treatment SMA1 is a fatal condition presenting with progressive wasting and weakness of the skeletal muscles that will lead to death in 90% of the patients by 20 months of age.
- Treatment of SMA1 patients with either nusinersen or onasemnogene needs to start early, within the first few months of life, or ideally pre-symptomatically, in order to have the biggest benefit.
- Treatment with onasemnogene would have the huge advantage of a single iv administration in contrast to repeated intrathecal administrations with nusinersen, the only current licenced drug treatment for SMA1 in the UK.
- The safety profile of the treatment in patients with SMA1 so far looks very promising, keeping in mind that patients with SMA1 are extremely vulnerable.
- The trial results with onasemnogene in SMA1 have shown a clear positive effect on quality of life and life expectancy.

Thank you for your time.

Please log in to your NICE Docs account to upload your completed statement, declaration of interest form and consent form.

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NICE National Institute for Health and Care Excellence

Highly Specialised Technology Evaluation - Patient expert statement

Onasemnogene abeparvovec for treating type 1 spinal muscular atrophy [ID1473]

Thank you for agreeing to give us your views on this technology and its possible use in the NHS.

You can provide a unique perspective on conditions and their treatment that is not typically available from other sources.

To help you give your views, please use this questionnaire with our guide for patient submissions.

You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type.

Information on completing this expert statement

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- We are committed to meeting the requirements of copyright legislation. If you intend to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Your response should not be longer than 10 pages.

About you	
1.Your name	**Dr Gennadiy Ilyashenko**
2. Are you (please tick all that apply):	☐ a patient with the condition? ☒ a carer of a patient with the condition? ☒ a patient organisation employee or volunteer?

	☐ other (please specify):
3. Name of your nominating organisation	TreatSMA
4. Did your nominating organisation submit a submission?	☒ yes, they did ☐ no, they didn't ☐ I don't know
5. Do you wish to agree with your nominating organisation's submission? (We would encourage you to complete this form even if you agree with your nominating organisation's submission)	☒ yes, I agree with it ☐ no, I disagree with it ☐ I agree with some of it, but disagree with some of it ☐ other (they didn't submit one, I don't know if they submitted one etc.)

6. If you wrote the organisation submission and/ or do not have anything to add, tick here. (If you tick this box, the rest of this form will be deleted after submission.)	☐ yes
7. How did you gather the information included in your statement? (please tick all that apply)	☒ I have personal experience of the condition ☐ I have personal experience of the technology being appraised ☒ I have other relevant personal experience. Please specify what other experience: ☒ I am drawing on others' experiences. Please specify how this information was gathered:
Living with the condition	
8. Did you have any difficulty or delays in receiving a diagnosis; appropriate treatment or helpful information about the condition?	There was a significant delay in receiving the diagnosis. In fact if we had remained on the NHS we would have to wait an additional 3-4 months! We paid privately to see a paediatrician, followed by a neuromuscular consultant and genetic testing. At the time of diagnosis there was no helpful information about the condition. The condition was never publicised and even though there is methodology to do newborn screening, it is not available on the NHS. Most of the information available would tell us that our child was going to die before the age of 2. We had little or no support from the NHS or charitable organisations. The diagnosis has completely demoralised our family. Four years on we are still experiencing depression, anger and heartbreak. The impact was felt through the whole family. It did not affect

What was the impact of this you and your family?	just parents, but reverberated through all of our extended family. As well as emotional stress, the financial burden to family is excessive. The cost of equipment, physiotherapy and living has gone up, at the same time my wife had to give up her work thus halving the income. The NHS and the social system does the bare minimum to support families and EVERYTHING is a battle. SMA families are permanently exhausted!
9. What is it like to live with the condition? What do carers experience when caring for someone with the condition? Please describe if you have had to adapt your and your family's life: physical health; emotional wellbeing; everyday life including; ability to work, where you live, adaptations to your home, financial impact, relationships and social life. If you are the parent of an affected child, please also include their ability to go to school, develop emotionally, form friends and participate in	1. **What is it like to live with the condition:** From the observation of SMA families and personal experience: living with SMA is difficult. Everyday tasks we take for granted are either challenging or nearly impossible for the SMA patients. From toileting to eating, to brushing teeth, to turning in bed, to ability to cope with respiratory infections, to being "independent" – these tasks are very hard. It is the physical manifestation of the condition that causes the biggest issues. Every movement takes longer and depletes the stamina very fast. **2. What do carers experience:** There are several aspects that must be taken into account here, however this could be divided into mental and physical. The emotional journey through this is something that is very unique to the family. However, I do not know a single family which said that SMA enriched their lives. I do know a few who committed suicide because of SMA and being a carer of someone with SMA is hard. You have to make numerous sacrifices which many people do not understand. For example, during the colder months staying away from public places to reduce chances of getting a respiratory infection – this leads to isolation and loneliness of both carer and child. On-going worry about what to do next, how to get the next best equipment, how to make sure that the child has a safe way to go to school, how to make sure that the person can attend work safely – something that constantly drives the carer/s crazy. As a carer we think how we can set up a life for the child for the years AFTER we are dead. For many people it is too much and they give up. Families, which otherwise would have been happy, fall apart and eventually isolation instigate suicides and even murder of children. Physical experience is highly relevant to this appraisal in particular. On-going exhaustion leads to increased health problems for the carers. Lifting children causes back problems. Lack of suitable

school and social life. What is the effect on any siblings?	sleep has been linked to the development of Alzheimer's disease later in life. Muscle strain injuries are also not uncommon for carers. All of this adds up to a large total bill for the NHS. Basically, being a carer for someone with SMA means you have to be switched on 24/7 365 days of the year for the rest of your life. 3. Adaptation to life with SMA: physical health: a) Most people with SMA have severe respiratory issues due to their inability to have an effective cough and weak breathing muscles. Often SMA people find themselves in ICU, PICU at least once a year to treat a common cold. In a number of cases this can be much more. In order to prevent this, many families remain indoors for the duration of colder months and reduce their contact with the outside world to a minimum. The use of BiPAP and Cough Assist is a must for most people with SMA Type 1 and type 2 and is strongly recommended for type 3. b) Gastrointestinal problems can also arise in many cases. Constipation is one of the most common problems.- ongoing use of medicines and finding a suitable diet is needed, however as there is little known about diet in SMA this can be tricky. c) Lack of movement also affects bone density leading to fragile bones. Weak torso muscles allow for development of scoliosis in almost all cases – which enhances other problems (including breathing) and almost always requires a surgical intervention. Lack of walking means that hip sockets do not develop and therefore another type of surgery is often required to correct the problem. – SO hoisting, wheelchairs, suitable physiotherapy equipment must be purchased and installed. In our household we now have: Powerchair (£25k) Wheelchair (£3k), Innowalk (£15k), Stander (£3k) and smaller equipment (£3k). None is supported by NHS or social services. House adaptations are also a must as level access is needed everywhere as well as a suitable bathing room, toileting system and hoisting to enable transfers. Beds and cushions to prevent sores are also vital as well as suitable cars for driving and carrying equipment. The list is endless!

	emotional wellbeing: a) This is generally affected a lot within the SMA community. The use of anti-depressants is not uncommon. Seeing therapists and enhancing emotional wellbeing of the carer and patient through exercise can be done, however this requires dedicated time and often this may not be the case. In some severe cases communication with children can be limited as they do not develop the ability to talk and therefore expression of emotion is very hard. Some recent advances with IT enables this communication now, but it requires specialist set up and costs money. The devices for this cost around £10,000. everyday life including: a) ability to work – Many people with SMA hold steady jobs and have successful careers! Baroness Jane Campbell sits in the House of Lords! My daughter from an early age is involved in child modelling. However this all depends on the access to buildings, and their strength. As the condition progresses without treatment the ability to do work becomes harder. Eventually people who work will lose their ability to drive their wheelchair or type and they will lose their job. Often buildings are not accessible and therefore people with SMA will miss out on such opportunities. Carers must also adapt to different working environments. My wife had to give up her work to look after our child. I have to support the family and bring in the income. I have to be very careful how I deal with people outside my family to prevent bringing infections into the home and after I finish work I have to give my wife respite so she can have a break! The mental tiredness does affect the quality of work I can produce. I have found that it is increasingly difficult for me to remain focused, yet I am not given a choice. b) adaptations to your home – In our case specifically we had to move from a comfortable accommodation into a council housing because we could not adapt anything where we lived and there was no level access to the flat. This is often the case for many families. Those who have their own houses still have to make adjustments. For example rearranging the house to have the living room as a ground floor bedroom and installing an ensuite bathroom with required taps (often must be temperature and touch controlled because if you and me put our hand under a hot tap we can quickly pull it out, a person with SMA will simply burn their hand), adjustable sinks (to get wheelchairs under), bath/shower chairs and hoisting. Kitchens are often overlooked, but we do need to have accessible kitchens which also means rethinking how things are done. Basically, to

	make a house accessible requires lots of work and money. As a person with no physical disability we do not take these things into account, but they must be considered! c) financial impact – The loss of earnings is phenomenal. In our family we went from a happy mid-range to single income almost over night. Adding equipment and physiotherapy on top and you have a financial disaster. Most SMA families will ask for financial support to buy equipment from one charity or the other. Often multiple charities will have to step up to help. d) relationships – There is massive strain on the relationship within families. People are tired, highly charged emotionally and thus a perfect storm for fall outs. Many families are broken apart by the condition. Even when strong relationships come across SMA it grinds these down. e) social life – In the case of my family we basically do not have social life anymore. Some people are still trying to see friends and family and have a bit of social interaction, but this becomes harder and very often the people who we interact with are other SMA families. The child's ability to go to school: Children with SMA have exceptional levels of intellect. Repeat studies show that they have higher than average IQ and have brilliant minds. Any intellectual and cognitive developments are only hampered by the environment we live in. This simply reflects everyday life. However, in order to be able to access mainstream education an EHCP and similar provisions must be introduced to help people with SMA to carry out physical tasks. For example adaptations within school to allow accessibility, one-to-one help with simple physical tasks like writing. Many stronger SMAers are capable of using modern IT to do their homework and as long as there is suitable physical support and provisions made the child is capable of attending the school. During the winter seasons the school attendance is significantly reduced due to illnesses and if the school does not provide a suitable remote teaching platform, the child's education is damaged. So whilst SMA does not preclude the child's education, it does make things difficult and how well the child is included in the school environment really depends on the school. The child's development emotionally:

	SMA children could have normal emotional development. However, due to stress experienced by the parents and caregivers, children with SMA can develop certain anxieties and issues. Saying that, it is reflective of the environment the child lives in. There are many SMA children who are loved far more than non-SMA children and they develop into kind and caring adults. One trait is obvious though, is that SMA children can influence the emotional state of parents more so than non-SMA children. Making friends I cannot specifically say for all SMA children here, but I find that my child makes friends with ease. Participation in school and social life The level of participation in school and social life would reflect that of the parents and varies from family to family. However if the aspect of a social life is not adapted to be physically accessible then it automatically excludes the children and adults with SMA. SMA itself does not stop people with this condition from participation, but lack of adaptation does. However… as the condition progresses and weakness grows the participation becomes harder. Any activity requires stamina and at some point this will be depleted far too much. Again, if you have a loving family around they will work out what to do, if you do not, loneliness will eventually take over.
Current treatment of the condition in the NHS	
10. What do you think of current treatments (if they exist) and care available on the NHS? What are the things they do not do well enough?	The current palliative care is unacceptable in the world where new treatments are becoming more widespread. The palliative approach does not do anything well as this condition is progressive and symptom management now can be viewed as throwing good money after bad. It does not address the patient's need. It excludes innovation. It prevents a happy life. There is Nusinersen MAA treatment which is currently undergoing evaluations. The treatment is effective, however it is beyond the scope of this appraisal. What I would like to add though is that had my child been

	less than 2 years old I would have switched from Nusinersen to Gene Therapy instantly.
11. Is there an unmet need for patients with this condition?	Absolutely. A young child treated with Gene Therapy could potentially avoid many issues arising from life with SMA. This must be applied to ALL newly diagnosed patients within the weight limit as well as those who could be moved from Nusinersen to GT safely.
Advantages of the technology (treatment)	
12. What do you think are the advantages of the treatment? Consider things like the progression of the disease, physical symptoms, pain, level of disability, mental health and emotional health, ability to work, family life, social life. If you are the parent of an affected child, please also include their an improvement in the ability to go to school, develop emotionally, interact with their siblings, form friends	The treatment has many advantages. In clinical trials a single dose has shown brilliant results compared to the natural history of the condition. The most important point here is that the life of the patient can be saved. Without treatment life expectancy for the SMA Type 1 patient is 2 years; type 2 teenage years though with modern interventions like BiPAP, Cough Assists, surgeries this could be into adulthood. With the treatment people with SMA are fully expected to have much longer life expectancy. In most cases the data clearly shows that progression of the condition is halted and very often reversed. Since the physical weakness is reduced, the quality of life for both patient and carer is improved. As discussed before SMA children have excellent levels of intelligence, but lack physical abilities. Enhancement of those abilities will unequivocally lead to a better quality of life and higher achievements. After all, if you do not have to fight for every breath of air you can write a book (for example). Higher levels of mobility are expecting to reduce many other problems and stronger bodies should be able to prevent scoliosis and other complications due to the nature of the condition. It is possible and plausible to expect that all aspects of life will be improved by having access to the treatment. (My personal experience with the treatment Nusinersen clearly shows that many aspects of life can be and are improved! I expect similar or even better results from Zolgensma. The additional benefit is a

and participate in school and social life.	single dose treatment. However caution must be taken about viral loadings as other issues can come up as problems).
13. How easy or difficult is it to take the treatment? What is the impact you and the family in terms or travel and receiving the treatment?	The treatment is a single dose. It is expected that there will be no follow up treatment thus making this a pretty good starting point. Many families travel 1000 of miles to get this treatment, should this become available through the NHS, many families would be okay to travel required distances.
Disadvantages of the technology (treatment)	
14. What do patients or carers think are the disadvantages of the technology? Consider how the treatment is taken and where? Are there side effects, what are they, how many are there, are they long term or short term and what impact do they have? Are there any aspects of the condition that the treatment	The biggest disadvantage of the treatment is for those who are too old or too heavy thus requiring higher viral does and expecting complications associated with this. Costs.

does not help with or might make worse? Are there any disadvantages to the family: quality of life or financially?	
Patient population	
15. Are there any groups of patients who might benefit more or less from the treatment than others? If so, please describe them and explain why.	The younger the patient the higher advantage and benefits. All newly diagnosed patients will benefit the most from the treatment. Patients who are older may not benefit as much mainly because the loading doses required cannot be done safely.
Equality	
16. Are there any potential equality issues that should be taken into account when considering this condition and the treatment?	**Yes. The treatment should be available to ALL newly diagnosed regardless of their type of SMA. If a child is diagnosed young with any type of SMA the effects of Gene Therapy have shown that it is an effective treatment thus halting the progression of the condition. No one should be discriminated against for having Type 1, 2 or 3 as this would be an effective treatment for all types when young and would improve the quality of life for both the person with SMA and the family.**

Other issues	
17. Are there any other issues that you would like the committee to consider?	

Key messages

19. In up to 5 bullet points, please summarise the key messages of your statement:

- Onasemnogene abeparvovec is an innovative treatment that currently addresses an unmet medical need.
- Current palliative care does not provide a suitable approach to SMA.
- Life with SMA has a significant impact on the people with SMA, immediate and extended family, affecting both physical and mental health of many people involved.
- The treatment should be available to ALL newly diagnosed regardless of type as long as it is within safety limits.

Thank you for your time.

Please log in to your NICE Docs account to upload your completed statement, declaration of interest form and consent form.

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Onasemnogene abeparvovec for treating spinal muscular atrophy

HST REPORT

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BMJ Technology Assessment Group

Title: Onasemnogene abeparvovec for treating spinal muscular atrophy

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Rider on responsibility for report
The views expressed in this report are those of the authors and not necessarily those of the NIHR HTA Programme. Any errors are the responsibility of the authors.

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Contributions of authors:

Steve Edwards	Critical appraisal of the company's submission; validated the statistical analyses; provided feedback on all versions of the report. Guarantor of the report
Samantha Barton	Critical appraisal of the company's updated submission; critical appraisal of the clinical evidence; cross checking of company's search strategies; and updated the summary, background and clinical results sections
Victoria Wakefield	Critical appraisal of the company's updated submission; critical appraisal of the clinical evidence; cross checking of company's search strategies; and assisted with updating the clinical results sections
Tracey Jhita	Critical appraisal of the company's updated submission; critical appraisal of the economic model; cross checking of company's search strategies; critical appraisal of the economic evidence; carried out the economic analyses; and drafted the economic sections

All authors read and commented on draft versions of the ERG report.

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Abbreviation	In full
AAV9	Adeno-associated virus subtype 9
AE	Adverse event
AESI	Adverse event of special interest
AIC	Akaike Information Criterion
BIC	Bayesian Information Criterion
BiPAP	Bi-level positive airway pressure
BSC	Best supportive care
CASP	Critical Appraisal Skills Programme
CHOP-INTEND	Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders
CMAP	Compound muscle action potential
CNS	Central nervous system
CS	Company submission
CSR	Clinical Study Report
CTCAE	Common Terminology Criteria for Adverse Events
ddPCR	Droplet digital polymerase chain reaction
EFS	Event-free survival
EMA	European Medicines Agency
ERG	Evidence review group
EQ-5D	EuroQol-five dimension
FAS	Full analysis set
FDA	United States Food and Drug Administration
GP	General Practitioner
HCRU	Healthcare resource utilisation
HINE-2	Hammersmith Infant Neurological Examination
HRQoL	Health-related quality of life
HST	Highly specialised technology assessment
HSUV	Health state utility value
ICER	Incremental cost-effectiveness ratio
IPD	Individual patient data
ITC	Indirect treatment comparison
ITT	Intention-to-treat
IV	Intravenous
KM	Kaplan Meier
MUNE	Motor unit number estimation
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
NINDS	National Institute of Neurological Disorders and Stroke
NIV	Non-invasive ventilation
NRA	Non-respiratory muscle aid
OS	Overall survival
PAV	Permanent assisted ventilation
PNCR	Pediatric Neuromuscular Clinical Research network
PSA	Probabilistic sensitivity analysis
QALY	Quality adjusted life year

QoL	Quality of life
qPCR	Quantitative polymerase chain reaction
RCT	Randomised controlled trial
SAE	Serious adverse event
SAS	Safety analysis set
SD	Standard deviation
SE	Standard error
SLR	Systematic literature review
SMA	Spinal muscular atrophy
SMN	Survival motor neurone
TEAE	Treatment-emergent adverse event
TRAE	Treatment-related adverse event
TV	Tracheostomy
US	United States
US ICER	United States Institute for Clinical and Economic Review
UK	United Kingdom
WHO	World Health Organisation

1 SUMMARY

1.1 Critique of the decision problem in the company's submission

The company of onasemnogene abeparvovec (Zolgensma®; AveXis), hereafter referred to as onasemnogene, submitted to the National Institute for Health and Care Excellence (NICE) clinical and economic evidence in support of the effectiveness of a one-time onasemnogene treatment for infants with spinal muscular atrophy (SMA) type 1, a progressive neuromuscular disease. SMA is divided into five phenotypes (type 0 to 4) that are separated by age of symptom onset and maximal motor milestone achievement. The population of interest specified in the original scope for this Highly Specialised Technology (HST) was children with SMA type 1, which is characterised by development of symptoms before 6 months of age, never achieving the ability to sit, and a typical life expectancy of less than 2 years. The scope indicated a special consideration, data allowing, for use of onasemnogene in pre-symptomatic patients, that is, those with no symptoms but a genetic diagnosis of SMA and a genotype indicative of likely development of SMA type 1. At the time of writing of the ERG's report, NICE informed the ERG that the population of interest had been updated to reflect the marketing authorisation for onasemnogene and comprised those with:

- 5q (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.

The ERG notes that the population with a clinical diagnosis of SMA type 1 is equivalent to the population of interest in the original scope. Considering those with 5q SMA with a bi-allelic mutation in the SMN1 gene and up to 3 copies of the SMN2 gene, as highlighted by the company, the population could potentially capture those with a clinical diagnosis of SMA type 2 or SMA type 3. However, in their response to clarification, the company emphasised that recommendations for use of onasemnogene for those with a bi-allelic mutation in the SMN1 gene and up to three copies of the SMN2 gene relate to a genotype predictive of development of SMA type 1, that is, pre-symptomatic infants for whom symptoms are likely to manifest within the timeframe for a clinical diagnosis of SMA type 1.

People with SMA type 1 have a missing or dysfunctional survival motor neuron (SMN) 1 gene on chromosome 5q13. For those without a functional SMN1 gene, the higher the copy number of the SMN2 gene, the more SMN protein is produced by their cells. Thus, SMA disease severity is related in some way to SMN2 gene copy number. However, there is an overlap and continuum between SMN2 copy number and SMA type, which means that copy number is not considered to be a reliable predictor of the age of onset of symptoms, and, therefore, SMA type. Typically, having one or two copies of the

SMN2 gene is associated with development of SMA type 1, with most people having a single copy (96%) or two copies (79%) of the SMN2 gene presenting with SMA type 1. However, a proportion of cases with three copies of SMN2 go on to develop SMA type 1 (~20%).

Onasemnogene is a gene therapy that replaces the SMN1 gene and is administered as a single peripheral intravenous (IV) infusion with dosing adjusted by body weight. In March 2020, onasemnogene was granted a conditional marketing authorisation by the European Medicines Agency (EMA) that encompassed those with a clinical diagnosis of SMA type 1 and children with no symptoms of SMA but identified as having a genotype indicative of development of SMA.

The evidence informing the clinical efficacy and safety of onasemnogene therapy for patients with SMA type 1 presented in the company's submission (CS) is derived from single arm, open-label studies. For infants with a clinical diagnosis of SMA type 1, the company presents results from two completed studies, START and STR1VE-US, together with a naïve pooled analysis of the two studies. Longer-term data are available from LT-001, which is a follow-up study enrolling infants completing follow-up in START. A third trial in symptomatic SMA type 1 is ongoing, STR1VE-EU. Data from STR1VE-EU provides some supportive evidence on the clinical effectiveness of onasemnogene, but the data are immature and do not inform the economic modelling. The company also described the ongoing SPR1NT study, which recruited (enrolment is complete) patients yet to develop symptoms (hereafter referred to as pre-symptomatic) but identified as having a genotype predictive of SMA type 1. As highlighted earlier, patients eligible for SPR1NT were those identified as having a bi-allelic mutation in the SMN1 gene and up to three copies of the SMN2 gene.

The original scope issued by NICE specified the population of interest to be children with SMA type 1, with no specification of SMN2 gene copy number. Given that the updated scope limits the population of interest for a genetic diagnosis of SMA to those with up to three copies of the SMN2 gene, the ERG considers it would be helpful to outline the influence of SMN2 copy number in SMA. START (N=15) and STR1VE-US (N=22) involved patients with SMA type 1, two copies of the SMN2 gene, and age of less than 6 months at symptom onset. Although a proportion of children with one (7%) or three (20%) copies of the SMN2 gene are reported to develop SMA type 1, the ERG's clinical experts communicated that time of symptom onset, rather than copy number of SMN2 gene, is a stronger predictor of SMA type, severity of symptoms and likelihood to reach key motor milestones. Given that patients had symptom onset at younger than 6 months in START and STR1VE-US, the ERG considers the populations in the studies to be relevant to the decision problem and to be representative of patients with a clinical diagnosis of SMA type 1 in England. The ERG notes that START included two cohorts, with the cohorts receiving different doses of onasemnogene. The first three patients received a single intravenous "low dose" (6.7×10^{13} vg/kg; Cohort 1), whereas the next 12 patients were given a single intravenous "therapeutic dose" (2.0×10^{14} vg/kg; Cohort 2). Onasemnogene was administered at a dose

of 1.1 x 10^{14} vg/kg in STR1VE-US. For START, given the difference in dose received between the two cohorts, the ERG considers only Cohort 2 to be relevant to the decision problem. With only 34 patients receiving a therapeutic dose of onasemnogene in the START and STR1VE-US, and the limited length of follow-up in the studies, the ERG considers there is, at this time, uncertainty around the magnitude of the true effectiveness of onasemnogene.

The original NICE scope specified the comparators as best supportive care (BSC) and nusinersen (subject to NICE appraisal). Nusinersen was approved in July 2019 for routine commissioning in England for use in all patients with 5q SMA (pre-symptomatic SMA, or SMA types 1, 2 or 3) as part of a managed access agreement and as yet is not considered established standard of care. As per the revised scope, nusinersen is no longer considered a comparator of interest for this appraisal.

To enable the comparison between onasemnogene and BSC, the company identified cohorts of patients from the SMA natural history studies PNCR and NeuroNext to use as historical controls. A randomised trial comparing nusinersen versus a sham control arm in which patients received BSC (ENDEAR) was also identified as a source of relevant comparator data. Hereafter PNCR, NeuroNext, and ENDEAR are collectively referred to as SMA type 1 natural history studies. BSC of infants with SMA type 1 involves mechanical ventilation to help ease breathing difficulties due to decline in muscle function, interventions (e.g., oral suctioning or physiotherapy) to maintain airway clearance and to cough, and mechanical feeding as swallowing and feeding difficulties increase over time. Although the NeuroNext and the PNCR studies were based in the USA, and ENDEAR is a multicentre, international trial with few patients recruited in the UK, the ERG's clinical experts consider the BSC provided in these studies is broadly comparable to BSC in UK clinical practice. The ERG notes that use of life-extending care, such as permanent-assisted ventilation (PAV) by tracheostomy and non-invasive ventilation (NIV), varies between countries and has changed over time. In the UK, there has been a shift towards increased uptake of NIV in clinical practice, which may not be reflected within the SMA natural history studies. In addition, for patients with SMA type 1 who need PAV, tracheostomy is used rarely in the UK and is a more common procedure in the USA. Disparity in rate of tracheostomy will likely have an impact on overall survival (OS) in the natural history studies as patients who have a tracheostomy can live for many years, which is likely to be overestimated in studies carried out in the USA compared with UK clinical practice.

The CS includes evidence on outcomes capturing motor function, respiratory function, and speech and communication. Data are also available for a composite outcome encompassing survival without the need for permanent ventilation. Data are not are not presented for the specified outcome of complications of SMA. However, many complications of SMA type 1 will be captured within the adverse events experienced during the studies, for example, occurrence of scoliosis. Data are reported for a patients' ability to thrive, their nutritional status and their capability to swallow, which are not

included in the outcomes of interest to the decision problem, but all of which have been highlighted by the ERG's clinical experts as clinically relevant outcomes in SMA. Health-related quality of life (HRQoL) data were not collected in any of the onasemnogene studies for SMA type 1.

1.2 Summary of clinical effectiveness evidence submitted by the company

The primary objective of the START study was to evaluate the safety of onasemnogene whereas efficacy (achieved motor milestones and time to death or PAV) was a secondary objective. As noted above, START comprised two cohorts, of which the ERG considers the cohort receiving the therapeutic dose (Cohort 2) of onasemnogene to be relevant to the decision problem. Additionally, data for START Cohort 2, and not Cohort 1, inform the economic modelling. The trial, which is completed, followed all patients for 24 months after treatment with onasemnogene. However, the trial was not powered to assess efficacy outcomes and these were performed without a statistical analysis plan and so should be considered descriptive.

STR1VE-US is a Phase III, multicentre study carried out in the USA with primary objectives of determining the efficacy of onasemnogene by demonstrating achievement of sitting without support for ≥30 seconds up to and including 18 months of age, and evaluating survival (alive and free from PAV) at 14 months of age. End of study visit was planned for when the patient reached 18 months of age. Patients with 1 or 2 copies of SMN2 were eligible for inclusion in STR1VE-US, but all those enrolled had 2 copies of the gene.

START and STR1VE-US have complete follow-up for all patients but due to the maximum follow-up of 2 years (START) and at 18-months of age (STR1VE-US) in the trials, there is some uncertainty around the long-term development of patients treated with onasemnogene. The uncertainty will reduce when the follow-up studies LT-001 and LT-002 report results of up to 15 years' follow-up.

All patients in Cohort 2 of START were alive and without permanent ventilation 24 months after dosing with onasemnogene. In STR1VE-US, one patient died at age 7.8 months and the parents of a second patient withdrew consent at age 11.9 months, at which time the patient required ≥16 hours of non-invasive BiPAP ventilator support for ≥14 consecutive days. In the natural history studies of SMA type 1, 50% to 70% of those assessed were reported to have died or be in need of PAV at 13-14 months of follow up.

Without treatment, infants with SMA type 1 rarely develop motor skills. After receiving onasemnogene, START and STR1VE-US report a large proportion of infants achieve major motor milestones, with events being confirmed by video and central review. In Cohort 2 of START, 91.7% of patients were able to hold their head erect without support for ≥3 seconds and sit with support, 75% were able to sit

alone for ≥30 seconds, 16.7% of were able to walk alone. In LT-001, the follow-up study to START, at the 31 December 2019 data cut, all enrolled patients were reported to have maintained their achieved motor milestones, with [redacted] patients gaining new motor milestones during follow-up.

In STR1VE-US, by 18 months of age, 86.4% of patients achieved motor milestone(s), confirmed by independent central video review. At baseline, two patients were able to hold their heads erect, and, after receiving onasemnogene, an additional 17 (85.0%) patients were able to hold their head erect. Other achievements included 13 patients being capable of turning from back to side, and 14 patients being able to sit alone without support for ≥30 seconds (Bayley definition) and for ≥10 seconds (WHO definition). For the 14 (63.6%) achieving the milestone of independent sitting for ≥30 seconds, the median age at which the milestone was first attained was 12.6 months (range 9.2 to 18.6 months).

SPR1NT is an ongoing Phase III multicentre study enrolling pre-symptomatic patients with SMA and an SMN copy number associated with SMA type 1 or 2, that is, those with bi-allelic deletion of SMN1, and two or three copies of SMN2. Patients must also have been ≤6 weeks of age at the time of gene replacement therapy. The objective of SPR1NT is to evaluate both safety and efficacy of onasemnogene. Efficacy will be demonstrated by:

- for those with two copies of SMN2, independent sitting for at least 30 seconds up to 18 months of age;
- for those with three copies of the SMN2 gene, the ability to stand without support for at least 3 seconds up to 24 months of age.

As of December 2019, 30 patients were enrolled in SPR1NT, which is more than the planned 27 patients, and data are presented from the 31 December 2019 efficacy data cut. All patients involved in SPR1NT, were alive and free of permanent ventilation at their last study visit prior to the 31 December 2019 data cut. Despite the short follow up and immature data in SPR1NT, motor milestone achievements seem consistent with normal, age-appropriate development, potentially demonstrating the benefit of early treatment with onasemnogene. However, because SPR1NT enrolled patients before symptoms manifested, it must be borne in mind that the type of SMA a patient would have gone on to develop is unknown. To be eligible for SPR1NT, patients could have two or three copies of SMN2, and therefore a proportion, the size of which cannot be reliably predicted, is likely to develop types of SMA other than type 1.

To provide clinical inputs for the cost-effectiveness analysis of onasemnogene, the company pooled data from the completed START (N=12) and STR1VE-US (N=22) studies. The pooled dataset was generated by totalling the number of events per milestone (e.g., sitting independently and walking independently) in each 6-month follow-up period, to correspond with the 6 monthly cycle implemented

in the economic model. The comparison of onasemnogene with BSC informing the economic model is an unanchored, naïve comparison, as no adjustment has been made for differences (known or unknown) in study populations or differences in study effects. Although the ERG noted some differences in baseline characteristics for START and STR1VE-US compared with the studies informing BSC, given the small sample size, the ERG considers that adjusting for known prognostic indicators, as well as potential confounders, could potentially reduce the effective sample size without necessarily increasing precision or accuracy of the results. Proportion of patients achieving motor milestones were comparable between START and STR1VE-US, and, as such, are comparable with the results generated by the pooled analysis. Thus, the ERG considers the unadjusted results are the best available evidence to inform the decision problem, at this time.

A difference in outcome assessment between START Cohort 2 and STR1VE-US implemented in the pooled analysis was noted in the time threshold for independent sitting, which was sitting alone for ≥30 seconds for STR1VE-US compared with sitting alone for ≥5 seconds for START. Applying a threshold of ≥30 seconds independent sitting in START resulted in the omission of two patients from the analysis, compared with the use of the ≥5 second threshold. The company considers the loss of two patients from the independent sitting analysis to result in a pessimistic model because the two patients, who remain in the non-sitting health state in the requested scenario, went on to [redacted]. Overall, the ERG considers the pooled analysis to be appropriate for decision-making, with consideration of the highlighted caveat around threshold for independent sitting.

As of the latest data available across the four studies, 100 patients had received an IV infusion of onasemnogene, with 97 administered the recommended therapeutic dose of onasemnogene. Of the 97 patients who received the therapeutic dose, 96 (99%) experienced at least one treatment-emergent adverse event (TEAE) and 56 (58%) were reported to have a TEAE considered by the investigator to be related to onasemnogene. The most frequently reported TEAEs and considered related to onasemnogene (therapeutic dose) across START, STR1VE-US, STR1VE-EU, and SPR1NT included increase in level of transaminases, increase in level of aspartate aminotransferase, and increase in level of alanine aminotransferase.

The ERG's clinical experts commented that development of scoliosis in patients with SMA is an important outcome and thus the ERG requested, during second round of clarification, that the company provide data on occurrence of scoliosis, which was captured as an AE. Across START, STR1VE-US,

STR1VE-EU and SPR1NT, 13 (11.3%) patients have been recorded as experiencing a scoliosis TEAE, with only one patient reported as having scoliosis at baseline. The company reported that a second patient from START also had scoliosis at baseline but is presumed to have had surgery as there is no record of the patient as having a scoliosis TEAE during follow-up. In general, the occurrence of scoliosis and kyphoscoliosis is low across the studies, but, as highlighted by the ERG's clinical experts, the duration of follow-up is also short in terms of capturing the development of scoliosis.

Similar to the population in START and STR1VE-US, the natural history cohorts in PNCR, NeuroNext and ENDEAR were all limited to infants with SMA type 1 who had two copies of SMN2. However, the natural history studies have different issues in terms of their comparability with START and STR1VE-US: ENDEAR survival data are limited by the relatively short follow-up (13 months); NeuroNext used a less stringent definition of PAV that means event free survival (EFS, defined as PAV or death) will be overestimated compared with PNCR and ENDEAR; and PNCR was partly retrospective in design with a potential risk of selection bias and reliance on adequate record-keeping. In addition, all three SMA type 1 natural history studies are limited by small sample sizes. The three studies are also likely to overestimate OS compared with UK clinical practice as most study sites were in the USA, where tracheostomy is more commonly used than in the UK for patients with SMA type 1 who need PAV. The ERG considers all three studies to have major limitations but prefers NeuroNext because of the prospective design and the maturity of the data. The comparisons between the population derived from combining those enrolled in START and STR1VE-US and any of the natural history data sets were unplanned and naïve; that is, no adjustments were made for differences in patient baseline characteristics or any other factors that may confound the results.

1.3 Summary of cost effectiveness evidence submitted by the company

In August 2019, the company submitted clinical and cost-effectiveness evidence to support the recommendation for onasemnogene to be used for treatment of infants with SMA type 1. Based on the company's submission, the ERG produced an interim report which reviewed and critiqued the company's evidence and put forth recommendations for structural changes to the model and clinical data used, as well as its preferred assumptions for the economic analysis.

In May 2020, the company provided NICE with a supplementary appendix to their original submission and a revised cost-effectiveness analysis for the symptomatic SMA type 1 population. The company's revised analysis addressed the issues with the model and reflected all of the ERG's preferred assumptions. As such, the ERG's summary and critique of the company's economic evaluation provided in this report reflects the company's revised base case, including the accepted ERG preferred assumptions, presented in the company's supplementary appendix.

As mentioned previously, in March 2020 the company received a positive opinion from the Committee for Medicinal Products for Human Use (CHMP) for onasemnogene and the proposed indication was widened to include both patients with diagnosed SMA type 1 and the pre-symptomatic population. In the company's supplementary appendix, only clinical evidence was presented for the pre-symptomatic population. The main body of cost-effectiveness evidence submitted by the company was for the symptomatic SMA type 1 population, but in response to clarification questions the company provided two scenarios exploring the cost-effectiveness of onasemnogene for the pre-symptomatic population using the symptomatic SMA type 1 model (discussed at the end of this section).

The patient population considered by the company for the economic model are infants with symptomatic SMA type 1. However, based on the patient characteristics of the main clinical trials for onasemnogene in the symptomatic SMA type 1 population (START and STR1VE-US), the modelled 5q13 SMA type 1 population is further defined to include patients with two copies of the SMN2 gene and age of six months or less at the time of gene replacement therapy. The ERG considers the modelled population to be reflective of the SMA type 1 population in the updated NICE final scope and of the SMA type 1 population in England but does not reflect the pre-symptomatic population.

The intervention and comparator considered in the economic analysis is onasemnogene and BSC, respectively, in line with the NICE final scope. Nusinersen was also included in the original NICE final scope, as it was recently (July 2019) approved for use through a managed access agreement in England for use in all patients with 5q SMA (pre-symptomatic SMA, or SMA types 1, 2 or 3). However, nusinersen is not yet considered established standard of care and has therefore been removed from the updated NICE final scope. Therefore, nusinersen is not a comparator of interest for this appraisal.

Onasemnogene is a one-time, single IV treatment. A dose of onasemnogene for the IV infusion is calculated based on patient weight and is received at a dose of 1.1×10^{14} vg/kg, with the infusion lasting approximately 60 minutes. The comparator (BSC) comprises standard respiratory, gastrointestinal and nutritional care delivered by a multidisciplinary team, which the ERG considers appropriate based on consultations with clinical experts.

A single *de novo* economic model was developed in Microsoft© Excel to assess the cost-effectiveness of onasemnogene compared with BSC for treating patients with symptomatic SMA type 1. The structure of the model is a six-state Markov chain, with the health states reflective of motor function milestones achieved, need for permanent ventilation and death. Furthermore, the model is sub-divided into two time horizons; a short-term (three years) model informed by clinical study data and a long-term (lifetime) extrapolation model.

The health states D (not sitting) and E (PAV) reflect the natural history of patients with symptomatic SMA type 1. For patients treated with onasemnogene, transitions to higher functioning health states C (sitting), B (walking) and A (within a broad range of normal development) are possible. All patients enter the short-term model in the D state. At the end of every model cycle (up to three years) patients can remain in their current health state, transition to higher functioning health states (C and B) if they have achieved motor function milestones, or transition to the E state if their health is deteriorating and they require permanent ventilation. From any health state, patients can also transition to the death state. It should be noted that patients can only transition to the E state from the D state and no backward transitions from higher functioning health states are permitted.

At the end of the short-term model, if patients are in the C state, they remain there until death. For patients in the B state, it was assumed that if they are able to walk independently before the age of 2 (which 2 patients in START and 1 patient in STR1VE-US achieved), then at the age of 5 these patients transitioned to the A state. Patients in the D state could still transition to the E state, but not to any of the higher functioning health states. The company assumed for the base case, that once a patient achieved a motor function milestone, they would not regress to lower functioning health states.

The cycle length used in the short-term model is 6 months, which is reflective of the assessment timepoints in START. Follow-up assessment timepoints in STR1VE-US were monthly. Annual cycles were used for the long-term model. Half cycle correction was applied in the model. The perspective of the analysis is based on the UK National Health Service (NHS), with costs and benefits discounted using a rate of 3.5% as per the NICE reference case.

Estimates of treatment effectiveness in the short-term model are based on pooled motor milestone data from the START and STR1VE-US trials. Motor milestone achievement was a secondary efficacy endpoint in START and in STR1VE-US, independent sitting for ≥30 seconds was a co-primary endpoint and other motor milestone achievements were included as exploratory efficacy endpoints.

Confirmation of motor milestone achievement in START and STR1VE-US was based on video recordings of the CHOP-INTEND, Bayley Scales, submitted home videos and physical examinations sent to an independent central reviewer. The CHOP-INTEND and Bayley Scales were assessed monthly until 12 months post-dose and then quarterly until end of study. Development Milestones/Gross Motor Skills Checklist at physical therapy assessments were assessed every six months.

In STR1VE-US, one patient went on to permanent ventilation and one patient died, thus in the short-term model for patients treated with onasemnogene, transitions from the D state to the E state and D to death were modelled. It should be noted that in START, no patients went on to permanent ventilation or died. In the pooled dataset, three patients were observed to be walking by 2 years of age, 22 patients

were observed to be sitting unassisted and seven patients remained in the not-sitting state, when using a ≥5 second threshold for sitting in START and a ≥30 second threshold for sitting in STR1VE-US. However, in START, patients were followed up to 24 months post-dose (approximately 30 months of age), whereas in STR1VE-US, patients were followed up to 18 months of age. The company highlighted that it is clinically plausible for some patients between 18 and 30 months of age in STR1VE-US to attain higher functioning motor milestones and have assumed for the pooled dataset that there will be one additional independent sitter and one additional independent walker, added to the last cycle of the short-term model.

The threshold used for sitting unassisted was if a patient was observed to sit unassisted for ≥5 seconds (item 22 on the Bayley-III scale). It should be noted that different definitions of sitting independently were used in trials for the pooled dataset (sitting unassisted for ≥5 seconds in START and ≥30 seconds in STR1VE-US). However, as a longer duration of sitting independently was used in STR1VE-US, it implicitly means that all the patients who could sit unassisted for more than 30 seconds could also sit unassisted for more than five seconds. The company stated that an "offset" approach is used to calculate the percentage of patients moving into higher functioning health states, such that motor milestones achieved during a model cycle are accounted for in the following model cycle.

For the BSC arm of the model, no patients achieve any motor milestones based on observed data from natural history studies. Thus, BSC patients can only transition from the D state to the E state (PAV) or death, based on EFS and OS data.

For the short-term model Kaplan-Meier (KM) EFS and KM OS data were used directly to inform the D state. In the onasemnogene arm, pooled EFS and OS KM data from START and STR1VE-US were used. In START, EFS was defined as time from birth to either (a) requirement of ≥16-hour respiratory assistance per day (includes bi-level positive airway pressure [BiPAP]) continuously for ≥2 weeks in the absence of an acute reversible illness, excluding perioperative ventilation or (b) death. In STR1VE-US, EFS was defined as avoidance of either (a) death or (b) permanent ventilation, at 14 months. The definition of permanent ventilation in STR1VE-US was as follows: tracheostomy or the requirement of ≥16 hours of respiratory assistance per day (via non-invasive ventilatory support) for ≥14 consecutive days in the absence of an acute reversible illness, excluding perioperative ventilation.

The BSC arm was informed using EFS and OS KM data from the natural history study, NeuroNext. EFS in NeuroNext was defined as alive without tracheostomy. OS data from NeuroNext included patients who were alive and on PAV. As such, the company adjusted/disaggregated their analysis of KM OS data from NeuroNext to censor patients at the point in time which they receive PAV. The company state that this approach allows as much of the OS data as possible to be used in the calculations.

For the long-term model, EFS and OS informing the D state for both arms of the model were based on extrapolations of data from NeuroNext using standard parametric survival distributions (exponential, Weibull, Gompertz, log-normal, log-logistic and generalised gamma). Based on the ERG's preferred distribution in the interim ERG report, the company implemented the Weibull distribution to extrapolate EFS and OS in the long-term model. The Weibull distribution was considered to be a more plausible extrapolation by the ERG as it naturally declined down to four years, which was the point in the time the company used to truncate survival in its original submission. Based on the selected survival distributions for EFS and OS, per cycle transition probabilities for D to death and D to E state transitions were calculated.

For the E state, OS KM data for SMA type 1 patients requiring PAV are derived from a study by Gregoretti *et al*. 2013. The study was a retrospective chart review of 194 SMA type 1 patients in Italy, which estimated long-term survival for 3 cohorts of patients; no treatment (NT arm, n=121), non-respiratory aid (NRA arm, n=31) or tracheostomy and invasive mechanical ventilation (TV arm, n=42). In line with the methodology adopted in the US ICER report and based on the preferred analysis put forth in the interim ERG report, the company used the NRA cohort to inform OS for the E state. The NRA cohort was deemed suitable for use in the model as the proportion of patients receiving tracheostomy is similar to UK clinical practice.

Standard parametric survival distributions were used to extrapolate the NRA KM OS data. Based on the AIC/BIC statistics and visual inspection of the extrapolations, the company chose the exponential distribution. Due to plateaus in all the extrapolations, the company truncated OS to zero at 16 years, which was deemed to be clinically plausible by the company's clinical experts.

The company used the extrapolation of the NRA KM OS data for the E state for both the short and long-term model and stated this was to avoid overfitting the model to the study population observed in Gregoretti *et al*. 2013 and to ensure transition probabilities remained relatively constant over time. Furthermore, OS for the E state is the same for both the onasemnogene and BSC arms of the model.

In lieu of any long-term data for SMA type 1 patients who are able to sit unassisted for ≥ 5 seconds or more, the company assumed that OS for the C state will be similar to that of SMA type 2 patients. Long-term KM OS data for the C state was derived from Zerres *et al*. 1997, which was a 52-year prospective and retrospective genetic study of SMA type 2 patients. Standard parametric survival distributions were used to extrapolate the KM OS data digitised from the Zerres *et al*. 1997 publication. Based on the AIC/BIC statistics and visual inspection of the extrapolations, the company chose the generalised gamma distribution. No truncation was applied to the selected survival curve. Furthermore, the extrapolated survival curve is used only for the long-term model. Based on data from START and

STR1VE-US, no patients who achieved the ability to sit unassisted died and as such, 100% survival for the C stated is assumed for the short-term model.

The company assumed that patients who could walk unassisted followed the natural history of SMA type 3 patients in terms of OS, which they state is not significantly different to that of the general population, based on a study by Zerres *et al*. 1997. As such, OS for both the A state (within a broad range of normal development) and the B state for both the short and long-term models is based on UK life tables for 2014-16. For the short-term model, OS is 100% to reflect that no patients who are able to walk died in START or STR1VE-US.

HRQoL data were not collected in any of the onasemnogene trials for SMA type 1, the nusinersen SMA type 1 trials and the SMA type 1 natural history studies identified in the clinical effectiveness SLR. The company chose the same health state utility values (HSUVs) as those used in the base case of a published cost-effectiveness analysis of nusinersen and onasemnogene by the US Institute for Clinical and Economic Review (US ICER) report (including the application of on-treatment utilities) to inform the economic model. Disutilities associated with adverse events were not included in the company's model or US ICER assessment and the company justified this approach stating the difficulty in separating utilities due to treatment from the complications associated with SMA, which are already accounted for in the HSUVs.

Costs included in the model include the following:

- Acquisition and administration costs associated with the intervention; and
- Health state costs consisting of drugs, medical test, medical visits, GP and emergency costs, health material, hospitalisations and social services costs.

For the pre-symptomatic population, the main trial assessing onasemnogene in the pre-symptomatic population is SPR1NT. The company stated that data from SPR1NT are not sufficiently mature to inform a full cost-effectiveness analysis. Instead, the company provided two scenarios using the economic model for the symptomatic SMA type 1 population. For the company's pre-symptomatic population scenario analyses, the symptomatic SMA type 1 model is adapted to improve motor milestone achievements, EFS and OS in the short-term model for the onasemnogene arm. All other parameters and assumptions for the SMA type 1 analysis hold for the scenarios. The company acknowledged that the patient pathway, and in particular costs for the pre-symptomatic population are different compared to the symptomatic SMA type 1 patient pathway but consider that costs would be overestimated for the scenarios.

1.4 ERG commentary on the robustness of evidence submitted by the company

1.4.1 Strengths

Clinical

Despite the limitations of the START and STR1VE-US trials with their single-arm, open-label design and small sample size, the magnitude of effect in the 34 patients who received the therapeutic dose of onasemnogene is large enough to indicate that onasemnogene provides a substantial health benefit compared with BSC.

Economic

The company based much of its approach to the cost-effectiveness analysis on an independently developed model to evaluate the use of onasemnogene in the USA and implemented all of the ERG's preferred assumptions from the interim ERG report.

1.4.2 Weaknesses and areas of uncertainty

Clinical

The sample sizes for the studies informing the efficacy of onasemnogene and BSC are small, which means that differences across studies in baseline characteristics (such as age at treatment or age at symptom onset) or single outcome events are likely to impact on the absolute results. Additionally, the accuracy and precision of the findings could also be unstable due to chance events.

Partly due to the small study sample sizes, only naïve comparisons could be made between onasemnogene and BSC; that is, no adjustments were made for differences in patients' baseline characteristics or other factors that may confound the results. In addition, the natural history studies, PNCR, NeuroNext and ENDEAR, enrolled patients either primarily or exclusively in the USA where tracheostomy is much more commonly used than in the UK for patients with SMA type 1 who need PAV. Tracheostomy can keep patients alive for several years and OS is therefore likely to be longer in studies carried out predominantly in the USA compared with UK clinical practice. Thus, there is uncertainty in the comparability of the results of each of the SMA type 1 natural history studies with START and STR1VE-US and with UK clinical practice.

There is a lack of data on the long-term efficacy and safety of onasemnogene therapy. In LT-001, no patient has lost motor milestones achieved during START, with a follow-up of 4.4 years. However, no longer-term data is available to inform the likely trajectory of infants with SMA type 1, and so it is

unknown whether they may gain further motor function as they grow older, stay at the functional level they have achieved, or if their functional ability may eventually decline.

Economic

In the interim ERG report, the ERG had several concerns which were accepted by the company and implemented in their revised base case analysis. However, with introduction of the pooled data set using START and STR1VE-US, and the expansion of the marketing authorisation to include pre-symptomatic patients, the ERG considers that the company's analysis still has some issues. With regards to the use of the pooled dataset, the ERG considers that pooling the data from the two trials of onasemnogene is reasonable, but that the differences in trial follow-up and thresholds for determining sitting independently and the company's approach to account for the differences introduces additional uncertainty into the analysis. The ERG's clinical experts considered that the assumption of an additional independent sitter might be reasonable but were cautious about assuming an additional independent walker and caveated their opinion by stating that none of the assumptions are founded in evidence. Thus, the ERG's preference was to use only the observed motor milestones in START and STR1VE-US to produce a conservative estimation of the cost-effectiveness of onasemnogene for symptomatic SMA type 1.

The different definition of patients achieving the ability to sit independently in the pooled analysis (sitting unassisted for ≥5 seconds in START and ≥30 seconds in STR1VE-US) was a concern for the ERG. In the interim ERG report, sitting unassisted for ≥5 seconds in START was accepted despite the ERG's clinical experts stating that the threshold was not clinically relevant and preferred the threshold of sitting unassisted for ≥30 seconds. The ERG considered that the loss of two patients from the data set who did achieve the milestone of sitting unassisted for ≥30 seconds or more (albeit not video confirmed) in the follow-up study to START (LT-001) was overly conservative and still maintains this view. Furthermore, as the threshold in STR1VE-US was longer, all patients who are included in the C state (sitting independently) implicitly meet the ≥5 seconds threshold. Nonetheless, the ERG explored the use of the ≥30 seconds threshold in its preferred assumptions and this had a substantial upward impact on the ICER.

With regards to the inclusion of the pre-symptomatic population in the marketing authorisation and the updated NICE final scope, the company's use of the symptomatic SMA type 1 to produce scenarios assessing the cost-effectiveness is considered by the ERG to be problematic. A key assumption made by the company for the scenarios is that the pre-symptomatic patient population (up to three copies of the SMN2 gene) covers a genotype that is predictive of SMA type 1. The ERG's clinical experts stated that pre-symptomatic patients with up to three copies of the SMN2 gene can potentially develop symptomatic SMA type 1, 2 or 3 and the proportions vary by SMN copy number. For the scenarios, the

company relied heavily on the interim data from SPR1NT demonstrating attainment of age appropriate milestones for patients to inform their assumptions, but a proportion of these patients may have developed symptomatic SMA type 2 or 3 and these patients are more likely be able to sit independently (type 2 and 3) and walk independently (type 3 only) irrespective of being treated with onasemnogene.

The ERG considers that assuming all pre-symptomatic patients would have developed symptomatic SMA type 1 is flawed but the evidence base to understand what type of SMA pre-symptomatic patients might go on to develop is limited. Furthermore, the company has acknowledged the challenges and limitations in developing robust cost-effectiveness analysis for the pre-symptomatic population before the SPR1NT trial is completed. The ERG agrees with the company that using the symptomatic SMA type 1 economic model for the scenarios may not accurately reflect costs for the proportion of patients treated with onasemnogene who may have developed symptomatic SMA type 1 but in the absence of data, the ERG cannot predict if the company's assumption that costs would be lower for pre-symptomatic patients with a genotype predictive of SMA type 1 is true.

1.5 Summary of exploratory and sensitivity analyses undertaken by the ERG

The ERG conducted several exploratory analyses in addition to the scenarios provided by the company for the symptomatic SMA type 1 population during the clarification stage, to test the impact of changes in the data and assumptions used by the company on the ICER. However, the ERG only made one change to the company's base case which was to remove the assumption of an additional independent sitter and independent walker from pooled dataset (only observed motor milestones from START and STR1VE-US used in the short-term model). Table A presents the ERG's preferred ICER.

Table A. ERG preferred base case results

Results per patient	Onasemnogene	Best supportive care	Incremental value
Company's base case			
Total Costs (£)	[redacted]	£381,131	[redacted]
QALYs	10.21	0.21	10.00
ICER	-		[redacted]
Removal of the assumption of an additional independent sitter and independent walker from pooled dataset			
Total costs (£)	[redacted]	381,131	[redacted]
QALYs	9.56	0.21	8.29
ICER	-		[redacted]
ERG's preferred base case ICER			[redacted]

Abbreviations: ERG, evidence review group; HSUVs, health state utility values; ICER, incremental cost-effectiveness ratio; KM, Kaplan Meier; NRA; non-respiratory aid; OS, overall survival; QALYs, quality-adjusted life years, US, United States.

The ERG presents a scenario around the preferred base-case to reflect the ERG's clinical experts view that that sitting independently for ≥30 seconds or more was a more meaningful threshold than ≥5

seconds, which was used for the START dataset. However, by adjusting the threshold for START, two patients no longer contribute to the C state, but evidence from the follow-up study, LT-001, demonstrates that these two patients do go on to achieve sitting independently for ≥30 seconds. Nevertheless, it is important to consider the ERG's preferred base case ICER in the context of the clinical expert view and as such, Table B presents the ERG's preferred base case, including the threshold of ≥30 seconds for sitting independently.

Table B. ERG's base case results for onasemnogene versus BSC including threshold for sitting independently of ≥30 seconds

Treatment	Total costs	Total LYs	Total QALYs	Incremental costs	Incremental LYs	Incremental QALYs	ICER (£/QALY)
BSC	381,131	2.15	0.21	-	-	-	-
Onasemnogene + BSC	[redacted]	14.08	8.96	[redacted]	11.94	8.75	[redacted]

Abbreviations: BSC, best supportive care; ICER, incremental cost-effectiveness ratio; LYs, life years; QALY, quality-adjusted life year.

2 BACKGROUND

In August 2019, the company submitted evidence in support of the clinical and cost effectiveness of onasemnogene abeparvovec, hereafter referred to as onasemnogene, in the treatment of infants with spinal muscular atrophy (SMA) type 1. At that time, the Evidence Review Group (ERG) produced an interim report for the National Institute for Health and Care Excellence (NICE) that provided a critique of the evidence outlined in the company's submission to the Highly Specialised Technology (HST) programme. Subsequently, in May 2020, the company submitted an appendix to their original full submission that detailed additional supportive evidence on the clinical effectiveness of onasemnogene in treatment of SMA type 1. The company also reported a revised cost-effectiveness analysis for the symptomatic SMA type 1 population that accommodated the ERG's preferred assumptions and addressed issues with the model as highlighted by the ERG. Additionally, NICE informed the ERG that the population of interest in the scope had been updated to reflect the marketing authorisation for onasemnogene.[1] Below, the ERG has updated the appropriate sections of its interim report to incorporate the supplementary evidence provided by the company in May 2020 and to reflect the update to the scope.

2.1 Critique of company's description of underlying health problems

The full company submission (CS), Section 6, provides a comprehensive description of SMA type 1 and the impact the disease has on patients and carers. Below is an overview of the information available in the CS.

SMA is a progressive neuromuscular disease, with SMA type 1 presenting in babies aged younger than 6 months. SMA is a clinical continuum that is divided into five phenotypes (Type 0 to 4), which are historically related to the age at onset and the maximal motor milestone achieved (Table 1).[2] Younger age of onset is associated with greater severity of disease and reduced life expectancy.[3] Infants with SMA type 1 show onset of disease before six months of age and never achieve the ability to sit.[3]

Table 1. Spinal muscular atrophy classification (reproduced from CS, Table 5)

Type	Age at symptom onset	Maximum Motor Function	Life Expectancy	*SMN2* Copy No.
0	Foetal	Nil	Days–Weeks	1
1	<6 months	Never sits	<2 years	1, **2**, 3
2	6–18 months	Never walks	20–40 years	2, **3**, 4
3	1.5–10 years	Walks, regression	Normal	3, **4**, 5
4	>35 years	Slow decline	Normal	4, 5

Numbers in bold indicate the predominant SMN2 copy number that defines the SMA type; the other copy numbers represent a small percentage of the designated SMA type. Source: Adapted from Kolb *et al*. 2011[2].
Abbreviations: SMN2, survival motor neurone 2 gene.

SMA is caused by mutations in chromosome 5q in the survival motor neuron (SMN) 1 gene and the resulting disrupted production of SMN protein. SMN protein is made by both the SMN1 and SMN2 genes. Typically, each cell has two copies of the SMN1 gene, and one or two copies of the SMN2 gene. However, the number of copies of the SMN2 gene can vary, with some people having up to eight copies of the gene.[4, 5] In people with SMA, the SMN1 gene is either absent or mutated. For those without a functional SMN1 gene, the higher the copy number of the SMN2 gene, the more SMN protein is produced by their cells. Thus, SMA disease severity is related to the SMN2 gene copy number.[4, 5] Additionally, some infants have a variation in their SMN2 gene (referred to as c.859G>C variant) that is potentially a positive disease modifier, being associated with less severe phenotypes and milder symptoms.[6] For most people, expression of SMN protein from SMN2 gene is insufficient to compensate for the loss of production arising from dysfunction of the SMN1 gene.

Absence of SMN protein leads to deterioration, and eventually death, of motor neurons, which are a specialised type of cell located in the central nervous system and are responsible for controlling voluntary and involuntary muscle movement. Loss of motor neuron function leads to progressive muscle weakness, loss of movement and physical disability.[2, 3] As well as affecting patients' musculoskeletal system, SMA also impacts on their respiratory and gastrointestinal systems. SMA is the most common genetic cause of death in infants.[7]

SMA type 1 is the most common form of SMA, accounting for approximately 60% of all cases of the disease, with an estimated incidence of 9.4 per 100,000 live births.[8, 9] SMA type 1 is associated with a particularly poor prognosis and early mortality; most infants do not survive to their second birthday unless they receive ventilatory support.[3, 10] As noted above, symptoms appear early (before 6 months) and include profound muscle weakness, inability to lift head/poor head control, and swallowing and feeding difficulties.[3] By definition, patients with SMA type 1 never develop the ability to sit independently; those with SMA type 1 never gain developmental milestones after initial presentation and are often described as 'floppy' babies.[11, 12] Patients suffer from a range of severe problems, including pulmonary, nutritional and gastrointestinal complications. Despite these symptoms, cognitive ability is normal and infants with SMA type 1 are alert and aware.[3]

Symptoms of SMA type 1 are typically first noticed by health visitors or a general practitioner (GP), but are sometimes picked up at the neonatal unit by a neuromuscular specialist.[13] A clinical diagnosis of SMA type 1 is typically made by a paediatric neurologist, prompted by severe muscle weakness. The diagnosis is confirmed by genetic testing of SMN1, with the absence of a functional SMN1 gene providing a diagnosis of SMA.[14] Further genetic testing may be performed to determine SMN2 copy number.[15]

Although the number of copies a person has of the SMN2 gene is linked with severity of symptoms, there is an overlap and continuum between SMN2 copy number and SMA type. In pre-symptomatic patients, there is consensus that SMN2 copy number is the best available predictor of clinical severity, but it is also acknowledged that there are limitations in the predictive value of SMN2 copy in estimating the age of onset of symptoms, and therefore SMA type.[110] Typically, having one or two copies of the SMN2 gene is associated with development of SMA type 1, with most people with a single copy (96%) or two copies (79%) of the SMN2 gene presenting with SMA type 1 (Table 2).[16] However, a proportion of cases with three copies of SMN2 go on to develop SMA type 1 (~20%; Table 2). Cases with three SMN2 copies are the most challenging to predict in terms of SMA type, given that the copy number is linked with SMA types 1, 2, and 3 (Table 2).

Table 2. SMA type and copy number of SMN2 gene[16]

		SMN2 copy number					
SMA type	**Number of people**	**1**	**2**	**3**	**4**	**5**	**6**
1	1,256	88 (7%)	919 (73%)	245 (20%)	3 (<1%)	1 (<1%)	0 (0%)
2	1,160	4 (<1%)	192 (16%)	902 (78%)	59 (5%)	3 (<1%)	0 (0%)
3	1,043	0 (0%)	54 (5%)	515 (49%)	455 (44%)	16 (2%)	3 (<1%)
Abbreviations: SMA, spinal muscular atrophy; SMN2, survival motor neurone 2 gene.							

The profound muscle weakness caused by SMA type 1 impacts on every aspect of an infant's life.[17, 18] Infants with SMA type 1 will never sit, walk, talk, or achieve any developmental milestones and their lives are defined by hospital stays and ever-increasing levels of medical interventions. Nutritional and ventilatory support can help keep infants alive for years, but the procedures are often traumatic and invasive, with significant morbidity and diminished quality of life (QoL), potentially prolonging suffering rather than relieving the burden of disease.[19]

SMA also has substantial effects on families and carers, including the impact of caring for the patient, the need for specialist equipment and ongoing emotional, financial and social impacts.[11] Caregivers face a constant physical and emotional burden, are limited in their ability to interact with direct and wider family networks, and face financial pressure due to time off paid employment to attend frequent hospital visits and providing care at home. Caregivers also must make difficult decisions around extending their child's life via interventions that may worsen their QoL.[17]

2.2 Critique of company's overview of current service provision

The CS provides an accurate overview of the current management of SMA, a synopsis of which is provided below.

There is currently no effective therapy available in routine clinical practice in England for the treatment of SMA. SMA type 1 is managed with multidisciplinary best supportive care (BSC) comprising

management of nutritional and respiratory support, and orthopaedic care of the infants. BSC does not halt SMA type 1 disease progression and is primarily given as a palliative measure. In England, BSC is delivered by a network of centres with expertise in neuromuscular disorders, and the team providing the treatment includes neuromuscular specialists and nurses, respiratory and orthopaedic specialists, nutritionists/dieticians, occupational therapists, community nurses, health visitors, and social workers.[13] Parents play a key role in the care of infants with SMA type 1,[13] but according to the ERG's clinical experts access to community and social care in the UK, and thus the burden for parents, varies geographically.

No guidance has been published by the National Institute for Health and Care Excellence (NICE) on the standard care pathway for SMA. However, guidelines on the management of patients with SMA are provided by the International Standards of Care for Spinal Muscular Atrophy (Table 3). The recommendations are categorised according to motor function status (non-sitters, sitters and walkers) rather than SMA type (Types 0 to IV), with non-sitters being analogous to SMA type 1.[14, 19]

Nusinersen was granted reimbursement in England in July 2019 for use in patients with pre-symptomatic SMA, SMA types 1, 2 or 3 as part of a managed access agreement. Nusinersen increases the proportion of exon 7 (critical for production of fully functional SMN protein) inclusion in SMN2 messenger ribonucleic acid (mRNA) transcripts, which leads to retention of exon 7 in the SMN2 mRNA. Thus, when SMN2 mRNA is produced, the mRNA can be translated into functional full length SMN protein, thereby increasing the level of SMN protein in the central nervous system (CNS). Given as an intraspinal injection, nusinersen is a lifetime treatment and is currently the only available disease-modifying therapy for SMA. At the time of writing, nusinersen is not considered established clinical practice in England for the management of SMA, but, should more robust evidence on the effectiveness of nusinersen become available, use of nusinersen could become routine in the management of SMA.[20, 21]

Table 3. Clinical management recommendations for patients with SMA (classified as non-sitters and analogous to patients with SMA type 1) from the consensus statement by the International Conference on the Standard of Care for SMA (reproduced from CS, Table 7)

Type of care	
Pulmonary care	• Airway clearance o Assisted cough o Oral suctioning o Physiotherapy/respiratory therapy o Manual chest therapy o Cough insufflator/exsufflator • Bilevel NIV • Immunisations • Tracheostomy
Gastrointestinal and nutritional care	• Referral to specialist dietitian for feeding therapy/modification • Placement of a nasogastric or nasojejunal tube or gastrostomy • Avoidance of fasting during acute care • Adequate hydration and electrolyte balance • Use of bowel regulation medications
Managing musculoskeletal system problems and related functional impairments	• Use of thoracic bracing • Use of cervical bracing for head support • Use of postural and positioning supports • Mobile arm supports to assist upper extremity function • Use of orthoses for limb positioning & stretching • Use of seating and mobility systems
Abbreviations: NIV, non-invasive ventilation; SMA, spinal muscular atrophy. Sources: Finkel *et al.* 2018 and Mercuri *et al.* 2018.[14, 19]	

In May 2019, onasemnogene had yet to receive a marketing authorisation from the European Medicines Agency (EMA), and the population of interest to the decision problem was specified as children with SMA type 1. In March 2020, onasemnogene was granted a conditional marketing authorisation by the EMA that encompassed children with a genetic diagnosis of SMA and no symptoms, as well as those with a clinical diagnosis of SMA type 1.[22] In line with the marketing authorisation, the company anticipates that the therapy will be used for the treatment of patients:[22]

- with symptomatic SMA type 1;
    - that is, those with a bi-allelic mutation in the SMN1 gene and a clinical diagnosis of SMA type 1;

  and

- with no symptoms of SMA (hereafter referred to as pre-symptomatic) but identified as having a genotype indicative of development of SMA;
    - that is, those found to have a bi-allelic mutation in the SMN1 gene and up to three copies of the SMN2 gene.

Subsequently, NICE revised the scope of the HST to reflect the marketing authorisation for onasemnogene.[1] The ERG notes that the population with a clinical diagnosis of SMA type 1 is equivalent to the population of interest in the original scope.[23] Considering those with 5q SMA with a bi-allelic mutation in the SMN1 gene and up to 3 copies of the SMN2 gene, the ERG appreciates that the population could potentially capture those with a clinical diagnosis of SMA type 2 or SMA type 3, based on copy number of the SMN2 gene. However, taking together the company's response to clarification around the proposed population eligible for treatment with onasemnogene and inclusion criteria for the key trial evaluating those with a genetic diagnosis of SMA (SPR1NT), the ERG considers that SMA with a bi-allelic mutation in the SMN1 gene and up to 3 copies of the SMN2 gene pertains to pre-symptomatic infants, and does not encompass infants with a clinical diagnosis of SMA type 2 or type 3.

Clinical data suggest there is a clear benefit in starting treatment with onasemnogene as early as possible, before a substantial loss of muscle motor neurons have occurred.[24] Onasemnogene is, therefore, expected to be used in patients newly diagnosed with SMA type 1.

The administration of onasemnogene will need to take place in specialist infusion centres across England, with the centres likely located within current neuromuscular centres with appropriate facilities for the treatment of patients with SMA type 1. Patients and their families may require assistance with travel to the specialist infusion centres, depending on the condition of the child.

In England, there is currently no national screening programme for SMA in new-born babies, and, therefore, cases of pre-symptomatic SMA are identified through genetic testing referrals arising from a sibling history of SMA.

Patients will require a test, prior to treatment, for the antibody against the adeno-associated vector serotype 9 (AAV9) virus capsid, which is used to deliver the gene. An immune response to the AAV9 capsid will occur after infusion of onasemnogene. To manage a possible increase in liver transaminases, all patients should receive oral prednisolone 24 hours prior to onasemnogene administration, with continued administration of prednisolone for 30 days after treatment, followed by a tapering of prednisolone depending on clinical assessment of the patient. Following administration of onasemnogene, patients will also require monitoring of liver function, platelet, and cardiac troponin I at regular intervals.[25]

The diagnosis of SMA type 1 and long-term follow-up of patients post onasemnogene administration will continue to be the responsibility of the patient's nearest neuromuscular centre. Health practitioners potentially making a diagnosis of SMA type 1 must be aware of, and able to, offer a rapid path to onasemnogene treatment. In addition, national highly specialised commissioning and oversight will be

essential to ensure timely and effective referral paths are in place between the community, neuromuscular centres and specialist infusion centres. The initiation of testing for AAV9 antibodies as part of the screening of patient eligibility for administration of onasemnogene will be a new responsibility for neuromuscular centres if onasemnogene becomes available in England. However, the AAV9 testing of patients will be funded and coordinated by the company. The company anticipates that the network of specialised paediatric neuromuscular services that is already commissioned for the provision and delivery of BSC to patients with SMA type 1 will be able to manage patients long term following treatment with onasemnogene.

The company envisage that onasemnogene will reduce the need for invasive and non-invasive pulmonary support and nutritional support for patients with SMA type 1. In addition, there could be a decline in the need for time in intensive care units and palliative care, decreasing the burden on caregiver and NHS services.[26] Other potential reductions in resource requirements, as a result of treatment with onasemnogene, include the use of pharmacological treatments such as antibiotics and the need for mobility equipment and devices.[13]

3 CRITIQUE OF COMPANY'S DEFINITION OF DECISION PROBLEM

Below is a discussion and critique of the decision problem addressed by the company. The ERG provides a critique of how closely the information available in the company's original submission (CS) and the supplementary appendix aligns with the requirements outlined in the original scope issued by the National Institute for Health and Care Excellence (NICE),[23] and the newly revised scope.[1] A summary of the decision problem as originally outlined by NICE, together with the rationale for any deviation from the decision problem as presented in the company's original submission is available in Table 4. As noted in Section 2, a marketing authorisation for onasemnogene has been granted subsequent to the submission of the original CS and ERG interim report, and the scope has been revised in line with the marketing authorisation. For clarity and to avoid confusion, the ERG has preserved the description of the decision problem as reported in the company's original submission and the ERG's interim report.

Table 4. Summary of decision problem as outlined in the company's original submission (adapted from CS Table 2)

	Original scope issued by NICE[23]	Variation from scope in the submission	Rationale for variation from scope
Population	Children with SMA type 1	As per draft pre-invite scope, however, onasemnogene abeparvovec is expected to be used in infants who are newly diagnosed with SMA type 1 or with a genotype predictive of SMA type 1 (i.e. the incident population) [redacted][a]	Clinical data suggest there are potential benefits in starting treatment as early as possible, therefore onasemnogene abeparvovec is expected to be used in the newly diagnosed (incident) SMA type 1 population or infants with a genotype predictive of SMA type 1 only
Intervention	Onasemnogene abeparvovec	As per scope, but for clarity the intervention is: onasemnogene abeparvovec delivered via a single IV infusion	N/A
Comparator(s)	Best supportive care Nusinersen (subject to ongoing NICE appraisal)	As per scope	N/A
Outcomes	The outcome measures to be considered include: • Motor function (including, where applicable, age-appropriate motor milestones such as sitting, standing, walking) • Frequency and duration of hospitalisation. • Speech and communication • Respiratory function • Complications of SMA (including, for	As per scope, but a composite endpoint of permanent ventilation-free survival – often termed as event-free survival (EFS) in the assessment of SMA type 1 – is also assessed As per scope, but health-related quality of life of caregivers will be explored in modelling scenario analyses only	EFS (defined as survival free from permanent ventilation) is a primary or secondary efficacy endpoint in the onasemnogene abeparvovec clinical trial programme Due to the lack of robust utilities for caregivers of SMA type 1 patients

	example, scoliosis and muscle contractures) • Need for non-invasive or invasive ventilation • Mortality • Adverse effects of treatment • Health-related quality of life (for patients and carers) Clinical effectiveness • Overall magnitude of health benefits to patients and, when relevant, carers • Robustness of the current evidence and the contribution the guidance might make to strengthen it • Treatment continuation rules (if relevant)		
Subgroups to be considered	Within the proposed label, heterogeneity of health benefits within the population will be explored	As per scope, heterogeneity of health benefits within the population is explored qualitatively but no formal quantitative subgroups are presented	N/A
Nature of the condition	• Disease morbidity and patient clinical disability with current standard of care • Impact of the disease on carer's quality of life	As per scope	N/A

	• Extent and nature of current treatment options		
Cost to the NHS and PSS, and Value for Money	• Cost effectiveness using incremental cost per quality-adjusted life year • Patient access schemes and other commercial agreements • The nature and extent of the resources needed to enable the new technology to be used	As per scope Potential patient access schemes or other commercial agreements will be explored with NICE and NHS England, during this appraisal process, if required	N/A
Impact of the technology beyond direct health benefits, and on the delivery of the specialised service	• Whether there are significant benefits other than health • Whether a substantial proportion of the costs (savings) or benefits are incurred outside of the NHS and personal and social services • The potential for long-term benefits to the NHS of research and innovation • The impact of the technology on the overall delivery of the specialised service	As per scope, however, the assessment of caregiver productivity loss, caregiver/patient out of pocket costs and patient educational achievement/ workforce participation are explored via modelling scenario analyses only	Limited UK-specific data for the SMA type 1 population in relation to costs incurred outside of the NHS and PSS exists, therefore, impacts of the technology beyond direct health benefits are explored by modelling scenario analyses only in Section 5.4.2

	• Staffing and infrastructure requirements, including training and planning for expertise		
Special considerations, including issues related to equality	• There are no special considerations in equality regarding prescribed characteristics, however, the practicalities of families having to travel for treatment at specialised centres should be considered • Guidance will only be issued in accordance with the marketing authorisation • If evidence allows, and included within the marketing authorisation, consideration may be given to a subgroup of people with pre-symptomatic disease • Guidance will take into account any Managed Access Arrangements	As per scope	N/A

[a] As noted in Section 2, a marketing authorisation for onasemnogene has been granted subsequent to the submission of the original CS and ERG interim report. For clarity and to avoid confusion, the ERG has preserved the description of the decision problem as reported in the company's original submission and the ERG's interim report.

Abbreviations: ERG, Evidence Review Group; N/A, not applicable; NHS, National Health Service; NICE, National Institute for Health and Care Excellence; PSS, personal social services; SMA, spinal muscular atrophy.

3.1 Population

The initial scope issued by NICE specified the population of interest to be children with spinal muscular atrophy (SMA) type 1.[23] The scope indicated a special consideration, data allowing, for use of onasemnogene in pre-symptomatic patients, that is, those with no symptoms but a genetic diagnosis of SMA and thought likely to develop SMA type 1. At the time of writing of the ERG report, NICE informed the ERG that the population of interest had been updated to reflect the marketing authorisation for onasemnogene:[1]

- 5q (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.

In the original CS, data on the clinical effectiveness of onasemnogene were primarily derived from START (N=15),[24] which is a Phase 1 single arm study designed to evaluate the safety of onasemnogene in those with SMA type 1 and symptom onset at less than 6 months of age, and who had two copies of the SMN2 gene. Given that a proportion of children with one (7%) or three (20%) copies of the SMN2 gene are reported to develop SMA type 1 (Table 2), the ERG considers that focusing on those with two copies of the SMN2 gene potentially renders a slightly narrower population than specified in the scope issued by NICE.

In the original CS, the company described several ongoing studies evaluating onasemnogene as supporting evidence for the results from START.[24] In particular, STR1VE-US[27] (N=22) and STR1VE-EU[28] (N=33) are Phase III single-arm studies that enrolled children with a clinical diagnosis of SMA type 1 and who had one or two copies of the SMN2 gene. Additionally, SPR1NT[29] (N=29) enrolled pre-symptomatic patients identified as having a genetic profile indicative of development of SMA type 1 or type 2, that is, those with bi-allelic deletion of SMN1 and with two or three copies of SMN2.

In the subsequent supplementary appendix, the company provides a pooled analysis of data from START[24] and STR1VE-US[27] to provide a more robust estimate for key clinical outcomes for patients with symptomatic SMA type 1 after receiving treatment with onasemnogene. The ERG considers the pooling of data to be appropriate (discussed in greater detail in Section 4.3.4), but notes that a proportion of children who develop SMA type 1, that is, those with three copies of the SMN2 gene, are not represented in the studies. The ERG's clinical experts communicated that time of symptom onset, rather than copy number of SMN2 gene, is a stronger predictor of severity of symptoms and likelihood to reach key motor milestones. Thus, the ERG proposes excluding those with three copies of the SMN2

gene is unlikely to impact on the estimate of clinical effectiveness of onasemnogene in infants with symptoms of SMA and a clinical diagnosis of SMA type 1.

As per the conditional marketing authorisation for onasemnogene (described in Section 2.2), the therapy is available for administration to infants with a bi-allelic mutation in the SMN1 gene and up to 3 copies of the SMN2 gene. As per the company's response to clarification around the proposed population eligible for treatment with onasemnogene, the ERG notes that SMA with a bi-allelic mutation in the SMN1 gene and up to 3 copies of the SMN2 gene pertains to pre-symptomatic infants. As noted earlier, the relationship between SMN2 gene copy number and SMA type is a continuum (Table 2), and, as commented by the ERG's clinical experts, it is challenging to reliably identify infants who will go on to develop SMA type 1 or SMA type 2 at a pre-symptomatic stage based on SMN2 copy number. The key studies evaluating onasemnogene in the management of SMA type 1, START, STR1VE-US and STR1VE-EU, are all single arm studies and, as such, afford no data on effectiveness of the comparator of best supportive care (BSC; see section 3.3). To provide estimates on the effectiveness of BSC, the company identified and extracted data from two studies of the natural history of SMA type 1 (NeuroNext[30, 31] and PNCR) and the sham control arm of a randomised controlled trial of nusinersen (ENDEAR[32]), which is disease-modifying treatment for SMA (all types). Hereafter PNCR, NeuroNext, and ENDEAR are referred to as SMA type 1 natural history studies. The populations of the identified studies are similar to that of START:

- ENDEAR[32] enrolled patients with SMA type 1, two copies of the SMN2 gene, and symptom onset at ≤6 months of age;

- NeuroNext[30, 31] enrolled patients with SMA type 1 and symptom onset at age ≤6 months and pre-symptomatic patients who had been genetically tested prior to enrolment. Only patients with symptomatic SMA type 1 and two copies of SMN2 are included in analyses presented in the CS;

- PNCR enrolled patients with SMA type 1 and 2. The cohort of patients with two copies of SMN2 (AveXis PNCR NeuroNext report[30] and Finkel *et al.* 2014[33]) is described within the CS. For the purposes of the economic model, the PNCR cohort is implemented in two scenarios. One scenario involves the PNCR cohort alone and comprises patients with 2 copies of SMN2 gene and SMA type 1 (n=23). A second scenario involves a cohort (n=26) combining patients from Italy, where SMN2 copy number is not available, as described in De Sanctis *et al.*[34], with patients from the PNCR database. The population in the combined cohort applied in scenario analysis in the economic model is in line with the NICE final scope[1] but a mismatch compared with the more specific population enrolled in START (limited to two copies of the SMN2 gene), which is informing the efficacy and safety data for onasemnogene.

The ERG's clinical experts confirm that the populations in START and the natural history cohorts are representative of patients with SMA type 1 in England. However, there are differences in, for example, the health care settings across START, the natural history studies and the ongoing onasemnogene studies. A key difference across studies is that, for studies based in the USA, a larger proportion of patients go on to receive tracheostomy compared with UK clinical practice, which could affect the applicability of the findings from analyses of survival.

3.2 Intervention

Onasemnogene acts by replacing the missing or dysfunctional SMN1 gene associated with SMA with a new, working copy of a human SMN gene. Replacement of the nonworking SMN gene restores cellular expression of the SMN protein. The adeno-associated vector serotype 9 (AAV9)-derived viral vector used to deliver the gene has a high affinity for motor neurones and skeletal cells and it crosses the blood–brain barrier, allowing effective dosing of the motor neurons in the central nervous system (CNS). Onasemnogene is administered as a single peripheral IV infusion;[25] the dosing is adjusted by body weight so that patients receive 1.1 x 10^{14} vector genome copies per kg (vg/kg). The company's summary of the mechanism of action of onasemnogene is described in Box 1.

The key study START includes two cohorts: Cohort 2 received the recommended dose whereas cohort 1 received a lower dose and at an older age. Only data for the recommended dose of onasemnogene from Cohort 2 have been used to inform the economic modelling.

Box 1. Mechanism of action of onasemnogene (reproduced from CS, Box 1)

Onasemnogene abeparvovec replaces the *SMN* gene which is missing (or dysfunctional) in patients with SMA type 1. The *SMN* gene present in onasemnogene abeparvovec is located in a viral vector (AAV9) which acts as a vehicle to carry the gene into patients' cells. As the vector contains no genes from the AAV9 virus, it is incapable of replicating itself. Once inside the cell, the vector releases an *SMN* gene into the cell nucleus. The onasemnogene abeparvovec *SMN* gene is designed not to integrate into the patient chromosome, but rather to reside as a DNA episome – a DNA molecule that exists independently of chromosomal DNA. This means that the AAV9 vector delivers a functional copy of a human *SMN* gene without modifying patients existing chromosomal DNA. The inserted *SMN* gene is in a 'transcription-ready' state (ready to be turned into a genetic messenger [mRNA] telling patients' cells to make SMN protein) as it contains a region of DNA (called a promoter) that initiates transcription of the *SMN* gene. This rapid and sustained production of SMN protein is critical to preventing motor neurone cell death and enabling motor function gains so that patients can achieve key developmental and motor milestones. The introduction of a stable *SMN* gene that remains in non-mitotic (non-dividing) cells indefinitely enables continuous and sustained SMN protein expression, eliminating the need for repeat administration of onasemnogene abeparvovec.
Abbreviations: AAV9, adeno-associated vector serotype 9; DNA, deoxyribonucleic acid; mRNA, messenger ribonucleic acid; SMA, spinal muscular atrophy.

Onasemnogene gained regulatory approval by the US Food and Drug Administration (FDA) in May 2019. As noted in Section 2.2, onasemnogene was granted a marketing authorisation by the European Medicines Agency (EMA) in March 2020.

3.3 Comparators

The original NICE scope defined the comparators as best supportive care (BSC) and nusinersen (subject to NICE appraisal).[23] Nusinersen was approved in July 2019 for routine commissioning in England for use in all patients with 5q SMA (pre-symptomatic SMA, or SMA types 1, 2 or 3) as part of a managed access agreement but is not yet considered established standard of care.[20, 21] As per the revised scope, nusinersen is no longer considered a comparator of interest for this appraisal.[1] The company provided an indirect treatment comparison (ITC) between onasemnogene and nusinersen in the original CS, but as nusinersen is not considered a comparator of interest this analysis is not described or critiqued further by the ERG. The ERG considers that only comparator of relevance is BSC, irrespective of whether onasemnogene has been given with the goal of preventing development of symptoms in patients identified as having a genotype associated with SMA type 1 or as a treatment in those with a clinical diagnosis of SMA type 1.

The key studies evaluating the clinical effectiveness of onasemnogene (START, STR1VE-EU, STR1VE-US for symptomatic and SPR1NT for pre-symptomatic patients) are all single arm studies. To provide a comparison of onasemnogene with BSC for the treatment of SMA type 1, the company identified three studies looking at the natural history of SMA type 1; the comparator arm within the randomised controlled trial (RCT) of nusinersen (ENDEAR),[32] which is a sham procedure, and two cohorts of the natural history of SMA type 1 (NeuroNext[30, 31] and PNCR[30, 33]).

As described in Section 2.2, the care of infants with a clinical diagnosis of SMA type 1 in England is informed by guidelines from the International Standards of Care for Spinal Muscular Atrophy, and BSC involves mechanical ventilation to help ease breathing difficulties due to decline in muscle function, interventions such as oral suctioning or physiotherapy to maintain airway clearance and to cough, and mechanical feeding as swallowing and feeding difficulties increase over time. The comparator (BSC) considered within the company's health economic analyses comprises standard respiratory, gastrointestinal and nutritional care delivered by a multidisciplinary team.

Although both the NeuroNext and the PNCR studies were based in the USA and ENDEAR is a multicentre, international trial with few patients recruited in the UK, the ERG's clinical experts consider the BSC provided in these studies broadly comparable to BSC in UK clinical practice. However, the experts noted that use of life-extending care, such as permanent assisted ventilation (PAV) by tracheostomy and non-invasive ventilation (NIV), varies between countries and has changed over time. In the UK, there has been a shift towards increased uptake of NIV in clinical practice, which may not

be reflected within the SMA natural history studies.[35] In addition, for patients with SMA type 1 who need PAV, tracheostomy is used rarely in the UK compared with USA. The difference across studies in rate of tracheostomy will have an impact on OS, which is likely to be overestimated in studies carried out in the USA compared with UK clinical practice. The merits of the studies informing the comparison with BSC are discussed in Section 4.2.

3.4 Outcomes

The NICE final scope[1] lists the following outcomes:

- motor function (including, where applicable, age-appropriate motor milestones such as sitting, standing, walking);
- frequency and duration of hospitalisation;
- speech and communication;
- respiratory function;
- complications of SMA (including, for example, scoliosis and muscle contractures);
- need for non-invasive or invasive ventilation;
- mortality;
- adverse effects of treatment;
- health-related quality of life (HRQoL, for patients and carers).

The CS includes evidence on outcomes capturing motor function, respiratory function, and speech and communication. Data are also available for a composite outcome encompassing survival without the need for permanent ventilation. Motor function, measured as achieving motor milestones, were mainly assessed using Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders, CHOP-INTEND, a scale developed and validated for use specifically to monitor motor function status amongst children with SMA type 1. Data are not are not presented for the specified outcome of complications of SMA. However, the ERG notes that many complications of SMA type 1 will be captured within the adverse events that occurred during the studies, for example, occurrence of scoliosis.

Data are reported for a patients' ability to thrive, their nutritional status and their capability to swallow, which are not included in the outcomes of interest to the decision problem, but all of which have been

highlighted by the ERG's clinical experts as clinically relevant outcomes in SMA. Definitions for all outcomes are provided in the appropriate section on clinical effectiveness of onasemnogene.

HRQoL data were not collected in any of the onasemnogene studies for SMA type 1. In addition, HRQoL data were not captured in the ENDEAR trial or the SMA type 1 natural history studies PNCR and NeuroNext. HRQoL data to inform the patient health state utility values in the cost-effectiveness model were, therefore, derived from multiple other sources. These are described and the appropriateness of them are discussed in Section 5.3.8. The company has explored the HRQoL of caregivers only in scenario analyses due to the lack of robust utilities for caregivers of SMA type 1 patients.

3.5 Subgroups

NICE has requested that, if evidence allows, consideration be given to a subgroup of patients with pre-symptomatic disease. The ERG considers that the marketing authorisation for onasemnogene encompasses pre-symptomatic patients, that is, those with a genetic diagnosis of SMA. Data from the ongoing SPR1NT study, a study enrolling exclusively pre-symptomatic patients, are presented in Section 4.3.2.

3.6 Special considerations

In Table 4, the company states that there are no special considerations in equality regarding prescribed characteristics but comment that the practicalities of families having to travel for treatment at specialised centres should be considered.

4 CLINICAL EFFECTIVENESS

4.1 Critique of the methods of review

The company carried out several systematic literature reviews (SLRs) to identify evidence for:

- the clinical efficacy and safety of onasemnogene versus competing interventions for spinal muscular atrophy (SMA);
- health related quality of life (HRQoL) and utilities for onasemnogene versus competing interventions for SMA;
- economic burden of onasemnogene versus competing interventions for SMA;
- the natural history of SMA type 1.

Full details of the methods and results of the SLRs were provided in a separate reference of the submission.[36] The company's SLRs of clinical efficacy of onasemnogene and natural history of SMA type 1 are summarised in Table 5, together with the Evidence Review Group's (ERG's) critique of the appropriateness of the methods implemented. The SLRs for HRQoL and economic burden of onasemnogene and competing interventions are described and discussed in Section 5.2.

The main purpose of the clinical efficacy and safety SLR was to identify all relevant studies that could inform the comparison of onasemnogene with other interventions for SMA. As stated in Section 3.3, best supportive care (BSC) is the only comparator relevant to this appraisal as nusinersen is not considered a comparator of interest to the decision problem. Relevant studies identified in the clinical efficacy SLR are therefore limited to those of onasemnogene. Studies informing the outcomes of BSC were primarily identified through the SLR of the natural history of SMA type 1. Records retrieved by the four systematic literature searches were cross-referenced across the systematic reviews such that if any article identified by one of the reviews was also relevant to another review it was accounted for in both reviews.

From the company submission (CS), it seems a fifth SLR was conducted with the goal of identifying evidence to enable a comparison of onasemnogene and nusinersen (CS, Section 9.8.1). The SLR focusing on onasemnogene versus nusinersen was in addition to the efficacy and safety SLR on onasemnogene versus competing interventions that also included a search for studies evaluating nusinersen. The additional SLR had similar inclusion criteria, but was much less rigorous in terms of methods, with fewer sources searched, a significantly simpler search strategy, and sifting, appraisal and data extraction done by only one reviewer. It is unclear why this SLR was conducted in light of the more comprehensive efficacy and safety SLR already performed. No information was provided about

the search date for the additional SLR, neither was a PRISMA diagram provided to show the results of the SLR. However, as nusinersen is not considered a comparator of interest for this appraisal, the methods for identifying nusinersen trials are of limited importance.

As part of its critique of the supplementary appendix, the ERG noted that the SLRs appeared not to have been updated for the additional submission. The company clarified that update searches had been performed but the finalised SLR report was not available by the deadline for submission of the appendix. In their clarification response, the company indicated that the update to the SLR for natural history studies was expanded to include SMA types 1 through 3, with the goal of providing studies to inform the C state and B state of the economic model, if needed. All studies relevant to the clinical effectiveness and safety of onasemnogene were retrieved by the primary SLR, and data from latest data-cuts or final results for each study were reported in the supplementary appendix.

Table 5. Summary of the ERG's critique of the company's SLRs of clinical efficacy and safety, and SMA type 1 natural history studies

Review step	CS Section	ERG critique
Data sources	CS Section 9.1.1.1[36]	**The ERG considers the sources and dates searched appropriate.** MEDLINE, EMBASE, EconLit, CENTRAL, trial registries (USNIHCTR, EUCTR, WHO ICTRP, and clinicalstudyresults.org), conference proceedings (WMS 2018, AAN 2018, ICNMD 2018, CNS 2017, AANEM 2017), reference lists of SLRs and of US ICER report[a].
Search strategies	CS Appendix 17.1.1 and 17.1.4[36]	**The ERG is satisfied that searches would have identified all evidence relevant to the decision problem.** Search strategies combined comprehensive terms for the population and interventions, medical subject headings, and study design filters. Search date: 11 March 2019. Update search: March 2020.
Inclusion criteria	CS Section 9.2[36]	**The ERG considers it likely that no relevant evidence was excluded based on the eligibility criteria used.** Inclusion criteria reproduced in Appendix 10.1. Criteria were at least as broad as the NICE final scope. Included interventions were well beyond the scope of this appraisal. Natural history studies were limited to RCTs or prospective cohorts with ≥ 12 months of follow-up, whereas similar restrictions were not applied for the clinical efficacy search.
Screening and data extraction	CS Section 9.1.1.1[36]	**The ERG considers the methods described to be robust.** Independent duplicate screening and data extraction by two reviewers with predefined criteria; discrepancies resolved by consensus/with a third reviewer, screening results summarised in PRISMA diagrams and data extraction clearly described. However, the ERG notes that natural history studies with a retrospective component (e.g., PNCR) were included in the review, which does not reflect the specified inclusion criterion for studies on natural history.

Quality assessment	CS Section 9.1.1.1[36] and 9.5, Appendix 17.4.1.1 and 17.4.1.4	**The ERG considers the company's quality assessments of studies to be satisfactory.** Quality assessment was done independently by two reviewers. The RCT ENDEAR[32] was assessed using the Cochrane RoB tool.[37] START[38], STR1VE-US[27] and the observational studies informing the comparator, NeuroNext[31, 39] and PNCR[33], were assessed using the Newcastle-Ottawa scale.[40] Quality assessments of STR1VE-EU,[28] SPR1NT,[29] and LT-001[41] were not provided.
[a] The US ICER report was not formally included in the SLR as it was published after the date on which the SLR was conducted. Abbreviations: AAN, American Academy of Neurology; AANEM, American Association of Neuromuscular & Electrodiagnostic Medicine; CASP, Critical Appraisal Skills Programme; CENTRAL, Cochrane Central Register of Controlled Trials; CNS, Child Neurology Society; CS, company's submission; ERG, Evidence Review Group; EUCTR, European Union Clinical Trials Register; ICNMD, International Congress on Neuromuscular Diseases; NICE, National Institute for Health and Care Excellence; PRISMA, Preferred Reporting Items for Systematic Reviews and Meta Analyses; RCT, randomised controlled trial; RoB, risk of bias; SLR, systematic literature review; SMC, Scottish Medicine Consortium; US ICER, US Institute for Clinical and Economic Review's; USNIHCTR, US National Institutes of Health Clinical Trial Registry; WHO ICTRP, World Health Organization International Clinical Trials Registry Platform; WMS, World Muscle Society.		

Twenty studies reported across 22 publications were identified for inclusion in the clinical efficacy and safety review. However, not all studies were of relevance to the decision problem as the total includes studies assessing any of the broad list of interventions specified in the inclusion criteria (Table 64, Appendix 10.1). Studies evaluating interventions or populations (e.g., SMA type 2) not of relevance to the decision problem were not assessed.

During the cross-referencing of publications across the four SLR topics, only one study (ENDEAR[32]), identified from the review of clinical efficacy and safety, was deemed relevant for inclusion in the natural history SLR. In addition to the ENDEAR RCT, four additional studies were included in the review of natural history of SMA type 1, although one of these studies (Finkel *et al*. 2014b[42]) does not feature in the clinical or cost effectiveness result sections of the original CS. The company states that Finkel *et al.* 2014b was not included due to limitations in design (single site in the USA) and small sample size (N=7). The ERG agrees with the company that the other included natural history studies provide more robust data for clinical outcomes of BSC. The relative merits of the natural history studies are described and discussed in Sections 4.2.4 and 4.2.4.1. PRISMA diagrams for SLRs of literature on clinical effectiveness of onasemnogene and the natural history of SMA type 1 are available in Appendix 10.2.

The company also identified three ongoing and unpublished onasemnogene studies for which interim data are presented in both the CS and the supplementary appendix (STR1VE-EU[28], SPR1NT[29], LT-001[41]), and one long term follow up study which is yet to report results (LT-002[43]). The studies were selected based on the same inclusion and exclusion criteria as the published studies. No other details were provided around how the ongoing studies were identified. A pooled analysis of STR1VE-US and START informs the cost-effectiveness analysis, with the pooled data available in both the original CS and supplementary appendix. The results of the pooled analysis, together with the ERG's critique, are reported in Section 4.3.3. The company informed that the next interim data cut for the ongoing studies LT-001, SPR1NT, and STR1VE-EU, is planned for [redacted] but data will not be available until

[redacted]. The long-term follow-up study of patients in phase 3 onasemnogene studies, LT-002, commenced in September 2019 but, at the time of writing of the ERG's interim report, had yet to enrol any patient treated with IV onasemnogene (only intrathecally treated patients had been enrolled).

In summary, the studies informing the clinical and/or cost effectiveness analysis in the CS are: two completed onasemnogene studies (START[24], STR1VE-US[27]), three ongoing onasemnogene studies (STR1VE-EU[28], SPR1NT[29], LT-001[41]), and three natural history studies informing the estimates for BSC (PNCR[30], NeuroNext[30], ENDEAR[32], Table 6).

The ERG highlights that the ENDEAR trial, which was identified in the efficacy and safety SLR and informs the outcomes of BSC, was not described or used as a comparator for onasemnogene in the clinical effectiveness reported in the CS. However, ENDEAR was implemented in scenario analyses for evaluation of cost effectiveness of onasemnogene. Additionally, one of the natural history studies, PNCR, has been included in the review despite applying both retrospective and prospective enrolment of patients, which is contrary to the SLR inclusion criteria (Table 5). An alternative source of BSC data used in the economic model, De Sanctis *et al.* 2016[34], is a retrospective study comprising patients from the PNCR cohort, as well as patients from other cohorts. De Sanctis *et al.* 2016 was identified during full text screening as part of the SLR but was not included in the company's review, the ERG assumes because of its retrospective study design. The merits of the individual BSC studies, in terms of which is most applicable to UK clinical practice and which is the most appropriate to inform the comparison with onasemnogene based on START, are discussed in Sections 4.2 and 4.3.

Table 6. Included studies informing the clinical and/or cost effectiveness in the CS

Study name	Population	Intervention	Comparator
START[26, 44]	• SMA type 1 possessing 2 copies of SMN2 without c.859G>c modification in exon 7 • Aged ≤6 months • Symptom onset at ≤6 months • N=12	Onasemnogene	No comparator
STR1VE-US[27, 45]	• SMA type 1 with 1 or 2 copies of SMN2 • <6 months of age at the time of gene replacement therapy • N=22	Onasemnogene	No comparator
STR1VE-EU[28, 45]	• Symptomatic SMA type 1 with 1 or 2 copies of SMN2 • <6 months of age at the time of gene replacement therapy • Enrolled N=33	Onasemnogene	No comparator
SPR1NT[29, 45]	• Pre-symptomatic patients with genetically diagnosed SMA with 2 or 3 copies of SMN2 • ≤6 weeks of age at the time of gene replacement therapy • Planned N=≥27 evaluable patients	Onasemnogene	No comparator

	• Enrolled = 29: 2 copies of SMN2, N=14 3 copies of SMN2, N=15		
LT-001 (extension of START)[41, 46]	• Patients treated with onasemnogene abeparvovec in Study AVXS-101-CL-101 (enrolled N=13)	Onasemnogene	No comparator
PNCR*[30, 33]	• SMA type 1 and 2 (N=34), including SMA type 1 with 2 copies of the SMN2 gene (N=23)	BSC	No comparator
NeuroNext[30, 31, 39]	• SMA type 1 (N=26) 2 copies of the SMN2 gene, N= 16 • Age ≤6 months at enrolment and born between 36 and 42 weeks of gestation • Asymptomatic infants who had been genetically tested prior to enrolment	BSC	No comparator
ENDEAR[32]	• SMA type 1 with homozygous deletion or mutation in the SMN1 gene and 2 copies of SMN2 • Aged ≤7 months at screening • Symptom onset at ≤6 months	Nusinersen	Placebo (n=41, sham procedure)
De Sanctis 2016[34]	• SMA type 1 (N=33), including onset of symptoms <6 months of age (N=26), SMN2 copy number not reported	BSC	No comparator
Abbreviations: BSC, best supportive care; CS, company's submission; SMA, spinal muscular atrophy.			

Overall, the ERG considers that the company's SLR methods followed recommended practices and the ERG is satisfied that all relevant evidence was identified. However, the company has been inconsistent in applying set inclusion criteria resulting in the inclusion and use of the PNCR cohort and De Sanctis *et al.* 2016, despite these being part or fully retrospective in nature.

4.2 Critique of trials of the technology of interest, their analysis and interpretation

There are seven studies in the onasemnogene clinical trial programme, as depicted in Figure 1 and summarised in Table 7. The studies comprise six studies evaluating onasemnogene in SMA type 1 and one study in pre-symptomatic patients identified as having a genotype associated with potential development of SMA type 1.

As can be seen in Figure 1, studies in those with a clinical diagnosis of SMA type 1 are the Phase I/II trial START,[24] and three Phase III trials (STR1VE-US[27] and STR1VE-EU[28], STR1VE-APAC). Additionally, there are two long-term follow-up studies — LT-001,[41] which is the extension of START, and LT-002,[43] which is the long-term follow up study of the Phase III studies. SPR1NT[29] is the Phase III study enrolling pre-symptomatic patients. STR1VE-US and START are complete and data derived from the studies are pooled to inform the cost-effectiveness analysis of onasemnogene. Interim data from the ongoing STR1VE-EU, LT-001, and SPR1NT studies are also presented in the clinical-effectiveness section of the CS and supplementary appendix as supporting evidence on the clinical

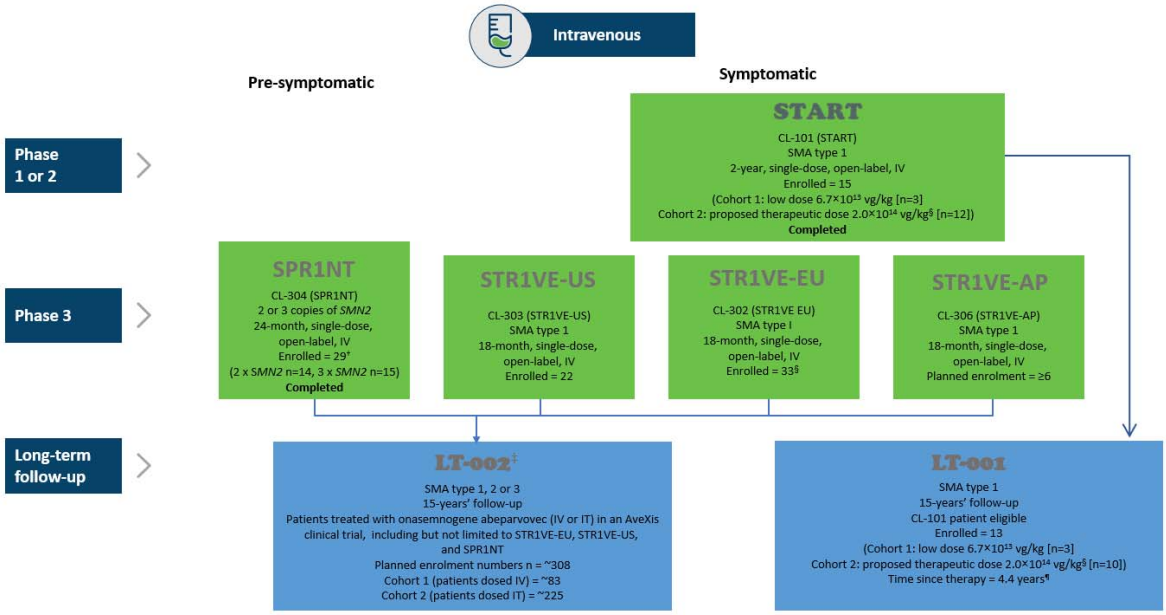
effectiveness of onasemnogene. No results are reported for LT-002 or for STR1VE-APAC, which is an ongoing Phase III study with sites located in Japan, South Korea, and Taiwan.

The ERG notes that, in the original CS appendix, the company reported that intrathecal administration of onasemnogene is being investigated in patients with SMA type 2 in AVXS-101-CL-102 (STRONG). However, intrathecal administration is not relevant to the NICE decision problem and thus this study is not discussed further.

The company also reported in the original CS appendix that AveXis is sponsoring a prospective Global SMA Disease Registry (RESTORE, AVXS-101-RG-001). The aim of the registry is to follow a minimum of 500 patients with SMA (genetically confirmed on or after 24 May 2018) until death or for up to 15 years, with the cohort including approximately 20% of patients treated with existing or upcoming approved treatments, such as onasemnogene. The current data available from the registry are limited to [redacted] patients and outcome data presented in the CS appendix were limited to survival data reporting [redacted] are still alive as of 31 January 2020 data cut. The ERG does not discuss these data further as data are not available for other outcomes of relevance to the NICE decision problem.

All onasemnogene studies in the company's clinical development programme have an open-label design, with all patients receiving a one-time dose of onasemnogene. Due to the lethality of SMA, the extremely poor prognosis for patients who do not receive treatment and the unprecedented efficacy and favourable safety profile observed in the START trial, it was considered unethical to include placebo arms in further onasemnogene trials. To enable the comparison between onasemnogene and BSC, the company identified cohorts of patients from the SMA natural history studies PNCR and NeuroNext to use as historical controls.[30, 31, 33] The comparisons with PNCR and NeuroNext were unplanned but mentioned in the clinical study report (CSR) of START. A comparison with PNCR was prespecified for one of the ongoing onasemnogene studies, STR1VE-US. The SMA type 1 natural history studies are described and discussed in Section 4.2.4.

Figure 1. Overview of the onasemnogene clinical trial programme (reproduced from CS appendix, Figure 1)



† Pre-symptomatic patients with four copies of SMN2 were eligible for enrolment in SPR1NT based on the original SPR1NT protocol but were later removed as per protocol amendment dated 27 September 2018. One patient with four copies of SMN2 was enrolled but excluded from the ITT efficacy population for Cohort 2 (three copies of SMN2) and is therefore not reported in the interim efficacy results; this patient remains part of the safety population.
‡ LT-002 commenced in September 2019; to date, seven patients are enrolled in LT-002.
§ Direct testing of the actual lot of IMP used in START by an improved and more fully qualified analytical method has determined the actual dose received by Cohort 2 as 1.1 x 1014 vg/kg. The same method has been used to establish an equivalent dose for the IMP in all Phase III trials.
¶ The median duration of therapy in LT-001 of patients treated with the therapeutic dose of onasemnogene abeparvovec in START (n=10) as of the 31 December 2019 (range 49.2 to 61.9 months).
Abbreviations: CS, company's submission; IV, intravenous; IMP, investigational medicinal product; SMA, spinal muscular atrophy.

Table 7. Summary of clinical studies of onasemnogene abeparvovec included in the submission (reproduced from supplementary appendix, Table 2)

	Symptomatic SMA type 1				**Pre-symptomatic SMA**
Characteristic	**START**	**LT-001**	**STR1VE-US**	**STR1VE-EU**	**SPR1NT**
Phase	Phase I/IIa	Long-term extension of START	Phase III	Phase III	Phase III
Status of study	Complete	Ongoing	Complete	Ongoing	Ongoing
Design	Open label, dose-escalation trial	Open label	Open label, single-arm, single-dose trial	Open label, single-arm, single-dose trial	Open label, single-arm, single-dose trial
SMA type	Type 1	Type 1	Type 1	Type 1	Genetically diagnosed and pre-symptomatic SMA
SMN2 copy number – permitted in protocol	2 copies	2 copies	1 or 2 copies	1 or 2 copies	2 copies (Cohort 1) or 3 copies (Cohort 2)[a]
SMN2 copy number – for patients enrolled	2 copies	2 copies	2 copies	2 copies	2 copies (Cohort 1) or 3 copies (Cohort 2)[a]
Patients with c.859G>c modification in exon 7 of *SMN2* included in efficacy analysis populations	No	No	No[b]	No[b]	No[b]
Intervention(s) and comparators(s)	Intervention: Onasemnogene abeparvovec Cohort 1 received low dose 6.7×10^{13} vg/kg[c]; Cohort 2 received therapeutic dose 2.0×10^{14} vg/kg[c] Comparator: natural history cohort[d]	Study drug was not administered in LT-001; patients were dosed in START	Intervention: Onasemnogene abeparvovec 1.1×10^{14} vg/kg Comparator: Natural history cohort[d]	Intervention: Onasemnogene abeparvovec 1.1×10^{14} vg/kg Comparator: Natural history cohort[d]	Intervention: Onasemnogene abeparvovec 1.1×10^{14} vg/kg Comparator: Natural history cohort[d]
Primary endpoint	Safety: AEs Laboratory evaluations Drug-induced liver injury Vital signs	Primary efficacy: Physical examinations to assess developmental milestones	Co-primary efficacy: Proportion of patients achieving functional independent sitting for ≥30	Primary efficacy: Proportion of patients achieving the milestone of sitting without support for	Primary efficacy: Two copies of *SMN2*: Proportion of patients achieving the ability of functional independent

	ECGs Immunologic response Primary efficacy: Survival[f]	New milestones demonstrated by patients which were not documented during START must be supported by video evidence	seconds[e] at the 18 months of age study visit Survival at 14 months of age[g]	at least 10 seconds[h] up to 18 months of age	sitting for ≥30 seconds up to 18 months of age Three copies of *SMN2*: Proportion of patients achieving the ability to stand without support for at ≥3 seconds up to 24 months of age
Status of enrolment	Complete	Complete	Complete	Complete	Complete
Patients enrolled as of 31 December 2019	3 (Cohort 1) 12 (Cohort 2)	3 (Cohort 1) 10 (Cohort 2)	22	33	14 (Cohort 1) 15 (Cohort 2)[a]
Follow-up period	24 months post dose	15 years	18 months of age	18 months of age	18 months of age (Cohort 1) 24 months of age (Cohort 2)
References	Mendell *et al*. 2017[44] Al-Zaidy et al. 2019[26] CSR[24]	Al-Zaidy *et al*. 2019[26] Protocol[47] Clinical overview (31 December 2019 data cut)[48] 180-Day efficacy update (31 December 2019)[49] 180-Day safety update (31 December 2019)[50]	Protocol[27] Clinical overview (31 December 2019 data cut)[48] CSR[51]	Protocol[52] Clinical overview (31 December 2019 data cut)[48] 180-Day efficacy update (31 December 2019)[49] 180-Day safety update (31 December 2019)[50]	Protocol[53] Clinical overview (31 December 2019 data cut)[48] 180-Day efficacy update (31 December 2019)[49] 180-Day safety update (31 December 2019)[50]

[a] Pre-symptomatic patients with four copies of *SMN2* were in the original SPR1NT protocol but later removed as per protocol amendment dated 27 September 2018. One patient with four copies of *SMN2* was enrolled and received an IV administration of onasemnogene but was excluded from the ITT efficacy population and is therefore not reported in the interim efficacy results from the 31 December data cut; this patient remains part of the safety population.
[b] Whilst inclusion criteria of the trial permitted those with the modifier mutation, the ITT population excludes those with the *SMN2* gene modifier mutation (c.859G>C) and no infants with the modifier mutation were enrolled.
[c] Direct testing of the actual lot of investigational product used in START by an improved and more fully qualified analytical method (droplet digital PCR) has determined the actual dose received by Cohort 1 to be 3.7×10^{13} vg/kg and the actual dose received by Cohort 2 to be 1.1×10^{14} vg/kg (the same method has been used to establish an equivalent dose for the IMP in all Phase III trials).
[d] Well characterised external datasets from SMA natural history studies (PNCR and NeuroNext[30]) are used to provide an external control comparator.
[e] Defined as Bayley Scales Gross Motor subset item #26: Child sits alone without support for ≥30 seconds.
[f] Defined as time from birth to either (a) requirement of ≥16-hour respiratory assistance per day (includes BiPAP) continuously for ≥2 weeks in the absence of an acute reversible illness, excluding perioperative ventilation or (b) death. This is described as a co-primary but is treated, statistically, as a secondary endpoint.
[g] Defined as avoidance of either (a) death or (b) permanent ventilation, at 14 months of age. Permanent ventilation is defined by tracheostomy or by the requirement of ≥16 hours of respiratory assistance per day (via non-invasive ventilatory support) for ≥14 consecutive days in the absence of an acute reversible illness, excluding perioperative ventilation.
[h] WHO definition: child sits up straight with head erect for ≥10 seconds; child does not use hands or arms to balance body or support position.
Abbreviations: AE, adverse event; BiPAP, bi-level positive airway pressure; CSR, clinical study report; ECG, electrocardiogram; IMP, investigational medicinal product; ITT, intention to treat; SMA, spinal muscular atrophy.

4.2.1 Study conduct

A brief overview of each of the studies evaluating onasemnogene, some of which are ongoing, is available below, with detailed summary tables outlining individual study methods available in Appendix 10.3. All studies in the onasemnogene trial programme are single arm and open-label. As noted above, given the lethal nature of SMA and the initial effectiveness of onasemnogene observed in START, it could be considered unethical to include placebo arms in studies evaluating onasemnogene. Considering the open-label nature of the studies, the ERG considers that bias in assessment of motor milestone outcomes is minimised by recording children during assessment of motor skills.

4.2.1.1 Symptomatic SMA type 1

START

START[24] is a Phase I/IIa, single centre study conducted in the USA with a study duration of 2 years (Table 66). Patients were eligible for enrolment in the trial if they had genetically-confirmed double-deletion of SMN1 exon 7 and two copies of SMN2. Patients were also screened for antibodies against AAV9, the presence of which would interfere with gene therapy using the AAV9 vector, as is the case with onasemnogene; those with anti-AAV9 antibody titres >1:50 were excluded (n=1). START included two cohorts, with the cohorts receiving different doses of onasemnogene. The first three patients received a single intravenous "low dose" of 6.7×10^{13} vector genomes (vg) per kilogram (kg) (Cohort 1), whereas the next 12 patients were given a single intravenous "therapeutic dose" of 2.0×10^{14} vg per kg (Cohort 2). The dosage given was initially determined by an early development stage quantitative polymerase chain reaction (qPCR) assay. Subsequent assessment of the doses administered in START by a more accurate analytical method (droplet digital PCR [ddPCR]) determined the actual doses to have been 3.7×10^{13} vg/kg and 1.1×10^{14} vg/kg given to Cohort 1 and 2, respectively. Due to the differences in onasemnogene dosing between Cohort 1 and 2, only Cohort 2 is deemed relevant to the NICE decision problem.

Due to elevated serum aminotransferase levels following dosing in the first patient, a protocol amendment added a prednisolone regimen of 1 mg/kg starting 24 hours before dosing through 30 days post-gene therapy administration. Concomitant treatment with nusinersen was not allowed during the 24 months of follow-up in START but was allowed in the long term follow-up study LT-001. The ERG notes that no patients withdrew from START or were lost to follow-up.

The primary objective of the study was an evaluation of the safety of onasemnogene and the primary outcome was treatment-related adverse events (TRAEs) of common terminology criteria for adverse events (CTCAE) grade three or higher. The secondary objective was the efficacy of onasemnogene, and the primary efficacy endpoint was the composite of time to death or permanent assisted ventilation

(PAV), defined as requirement of ≥16-hour respiratory assistance per day continuously for ≥2 weeks in the absence of an acute reversible illness, excluding perioperative ventilation. Secondary and exploratory outcomes included:

- motor milestone achievements;
- change from baseline in Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders (CHOP-INTEND) score;
- ability to thrive;
- nutritional status and swallowing function;
- motor neurone function.

During the first year of the study, patients were followed up on days 7, 14, 21, and 30, with subsequent monthly visits through to month 12. Various assessments of change in motor skills and muscle strength were implemented in START, as listed above. During the second year of the study, motor milestones of patients with CHOP-INTEND scores ≥62 was also assessed using the Bayley Scales and completed visits every 3 months, whereas all other patients completed monthly visits (subsequently changed to quarterly visits).

STRIVE-US

STR1VE-US[27] is a Phase III, multicentre study carried out in the USA that enrolled 22 patients with a clinical diagnosis of SMA type 1, 2 copies of SMN2, and age <6 months at the time of gene replacement therapy (Table 67). End of study visit was planned for when the patient reached 18 months of age. The intervention in STR1VE-US was a single dose of onasemnogene at 1.1 X 10^{14} vg/kg administered as a peripheral IV infusion over approximately 30–60 minutes, which is in line with the proposed licensed dose of onasemnogene.

The ERG notes that patients with 1 or 2 copies of SMN2 were eligible for inclusion, but all those enrolled had 2 copies of the gene. Additionally, although patients with the known SMN2 mutation that is a positive disease modifier (c.859G>C) were eligible for inclusion in STR1VE-US, no patient with the modifier mutation was enrolled in the study.

Of the 22 patients enrolled in STR1VE-US, three were lost to follow-up or withdrew:

- one patient died (not considered related to study drug) on Study Day 171 at the age of 7.8 months;

- one patient was lost from the study due to withdrawal of consent on Study Day 203 at the age of 11.9 months; the patient met the criteria for permanent assisted ventilation (PAV) status on Study Day 176 at the age of 11 months;

- one patient was discontinued at the age of 18 months due to an adverse event of respiratory distress (not considered related to study drug). The patient did not complete the Month 18 study visit, but at withdrawal (18 months of age) the patient was alive and not on PAV.

The primary objectives of STR1VE-US were to determine the efficacy of onasemnogene by demonstrating achievement of sitting without support for ≥30 seconds up to and including 18 months of age, and evaluating survival (alive and free from PAV) at 14 months of age compared with natural history data from PNCR. Secondary and exploratory outcomes in STR1VE-US included:

- achievement of motor milestones, including hold head erect without support, roll from back to both sides, sit with support, sit independently (>10 seconds; WHO Motor Developmental Milestones[54]), crawl, pull to stand, stand with assistance, stand alone, walk with assistance, walk alone;

- change from baseline in fine and gross motor components of the Bayley Scales of Infant and Toddler Development;

- change from baseline in gross motor function as determined by improvement CHOP-INTEND score;

- proportion of patients achieving CHOP-INTEND score ≥40, ≥50 and ≥58;

- change in peroneal nerve CMAP amplitude;

- age at which independent sitting (30 seconds) is first achieved;

Motor function of patients was assessed using both the Bayley Scales and CHOP-INTEND, which differs from assessment of motor milestones in START in which only patients who reached a score of 62 or more on the CHOP-INTEND scale were also assessed using the Bayley Scales.

STR1VE-EU

STR1VE-EU[28] is an ongoing Phase III study, of a similar design to STR1VE-US, with investigative sites located across Europe (Table 68). Follow-up is planned for up to 18 months after administration of onasemnogene. Akin to STR1VE-US, STR1VE EU enrolled patients with SMA type 1 and 1 or 2 copies of SMN2, and aged <6 months at the time of gene replacement therapy. The planned enrolment of 33 patients completed in May 2019, including patients from two UK sites. As with STR1VE-US,

although patients with 1 copy of SMN2 were eligible, all those enrolled had 2 copies of SMN2. The ERG notes that one patient was dosed at the age of 181 days and is therefore not included in the analyses of the ITT population. As of the 31 December 2019 data-cut, one patient was lost to follow-up due to death. The estimated completion date for STR1VE-EU is Q4 2020.

In contrast to STR1VE-US, in STR1VE-EU, the primary outcome is achievement of the developmental milestone of sitting without support for at least 10 seconds up to 18 months of age as determined the WHO Motor Development Milestones scale: assessment of motor skills using the Bayley Scales and CHOP-INTEND form part of the listed exploratory efficacy endpoints for STR1VE-EU.

Other exploratory outcomes evaluated in STR1VE-EU include:

- survival at 14 months of age;
- achievement of motor milestones, including hold head erect without support, roll from back to both sides, sit with support, crawl, pull to stand, stand with assistance, stand alone, walk with assistance, walk alone;
- maintain ability to thrive.

LT-001

LT-001[41] is the long-term follow up study of patients participating in the START study (Table 69). Thirteen of the 15 patients in START have enrolled in LT-001. The parents/carers of the two patients from START who did not continue into LT-001 were not required to provide a reason for the decision not to enrol in LT-001. The objective of LT-001 is to evaluate whether the highest milestone attained in START is maintained for up to 15 years post administration, with patients undergoing assessment annually. Capturing new motor milestone achievements was not originally part of LT-001. However, clinical investigators have observed patients reaching new motor milestones during LT-001, and data on such achievements are therefore prospectively being collated.

The latest data cut presented by the company was 31 December 2019: the median time since onasemnogene administration in patients treated with the therapeutic dose in START (Cohort 2) was 52.5 months (4.4 years) and the longest follow-up was 61.9 months (5.2 years) since dosing in START.

LT-002

LT-002[43] is the long-term follow up study for patients participating in any of the onasemnogene clinical trials with the exception of START (Figure 1; Table 70). The objective of the study is to collect long-term follow-up safety and efficacy data for patients with SMA type 1, 2, or 3 who were treated with onasemnogene in any clinical trial, and patients treated with onasemnogene in future studies may be

enrolled. The planned commencement date for LT-002 was September 2019, and the study is estimated to be completed in 2034. To date, no patients who have received intravenous onasemnogene have been enrolled in LT-002 and so the study is not discussed further in this report.

4.2.1.2 Pre-symptomatic SMA

SPR1NT

SPR1NT is an ongoing Phase III multicentre study enrolling pre-symptomatic patients with SMA and an SMN copy number associated with SMA type 1 or 2, defined by bi-allelic deletion of SMN1, and two or three copies of SMN2 (Table 71). Patients must also have been ≤6 weeks of age at the time of gene replacement therapy. As of December 2019, 30 patients were enrolled in SPR1NT, which is more than the planned 27 patients, and data are presented from the 31 December 2019 efficacy data cut. The estimated completion date for SPR1NT is Q4 2020 for the cohort of patients with two copies of SMN2, and Q2 2021 for the cohort of patients with three copies of SMN2.

The objective of SPR1NT is to evaluate both safety and efficacy of onasemnogene. Efficacy will be demonstrated by:

- for those with two copies of SMN2, independent sitting for at least 30 seconds up to 18 months of age;
- for those with three copies of the SMN2 gene, the ability to stand without support for at least 3 seconds up to 24 months of age.

Changes in CHOP-INTEND and Bayley Scales, as well as the achievement of other motor milestones, are also captured.

Given that SPR1NT enrols patients with a bi-allelic mutation of the SMN1 gene, without onasemnogene treatment, patients would most likely develop symptoms of SMA at some point in their life. There are cases of people having a bi-allelic mutation of the SMN1 gene and remaining asymptomatic in their lifetime, but these cases are rare and such people have been reported to typically have increased copy numbers of the SMN2 gene.[55, 56] Additionally, because SPR1NT enrolled patients before symptoms manifested, it cannot be stated with certainty which type of SMA a patient would have gone on to develop. To be eligible for SPR1NT, patients could have two or three copies of SMN2. Given that the association between SMN2 copy number and severity of symptoms is a continuum, if patients were to become symptomatic without treatment, the type of SMA they would have developed cannot be reliably predicted. SPR1NT Cohort 1 (N=14) comprises patients who have two copies of SMN2 and, based on reported data (Table 2), a large proportion (73%) is likely to develop symptoms within the timeframe that leads to a clinical diagnosis of SMA type 1. By contrast, SPR1NT Cohort 2 (N=15) is made up of

patients with three copies of SMN2, who are, therefore, more likely to develop SMA type 2 (78%) than SMA type 1 (20%). As a small proportion of patients with three copies of SMN2 (20%) would potentially develop SMA type 1, results from Cohort 2 are presented for completeness. The ERG notes that one patient with four copies of SMN2 was enrolled in SPR1NT but later excluded following a protocol amendment and is not included in the ITT efficacy analyses but still contributes to the safety data.

Taken together, the ERG considers that SPR1NT will provide evidence on the effectiveness of early treatment with onasemnogene, before symptoms manifest, of patients identified as having a bi-allelic mutation of SMN1 and a genotype predictive of SMA type 1, but recognises that a proportion (of unknown size) of the patients enrolled in SPR1NT are likely to be have SMA types other than SMA type 1.

4.2.2 Baseline characteristics

4.2.2.1 Symptomatic SMA type 1

Baseline characteristics from studies involving patients with symptomatic SMA type 1 have been collated into one table (Table 8) to facilitate comparison of characteristics. Differences in baseline characteristics between studies evaluating onasemnogene and the SMA type 1 natural history studies are discussed in Section 4.2.4.1.

The ERG's clinical experts confirmed that baseline characteristics across the studies are broadly comparable and representative of a patient presenting with symptoms of SMA type 1 in UK clinical practice (Table 8). However, the ERG's experts commented that, in terms of baseline requirement for ventilatory and feeding support, START more closely reflects the proportion of patients in UK clinical practice requiring such assistance at baseline, but also went on to emphasise that variations across studies in baseline characteristics could arise due to the small sample size of the studies.

Considering START, there is a marked difference between Cohort 1 and Cohort 2 in age at treatment, with patients in Cohort 1 treated with onasemnogene at a mean age of more than 6 months compared with 3.4 months for Cohort 2 (Table 8). Cohort 1 also had a lower (worse) CHOP-INTEND score than Cohort 2, and all three patients were on feeding and ventilatory support, indicating that they suffered from more advanced disease. As mentioned earlier, patients in Cohort 1 received a lower dose of onasemnogene than those in Cohort 2 (6.7×10^{13} vg/kg versus 2.0×10^{14} vg/kg), and, as a result, only Cohort 2 is deemed relevant to the NICE decision problem.

The baseline characteristics of the patients in STR1VE-EU are comparable with those of Cohort 2 from START. However, a key difference in the population enrolled in STR1VE-US from the other studies is that no patient required support in feeding or ventilation at baseline, whereas a proportion of patients in

both STR1VE-EU and START required some form of support with feeding (41.7% in Cohort 2 of START and [redacted]% in STR1VE-EU) or ventilation (8.3% in Cohort 2 of START and [redacted]% in STR1VE-EU; Table 8). The lack of requirement for feeding and ventilatory support at baseline in STR1VE-US suggests that enrolled patients have less severe disease than those in Cohort 2 of START and STR1VE-EU. A more detailed comparison of baseline characteristics of START and STR1VE-US (studies forming the pooled analysis) is available in Section 4.3.3.

Table 8. Baseline characteristics of studies evaluating onasemnogene in patients with SMA type 1 (reproduced from original CS, Table 21 [START], original CS appendix, Table 14 [STR1VE-US], original CS appendix, Table 15 [STR1VE-EU], and original CS appendix, Table 13 [LT-001], and additional data were taken from Table 4 on the clarification response supplied during critique of the supplementary appendix)

Characteristic	START			STR1VE-US	STR1VE-EU	LT-001
	Cohort 1 (N=3)	Cohort 2 (N=12)	All patients (N=15)	(N=22)	(N=33)	(N=13)
SMN2 copy number	2	2	2	2	2	2
Age at diagnosis, months					[redacted]	
• Mean	–	67.8 (days)	–	2.6		2.5 (SD 0.52)[j]
• Range	–	1, 137 (days)	–	0[g], 5.4	[redacted]	Age at baseline visit
Age at treatment[a], months					[redacted][h]	
• Mean (SD)	6.3 (0.75)	3.4 (2.06)	4.0 (2.21)	3.7 (1.61)[h]		–
• Min, Max	5.9, 7.2	0.9, 7.9	0.9, 7.9	0.5, 5.9	[redacted]	–
Sex						
• Female, %	66.7	58.3	60.0	12 (54.5)	[redacted]	7 (53.8)
• Male, %	33.3	41.7	40.0	10 (45.5)	[redacted]	6 (46.2)
Race, %						
• White	100	91.7	93.3	11 (50.0)	–	12 (92.3)
• Other	0	8.3	6.7	6 (27.3)	–	1 (7.7)
• Black or African American				3 (13.6)	–	–
• Asian				2 (9.1)	–	–

Ethnicity, % • Not Hispanic or Latino • Hispanic or Latino	 100 0	 83.3 16.7	 86.7 13.3	 18 (81.8) 4 (18.2)	 – –	 12 (92.3) 1 (7.7)
Weight, mean (SD), kg	6.6 (0.56)	5.7 (1.34)	5.9 (1.27)	5.8 (range 3.9, 7.5)	[redacted]	–
Gestational age at birth, weeks • n • Mean (SD)	 2 39.0 (1.41)	 10 38.5 (1.43)	 12 38.6 (1.38)	 – 39.05 (0.95)	 – 	 – –
Mean age at symptom onset, months (SD)	1.7 (1.15)	2.3 (1.47)	1.5 (0.99)	1.9 (1.24)	–	–
Mean age at genetic diagnosis, days (range)	33 (4–85)	60 (0–136)[c]	–	–	–	–
Mean CHOP-INTEND score (SD)[d]	16.3 (10.5)	28.2 (12.3)	25.8 (12.6)[e]	32.0 (9.69)	[redacted]	–
Swallowing thin liquid, n (%) • Yes • No	 0 (0.0) 3 (100)	 4 (33.3) 8 (66.7)	 4 (26.7) 11 (73.3)	 22 (100%) –	 [redacted] –	 – –
Non-oral feeding support, n (%) • Yes • No	 3 (100) 0	 5 (41.7) 7 (58.3)	 8 (53.3) 7 (46.7)	 0 (0) 22 (100)	 [redacted] –	 – –
Ventilatory support (invasive/non-invasive), n (%) • Yes • No	 3 (100) 0	 1 (8.3)[b] 11 (91.7)	 4 (26.7)[b] 11 (73.3)	 0 (0) 22 (100)	 [redacted] –	 – –

Familial history of SMA including affected siblings or parent carriers, n (%)						
• Yes	1 (33.3)	3 (25.0)	4 (26.7)	[redacted]	[redacted]	–
• No	2 (66.7)	8 (66.7)	10 (66.7)	[redacted]	[redacted]	–
• Unknown	0	1 (8.3)	1 (6.7)	[redacted]	[redacted]	–
Total number of days of prednisolone administration, mean (SD)	47.7 (14.1)[f]	73.8 (33.0)	68.6 (31.7)	73.7 (39.54)	–	–

[a] On day of onasemnogene abeparvovec administration.
[b] Does not include one additional patient in Cohort 2 who was receiving BiPAP at baseline but for whom data was mis-entered at the clinical site.
[c] In one patient in Cohort 2, the diagnosis was made prenatally, so an age of 0 was reported at the time of genetic diagnosis.
[d] Scores on the CHOP-INTEND scale of motor function range from 0 to 64, with higher scores indicating better function.
[e] Data for 'All patients' were calculated using CHOP-INTEND data for all patients (Listing 16.2.6.4-24).
[f] Includes one patient who did not receive prednisolone prophylactically but the corticosteroid began on Day 27.
[g] Some patients were diagnosed before 1 month of age. Because of rounding, age of diagnosis is reported as "0 months".
[h] Age = (dose date - date of birth + 1)/30.
[j] Age = (Visit Date - Date of Birth + 1) / 365.25.
Data reported for STR1VE-EU and LT-001 are based on 31 December 2019 efficacy data cut (data on file).
[i] n=32 – one patient ([redacted]) was dosed at the age of 181 days and was therefore not included for the ITT population.
Abbreviations: CHOP-INTEND, Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders; CS, company's submission; SD, standard deviation; SMA, spinal muscular atrophy.

4.2.2.2 Pre-symptomatic SMA

SPR1NT

Baseline characteristics of Cohort 1 and Cohort 2 of SPR1NT are generally comparable (Table 9), but patients in Cohort 2 were marginally [redacted] at time of treatment with onasemnogene compared with Cohort 1. All patients could swallow a thin liquid at baseline, as per inclusion criterion of SPR1NT.

Table 9. Baseline characteristics of SPR1NT for the Day 180 update (31 December 2019 data-cut), [reproduced from CS supplementary appendix, Table 16])

Characteristic	**Cohort 1**	**Cohort 2**
	Two copies of SMN2 (N=14)	**Three copies of SMN2 (N=15)**
Enrolment status at data cut	Completed	
Mean age at diagnosis[a], months (range)	[redacted]	[redacted]
Mean age[b] (range) at treatment, months	[redacted]	[redacted]
Mean (range) length/height at baseline, cm	[redacted]	[redacted]
Sex, n (%) • Female • Male	 [redacted] [redacted]	 [redacted] [redacted]
Race, n (%) • White • Other • Black or African American • Asian • American Indian or Alaska Native	 [redacted] [redacted] [redacted] [redacted] [redacted]	 [redacted] [redacted] [redacted] [redacted] [redacted]
Ethnicity, n (%) • Not Hispanic or Latino • Hispanic or Latino	 [redacted] [redacted]	 [redacted] [redacted]
Weight, kg (SD)	[redacted]	[redacted]
Reported swallowing thin liquid, n (%)[§]	[redacted]	[redacted]
Reported feeding support, n (%)[c]	[redacted]	[redacted]
Reported ventilatory support, n (%)[c]	[redacted]	[redacted]
Mean (range) score on CHOP-INTEND scale[d]	[redacted]	[redacted]

Familial history of SMA including affected siblings or parent carriers, n (%)	[redacted]	[redacted]

[a] For patients diagnosed in utero, rather than report negative ages age at diagnosis was reported as to 1 day old. Because of rounding, this is reported as "0 months".
[b] Age = (dose date - date of birth + 1).
[c] In order to be eligible for enrolment in SPR1NT, patients were required to be asymptomatic, able to swallow thin liquids, and free from ventilatory support.
[d] Scores on CHOP-INTEND scale of motor function range from 0 to 64, with higher scores indicating better function.
Source: 31 December 2019 efficacy data cut (data on file).[27]
Abbreviations: CHOP-INTEND, Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders; SD, standard deviation; SMA, spinal muscular atrophy.

4.2.3 Quality assessments

The company's quality assessment of START and STR1VE-US using the Newcastle-Ottawa scale are presented in Table 10 and Table 11, respectively, with the quality assessment of the natural history studies, PNCR and NeuroNext, available in Appendix 10.4. Quality assessments for the remaining onasemnogene studies were not presented in the CS. Given that all studies evaluating onasemnogene are open label and of single-arm design, the ERG considers that the designs of the studies are similar and, as such, strengths and limitations of the studies are comparable.

In short, for the completed START and STR1VE-US studies, the cohorts forming the studies are representative of the relevant targeted population (patients with SMA type 1), details of the intervention were clearly described, and follow-up was complete. However, the maximum follow-up of 18-months of age (STR1VE-US) and 2 years (START) in the trials is insufficient to assess the long-term effects of onasemnogene treatment on motor milestones, and event-free and overall survival. The comparability of the studies evaluating onasemnogene and the SMA type 1 natural history studies is discussed in Section 4.2.4.1.

Table 10. Company quality assessment of START (reproduced from CS supplementary appendix, Table 18)

Study name	**Mendell *et al*. 2017[44] (NCT02122952)**	
Newcastle Ottawa item	Score	Support
Selection: Representativeness of exposed cohort	*	Somewhat representative of the average SMA patient in the community
Selection: Selection of non-exposed cohort	NA	Single arm study, no non-exposed cohort
Selection: Ascertainment of exposure	*	Secure record; genetically confirmed SMA
Selection: Outcome not present at start of study	*	Assumed that patients requiring PAV were excluded from the study
Comparability: Comparability of cohorts	NA	Single arm study, study only examines exposed cohort
Outcomes: Assessment of outcome	*	Record linkage
Outcomes: Follow-up length	*	All patients 24 months' follow-up

Abbreviations: NA, not applicable; PAV, permanent assisted ventilation; SMA, spinal muscular atrophy.

Table 11. Company quality assessment of STR1VE-US using Newcastle-Ottowa Scale (reproduced from CS supplementary appendix, Table 19)

Study name	**STR1VE-US[27]**	
Newcastle Ottawa item	Score	Support
Selection: Representativeness of exposed cohort	*	Somewhat representative of the average SMA patient in the community
Selection: Selection of non-exposed cohort	NA	Single arm study, no non-exposed cohort
Selection: Ascertainment of exposure	*	Secure record; genetically confirmed SMA
Selection: Outcome not present at start of study	*	The co-primary efficacy endpoints were the proportion of patients who achieved functional independent sitting for at least 30 seconds at the 18 months of age study visit and survival at 14 months of age. By definition, children with SMA type 1 are never able to sit independently
Comparability: Comparability of cohorts	NA	Single arm study, study only examines exposed cohort
Outcomes: Assessment of outcome	*	Record linkage. Defined by the Bayley Scales of Infant and Toddler Development (Version 3), confirmed by video recording, as a patient who sits up straight with the head erect for at least 30 seconds
Outcomes: Follow-up length	*	Days 4 to End of Study at 18 months of age (or early termination)
Abbreviations: NA, not applicable; PAV, permanent assisted ventilation; SMA, spinal muscular atrophy.		

4.2.4 SMA type 1 natural history studies

To enable the comparison between onasemnogene and BSC, the company identified cohorts of patients from the SMA natural history studies PNCR and NeuroNext, for which the company has access to individual patient level data. The company implemented the PNCR cohort in two scenario analyses. One scenario involves the PNCR cohort alone and comprises patients with two copies of SMN2 gene and SMA type 1 (n=23). A second scenario involves a cohort (n=26) combining patients from Italy, where SMN2 copy number is not available, as described in De Sanctis *et al*.[34], with patients from the PNCR database. The ERG has not been able to assess fully the appropriateness of De Sanctis *et al.* 2016, as only limited information was presented, but based on the information provided the ERG considers the PNCR cohort to be the most relevant and appropriate to inform BSC.

The ERG provides a summary of the strengths and limitations of natural history studies identified by the company below, with a more detailed description of each study available in Appendix 10.5. Additionally, to complement the company's description of relevant comparator studies, the ERG has included a description of the control arm in ENDEAR, also identified as relevant through the company's SLRs, but only used in a scenario analysis in the company's health economic model.

The natural history studies all have different issues and merits in terms of their comparability with START or STR1VE-US. ENDEAR has the largest sample size (N=41), but especially survival data are limited by the relatively short follow-up in the study (13 months). NeuroNext has a small sample size (N=16) and the less stringent definition of PAV will lead to an overestimate of EFS in NeuroNext compared with PNCR and ENDEAR, but the likely size or direction of the effect on EFS compared with UK clinical practice is unclear. PNCR also has a small sample size (N=23) and, in addition, the study was partly retrospective in design with a potential risk of selection bias and reliance on adequate record-keeping.

4.2.4.1 Comparability of natural history studies with START and STR1VE-US and with UK clinical practice

Patients in PNCR, NeuroNext, ENDEAR, START and STR1VE-US were all classified as having SMA type 1 based on clinical characteristics and age of onset. START and ENDEAR were limited to patients with two copies of SMN2, and only patients with two copies of SMN2 were enrolled in STR1VE-US, which is equivalent to the cohorts derived from PNCR and NeuroNext and used in the CS. In addition, START and NeuroNext excluded patients with the SMN2 modifier mutation c.859G>C, and no patient with the modifier was enrolled in STR1VE-US.

Age at baseline was relatively similar between START, STR1VE-US and NeuroNext and slightly older at screening in ENDEAR (Table 77). In PNCR, which included both retrospectively and prospectively enrolled patients, mean age at enrolment was substantially higher (mean of 29.0 months [SD 41.7]; Table 77). Three of the 23 enrolled in PNCR were 7, 9 and 14 years old and on permanent assisted ventilation at the time of enrolment and a further four of the cohort were aged between 2 and 4 years at enrolment. The remaining patients were aged <2 years at the time of enrolment.

The ERG considers the retrospective enrolment in PNCR likely to be one of the main reasons for the greater proportion of patients requiring ventilator and non-oral feeding support at the time of the initial evaluation compared with the other studies (Table 77). However, there were marked differences in ventilator and nutritional support also between the remaining studies; a greater proportion of patients needed ventilatory support in NeuroNext and fewer patients needed nutritional support in ENDEAR and STR1VE-US, when compared with START. As the company notes, a more relevant comparison with PNCR is the ventilation support status at 6 months of age, with baseline support in the other studies. At 6 months of age, the majority of the PNCR cohort (91.3%) remained free of ventilator support, a higher percentage than was free of such support at baseline in the other studies. The larger proportion free of ventilator support suggests that the patients forming the PNCR cohort had less severe pulmonary dysfunction than the START cohort at similar ages. The indication that the START cohort may have a more severe/aggressive disease than that of ENDEAR and PNCR is also reflected in the mean age at diagnosis and time to onset of symptoms: mean age at diagnosis was substantially lower in START (2

months) compared with ENDEAR (3.9 months) and PNCR (5 months), as were onset of symptoms: 1.4 months for START compared with 2.2 and 3 months for ENDEAR and PNCR, respectively. Despite the early onset of symptoms in START compared with the other studies, motor function at baseline (START, STR1VE-US, and ENDEAR) and enrolment (PNCR, NeuroNext) was relatively similar across the studies with patients in STR1VE-US having the highest mean baseline CHOP-INTEND score at 32 (indicating better motor function) and NeuroNext the lowest at 20. The ERG notes the challenge in comparing CHOP-INTEND scores at enrolment for PNCR with the other studies because of the partly retrospective recruitment to the study and therefore the high mean age.

In the PNCR cohort, 4 patients (17.4%) received experimental SMA medication at baseline or during the study, including therapies thought to increase SMN expression, such as valproic acid. No-one in START, NeuroNext or ENDEAR received experimental SMA medications.

Differences in baseline characteristics across studies are likely to have a large impact on analyses because of the small sample sizes informing the studies. Conversely, because of the small sample sizes, variations in baseline characteristics could be due to chance. Differences in the definition of endpoints may also have an impact; NeuroNext captured tracheostomy-free survival, whereas survival in PNCR, ENDEAR, START and STR1VE-US was defined as the avoidance of death or permanent ventilation, which was specified as tracheostomy or requirement of ≥16 hours of ventilatory support for a period of ≥14 consecutive days (START, STR1VE-US and PNCR) or >21 consecutive days (ENDEAR) in the absence of an acute, reversible illness or a perioperative state. The difference in the definition of PAV will lead to an overestimate of event-free survival in NeuroNext compared with PNCR and ENDEAR.

Irrespective of the data source used to inform the natural history of SMA type 1 (NeuroNext, PNCR, or ENDEAR), patients who only receive BSC do not reach any motor milestone. However, the differences between ENDEAR, NeuroNext and PNCR in study methodology, outcome definitions and populations may be reflected in the differences in mortality outcomes observed between the studies (Table 12). At 13 months' follow-up the proportion of patients who had the composite outcome (permanent assisted ventilation or death) was 50% in NeuroNext and just under 70% in PNCR and ENDEAR, a difference which is sustained at the end of follow-up for NeuroNext and PNCR.

The results for overall survival for the natural history studies may also differ from the experience in UK clinical practice. NeuroNext and PNCR were both USA-based studies, as were a large number of the study sites in ENDEAR. According to the ERG's clinical experts, a larger proportion of SMA type 1 patients receive tracheostomy in the USA compared with UK clinical practice, where few patients undergo this type of surgery. Disparity in rate of tracheostomy will likely have an impact on overall survival in the natural history studies as patients who have a tracheostomy can live for many years, whereas patients on NIV >16 hours per day rarely survive past their second birthday. All three SMA

type 1 natural history studies are therefore likely to overestimate overall survival for patients with SMA type 1 compared with the survival of patients cared for in UK clinical practice.

In summary, the studies have different issues and merits in terms of their comparability with START and STR1VE-US;

- ENDEAR has the largest sample size (N=41), but data, especially survival data, are limited by the relatively short follow-up of the study;
- NeuroNext has a small sample size (N=16) and comparisons of event-free survival will be impacted by the less stringent definition of permanent ventilation in the study;
- PNCR also has a small sample size (N=23) and, in addition, the study was partly retrospective in design with a potential risk of selection bias and reliance on adequate record keeping.

The ERG considers all three studies to have major limitations but has a preference for NeuroNext because of its prospective design and the maturity of the event-free and overall survival data compared with the other studies.

Table 12. Mortality in SMA type 1 natural history studies

Characteristic	NeuroNext control (N=16)	PNCR control (N=23)	ENDEAR sham arm (N=41)
13-14 months follow-up[a] n (%)			
• Death	7 (43.8)	7 (30.4)	16 (39.0)
• Death or PAV	8 (50.0)	16 (69.6)	28 (68.3)
End of follow-up[b] n (%)			
• Death	8 (50.0)	11 (47.8)	16 (39.0)
• Death or PAV	10 (62.5)	18 (78.3)	28 (68.3)

[a] Follow-up 14 months for NeuroNext and PNCR; follow-up 13 months for ENDEAR
[b] End of follow-up in the studies were: NeuroNext, 24 months; PNCR, 36 months; ENDEAR, 13 months.
Abbreviations: PAV, permanent assisted ventilation; SMA, spinal muscular atrophy.

To support the appropriateness of the natural history cohorts as control groups for the comparison with onasemnogene, the company presented additional analyses examining individual patient matching between the PNCR or NeuroNext datasets and START. Twelve patients from PNCR and 12 from NeuroNext were matched to the patients in Cohort 2 of START. Patients were matched by genotype (patients in both cohorts had bi-allelic SMN1 deletions, 2 copies of SMN2), age at disease onset, nutritional and ventilatory support at 6 months of age, and baseline motor function (CHOP-INTEND score). It is unclear from the CS how patients were selected for matching, but, at the first round of clarification, the company provided outcome data for the matched populations in NeuroNext and PNCR. For NeuroNext, the matching has a limited effect on the outcome results (Table 13). However,

for the full and matched PNCR cohorts, there were larger differences in mortality (Table 13), which highlights the large uncertainty around the survival data for SMA type 1 patients on BSC, partly due to the small sample sizes of the cohorts.

Table 13. Summary of disease course in the PNCR and NeuroNext natural history cohorts (adapted from clarification response A1, Table 1)

Variable	NeuroNext control (N=16)	NeuroNext matched-pair (N=12)	PNCR control (N=23)	PNCR matched-pair (N=12)
Gastrostomy and ventilation support, n (%)				
Experimental SMA medication used (non-onasemnogene abeparvovec)	0	0	4 (17.4)	2 (16.7)
Gastrostomy tube placed	NA	NA	16 (69.6)	9 (75.0)
Ventilation support	NA	NA	18 (78.3)	9 (75.0)
CHOP-INTEND score >40 at any time >6 months of age n (%)	0	0	1 (4.3)	0
BiPAP or intubation (for ≥16 hours/day and ≥14 days), n (%)	NA	NA	13 (56.5)	5 (41.7)
Age reached, months, mean (SD)			10.2 (4.9)	6.8 (3.3)
Intubation, n (%)	2 (12.5)	2 (16.7)	NA	NA
Age reached, months, mean (SD)	12.1 (8.8)	12.3 (8.91)	NA	NA
Mortality or ventilation outcome – all data				
Mortality, n (%)	8 (50.0)	6 (50.0)	11 (47.8)	6 (50.0)
Age at death, months, mean (SD)	8.9 (4.1)	8.7 (4.5)	33.1 (53.1)	12 (10.4)
Composite of mortality or ventilation, n (%)	10 (62.5)	8 (66.7)	18 (78.3)	8 (66.7)
Age at composite of mortality or ventilation, months, mean (SD)	9.6 (4.8)	9.7 (5.3)	9.8 (4.4)	8.1 (3.4)
Alive and PAV – all data, n (%)	2 (12.5)	2 (16.7)	7 (30.4)	2 (16.7)
Alive and ventilation-free – all data, n (%)	6 (37.5)	4 (33.3)	5 (21.7)	4 (33.3)

Abbreviations: BiPAP, bi-level positive airway pressure; CHOP-INTEND, Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders; HINE, Hammersmith Infant Neurological Examination; NA, not available; SD, standard deviation; SMA, spinal muscular atrophy; PAV, permanent assisted ventilation; PNCR, Pediatric Neuromuscular Clinical Research; SMA, spinal muscular atrophy.

4.2.5 Outcomes and statistical approach used

4.2.5.1 Outcomes

The outcome definitions across the onasemnogene studies were broadly consistent, although not all outcomes were captured in all studies, with studies capturing different motor milestones. The combined endpoint of survival without permanent ventilation was used in the onasemnogene studies because a single endpoint of mortality was considered to underestimate the benefit of treatment. The survival of patients with SMA was defined by the avoidance of the combined endpoint of either (a) death or (b) permanent ventilation, defined as tracheostomy or the requirement of ≥16 hours of respiratory assistance per day (via non-invasive ventilatory support) for ≥14 consecutive days in the absence of an acute reversible illness, excluding perioperative ventilation.

The development of significant motor function milestones, such as independent sitting and standing with or without support, was assessed based on video reviews by an external expert. Compiled video recordings of the CHOP-INTEND, Bayley Scales, submitted home videos, and physical examinations were sent to a central reviewer for independent confirmation of development milestones.

CHOP-INTEND is a motor function scale developed and validated for use specifically to monitor motor function status and decline amongst children with SMA type 1.[57, 58] The CHOP-INTEND scale ranges from 0 to 64, with higher score indicating better functional status. The proportion of patients who achieved CHOP-INTEND thresholds of ≥40, ≥50, and ≥60 (START) or ≥58 (STR1VE-EU, STR1VE-US, and SPR1NT) was assessed in the onasemnogene clinical studies.

The Bayley Scales of Infant and Toddler Development (Version 3) are a standardised, norm-referenced assessment of developmental functioning across five domains: cognitive; language; motor; social-emotional; and adaptive behaviour.[59] The Bayley Scales are administered by a physical therapist and the mean score is 10, with standard deviation of ±3 points; thus, a scaled score of ≤7 on the Bayley Scales would be considered low.

The ability to thrive was defined as meeting the following:

1. ability to tolerate thin liquids as demonstrated through a formal swallowing test;
2. not requiring nutrition through mechanical support such as a feeding tube;
3. maintained weight within expected ranges based on age and gender norms at time of primary efficacy data cut-off.

The ERG notes that patients in START, STR1VE-US, and STR1VE-EU were required to have had a swallowing evaluation test performed prior to administration of onasemnogene, and be willing to use an alternative method to oral feeding if necessary. However, the inclusion criteria in SPR1NT were stricter with patients were required to be able to swallow thin liquids at enrolment.

Nutritional status and swallowing function were assessed as the number of patients who used non-oral feeding at any time from baseline to the efficacy analysis time points. Swallowing function was determined through video-fluoroscopic swallowing studies (only in START) or standard bedside swallowing tests and was assessed at baseline and every 6 months during the follow-up period.

Motor neurone function was assessed using two techniques. Compound muscle action potential (CMAP) amplitude was measured, which is an indicator of motor neurone health and denervation severity. Additionally, motor unit number estimation (MUNE) was used, which is a technique that

utilises electromyography to estimate the number of motor units in a muscle. Both CMAP and MUNE were recorded from surface electrodes.

4.2.5.2 Subgroup analyses

An exploratory *post-hoc* analysis assessing time to independent sitting based on age at treatment was presented. In addition, the company reported an exploratory scenario analysis in their economic evaluation (CS appendix, Section 8.2.1.1) that used subgroup data for motor milestones, overall survival and event-free survival derived from on patients treated at ≤3.5 versus >3.5 months of age in START and STR1VE-US: 3.5 months was chosen as a cut off as it is the median age at dosing across the START (Cohort 2) and STR1VE-US cohorts. The company highlights that the results of this should be interpreted with caution due to the small sample size and post-hoc nature of the analyses.

4.2.5.3 Analysis sets

The company describes the key different analysis sets used as intention to treat (ITT), full analysis set (FAS), and safety analysis set (SAS). Patients with the c.859G>C SMN2 gene modifier mutation were eligible for enrolment in STR1VE-US, STR1VE-EU and SPR1NT but were excluded from the ITT efficacy analyses, and assessed only as part of additional analyses. The ERG notes that, as of 31 December 2019, no patient with the c.859G>C mutation in SMN2 has been enrolled in any onasemnogene study.

Additional analysis populations were defined in some of the studies, for example:

- the ability to thrive ITT population in START, which included patients with a baseline CHOP-INTEND score of ≥20 who received an infusion of onasemnogene at the therapeutic dose of 2.0 x 10^{14} vg/kg and who did not require non-oral nutrition prior to infusion with onasemnogene; and

- efficacy completers population in STRIVE-US, which comprised all treated patients who reached 14 months of age for the survival endpoint or 18 months of age for the endpoint of achievement of functional independent sitting, OR all treated patients who meet discontinuation criteria, discontinue the study due to an AE or experience death.

Efficacy analyses for START were conducted at three time points:

- the date at which all patients had completed a study visit after reaching 13.6 months of age;

- when the last enrolled patient had a study visit after reaching 20 months of age;

- when all patients completed 24 months of post-dose follow-up.

According to the CS, the first two time points were selected to allow a comparison with the PNCR natural history study of SMA type 1 patients. However, in the CS, efficacy results from START are only reported for when patients reached 13.6 months of age and 24 months post-dose. In addition, based on the company's PNCR and NeuroNext database report, PNCR data are only reported for the 13.6-month timepoint, but data for NeuroNext are reported for 20 months.[30] The ERG notes that efficacy data are also reported at 13.6 months in STRIVE-US, with further data presented at study completion (18 months of age). Data for the ongoing onasemnogene studies are reported based on data-cuts from 31 December 2019.

Efficacy analyses conducted for START were performed without a statistical analysis plan and were considered descriptive. In the CS, the difference in time-to-event data (composite outcome of death or permanent ventilation) between START and PNCR or NeuroNext is reported as a log-rank test. The proportion of patients reaching different motor milestones are reported but no analysis has been presented comparing the rates in the CS. However, in the CSR of START, results of unplanned analyses comparing START to PNCR or NeuroNext are mentioned; a comparison of the proportions of patients reaching the milestone of independent sitting was analysed using a 1-sided Exact Binomial Test, with the value of 0.1% used in place of a zero to make computation of the p-value possible.

In STR1VE-US, one primary efficacy endpoint was specified as sitting without support, as confirmed through video evidence, at any visit, up to and including the study end visit carried out when the patient reached 18 months of age. Analysis was planned for the ITT population. In STR1VE-US, as in START, a one-sided Exact Binomial Test was also used to test the null hypothesis of p=0.1% at significance level of 0.025. The company planned to compare the proportion of patients surviving in STR1VE-US versus the natural history data of the matching cohort in PNCR using a two-sample Fisher's exact test. A second primary objective was evaluation of survival (alive and free from PAV) at 14 months of age compared with natural history data from PNCR.

LT-001 is a long-term follow-up study of patients from START with safety as the primary measure and no statistical analysis plan reported in the CS. In STR1VE-EU, the primary outcome is achievement of the developmental milestone of sitting without support for at least 10 seconds up to 18 months of age as determined the WHO Motor Development Milestones scale.

The primary efficacy endpoint in SPR1NT differs according to the number of SMN2 copies:

- patients with two copies of SMN2: independent sitting for at least 30 seconds up to 18 months of age, with analysis based on the ITT population. A one-sided Exact Binomial Test was used

compared with zero to test the null hypothesis of p=0.1% at significance level of 0.025. To make computation of the p-value possible, the value of 0.1% was used in place of a literal zero;

- patients with 3 copies of SMN2: the ability to stand without support for at least 3 seconds up to 24 months of age will be compared with the natural history data of the matching cohort using a two sample 2-sided superiority Fisher exact test with a significance level of 0.05.

4.2.6 Summary statement

The main evidence sources informing the clinical and cost effectiveness assessment of onasemnogene therapy for patients with a clinical diagnosis of SMA type 1 in the CS are the Phase I/II trial START and the Phase III study STR1VE-US. Data are also available from the long-term follow up study LT-001, which is an extension of START. The company also describes two ongoing Phase III onasemnogene trials, one in patients with SMA type 1 (STR1VE-EU) and one in patients with no symptoms of SMA but identified as having a genetic profile indicative of likely development of SMA type 1 (SPR1NT). The ongoing onasemnogene trials provide some supportive evidence for the clinical effectiveness of onasemnogene, and on the potential additional benefit from early treatment with onasemnogene. However, data from STR1VE-EU and SPR1NT are immature and do not inform the economic model. All onasemnogene studies are of an open-label, single arm design, with all patients receiving a one-time dose of onasemnogene.

The primary objective of START was to evaluate the safety of onasemnogene, whereas efficacy (assessed as achievement of motor milestones and time to death or PAV) was a secondary objective. Patients enrolled in START were divided into two cohorts: Cohort 1, consisting of three patients receiving a low dose of onasemnogene (3.7×10^{13} vg/kg), and Cohort 2 consisting of 12 patients who received the therapeutic dose of onasemnogene (1.1×10^{14} vg/kg), as recommended in the SmPC.[60] Only data for START Cohort 2 inform the economic model. The primary objectives in STR1VE-US were video evidenced achievement of sitting without support at any visit up to and including 18 months of age, and evaluating survival (alive and free from PAV) at 14 months of age: a total of 22 patients were enrolled in STR1VE-US.

START is a single centre trial run in the USA, and STR1VE-US is a multicentre study, also carried out in the USA. Both studies enrolled SMA type 1 patients with two copies of SMN type 2, who are representative of those seen in UK clinical practice. However, the small sample sizes of START and STR1VE-US means considerable uncertainty around the results of the studies as baseline characteristics of each patient and single outcome events are likely to impact on the absolute results, which may not be representative in the wider SMA type 1 population.

START and STR1VE-US have complete follow-up for all patients but due to the maximum follow-up of 2 years (START) and at 18-months of age (STR1VE-US) in the trials, there is considerable uncertainty around the long-term development of the patients treated with onasemnogene. The uncertainty will reduce when the follow-up studies LT-001 and LT-002 report results of up to 15 years follow-up.

Considering the pre-symptomatic population, as of December 2019, 30 patients were enrolled in SPR1NT, which is more than the planned 27 patients, and data are available from the 31 December 2019 efficacy data cut.

To enable the comparison between onasemnogene and BSC, the company identified cohorts of patients from the SMA natural history studies PNCR and NeuroNext, for which the company has access to individual patient level data. The company implemented the PNCR cohort in two scenario analyses. One scenario involves the PNCR cohort alone and comprises patients with two copies of SMN2 gene and SMA type 1 (n=23). A second scenario involves a cohort (n=26) combining patients from Italy, where SMN2 copy number is not available, as described in De Sanctis *et al*.[34], with patients from the PNCR database. The ERG has not been able to assess the appropriateness of De Sanctis *et al.* 2016 as only limited information was presented. Given the more detailed information available, the ERG considers the PNCR cohort to be the most relevant and appropriate to inform BSC out of the two.

A randomised trial comparing nusinersen versus a sham control arm in which patients received BSC (ENDEAR) was identified as another source of relevant comparator data but was also only used in a scenario analysis in the company's health economic model. Similar to the population in START and STR1VE-US, the natural history cohorts in PNCR, NeuroNext and ENDEAR were limited to patients with SMA type 1 and who had two copies of SMN2. The comparisons with either of the natural history data sets were unplanned and naïve; that is, no adjustments were made for differences in patient's baseline characteristics or other factors that may confound the results.

The natural history studies all have different issues and merits in terms of their comparability with START or STR1VE-US. ENDEAR has the largest sample size (N=41), but especially survival data are limited by the relatively short follow-up in the study (13 months). NeuroNext has a small sample size (N=16) and the less stringent definition of PAV will lead to an overestimate of EFS in NeuroNext compared with PNCR and ENDEAR, but the likely size or direction of the effect on EFS compared with UK clinical practice is unclear. PNCR also has a small sample size (N=23) and, in addition, the study was partly retrospective in design with a potential risk of selection bias and reliance on adequate record-keeping.

The small sample sizes of START, STR1VE-US and all three SMA type 1 natural history studies, mean that differences between studies in baseline characteristics (such as age at treatment or age at symptom onset) or single outcome events are likely to have a large impact on the results. In addition, the small sample sizes mean that the accuracy and precision of the findings could be unstable due to chance events. All three studies are also likely to overestimate OS compared with UK clinical practice as most study sites were in the USA where tracheostomy is more commonly used than in the UK for patients with SMA type 1 who need PAV.

The ERG considers all three natural history studies to have major limitations but has a preference for NeuroNext because of the prospective design and the maturity of the event-free and overall survival data compared with the other studies.

4.3 Clinical effectiveness results

4.3.1 Symptomatic SMA type 1

4.3.1.1 Survival without need for permanent ventilation

In START,[24] STR1VE-US,[27] and STR1VE-EU,[28] event-free survival was defined as being alive and without the need for permanent ventilation, which was specified as tracheostomy or the requirement of ≥16 hours of respiratory assistance per day continuously for ≥2 weeks in the absence of an acute reversible illness, excluding perioperative ventilation. Event-free survival was reported at various timepoints across studies. At the time points assessed, the proportion of children achieving event-free survival was high across the three studies, with no events reported for Cohort 2 of START (Table 14).

In STR1VE-US, two patients were classified as experiencing an event (Table 14). One patient died at age 7.8 months and the parents of the second patient withdrew consent at age 11.9 months, at which time the patient required ≥16 hours of non-invasive BiPAP ventilator support for ≥14 consecutive days (Table 14). Data for an additional patient who was withdrawn from the study were available for age at 18 months, at which time the patient was event free.

At the time of writing, STR1VE-EU is ongoing. Data are reported for a data cut of 31 December 2019, at which time study enrolment was complete, with 33 patients having received onasemnogene. Median age of patients at the last visit was 15.4 months (range: 6.9 to 18.6 months). As of the 31 December 2019 data cut, [redacted] One patient was excluded from the ITT population due to receiving onasemnogene at the age of 181 days.

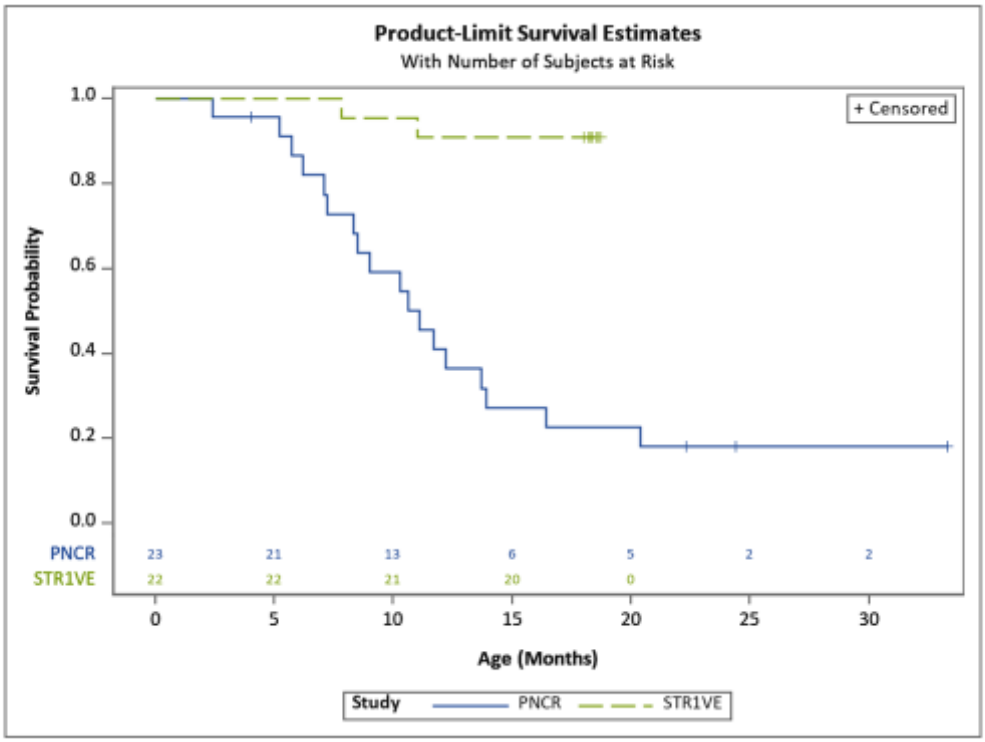
To illustrate the proposal that onasemnogene markedly prolongs ventilation-free survival in patients with SMA type 1, the company provided KM plots of time-to-event data from STR1VE-US and STR1VE-EU presented alongside time-to-event data from natural history datasets (STR1VE-US Figure 2, STR1VE-EU Figure 3).

Table 14. Event-free survival from START, STR1VE-US, STR1VE-EU and LT-001

Study	Number (N)	Time of follow-up	Survived without permanent ventilation	95% CI[c]	P value[d]
START[a]					
Cohort 1	3	≥13.6 months of age	3 (100%)	29.2 to 100	0.016
	3	24 months post dose	2 (66.67%)[f]	9.4 to 99.2	0.018
Cohort 2	12	13.6 months of age	12 (100%)	73.5 to 100	<0.001
	12	24 months post dose	12 (100%)	73.5 to 100	<0.001
STR1VE-US	22	>10.5 months of age	21 (95.5%)	NR	NR
	22	≥13.6 months of age	20 (90.9%	NR	NR
	22	18 months of age	20 (90.9%)	NR	NR
STR1VE-EU[b]	33	Median follow-up of 11.9 months (range 1.8 to 15.4)	[redacted]	[redacted]	[redacted]
LT-001[e]	10	Median age of children 4.5 years (range 4.3 to 5.6 years)	10 (100%)	NR	NR

[a] Results reported for ITT set.
[b] Study ongoing, data are from 31 December 2019 data cut. Median age of patients at their last visit was 15.4 months (range: 6.9 to 18.6 months). Of the patients assessed, [redacted].
[c] Confidence interval from the superiority 1-sided exact binomial test.
[d] Compared with the external natural history estimates of 25% for 13.6 months of age and 8% for 24 months post-dose using a 1-sample exact binomial test.
[e] Data based on 31 December 2019 data cut.
[f] One patient required permanent ventilation at approximately 29 months of age (22 months post-dose), but, after surgical ligation to address hypersalivation, the patient's ventilatory requirement reduced to below the 16 hours/day threshold.
Abbreviations: CI, confidence interval; ITT, intention to treat; NR, not reported.

Figure 2. Kaplan-Meier plot for event-free survival in STR1VE-US (Reproduced from CS appendix, Figure 12)



Natural history: The PNCR and NeuroNext profiles presented are the AveXis datasets used to provide an external control comparator.[30]

Figure 3. Kaplan-Meier plot for event-free survival in STR1VE-EU (31 December 2019 data cut; safety population; reproduced from CS appendix, Figure 17)

Natural history. The PNCR and NeuroNext profiles presented are the AveXis datasets used to provide an external control comparator.[30]

4.3.1.2 Motor function

Motor function milestones based on independent central review

Without treatment, infants with SMA type 1 rarely develop motor skills. After receiving onasemnogene, START, STR1VE-US and STR1VE-EU all report that a proportion of patients are able to sit

independently for 30 seconds or more, and hold their head erect without support (Table 15), with events being confirmed by video and central review. The ERG notes that the time points of assessment differed across the studies, with START reporting results at 24 months after dosing with onasemnogene, and STR1VE-US presenting data captured at 18 months of age for each patient. In the ongoing STR1VE-EU study, median age of patients at their last visit captured in the 31 December 2019 data cut was 15.4 months (range: 6.9 to 18.6 months), and results are therefore immature. The potential impact of the difference in timing of outcome assessment on interpretation of results is discussed in more detail in the critique of the pooled analysis of completed studies (Section 4.3.3).

Considering Cohort 2 of START, at baseline, none of the patients had achieved any of the listed motor milestones (Table 15), with the exception of bringing a hand to the mouth. At the assessment carried out at 24 months post-dose, 91.7% of patients were able to hold their head erect without support for ≥3 seconds and sit with support, 75% were able to sit alone for ≥30 seconds, and 16.7% of were able to walk alone (Table 15). The company presented results of a *post-hoc* analysis of the effect of age at onasemnogene administration on the motor milestone development based on patients in Cohort 2. The results suggest that early treatment is associated with improved outcomes, but the ERG notes that the analysis was *post-hoc* and based on small sample sizes and should therefore be interpreted with caution.

In LT-001, the follow-up study to START, at the 31 December 2019 data cut, all enrolled patients were reported to have maintained their achieved motor milestones, with [redacted] patients gaining new motor milestones during follow-up (Table 16):

- two gained the video-assessed milestone of 'stands with assistance';

[redacted]The ERG notes that no patient from Cohort 2 of START received additional SMA-targeted therapies (such as nusinersen) during the 24-month follow-up period of START. The use of other SMA-targeted therapies is permitted in LT-001 and data on use of nusinersen are available for the ten patients who enrolled in LT-001 (Table 16). As of the 31 December 2019 data cut, nusinersen treatment was ongoing in four of the patients enrolling from START (40.0%): the reasons for initiation of nusinersen therapy are not recorded in LT-001. The ERG notes the two patients who achieved the video-confirmed milestone of 'stands with assistance' during LT-001 have not been treated with nusinersen at any point.

In STR1VE-US, by 18 months of age, 86.4% of patients achieved motor milestone(s), confirmed by independent central video review (Table 15). At baseline, two patients were able to hold their heads erect, and, after receiving onasemnogene, an additional 17 (85.0%) patients were able to hold their head

erect. Other achievements included 13 patients being capable of turning from back to side, and 14 patients being able to sit alone without support for ≥30 seconds (Bayley definition) and for ≥10 seconds (WHO definition). For the 14 (63.6%) achieving the milestone of independent sitting for ≥30 seconds, the median age at which the milestone was first attained was 12.6 months (range 9.2 to 18.6 months). The milestone of independent sitting for ≥30 seconds was confirmed for 13 patients at the 18-month of age visit (p<0.0001). For the remaining patient, the patient was reported to have achieved the milestone of at 16 months of age, and [redacted]

[redacted] One patient achieving the video-confirmed motor milestones of crawls, pulls to stand, stands with assistance, walks with assistance, stands alone, and walks alone as defined by the Bayley gross motor scale (Table 15) was initially categorised as asymptomatic by the Investigator but subsequently re-classed as symptomatic due to the absence of patellar function.

At their last visit prior to the 31 December 2019 data cut, patients in STR1VE-EU were between 6.9 and 18.6 months of age. The video-confirmed developmental milestones achieved in STR1VE-EU (Table 15) [redacted]

Table 15. Summary of video-confirmed motor milestones achieved in START, STR1VE-US and STR1VE-EU (reproduced from CS, Table 30, and CS appendix, Tables 28 and 32)

Motor milestone	Study			
	START Cohort 2 (N=12)		STR1VE-US (N=22)	STR1VE-EU (N=32)
	13.6 months of age	24 months post dose	18 months of age	31 December 2019 cut off
Functional independent sitting, ≥30 seconds, (%; 95% CI[a]), p value[b])	41.7 (15.2 to 72.3) <0.001	75 (42.8 to 94.5) <0.001	14 (63.6)	[redacted]
Developed significant motor function milestones based on video reviews by external expert, %				
• Rolling (back to side from both sides)	75.0	75.0	13 (59.0)[g]	[redacted]
• Hold head erect ≥3 seconds, unsupported	91.7	91.7	17/20 (85.0)[e,f]	[redacted]
• Sits with support	91.7	91.7	–	[redacted]
• Sits alone ≥5 seconds	75.0[c,d]	91.7	–	
• Sits alone ≥10 seconds	58.3[c]	83.3	14 (63.6)[i]	[redacted]
• Sits alone ≥15 seconds	50.0[c]	75.0	–	[redacted]

• Sits alone ≥30 seconds	41.7[c]	75.0	14 (63.6)[h]	[redacted]
• Stands with assistance	16.7	16.7	1 (4.5)[l]	[redacted]
• Stands with assistance – holding stable object	–	–	–	[redacted]
• Stands alone	16.7	16.7	1 (4.5)[m]	
• Walks with assistance	16.7	16.7	1 (4.5)[n]	[redacted]
• Walks alone	16.7	16.7	1 (4.5)[o]	
• Crawls	–	–	1 (4.5)[j]	[redacted]
• Crawls at least 3 movements	–	–	–	[redacted]
• Pulls to stand	–	–	1 (4.5)[k]	–

[a] Confidence interval from the superiority 1-sided exact binomial test.
[b] Compared with zero using a 1-sided exact binomial test. To make computation of the p-value possible, the value of 0.1% was used in place of a literal zero.
[c] Patients are included in multiple categories for the "sits alone" milestone. Patients sitting ≥30 seconds are included in the totals for ≥15 seconds, ≥10 seconds, and ≥5 seconds.
[d] The source table and listing include a milestone identified as "Sits alone <10 seconds". The external reviewer confirmed that this milestone was defined as "Sits alone ≥5 seconds" and that is how it is labelled here.
[e] Two infants who were able to hold head erect for ≥3 seconds without support at screening visit are not included.
[f] Bayley Scales gross motor subtest item #4: Child holds head erect for at least 3 seconds without support.
[g] Bayley Scales gross motor subtest item #20: Child turns from back to both right and left sides.
[h] Bayley Scales gross motor subtest item #26: Child sits alone without support for at least 30 seconds.
[i] WHO MGRS definition: Child sits up straight with head erect for at least 10 seconds. Child does not use arms or hands to balance body or support position.
[j] Bayley Scales gross motor subtest item #34: Child makes forward progress of at least 5 feet by crawling on hands and knees.
[k] Bayley Scales gross motor subtest item #35: Child raises self to standing position using chair or other convenient object for support.
[l] Bayley Scales gross motor subtest item #33: Child supports his or her own weight for at least 2 seconds, using your hands for balance only.
[m] Bayley Scales gross motor subtest item #40: Child stands alone for at least 3 seconds after you release his or her hands.
[n] Bayley Scales gross motor subtest item #37: Child walks by making coordinated, alternated stepping movements.
[o] Bayley Scales gross motor subtest item #43: Child takes at least 5 steps independently, displaying coordination and balance.
[p] WHO MGRS definition: Child alternately moves forward or backward on hands and knees. The stomach does not touch the supporting surface. There are continuous and consecutive movements, at least 3 in a row.
[q] WHO MGRS definition: Child stands in upright position on both feet, holding onto a stable object (e.g., furniture) with both hands without leaning on it. The body does not touch the stable object, and the legs support most of the body weight. Child thus stands with assistance for at least 10 seconds.
Note: In STR1VE-EU, patient [redacted] was dosed at 181 days of age and is not included in the ITT population; this patient had not achieved any motor milestones as of the 31 December 2019 data-cut.
Abbreviations: CI, confidence interval; ITT, intention to treat; NR, not reported.

Table 16. Highest development milestone achievement in START for Cohort 2 and LT-001 and nusinersen usage (as of 31 December 2019, adapted from CS appendix, Table 27)

Patient	Maximum significant milestone achieved in START[a]	START end visit date	LT-001 baseline visit date	New maximum significant milestone achieved in LT-001		Nusinersen usage in LT-001			
				Central reviewer video-confirmed	Clinician assessed	Start date	Usage at LT-001 baseline visit	Usage at LT-001 1-year visit	Usage at LT-001 2-year visit
Cohort 2 (therapeutic dose)									
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]						
[redacted]	[redacted]	[redacted]	[redacted]						

[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

[a] Sitting unassisted definitions were: ≥5 seconds as per item 22 of the Bayley-III Scales gross motor subtest, ≥10 seconds as per the World Health Organization (WHO) criteria, and ≥30 seconds as per item 26 of the Bayley-III Scales gross motor subtest.

[b] The data listing describes milestone as “Sits alone <10 seconds”. The external reviewer confirmed that this milestone was defined as “Sits alone ≥5 seconds” and that is how it is labelled here.

[c] Reported at baseline visit. Sits unassisted ≥30 seconds as per item 26 of the Bayley-III Scales gross motor subtest. Listing 16.2.5, List of Clinician Assessed Milestones Reported, 31 December 2019.

[d] Patient [redacted] stopped nusinersen use on 13 August 2018 and then re-started on 12 February 2019.

[e] Patient also described as ‘sitting without support for ≥15 seconds’ per the Nationwide Children’s Hospital (NCH) definition in the Gross Motor Skills checklist in START Listing 16.2.15-24.

[f] Reported at Year 1 visit. Stands with assistance as per WHO criteria of stands with assistance. Listing 16.2.5, List of Clinician Assessed Milestones Reported, 31 December 2019.

[g] As reported in: Listing 16.2.1 Listing of Clinician Assessed Milestones Reported.

Note: Listing 16.2.1 does not state the time period for milestone attainment, however, milestones are defined in the LT-001 protocol, with sitting unassisted defined as item 26 in the Bayley-III Scales gross motor subtest. Abbreviations: Apr, April; Dec, December; Feb, February; Jun, June; N/A, not applicable; Nov, November; secs, seconds; Oct, October; Sep, September.

CHOP-INTEND

As described in Section 4.2, CHOP INTEND is 16-item scale developed to evaluate the motor skills of people with SMA type 1.[57, 58] The system comprises 16 items, each of which is graded on a scale of 0 to 4 where 0 is equivalent to and a score of 4 denotes complete response. Thus, CHOP-INTEND scale ranges between 0 and 64-points, where higher scores indicate better motor function. An increase in score by 4 points is a clinically meaningful improvement.

Baseline CHOP-INTEND scores were [redacted] (Table 17), [redacted] than baseline score in STR1VE-US, indicating populations with [redacted] impaired motor function than in STR1VE-US. Improvements in CHOP-INTEND score from baseline were captured across the three studies (Table 17). In START, patients in Cohort 2 were assessed as having an increase in CHOP-INTEND score from baseline of 24.6 points (n=12) at 13.6 months of age, which rose further to 30.7 points (n=6) by 24 months of age. For STR1VE-US and STR1VE-EU, changes in CHOP-INTEND score were captured at 1, 3 and 6 months after administration of onasemnogene. [redacted] in CHOP-INTEND from baseline were noted from one time point assessment to the next in both STR1VE US and STR1VE-EU, with [redacted] recorded for the two studies (Table 17).

The company also evaluated the proportion of patients achieving CHOP-INTEND threshold scores as an exploratory analysis. For the completed studies, START and STR1VE-US, the proportion achieving a threshold score of ≥40 were comparable (Table 17). However, a larger proportion of patients in START achieved a threshold score of ≥50 or ≥60 compared with STR1VE-US (Table 17), with 33.3% and 22.7% of patients in START and STR1VE-US, respectively achieving a score of ≥60. In START, of the four patients reaching the threshold score of ≥60, two achieved the maximum score of 64, indicating normal functional status.

[redacted] seen in the CHOP-INTEND score were [redacted], as depicted in Figure 4 for START, Figure 5 for STR1VE-US and Figure 6 for STR1VE-EU.

Table 17. Summary of improvement in CHOP-INTEND scores across START, STR1VE-US, and STR1VE-EU

Outcome	Study			
	START Cohort 2 (N=12)		STR1VE-US (N=22)	STR1VE-EU (N=32)
	13.6 months of age	24 months post dose	18 months of age	31 December 2019 cut off
Mean baseline CHOP-INTEND score (SD)	28.2 (12.3)		32.0 (9.69)	[redacted]
Mean change from baseline in CHOP-INTEND score, study end	+24.6	+30.7	NR	NR
• Month 1	NR	+9.8	+6.9 (5.35)	[redacted]
• Month 3	NR	+15.4	+11.7 (6.40)	[redacted]
• Month 6	NR	NR	+14.6 (7.04)	[redacted]
Proportion of patients in the FAS who achieved CHOP-INTEND scores, final data cut for each study				
• ≥40, % (SD; p value[a])	91.7% (p<0.001)	91.7% (p<0.001)	21 (95.5%)	[redacted]
• ≥50, % (p value[a])	83.3% (p<0.001)	91.7% (p<0.001)	14 (63.6%)	[redacted]
• ≥60, % (p value[a])	25.0% (p<0.001)	33.3% (p<0.001)	5 (22.7%)	[redacted]

[a] Compared with zero using a 1-sided exact binomial test. To make computation of the p-value possible, the value of 0.1% was used in place of a literal zero.
Abbreviations: NR, not reported; SD, standard deviation.

Figure 4. CHOP-INTEND response in START (full analysis set) (reproduced from CS, Figure 10)

Notes: Cohort 1 received the low dose of onasemnogene abeparvovec (6.7 x 10^{13} vg/kg) and Cohort 2 received the therapeutic dose of onasemnogene abeparvovec (2.0 x 10^{14} vg/kg). Patient [redacted] were in Cohort 1 and Patients [redacted] were in Cohort 2 of START. Dashed lines denote time between missed or partial CHOP-INTEND assessments and the solid lines denote time between visits when full CHOP-INTEND assessments were conducted. Data cut on August 7, 2017.
Abbreviations: CHOP-INTEND, Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders; CS, company's submission.

Figure 5. CHOP-INTEND response in STR1VE-US (ITT population) and START Cohort 2 (Reproduced from CS appendix, Figure 13)

Figure 6. CHOP-INTEND response in STR1VE-EU (31 December 2019 data cut, ITT population) (Reproduced from CS appendix, Figure 18)

Bayley Scales

As mentioned in Section 4.2, the Bayley Scales of Infant and Toddler Development (Version 3) are a standardised, norm-referenced assessment of developmental functioning across five domains: cognitive; language; motor; social-emotional; and adaptive behaviour.[59] A scaled score of ≤7 on the Bayley Scales would be considered low. A raw numerical score reflects how many items the infant can accomplish or gets imputed due to their starting position on the Bayley Scale. Infants with symptomatic SMA type 1 would be expected to have low or zero raw scores in the gross motor subset.

In START, only the four patients from Cohort 2 who scored ≥62 on the CHOP-INTEND scale were assessed on the Bayley Scales. The company reports that the mean Bayley fine motor subset scores

increased from [redacted] between the first visit at which Bayley scores were assessed and final visit. Mean gross motor subset raw scores also increased between the first and final visit from [redacted]. The increases in Bayley Scale scores reflect gains in motor function.

In STR1VE-US, by the age of 18 months, most patients had an improvement in performance on both the Bayley Scales gross motor and fine motor subtests. The mean change from baseline in the fine motor subtest raw scores was [redacted] and in the gross motor subtest mean raw score was [redacted] at the 18 months of age visit. The Bayley scale mean change from baseline in the subscales of cognitive assessments, expressive communication and receptive communication were [redacted]), [redacted] and [redacted], respectively. The company reported that the scores for the Bayley subscales were all within the range of normally developing children at all timepoints.

In STR1VE-EU, in the fine motor subtest, the mean raw score [redacted] points at 6 months after treatment with onasemnogene [redacted] points at 12 months post treatment. In the gross motor subtest, mean raw scores [redacted] at 6 and 12 months after treatment with onasemnogene, respectively.

4.3.1.3 Respiratory function

In START, the company reports that five patients (41.7%) in Cohort 2 required the use of temporary, reversible, invasive ventilatory support during the study. Ventilatory support was provided as endotracheal tube via mouth/nose, either when patients had an upper respiratory illness or pneumonia (three patients), or, was planned and used during a procedure or elective evaluation (four patients). All cases of invasive ventilatory support were temporary, single instances, and reversed on resolution of the acute illness or after the conclusion of the procedure or evaluation. No patient received a tracheostomy. The duration of ventilatory support ranged from 1 to 9 days.

No patient in START needed PAV, although chronic non-invasive ventilatory support (BiPAP) was required by all three patients in Cohort 1 and five patients in Cohort 2 at the 13.6 month data cut, which increased to six patients (50.0%) in Cohort 2 at the 24 month data cut. However, all three patients in Cohort 1 required ventilatory support at baseline, compared with only two patients in Cohort 2 at baseline. The ERG notes that five of the Cohort 2 patients who required ventilatory support with BiPAP have entered LT-001 and as of the 31 December 2019 data-cut were still requiring chronic non-invasive ventilatory support.

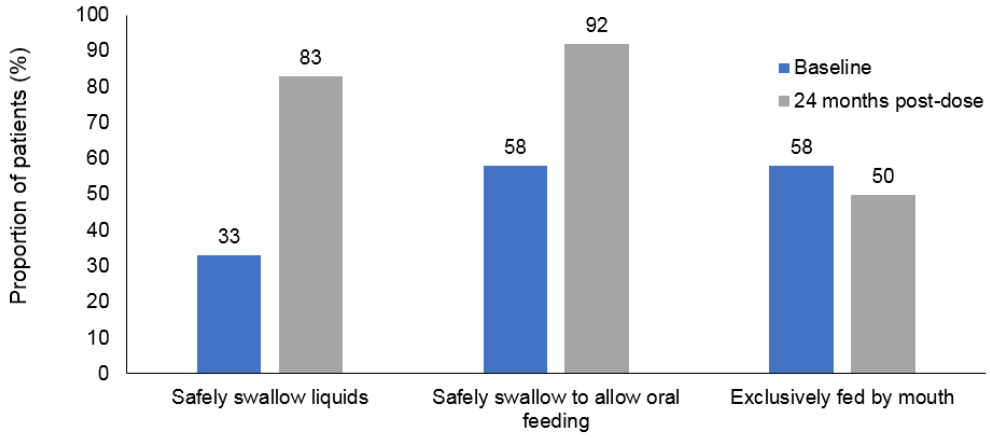
No patient required non-invasive ventilatory support at baseline in STR1VE-US. At the end of study visit, when the patient reached 18 months of age, 18 (81.8%) patients from the enrolled cohort remained independent of ventilatory support (as assessed by Trilogy BiPAP data; p<0.0001). The ERG notes that three (31.9%) patients required temporary non-invasive ventilatory support during STR1VE-US. One patient met the definition for permanent, non-invasive or invasive ventilatory support (as assessed by the Trilogy BiPAP data), with the patient reaching 11.0 months of age before requiring ventilatory support (study day 176).

As of the 31 December 2019 data cut, [redacted] in STR1VE-EU was in need of permanent ventilatory support, but [redacted] patients had required non-invasive ventilatory support during the study (BiPAP). [redacted] of the patients needing non-invasive ventilatory support during the study had required ventilatory support at baseline. [redacted].

4.3.1.4 Nutritional status and swallowing function

In START, at baseline, 53.3% of patients across Cohort 1 and Cohort 2 required non-oral feeding support. At 13.6 months of age, 60% of patients required non-oral feeding support, including all three patients in Cohort 1 and six patients in Cohort 2. Although the proportion of patients in Cohort 2 who fed exclusively by mouth decreased from 58% at baseline to 50% at 24 months post-onasemnogene administration, the proportion of patients able to safely swallow to allow for at least partial oral feeding increased from 58% at baseline to 92% at the end of the follow-up period (Figure 7).

Figure 7. Stabilisation or improvement in swallowing function in patients in Cohort 2 in START (reproduced from CS, Figure 14)



At study enrolment, all patients in STR1VE-US were able to swallow thin liquids and none required feeding support. Seven patients (31.8%) received non-oral feeding support at some point during the study, with four requiring only intermittent or transient [redacted] feeding support during the study. At the end of study visit, 19 patients (86.3%) were feeding without mechanical support. Of the three patients requiring feeding support at the end of study visit, two had gastrostomy-tube placement and one patient, who subsequently died, had [redacted] feeding support that was ongoing at the time death.

In STR1VE-EU, [redacted] patients were able to swallow thin liquids at time of enrolment into the study, and [redacted] required feeding support. By the 31 December 2019 data cut, [redacted] patients had received feeding support during the study, and [redacted] were receiving ongoing feeding support ([redacted]). The ERG notes that [redacted] patients who did not require feeding support at baseline were receiving feeding support at the 31 December 2019 data cut ([redacted]).

4.3.1.5 Ability to thrive

In START and STR1VE-US, a patient's ability to thrive was defined as the ability to tolerate thin liquids, not receiving nutrition through mechanical support and maintained weight (>3rd percentile for age and gender). In START, the ability to thrive was assessed for the seven patients in Cohort 2 who did not require non-oral nutrition prior to onasemnogene dosing. At 13.6 months of age, six of the seven (85.7%) patients maintained the ability to thrive, while at 24 months post-dosing, five out of seven patients had the ability to thrive (Table 18).

In STR1VE-US, compared with START, a smaller proportion of patients met the criteria for ability to thrive, with nine out of 22 patients (40.9%) achieving ability to thrive at 18 months of age (Table 18).

Table 18. Proportion of patients with the ability to thrive at 18 months of age in START and STR1VE-US (ITT population; reproduced from CS appendix, Table 31)

Outcome	START (N=7)	START (N=7)	STR1VE-US (N=22)
	13.6 months of age	24 months post-dose	18 months of age
Maintain ability to thrive			
n (%)	6 (85.7)	5 (71.4)	9 (40.9)
97.5% confidence interval[a]	42.1 to 99.64	29.0 to 96.3	18.6 to 66.4
p-value[a]	<0.001	<0.001	<0.0001
Subitems comprising the ability to thrive at 18 months of age			
Ability to tolerate thin liquids, n (%)	NR	NR	12 (54.5)
Does not receive nutrition through mechanical support, n (%)	NR	NR	19 (86.4)
Maintains weight consistent with age, n (%)	NR	NR	14 (63.6)

Outcome	START (N=7)	START (N=7)	STR1VE-US (N=22)
	13.6 months of age	24 months post-dose	18 months of age
[a] p-value and 97.5% confidence interval are from a one-sided exact binomial test. Abbreviations: CI, confidence interval; NR, not reported.			

4.3.1.6 Speech and communication

The ability of patients treated with onasemnogene to speak was not formally assessed as part of START. However, according to clinical observations, 11 (92%) patients in Cohort 2 of START had developed the ability to speak at 24 months post-dosing.[26] An additional evaluation of seven of the patients who developed the ability to speak was performed as a clinical service requested by the caregivers.[61] The patients were evaluated using the Bayley Scales for language resulting in scores in the range of normal childhood development, and the authors suggested that these children should be capable of schooling and have the potential for a good quality of life. Data on speech and communication were not available for STR1VE-US or STR1VE-EU.

4.3.2 Pre-symptomatic SMA

As touched on in Section 4.2.1, given that SPR1NT enrolled patients with a bi-allelic mutation of the SMN1 gene, without onasemnogene treatment, patients would most likely develop symptoms of SMA at some point in their life, but it is challenging to accurately predict the type of SMA likely to manifest. A large proportion of patients with two copies of SMN2 is likely to develop symptoms within the timeframe that leads to a clinical diagnosis of SMA type 1 (73%). By contrast, patients with three copies of SMN2 are more likely to develop SMA type 2 (78%), but a proportion will develop SMA type 1 (20%). Thus, the ERG presents results for both cohorts from SPR1NT.

4.3.2.1 Survival without need for permanent ventilation

All patients in SPR1NT, both cohorts, were alive and free of permanent ventilation at their last study visit prior to the 31 December 2019 data cut (Figure 8).

For patients in Cohort 1 (two copies of SMN2), the median duration of follow-up at last visit was 9.9 months (range 5.1 to 18.0 months), and the median age at last visit was 10.5 months (range 6.0 to 18.6). Patients in Cohort 2 (three copies of SMN2) had a median duration of follow-up at last visit of 9.0 months (range 2.0 to 13.9 months), and a median age at last visit of 9.6 months (range 3.3 to 15.1 months).

Figure 8. Kaplan–Meier plot for event free survival in Cohort 1 (two copies of SMN2) and Cohort 2 (three copies of SMN2) in SPR1NT (31 December 2019 data cut; ITT population) and plots for the natural history cohorts of NeuroNext and PNCR (reproduced from CS appendix, Figure 23)

4.3.2.2 Motor function

Motor function milestones based on independent central review

As highlighted in Section 4.2, primary efficacy outcome differed for the two cohorts:

- for those with two copies of SMN2, independent sitting for at least 30 seconds up to 18 months of age;
- for those with three copies of the SMN2 gene, the ability to stand without support for at least 3 seconds up to 24 months of age.

The ERG presents a combined overview of motor milestones, noting that patients with two copies of SMN2 would be considered likely to reach fewer motor milestones than those with three copies of SMN2.

Independent sitting

As of their last visit before the 31 December 2019 data cut, eight patients (out of 14 assessed) from Cohort 1 achieved the video-confirmed primary efficacy endpoint of sitting without support for ≥30 seconds (achieved between 5.7 and 11.8 months of age; Table 19) and seven had achieved the motor milestone within the expected WHO age range of <9.2 months. The remaining six patients who could not sit independently for ≥30 seconds at the data cut were all younger than 9.2 months of age.

For Cohort 2, [redacted] ([redacted]) patients were able to sit without support for ≥30 seconds, with [redacted] achieving sitting independently prior to 9.2 months of age, which is the 99th percentile for development of the motor milestone. The remaining [redacted] patients achieved sitting without support between the age of 9.3

and 12.0 months. Of the [redacted] patients who have yet to sit without support, [redacted] are younger than 9.2 months of age. [redacted] patients were able to sit without support for ≥10 seconds, according to the WHO Multicentre Growth Reference Study definition.

Walking alone

By the 31 December 2019 data cut, [redacted] ([redacted]) patients in Cohort 1 had achieved the milestone of standing alone, and [redacted] also achieved the milestone of walks alone according to WHO Multicentre Growth Reference Study definitions. The ERG notes that the company reported that the remaining Cohort 1 patients would not be expected to stand alone or walk alone as yet as they have not passed through the typical windows of achievement to develop these milestones.

As of their last visit before the 31 December 2019 data cut, four (26.7%) patients in Cohort 2 achieved the video-confirmed primary efficacy endpoint of standing without support for ≥3 seconds, with [redacted] also being able to stand alone as per the WHO Multicentre Growth Reference Study definition. Of the [redacted] patients capable of standing alone, [redacted] went on to be able to walk alone, meeting criteria for walking alone for both the Bayley Scale definition and the WHO Multicentred Growth Reference Study definition at the same visits and ages. One patient also achieved walking alone according to the WHO Mulitcentre Growth Reference Study definition at 12.4 months of age at the visit scheduled for 12 months of age. At the time of their last visit, all patients in Cohort 2 were younger than 16.9 months, which is the 99th percentile for development of standing alone. In addition, all patients were less than 17.6 months of age, which is the 99th percentile for development of walking alone.

Table 19. Video confirmed developmental milestones (ITT population) in SPR1NT (31 December 2019 data cut; reproduced from CS appendix, Table 34)

Milestone achieved		**Cohort 1 (two copies SMN2) (N=14)**	**Cohort 2 (three copies SMN2) (N=15)**
Holds head erect for ≥3 seconds without support[a]		[redacted]	[redacted]
Turns from back to both right and left sides[b]		[redacted]	[redacted]
Sits alone without support for ≥30 seconds[c]		8 (57.1)	[redacted]
Sits alone without support for ≥10 seconds[d]		[redacted]	[redacted]
Crawls at least 5 feet[e]		[redacted]	[redacted]
Crawls at least 3 movements[f]		[redacted]	[redacted]
Stands with assistance	Supports own weight for ≥2 seconds[g]	[redacted]	[redacted]
	Stands holding a stable object[h]	[redacted]	[redacted]
Pulls to stand[i]		[redacted]	[redacted]
Stands alone	≥3 seconds[j]	[redacted]	4 (26.7)
	≥10 seconds[k]	[redacted]	[redacted]
Walks with assistance	Bayley Scales[l]	[redacted]	[redacted]
	WHO MGRS[m]	[redacted]	[redacted]
Walks alone	Bayley Scales[n]	[redacted]	[redacted]
	WHO MGRS[o]	4 (28.6)	3 (20.0)

[a] Bayley Scales gross motor subtest item #4: Child holds head erect for ≥3 seconds without support.
[b] Bayley Scales gross motor subtest item #20: Child turns from back to both right and left sides.
[c] Bayley Scales Gross Motor subset item #26: Child sits alone without support for ≥30 seconds.
[d] WHO definition: child sits up straight with head erect for ≥10 seconds; child does not use hands or arms to balance body or support position.
[e] Bayley Scales gross motor subtest item #34: Child makes forward progress of at least 5 feet by crawling on hands and knees.
[f] WHO definition: Child alternately moves forward or backward on hands and knees. The stomach does not touch the supporting surface. There are continuous and consecutive movements, at least 3 in a row.
[g] Bayley Scales gross motor subtest Item #33: Supports weight. Child supports his or her own weight for ≥2 seconds, using your hands for balance only.
[h] WHO definition: Child stands in upright position on both feet, holding onto a stable object (e.g. furniture) with both hands without leaning on it. The body does not touch the stable object, and the legs support most of the body weight. Child thus stands with assistance for ≥10 seconds.
[i] Bayley Scales gross motor subtest item #35: Child raises self to standing position using chair or other convenient object for support.
[j] Bayley Scales gross motor subtest item #40: Child stands alone for at least 3 seconds after you release his or her hands.
[k] WHO MGRS definition: Standing alone. Child stands in upright position on both feet (not on the toes) with the back straight. The legs support 100% of the child's weight. There is no contact with a person or object. Child stands alone for at least 10 seconds.
[l] Bayley Scales gross motor subtest item #37: Child walks by making coordinated, alternated stepping movements.
[m] WHO MGRS definition: Walking with assistance Child is in upright position with the back straight. Child makes sideways or forward steps by holding onto a stable object (e.g. furniture) with 1 or both hands. One leg moves forward while the other supports part of the body weight. Child takes at least 5 steps in this manner.
[n] Bayley Scales gross motor subtest item #43: Child takes at least 5 steps independently, displaying coordination and balance.
[o] WHO MGRS definition: Walking alone Child takes at least 5 steps independently in upright position with the back straight. One leg moves forward while the other supports most of the body weight. There is no contact with a person or object.
Abbreviations: CS, company submission; ITT, intention to treat; WHO, World Health Organization.

CHOP-INTEND

As per the protocol, CHOP-INTEND data were assessed only in patients with 2 copies of SMN2 (Cohort 1). The mean baseline CHOP-INTEND score in Cohort 1 was 46.1 (SD 8.77), and, as of the 31 December 2019 data cut, the mean increase in score from baseline after treatment with onasemnogene was:

- 3.9 points (SD 8.28) at 1 month (n=14);
- 12.1 points (SD 9.87) at 3 months (n=9);
- 16.3 points (10.06) at 6 months (n=7).

The improvement in CHOP-INTEND scores for Cohort 1 overtime by age are generally comparable with the results of healthy controls and substantially improved compared to the historical cohort of SMA patients from NeuroNEXT (Figure 9).

All 14 patients in Cohort 1 achieved a CHOP-INTEND score of ≥50 by 6 months of age, and 13 (92.9%) achieved a CHOP-INTEND score ≥58 by 9 months of age. Nine patients (64.3%) have achieved three consecutive CHOP-INTEND scores ≥58, and will not undergo additional CHOP-INTEND examinations as per the SPR1NT study protocol. As of the 31 December 2019 data cut, 12 (85.7%) patients have achieved CHOP-INTEND scores ≥60: one patient will no longer be able to demonstrate a CHOP-INTEND score ≥60 as they have achieved three consecutive CHOP-INTEND scores ≥58 (59, 58, and 58) and, therefore, will not be eligible for further assessment using CHOP-INTEND.

Figure 9. CHOP-INTEND response in Cohort 1 in SPR1NT (31 December 2019) (ITT population) and juxtaposed healthy infants (reproduced from CS appendix, Figure 28)

† The NeuroNext CHOP-INTEND score estimate for healthy infants is a model-based estimate of motor function in healthy infants. The green shaded area denotes the 95% CI around the estimate [39].
‡ The NeuroNext SMA data are model-based estimates of an SMA cohort excluding *SMN2* >2. The grey shaded area denotes the 95% CI around the estimate.
Dotted line at CHOP-INTEND score of 40: A score ≥40 is beyond that reported in the literature for maximum transiently achieved function amongst symptomatic patients with SMA type 1 beyond 6 months of age (1).

Bayley scales

The gross and fine motor subtests of the Bayley Scales were administered at baseline, 1 month after receiving onasemnogene, and every 3 months beginning at 3 months of age.

In Cohort 1, at their most recent visit before the 31 December 2019 data cut, seven (50%) patients had Bayley gross motor subtest scaled scores within 2 SD of the mean for age (i.e., scaled score ≥4) and all patients had Bayley scale fine motor subtest scaled scores within 2 SD of the mean for age (i.e., scaled score ≥4). The Bayley scale fine motor subtest mean raw score improved from baseline by:

In the Bayley gross motor subtest, the mean raw score improved from baseline by:

- 0.9 (SD 1.94) points at 1 month (n=14);
- 16.6 (SD 4.37) points at 6 months (n=8);
- 29.3 (SD 10.84) points at 12 months (n=4);
- 33.5 (9.40) points at 15 months (n=4).

In Cohort 2, at their most recent visit prior to the 31 December 2019 data cut, all patients (n=15) had Bayley gross motor subtest scaled scores within 2 SD of the mean for age (i.e. scaled score ≥4), and

fourteen (93.3%) had Bayley fine motor scaled scores within 2 SD of the mean for age (i.e. scaled score ≥4). In Cohort 2, the Bayley scale fine motor subtest mean raw score improved from baseline after administration of onasemnogene by:

- [redacted].

In the Bayley gross motor subtest, the mean raw score for Cohort 2 improved from baseline by:

- 2.6 (SD 2.26) points at 1 month (n=13);
- 17.5 (SD 4.42) points at 6 months (n=6);
- 32.0 (SD 2.31) at 11 months (n=4).

4.3.2.3 Respiratory function

As of the 31 December 2019 data cut, no patient in SPR1NT required any ventilatory support, including non-invasive ventilatory support.

4.3.2.4 Nutritional status and swallowing function

In order to be eligible for enrolment in SPR1NT, patients were required to be asymptomatic, able to swallow thin liquids, and free from ventilatory support. At the 31 December 2019 data cut, 14 of 30 (46.7%) patients had completed at least their 12-month swallow evaluation, including eight patients in Cohort 1 and six patients in Cohort 2: one patient who was identified as having four copies of SMN2 was also assessed at 12 months. All patients had normal swallow at all timepoints, with the exception of one (unclear to which cohort patient was enrolled) for whom normal swallow was not noted at their 6-month swallow evaluation.

4.3.3 Adverse effects

Adverse effects are reported from all onasemnogene studies, that is, those involving patients with symptomatic SMA type 1 and pre-symptomatic SMA, and are presented alongside each other as types of adverse effect experienced with onasemnogene are not expected to differ between those with and those without symptoms. Safety results are presented from the completed START and STR1VE-US studies, and for the 31 December 2019 data cut for ongoing STR1VE-EU and SPR1NT.

As of the latest data available across the four studies, 100 patients had received an IV infusion of onasemnogene, with 97 administered the recommended therapeutic dose of onasemnogene. Of the 97 patients who received the therapeutic dose, 96 (99%) experienced at least one treatment-emergent adverse event (TEAE) and 56 (58%) were reported to have a TEAE considered by the investigator to

be related to onasemnogene (Table 20). Forty-five (46%) patients had at least one SAE, and 39 (40%) had at least one TEAE that was of Grade 3 severity or higher. The most frequently reported TEAEs (occurring in ≥5% of patients) and considered related to onasemnogene (therapeutic dose) across START, STR1VE-US, STR1VE-EU, and SPR1NT were:

- increase in level of transaminases (12.4%);
- increase in level of aspartate aminotransferase (9.3%);
- increase in level of alanine aminotransferase (8.2%);
- vomiting (8.2%);
- hypertransaminasemia (8.2%).

Two patients, one in STR1VE-US and one in STR1VE-EU, discontinued from their respective study due to TEAEs that resulted in death. One death was attributed to respiratory arrest and the other to respiratory distress and hypoxic-ischemic encephalopathy, with both deaths considered unrelated to onasemnogene by the investigator. In addition, one patient discontinued from STR1VE-US because of a TEAE of respiratory distress, which was also deemed by the investigator to be unrelated to onasemnogene.

Table 20. Overview of TEAEs for START, STR1VE-US, STR1VE-EU and SPR1NT (31 December data cut; reproduced from CS appendix, Table 36)

TEAEs	**START**			**STR1VE-US**	**STR1VE-EU**	**SPR1NT**	**All patients**
	Cohort 1 **n (%) (N=3)**	**Cohort 2** **n (%) (N=12)**	**All patients** **n (%) (N=15)**	**n (%) (N=22)**	**n (%) (N=33)**	**n (%) (N=30[a])**	**n (%) (N=100)**
Patients with ≥1 TEAE	3 (100)	12 (100)	15 (100)	22 (100)	32 (97.0)	30 (100)	99 (99.0)
TEAE ≥Grade 3 severity	3 (100)	10 (83.3)	13 (86.7)	10 (45.5)	13 (39.4)	6 (20.0)	42 (42.0)
TEAEs related to study treatment[b]	1 (33.3)	3 (25.0)	4 (26.7)	12 (54.5)	24 (72.7)	17 (56.7)	57 (57.0)
Serious TEAEs	3 (100)	10 (83.3)	13 (86.7)	10 (45.5)	19 (57.6)	6 (20.0)	48 (48.0)
TEAE causing study discontinuation	0	0	0	2 (9.1)	1 (3.0)[d]	0	3 (3.0)
TEAE resulting in death	0	0	0	1 (4.5)[c]	1 (3.0)[d]	0	2 (2.0)

[a] The safety data reported from SPR1NT as of the 31 December 2019 data cut includes 14 patients with two copies of SMN2, 15 patients with three copies of SMN2, and one patient with 4 copies of SMN2.
[b] Adverse events were considered related to treatment if the event is classified as unknown, possibly, probably or definitely related to study treatment.
[c] Patient [redacted] died due to respiratory arrest considered unrelated to onasemnogene abeparvovec by the Investigator.
[d] Patient [redacted] discontinued the study due to AEs of respiratory distress and hypoxic-ischaemic encephalopathy in death.
Source: 31 December 2019 Safety Update.[62]
Abbreviation: TEAE, treatment emergent adverse event.

The SmPC[60] for onasemnogene specifies that liver function, platelet counts, and cardiac troponin-I levels must be monitored after treatment to assess the immune response to the AAV9 capsid. In addition, to dampen the immune response, immunomodulation with corticosteroids (prednisolone) is recommended. The ERG notes that all liver-related AEs or TEAEs of increased liver transaminase, alanine aminotransferase, aspartate aminotransferase, liver function, or hepatic enzyme, across START, STR1VE-US, STR1VE-EU and SPR1NT were deemed to be related to onasemnogene by study investigators. The company reported that, in general, in SPR1NT, an increase in transaminases occurred in most patients during the first month after treatment and declined thereafter. The ERG is unsure whether the same pattern in transaminase abnormalities was also seen in START, STR1VE-US and STR1VE-EU.

In START, four (27%) patients had a liver-related AE, with increased level of transaminases reported in three patients, and increased aspartate aminotransferase and increased transaminases noted for the remaining patient. All AEs resolved within the observation period in START.

Seven patients in STR1VE-US were reported to have TEAEs of increased liver transaminase, alanine aminotransferase, aspartate aminotransferase, liver function, or hepatic enzyme. For two patients, the increases were sufficient for the AE to be categorised as SAEs (alanine aminotransferase and aspartate aminotransferase increased in one patient, and transaminases increased in the other).

Liver-related adverse events were reported in 16 patients in STR1VE-EU, including hepatic steatosis, hypertransaminasemia, and increased transaminases, alanine aminotransferases, aspartate aminotransferases, gamma-glutamyl transferases, and hepatic enzyme. Of these, two events in one patient were considered serious. Additionally, the same patient experienced a serious thrombocytopenia event that was accompanied by multi-organ system failure secondary to respiratory distress. The thrombocytopenic event was assessed by the investigator as being possibly related to onasemnogene.

Eight (36.4%) patients in STR1VE-US had events categorised as thrombocytopenia, with four considered by the investigator as related to onasemnogene. In addition, one patient in SPR1NT experienced transient thrombocytopenia and another experienced decrease in platelet count, which resolved without any sequelae.

The ERG notes that no patient in the onasemnogene intervention studies experienced clinically significant cardiac toxicity (tachycardia, bradycardia, or pre-existing congenital heart defects events were considered not clinically significant) or sensory abnormalities suggestive of dorsal root ganglia cell inflammation.

The ERG's clinical experts commented that development of scoliosis in patients with SMA is an important outcome and thus the ERG requested, during clarification, that the company provide data on occurrence of scoliosis, which was captured as an AE. In their response, the company flagged that there is also a separate MedDRA code for 'kyphoscoliosis', and supplied data for the number of patients experiencing a TEAE of scoliosis or kyphoscoliosis (Table 21). The ERG notes that 11 (11.3%) patients across the four studies have been recorded as experiencing a scoliosis TEAE, with only one patient reported as having scoliosis at baseline. The company reported that a second patient from START also had scoliosis at baseline but is presumed to have had surgery as there is no record of the patient as having a scoliosis TEAE during follow-up. No patient was recorded as having kyphoscoliosis at baseline, although one patient in STR1VE-US was reported to have experienced kyphoscoliosis as a TEAE. In general, the ERG notes that the occurrence of scoliosis and kyphoscoliosis is low across the studies, but, as highlighted by the ERG's clinical experts, the duration of follow-up is also short in terms of capturing the development of scoliosis.

Table 21. Aggregated data of scoliosis and kyphoscoliosis in patients treated with IV onasemnogene abeparvovec using the safety population (adapted from company response to CQs 02 July 2020, Tables 8 and 9)

	START Cohort 2 (N=12)	**STR1VE-US (N=22)**	**STR1VE-EU (N=33) (interim)**	**SPR1NT (N=30) (interim)**
Scoliosis at baseline, n (%)	2/12 (16.7%)[a]	0/22	0/33	0/30
Patients with scoliosis TEAE, n (%)	1/12 (8.3%)	9/22 (40.9%)	1/33 (3.0%)	0/30
Total scoliosis TEAE events	1	12	1	0
Kyphoscoliosis at baseline, n (%)	0/12	0/22	0/33	0/30
Patients with kyphoscoliosis TEAE, n (%)	0/12	1/22 (4.5%)	0/33	0/30
Total kyphoscoliosis TEAE events	0	1	0	0

[a] For one of the two patients who had scoliosis at baseline, while no TEAE of scoliosis is reported for this patient, scoliosis surgery is presumed due to the record a TEAE of 'wound infection secondary to scoliosis surgery'.
Abbreviation: TEAE, treatment-emergent adverse event.

In LT-001, only SAEs and AESIs are being collected, where AESIs are listed as: gene therapy-related AEs; liver function enzyme elevations; new incidences of a malignancy or hematologic disorder; new incidences or exacerbations of pre-existing neurologic or autoimmune disorders; and sensory abnormalities suggestive of dorsal root ganglionopathy.

As of the 31 December 2019 data cut, eight (61.5%) of the 13 patients enrolled in Study LT-001 were reported to have had at least one AE, and all the patients with an AE having experienced at least one serious AE (Table 22). No patient in LT-001 had a TEAE considered by the investigator to be related to onasemnogene and no TEAE resulted in study discontinuation or death. In addition, it was reported

that no clinically significant events of cardiac toxicity or sensory abnormalities suggestive of dorsal root ganglia cell inflammation have been reported.

Table 22. Overview of patients with TEAEs in LT-001 (31 December 2019 data cut 9reproduced from CS appendix, Table 37)

	Cohort 1 6.7×10^{13} vg/kg n (%) (N=3)	**Cohort 2 2.0×10^{14} vg/kg n (%) (N=10)**	**All patients n (%) (N=13)**
Patients with ≥1 TEAE	1 (33.3)	7 (70.0)	8 (61.5)
TEAE ≥ Grade 3 severity	1 (33.3)	7 (70.0)	8 (61.5)
Serious TEAEs	1 (33.3)	7 (70.0)	8 (61.5)
TEAEs related to study treatment[a]	0	0	0
TEAE causing study discontinuation	0	0	0
TEAE resulting in death	0	0	0

[a] Adverse events were considered related to treatment if the event is classified as unknown, possibly, probably or definitely related to study treatment.
Source: 31 December 2019 Safety Update[62]
Abbreviation: TEAE, treatment emergent adverse event.

4.3.3.1 Hospitalisation

The ERG notes that hospitalisation was specified in the NICE scope as an outcome of interest. The only results for hospitalisation provided by the company were derived from START and were presented in the original CS. At the final assessment, 13 (86.7%) of 15 patients experienced at least one hospitalisation during the study, including all three patients in Cohort 1 and 10 (83.3%) patients in Cohort 2. The mean annualised hospitalisation rates were 0.81 hospitalisations/year (standard error [SE] 0.17) for Cohort 1, 2.08 (SE 0.68) for Cohort 2, and 1.83 (SE 0.53) for the full study population. The company compared these results with the hospitalisation rates of patients with SMA type 1 in natural history studies, which have been reported to range from 4.2 hospitalisations/year in a USA-based study published in 2017,[63] to 7.6 hospitalisations/year in the first 3 years of life in a single centre UK study from 2011.[64]

For Cohort 2, the mean proportion of study time hospitalised was 4.4% (range: 0% to 18.3%); 10 (83%) patients were hospitalised <10% of the time, and none was hospitalised for ≥20% of the time. For the ten patients who were hospitalised, the mean length of stay per hospitalisation was 6.7 days (range: 3 to 12.1).

4.3.4 Pooled analysis

4.3.4.1 Methods

As mentioned earlier, to provide clinical inputs for the cost-effectiveness analysis of onasemnogene, the company pooled data from the completed START (N=12) and STR1VE-US (N=22) studies. The pooled dataset was generated by totalling the number of events per milestone (e.g., sitting independently

and walking independently) in each 6-month follow-up period, to correspond with the 6 monthly cycle implemented in the economic model.

The comparison of onasemnogene with BSC informing the economic model is an unanchored, naïve comparison, as no adjustment has been made for differences (known or unknown) in study populations or differences in study effects. Although the ERG noted some differences in baseline characteristics for START and STR1VE-US compared with the studies informing BSC (Section 4.2.4.1), given the small sample size, the ERG considers that adjusting for known prognostic indicators, as well as potential confounders, could potentially reduce the effective sample size without necessarily increasing precision or accuracy of the results. Thus, the ERG considers the unadjusted results are the best available evidence to inform the decision problem, at this time. Adjustment of data may be feasible on release of results from STR1VE-EU. Considering the naïve pooling of data from START and STR1VE-US, the ERG's clinical experts commented that the baseline characteristics of the populations enrolled in the two studies are sufficiently comparable for a naïve pooling of results.

The company reported that patients included in the pooled dataset were aged up to 36 months, which corresponds with cycle 6 of the economic model. The ERG notes that, in START, the duration of follow-up was a maximum of 24 months after administration of onasemnogene (approximately 30 months of age), whereas, in STR1VE-US, follow-up ceased when a child reached 18 months of age. The company proposed that using an 18-month age timepoint would underestimate the likely maximum milestone attainment and potential benefit from treatment with onasemnogene. Thus, the final proportions of patients in the pooled dataset for either sitting alone or walking independently were adjusted using an offset approach for inclusion in the economic model to take into consideration the timing of achieving the milestone. In addition, two assumptions were used in the economic model to mitigate for the differences in follow-up between START and STR1VE-US:

- the base case assumption includes one additional independent sitter and one additional independent walker between 24 months and 30 months of age in STR1VE-US, over and above empirical data. The rationale for the company's assumption is described in greater detail in Section 5.3.5.1.

- with the exception of sitting alone or walking independently, to account for the shorter follow up period in STR1VE-US compared with START, the last observation carried forward (LOCF) method was used for other outcomes for STR1VE-US patients between 18 months and 30 months of age and contributing to the pooled dataset. Applying LOCF meant that no further milestones were assumed to be gained, and, thus, the proportions observed sitting and walking at 18 months of age in STR1VE-US are assumed to remain the same up to 30 months of age.

Further details of the adjustments and assumptions used in the cost-effectiveness analysis are discussed in Section 5.4.

The ERG also notes that, for the outcomes of overall survival and event-free survival, the company converted the data into proportions using the pooled sample size of 34 patients as the denominator. Patients in STR1VE-US were censored from survival curves in the short-term model from 18 months to 36 months of age due to the absence of follow-up data beyond 18-months.

4.3.4.2 Baseline characteristics

The baseline characteristics of the pooled data set are provided, alongside the individual study baseline characteristics for START Cohort 2 and STR1VE-US, in Table 23. Race was markedly different between the studies, with 91.7% being white in START Cohort 2, compared with only 50% white in STR1VE-US. The ERG notes that the mean age at diagnosis of SMA type 1 and mean age at onasemnogene treatment were slightly higher in STR1VE-US compared with START Cohort 2.

Key differences between the studies are noted in the proportion of infants able to swallow thin liquids, and the requirement for support in feeding and ventilation. In STR1VE-US, no patient had difficulty swallowing thin liquids, or required support in feeding or ventilation at baseline (Table 23). By contrast, in START Cohort 2, 66.7% were unable to swallow thin liquids, 41.7% required non-oral feeding support and 16.6% required ventilatory support (includes one patient who was incorrectly recorded as not requiring ventilatory support at baseline). The lack of requirement for feeding and ventilatory support at baseline in STR1VE-US suggests that enrolled patients have less severe disease than those in Cohort 2 of START. However, as commented earlier, the ERG's clinical experts consider that the pooled dataset reflects the baseline characteristics of infants likely to be eligible for treatment with onasemnogene, and the ERG agrees with the company that it is appropriate to pool outcome data for the two studies.

Table 23. Baseline characteristics of START, STR1VE-US, and the POOLED dataset (reproduced from CQ response 02 July 2020, Table 4)

Characteristics	**START Cohort 2 (N=12)**	**STR1VE-US (N=22)**	**POOLED (N=34)**
SMN2 copy number x 2, n	12/12 (100%)	22/22 (100%)	34/34 (100%)
Gestational age at birth, weeks • N • Mean (SD)	 10 38.5 (1.43)	 22 39.045 (0.9501)	 32 38.9 (1.13)
Mean age at diagnosis, days (range)	67.8 (1, 137)	79.2 (1, 163)	75.1 (1, 163)
Mean age at symptom onset, months (SD)	2.3 (1.47)	1.9 (1.24)	2.0 (1.31)
Age at treatment, months • Mean (SD) • Min, Max	 3.4 (2.06) 0.93, 7.93	 3.73 (1.6096) 0.50, 5.90	 3.64 (1.76) 0.50, 7.93

Sex, n (%) • Female, % • Male, %	 7/12 (58.3%) 5/12 (41.7%)	 12/22 (54.5%) 10/12 (45.5%)	 19/34 (55.9%) 15/34 (44.1%)
Race, n (%) • White • Other	 11/12 (91.7%) 1/12 (8.3%)	 11/22 (50%) 11/22 (50%)	 22/34 (64.7%) 12/34 (35.3%)
Ethnicity, n (%) • Not Hispanic or Latino • Hispanic or Latino	 10/12 (83.3%) 2/12 (16.7%)	 18/22 (81.8%) 4/22 (18.2%)	 28/34 (82.4%) 6/34 (17.6%)
Weight, mean (range), kg	5.69 (5.45, 8.4)	5.83 (3.9, 7.5)	5.78 (3.6, 8.4)
Mean CHOP-INTEND score (range)	28.2 (12, 50)	32.0 (18, 52)	30.6 (12, 52)
Swallowing thin liquid, n (%) • Yes • No	 4/12 (33.3%) 8/12 (66.7%)	 22/22 (100%) 0/22 (0%)	 26/34 (76.5%) 8/34 (23.5%)
Non-oral feeding support, n (%) • Yes • No	 5/12 (41.7%) 7/12 (58.3%)	 0/22 22/22 (100%)	 5/34 (14.7%) 29/34 (85.3%)
Ventilatory support (invasive/non-invasive), n (%) • Yes • No	 1/12 (8.3%)† 11/12 (91.7%)	 0/22 (0%) 22/22 (100%)	 1/34 (2.9%)[a] 33/34 (97.1%)
Familial history of SMA including affected siblings or parent carriers, n (%) • Yes • No • Unknown	 3/12 (25%) 8/12 (66.7%) 1/12 (8.3%)	 7/22 (31.8%) 12/22 (54.5%) 3/22 (13.6%)	 10/34 (29.4%) 20/34 (58.8%) 4/34 (11.8%)
Total number of days of prednisolone administration, mean (SD)	73.8 (33.04)	73.7 (39.54)	73.7 (36.86)

[a] Does not include one additional patient in Cohort 2 who was receiving BiPAP at baseline but for whom data was mis-entered at the clinical site
Note: For age at diagnosis, patients who were diagnosed prior to birth have been assigned an age at diagnosis of 1 day.
Abbreviations: CHOP-INTEND, Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders; SD, standard deviation; SMA, spinal muscular atrophy; SMN, survival motor neuron.

4.3.4.3 Outcome assessment

As already discussed in Section 4.3.4.1, one of the key differences in outcome assessment in START Cohort 2 and STR1VE-US was the length of follow-up for the studies, which was only up to 18 months of age in STR1VE-US compared with 24 months after administration of onasemnogene in START Cohort 2 (approximately 30 months of age). The ERG agrees with the company that the 18-month follow-up in STR1VE-US may underestimate the clinical effectiveness of onasemnogene in terms of achievement of motor milestones and overall survival. The methods the company has used to account for the difference in follow-up between studies in the cost-effectiveness analysis is discussed further in Section 5.4.

The ERG also noted differences in definitions of clinical outcomes applied in START and STR1VE-US that could impact the interpretation of the results of the pooled analysis (outcome definitions for both studies are available in Appendix 10.5, Table 78). Key differences in outcomes between START Cohort 2 and STR1VE-US noted by the ERG are:

- the gross and fine motor subtests of the motor domain of the Bayley scale were administered at screening and at each monthly visit up to 18 months of age in STR1VE-US, whereas in START the Bayley Scale was only administered if a child reached or exceeded a CHOP-INTEND score of 60/64;

- attainment of Bayley Scales gross motor subtest item #22: Child sits alone without support for at least 5 seconds. Attainment of the outcome was not centrally reviewed and video-confirmed in STR1VE-US, but was, instead, clinician assessed during study visits using information from the Bayley individual item scores.

- assessment of walks alone: in START, achievement of independent walking was evaluated through the Attainment of Gross Motor Checklist ('takes independent steps') or the Motor Milestone Development Survey ('walks independently'), whereas, STR1VE-US determined independent walking using the Attainment of Bayley Scales gross motor subtest item #43 (child takes at least 5 steps independently, displaying coordination and balance).

The lack of data from START for change from baseline to maximum post-baseline value in Bayley Scales raw scores resulted in the company being unable to undertake a pooled analysis for this outcome.

4.3.4.4 Results

Pooled analysis informing company base case

The results of the pooled analysis are presented in Table 24, together with the results for the individual studies (START Cohort 2 and STR1VE-US). The ERG considers it important to highlight that the data in Table 24 comprise the empirical results of the pooled analysis and do not include the base case model assumption that there is one additional independent sitter and one additional independent walker in STR1VE-US, over and above the numbers observed during the trial period. Additionally, the ERG notes that the states within the economic model are "sits independently" and "walks independently", with no specification on timing of milestone, for example, sits independently for five seconds or longer. The differences between the empirical data from the pooled analysis and the data included in the base case for the economic model are discussed below.

The ERG notes that, for STR1VE-US, the number of patients reported as achieving the milestone of "sits alone for ≥5 seconds" includes one patient who achieved the milestone of "sits alone for ≥30

seconds" according to central review and video-confirmation, but who scored 0 (did not achieve) for the Bayley Scales gross motor subtest item of sitting alone without support for at least 5 seconds at the same visit. The company reported that they included the patient in the "sits alone for ≥5 seconds" based on the rationale that if a patient can sit for ≥30 seconds, they can sit for at least 5 seconds, a rationale with which the ERG agrees. However, the ERG notes that the company did not provide an explanation as to why the patient may have been recorded as unable to meet the milestone as assessed by Bayley scale.

Table 24. Clinical outcomes for the START, STR1VE-US, and POOLED analysis (reproduced from CQ response 02 July 2020, Table 1)

Outcome	**Results**		
	START (Cohort 2) (N=12) During trial period up to 24 months post-dose	**STR1VE-US (N=22) During trial period up to 18 months of age**	**POOLED (N=34)**
Survived without permanent ventilation, n (%)	12/12 (100%)	20/22 (90.9%)[a]	32/34 (94.1%)
Proportion of patients who achieved CHOP-INTEND scores[b], n (%)			
• ≥40	11/12 (91.7%)	21/22 (95.5%)	32/34 (94.1%)
• ≥50	11/12 (91.7%)	14/22 (63.6%)	25/34 (73.5%)
• ≥60	4/12 (33.3%)	5/22 (22.7%)	9/34 (26.5%)
Change from baseline to maximum post-baseline value in Bayley Scales raw scores, mean (SD)			
• Gross motor subset	N/A	16.0 (9.19)	N/A
• Fine motor subset	N/A	23.9 (6.60)	N/A
Developed significant motor milestones, n (%)			
• Sits alone ≥5 seconds[c]	11/12 (91.7%)	14/22 (63.6%)[d]	25/34 (73.5%)
• Sits alone ≥10 seconds[e]	10/12 (83.3%)	14/22 (63.6%)	24/34 (70.6%)
• Sits alone ≥30 seconds[f]	9/12 (75%)	14/22 (63.6%)	23/34 (67.6%)
• Stands with assistance[g]	2/12 (16.7%)	1/22 (4.5%)	3/34 (8.8%)

• Stands alone[h]	2/12 (16.7%)	1/22 (4.5%)	3/34 (8.8%)
• Walks with assistance[i]	2/12 (16.7%)	1/22 (4.5%)	3/34 (8.8%)
• Walks alone[j]	2/12 (16.7%)	1/22 (4.5%)	3/34 (8.8%)
• Independent of ventilatory support, n (%)	6/12 (50%)	15/22 (68.2%)	21/34 (61.8%)
Maintained the ability to thrive, n (%)	5/7 (71.4%)	9/22 (40.9%)	14/34 (41.2%)
Proportion of patients in the SAS receiving non-oral feeding support, n (%)	6/12 (50%)	3/22 (13.6%)	9/34 (26.5%)

[a] Reported at 14 months of age. Timepoint reported as it is the co-primary endpoint for STR1VE-US.
[b] Based on maximum post-baseline CHOP-INTEND score achieved.
[c] Bayley Scales gross motor subtest item #22: Child sits alone without support for at least 5 seconds used for STR1VE-US (not centrally reviewed/video-confirmed). "Sits alone <10 seconds" for START (centrally reviewed/video-confirmed). All patients in the 'sitting < 10 seconds' category were able to sit for at least 5 seconds.
[d] [redacted]
[e] WHO MGRS definition: Child sits up straight with head erect for at least 10 seconds. Child does not use arms or hands to balance body or support position (centrally reviewed/video-confirmed).
[f] Bayley Scales gross motor subtest item #26: Child sits alone without support for at least 30 seconds (centrally reviewed/video-confirmed).
[g] Bayley Scales gross motor subtest item #33: Child supports his or her own weight for at least 2 seconds, using your hands for balance only (centrally reviewed/video-confirmed).
[h] Bayley Scales gross motor subtest item #40: Child stands alone for at least 3 seconds after you release his or her hands (centrally reviewed/video-confirmed).
i Bayley Scales gross motor subtest item #37: Child walks by making coordinated, alternated stepping movements (centrally reviewed/video-confirmed).
j Bayley Scales gross motor subtest item #43: Child takes at least 5 steps independently, displaying coordination and balance used for STR1VE-US (centrally reviewed/video-confirmed). Gross Motor Checklist: 'takes independent steps' or the Motor Milestone Development Survey: 'walks independently' used for START (centrally reviewed/video-confirmed).
Abbreviations: CHOP-INTEND, Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders; CSR, clinical study report; SAS, safety analysis set; SD, standard deviation; WHO MGRS, World Health Organization Multicentre Growth Reference Trial.

Pooled analysis definition of sitting alone implemented in economic model

The ERG noted that the threshold for independent sitting used in the pooled analysis informing the company's cost-effectiveness analysis differed for START (≥5 seconds) and STR1VE (≥30 seconds). In the original submission, the company used data from only START in their economic model due to data availability. At that time, the company reported that they selected a threshold of 'independent sitting' of ≥5 seconds because:

- it reflects the earliest motor milestone that could be observed in clinical studies to indicate a treatment effect in patients with SMA type 1, because patients managed with BSC never attain the ability to sit;

- the approach used in the base case to incorporate motor milestone attainment is already conservative, as the motor milestones observed in the trials are 'offset' by a cycle when incorporated into the model;

- the definition of independent sitting in clinical trials of other SMA active therapies lack any reference to a time threshold (e.g., HINE-2);

- the outcome of 'sits alone for ≥5 seconds' in START was centrally reviewed and video-confirmed.

When pooling START and STR1VE-US the company used a threshold of 'independent sitting' for patients treated in STR1VE-US of sitting alone for ≥30 seconds and a threshold for patients in START of sitting alone for ≥5 seconds. The company reported their rationale for this was:

- in STR1VE-US, 'sits alone for ≥30 seconds' was centrally reviewed and video-confirmed, whereas this was not the case for 'sits alone for ≥5 seconds', which was clinician-assessed during study visits and based on the Bayley Scales individual item scores.

- the proportion of patients who achieved functional independent sitting for at least 30 seconds at the 18 months of age study visit was a co-primary efficacy endpoint in STR1VE-US.

The ERG notes that the number of independent sitters using the threshold of ≥5 seconds in STR1VE-US is in fact the same as the number of independent sitters using the threshold of ≥30 seconds (if the patient described in Section 4.3.4.3 is included as obtaining the ≥5 seconds). However, after discussion with clinical experts, the ERG considers a definition of independent sitting using the threshold of sits alone for ≥30 seconds is more clinically meaningful than the ≥5 seconds threshold. During the clarification stage, the ERG thus requested the company conduct a scenario analysis in which the threshold for independent sitting used in the economic model was ≥30 seconds for both START Cohort 2 and STR1VE-US.

The ERG notes that applying a threshold of ≥30 seconds independent sitting in START results in the omission of two patients from the analysis, compared with the use of the ≥5 second threshold. The company considers the loss of two patients from the independent sitting analysis to result in a pessimistic model because the two patients, who remain in the non-sitting health state in the requested scenario, went on to [redacted]

The company has, nevertheless, provided a scenario analysis for the pooled data whereby the proportion of patients who attain independent sitting is calculated using the sits alone for ≥30 seconds threshold in

the pooled analysis for both START and STR1VE-US. The ERG notes that the model base case assumption that includes one additional independent sitter and one additional independent walker in STR1VE-US, over and above empirical data, is also used in this scenario (see Section 5.4 for results). The clinical data from the pooled analysis that inform the scenario and the data implemented in the economic model are provided in Table 25.

Table 25. Milestone outcomes in START, STR1VE-US and POOLED: Empirical versus model base case assumption (reproduced from CQ response 02 July 2020, Table 5)

	Empirical[e]			**Base case assumption[e]** **Inclusive of the base case assumption: one additional sitter and one additional walker in STR1VE-US**		
	START (N=12) By 30 months of age	**STR1VE-US (N=22) By 18 months of age**	**POOLED (N=34)f By 30 months of age**	**START (N=12) By 30 months of age**	**STR1VE-US (N=22) By 30 months of age**	**POOLED (N=34)f By 30 months of age**
Non-sitters, n (%)[a]	1 (8.3%)	8 (36.4%)	9 (26.5%)	1 (8.3%)	7 (31.8%)	8 (23.5%)
Sits alone, n (%) base case definition[b]	11 (91.7%)	14 (63.6%)	25 (73.5%)[g]	11 (91.7%)	15 (68.2%)	26 (76.5%)[g]
Sits alone, n (%) scenario definition[c]	9 (75%)	14 (63.6%)	23 (67.6%)[g]	9 (75%)	15 (68.2%)	24 (70.6%)[g]
Walks alone[d]	2 (16.7%)	1 (4.5%)	3 (8.8%)	2 (16.7%)	2 (9.1%)	4 (11.8%)

[a] Includes one patient who died aged 7.8 months and one patient who met the permanent-assisted ventilation event endpoint aged 11 months in STR1VE-US.

[b] Sits alone calculated using the ≥30 seconds (item #26) outcome in STR1VE-US and the ≥5 seconds (item #22) outcome in START.

[c] Sits alone calculated using the ≥30 seconds (item #26) outcome in STR1VE-US and START

[d] Bayley Scales gross motor subtest item #43: Child takes at least 5 steps independently, displaying coordination and balance used for STR1VE-US. Gross Motor Checklist: 'takes independent steps' or the Motor Milestone Development Survey: 'walks independently' used for START.

[e] Numbers and percentages across the rows are greater than 100%, respectively, since patients can attain multiple milestones. For example, the patients who can walk alone can also sit alone

[f] For STR1VE-US patients contributing to the POOLED dataset last observation carried forward (LOCF) methodology is used, between 18 months and 30 months of age, to bridge the gap between the follow up period available for STR1VE-US versus START. Except for the two additional milestones described as part of the base case assumptions, no further milestones were gained so that the proportions observed sitting and walking at 18 months of age in STR1VE-US are assumed to remain the same up to 30 months of age in the POOLED analysis.

[g] For one patient in STR1VE-US the milestone of sits unassisted ≥30 seconds was not confirmed at the end of study 18 month visit but was observed at the 16-month and 17-month visit. This patient did sit unassisted for ≥5 seconds at the 18-month visit (as recorded in the Bayley Scale assessment, gross motor item #22.

Post hoc *exploratory analysis of effect of age at dosing on motor milestone development (≤3.5 months versus >3.5 months)*

During clarification, the ERG requested that the company conduct scenario analyses to explore the impact of age and baseline CHOP-INTEND score (high/low) on outcomes, similar to trial level analyses carried out for START. The company supplied *post hoc* exploratory analyses stratified by age at onasemnogene dose using an age threshold of '3.5 months' (Table 26), which was the median age in both START Cohort 2 and STR1VE-US. The company did not provide analyses based on CHOP-INTEND score, indicating that such analyses were not appropriate because there is no clinically-accepted definition of what constitutes a 'high' versus a 'low' CHOP-INTEND score at baseline. Additionally, the company commented that CHOP-INTEND score is not used to inform assessment of prognosis.

As for the other results presented for the pooled analyses, the results reported based on age at treatment with onasemnogene are observed data, thus they do not include the base case model assumption that there is one additional independent sitter and one additional independent walker in STR1VE-US, over and above the numbers observed during the trial period.

The ERG notes that the results of the subgroup analyses based on age suggest that earlier treatment with onasemnogene is associated with improved clinical outcomes (Table 26), and thus support the preliminary results observed in SPR1NT (infants with pre-symptomatic SMA). The ERG agrees with the company that the analyses should be interpreted with caution as they are based on small patient numbers and are *post hoc* analyses. Also, the ERG reiterates that the 3.5-month age threshold applied in the analyses has been determined statistically based on median age at treatment in START and STR1VE-US and there is no clinical rationale or evidence to support the use of 3.5 months as a threshold for treatment with onasemnogene.

Table 26. Motor milestones by age at dosing in Cohort 2 in START, STR1VE-US, and the POOLED dataset (adapted from CQ response 02 July 2020, Table 2)

	START, Cohort 2 (N=12)		STR1VE-US (N=22)		POOLED (N=34)		POOLED
	Dosing at ≤3.5 months of age (n=6)	Dosing at >3.5 months of age (n=6)	Dosing at ≤3.5 months of age (n=11)	Dosing at >3.5 months of age (n=11)	Dosing at ≤3.5 months of age (n=17)	Dosing at >3.5 months of age (n=17)	START Cohort 2 & STR1VE-US full population (N=34)
Age at dosing, months, mean	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	3.64
Motor milestone achievements							
Sits unassisted for ≥5 seconds[a], n	[redacted]	[redacted]	[redacted]	[redacted]	14/17 (82.4%)	[redacted]	25/34 (73.5%)
Median age, months (range)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Not reported
Sits unassisted for ≥30 seconds[b], n	[redacted]	[redacted]	[redacted]	[redacted]	14/17 (82.4%)	[redacted]	23/34 (67.6%)
Median age, months (range)[c]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Not reported
Walking unassisted[d]	[redacted]	[redacted]	[redacted]	[redacted]	3/17 (17.7%)	[redacted]	3/34 (8.8%)
Median age, months (range)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Not reported

[a] Bayley Scales gross motor subtest item #22: "Child sits alone without support for at least 5 seconds" used for STR1VE-US (not centrally reviewed/confirmed). [redacted]. "Sits alone <10 seconds" for START (centrally reviewed/video-confirmed). All patients in the 'sitting < 10 seconds' category were able to sit for at least 5 seconds.

[b] Bayley Scales gross motor subtest item #26: "Child sits alone without support for at least 30 seconds" used for both STR1VE-US and START (centrally reviewed/confirmed for both).

[c] [redacted]

[d] Bayley Scales gross motor subtest item #43 "Child takes at least 5 steps independently, displaying coordination and balance" used for STR1VE-US. Gross Motor Checklist: "takes independent steps" and the Motor Milestone Development Survey 'walks independently' used for START (centrally reviewed/video-confirmed for both).

4.3.5 Summary of clinical effectiveness

All patients in Cohort 2 of START were alive and without permanent ventilation 24 months after dosing with onasemnogene. In STR1VE-US, one patient died at age 7.8 months and the parents of a second patient withdrew consent at age 11.9 months, at which time the patient required ≥16 hours of non-invasive BiPAP ventilator support for ≥14 consecutive days. In the natural history studies of SMA type 1, 50 to 70% of those assessed were reported to have died or be in need of PAV at 13–14 months of follow up. Median OS was around 12 and 14 months in NeuroNext and PNCR, respectively, and was not reached in the BSC arm of ENDEAR. The ERG notes that OS for BSC is likely to be overestimated in the three natural history studies compared with UK clinical practice because they were mostly conducted in the USA where tracheostomy, which can keep patients alive for several years, is more commonly used than in the UK.

Without treatment, infants with SMA type 1 rarely develop motor skills. After receiving onasemnogene, START and STR1VE-US report a large proportion of infants achieve major motor milestones, with events being confirmed by video and central review. The ERG notes that the time points of assessment differed between the studies, with START reporting results at 24 months after dosing with onasemnogene, and STR1VE-US presenting data captured at 18 months of age for each patient. In Cohort 2 of START, 91.7% of patients were able to hold their head erect without support for ≥3 seconds and sit with support, 75% were able to sit alone for ≥30 seconds, 16.7% of were able to walk alone. In LT-001, the follow-up study to START, at the 31 December 2019 data cut, all enrolled patients were reported to have maintained their achieved motor milestones, with [redacted] patients gaining new motor milestones during follow-up.

In STR1VE-US, by 18 months of age, 86.4% of patients achieved motor milestone(s), confirmed by independent central video review. At baseline, two patients were able to hold their heads erect, and, after receiving onasemnogene, an additional 17 (85.0%) patients were able to hold their head erect. Other achievements included 13 patients being capable of turning from back to side, and 14 patients being able to sit alone without support for ≥30 seconds (Bayley definition) and for ≥10 seconds (WHO definition). For the 14 (63.6%) achieving the milestone of independent sitting for ≥30 seconds, the median age at which the milestone was first attained was 12.6 months (range 9.2 to 18.6 months).

In START, the company reports that five patients (41.7%) in Cohort 2 required the use of temporary, reversible, invasive ventilatory support during the study. No patient in START needed PAV, although chronic non-invasive ventilatory support (BiPAP) was required by five patients in Cohort 2 at the 13.6 month data cut, which increased to six patients (50.0%) at the 24 month data cut: two patients in Cohort 2 required ventilatory support at baseline. Five of the Cohort 2 patients who required ventilatory support with BiPAP have entered LT-001 and as of the 31 December 2019 data cut were still requiring chronic

non-invasive ventilatory support. In STR1VE-US, at the end of study visit, 18 (81.8%) patients from the enrolled cohort remained independent of ventilatory support (as assessed by Trilogy BiPAP data; p<0.0001). Three (31.9%) patients required temporary non-invasive ventilatory support during STR1VE-US. One patient met the definition for permanent, non-invasive or invasive ventilatory support (as assessed by the Trilogy BiPAP data), with the patient reaching 11.0 months of age before requiring ventilatory support.

In START, at baseline, 53.3% of patients across Cohort 1 and Cohort 2 required non-oral feeding support. At 13.6 months of age, 60% of patients required non-oral feeding support, including all three patients in Cohort 1 and six patients in Cohort 2. Although the proportion of patients in Cohort 2 who fed exclusively by mouth decreased from 58% at baseline to 50% at 24 months post-onasemnogene administration, the proportion of patients able to safely swallow to allow for at least partial oral feeding increased from 58% at baseline to 92% at the end of the follow-up period.

At study enrolment, all patients in STR1VE-US were able to swallow thin liquids and none required feeding support. Seven patients (31.8%) received non-oral feeding support at some point during the study, with four requiring only intermittent or transient [redacted] feeding support during the study. At the end of study visit, 19 patients (86.3%) were feeding without mechanical support. Of the three patients requiring feeding support at the end of study visit, two had gastrostomy-tube placement and one patient, who subsequently died, had [redacted] feeding support that was ongoing at the time death.

The ability of patients treated with onasemnogene to speak was not formally assessed as part of START. However, according to clinical observations, 11 (92%) patients in Cohort 2 of START had developed the ability to speak at 24 months post-dosing.

All patients involved in SPR1NT, both cohorts, were alive and free of permanent ventilation at their last study visit prior to the 31 December 2019 data cut. Despite the short follow up and immature data in SPR1NT, motor milestone achievements seem consistent with normal, age-appropriate development, potentially demonstrating the benefit of early treatment, but longer term data will be required to substantiate the promise of early treatment. Additionally, because SPR1NT enrolled patients before symptoms manifested, it must be borne in mind that the type of SMA a patient would have gone on to develop is unknown. To be eligible for SPR1NT, patients could have two or three copies of SMN2, and therefore a proportion, the size of which cannot be reliably predicted, is likely to develop types of SMA other than type 1.

To provide clinical inputs for the cost-effectiveness analysis of onasemnogene, the company pooled data from the completed START (N=12) and STR1VE-US (N=22) studies. The pooled dataset was generated by totalling the number of events per milestone (e.g., sitting independently and walking

independently) in each 6-month follow-up period, to correspond with the 6 monthly cycle implemented in the economic model. The comparison of onasemnogene with BSC informing the economic model is an unanchored, naïve comparison, as no adjustment has been made for differences (known or unknown) in study populations or differences in study effects. Although the ERG noted some differences in baseline characteristics for START and STR1VE-US compared with the studies informing BSC, given the small sample size, the ERG considers that adjusting for known prognostic indicators, as well as potential confounders, could potentially reduce the effective sample size without necessarily increasing precision or accuracy of the results. Thus, the ERG considers the unadjusted results the best available evidence to inform the decision problem, at this time.

In terms of the impact of differences in outcome assessment between START Cohort 2 and STR1VE-US on the pooled analysis, a disparity between the studies applied in the pooled analysis was the time threshold for independent sitting, which was sitting alone for ≥30 seconds for STR1VE-US compared with sitting alone for ≥5 seconds for START. Applying a threshold of ≥30 seconds independent sitting in START resulted in the omission of two patients from the analysis, compared with the use of the ≥5 second threshold. The company considers the loss of two patients from the independent sitting analysis to result in a pessimistic model because the two patients, who remain in the non-sitting health state in the requested scenario, went on to [redacted]. Overall, the ERG considers the pooled analysis to be appropriate for decision-making, with consideration of the highlighted caveat around threshold for independent sitting.

As of the latest data available across the four studies, 100 patients had received an IV infusion of onasemnogene, with 97 administered the recommended therapeutic dose of onasemnogene. Of the 97 patients who received the therapeutic dose, 96 (99%) experienced at least one treatment-emergent adverse event (TEAE) and 56 (58%) were reported to have a TEAE considered by the investigator to be related to onasemnogene. The most frequently reported TEAEs and considered related to onasemnogene (therapeutic dose) across START, STR1VE-US, STR1VE-EU, and SPR1NT included increase in level of transaminases, increase in level of aspartate aminotransferase, and increase in level of alanine aminotransferase.

The ERG's clinical experts commented that development of scoliosis in patients with SMA is an important outcome and thus the ERG requested, during clarification, that the company provide data on occurrence of scoliosis, which was captured as an AE. Across START, STR1VE-US, STR1VE-EU and

SPR1NT, 13 (11.3%) patients have been recorded as experiencing a scoliosis TEAE, with only one patient reported as having scoliosis at baseline. The company reported that a second patient from START also had scoliosis at baseline but is presumed to have had surgery as there is no record of the patient as having a scoliosis TEAE during follow-up. In general, the occurrence of scoliosis and kyphoscoliosis is low across the studies, but, as highlighted by the ERG's clinical experts, the duration of follow-up is also short in terms of capturing the development of scoliosis.

The only results for hospitalisation provided by the company were derived from START. At the final assessment, 13 (86.7%) of 15 patients experienced at least one hospitalisation during the study, including all three patients in Cohort 1 and 10 (83.3%) patients in Cohort 2. The mean annualised hospitalisation rates were 0.81 hospitalisations/year (standard error [SE] 0.17) for Cohort 1, 2.08 (SE 0.68) for Cohort 2, and 1.83 (SE 0.53) for the full study population. The company compared these results with the hospitalisation rates of patients with SMA type 1 in natural history studies, which have been reported to range from 4.2 hospitalisations/year in a USA-based study published in 2017, to 7.6 hospitalisations/year in the first 3 years of life in a single centre UK study from 2011.

4.4 Conclusions of the clinical effectiveness section

The main evidence sources informing the clinical and cost effectiveness assessment of onasemnogene therapy are for patients with a clinical diagnosis of SMA type 1 in the CS and are the Phase I/II trial START and the Phase III study STR1VE-US. Data are also available from the long-term follow up study LT-001, which is an extension of START. One ongoing study evaluates the use of onasemnogene as a treatment in patients with no symptoms of SMA but identified as having a genetic profile indicative of likely development of SMA type 1 (SPR1NT). The ongoing onasemnogene trials provide some supportive evidence for the clinical effectiveness of onasemnogene, and on the potential additional benefit from early treatment with onasemnogene. However, data from STR1VE-EU and SPR1NT are immature and do not inform the economic model. All onasemnogene studies are of an open-label, single arm design, with all patients receiving a one-time dose of onasemnogene.

START is a single centre trial run in the USA, and STR1VE-US is a multicentre study, also carried out in the USA. Both studies enrolled SMA type 1 patients with two copies of SMN type 2, who are representative of those seen in UK clinical practice. However, the small sample sizes of START and STR1VE-US generate some uncertainty around the results of the studies as baseline characteristics of each patient and single outcome events could have an impact on the absolute results reported for each study. START and STR1VE-US have complete follow-up for all patients but due to the maximum two-year (START) and maximum 18-month (STR1VE-US) follow-up in the trials, there is considerable uncertainty around the long-term development of the patients treated with onasemnogene. The

uncertainty will be resolved to some extent when the follow-up studies LT-001 and LT-002 report results of up to 15 years' follow-up.

To provide clinical inputs for the cost-effectiveness analysis of onasemnogene, the company pooled data from the completed START (N=12) and STR1VE-US (N=22) studies. The pooled dataset was generated by totalling the number of events per milestone (e.g., sitting independently and walking independently) in each 6-month follow-up period, to correspond with the 6 monthly cycle implemented in the economic model. The comparison of onasemnogene with BSC informing the economic model is an unanchored, naïve comparison, as no adjustment has been made for differences (known or unknown) in study populations or differences in study effects. Although the ERG noted some differences in baseline characteristics for START and STR1VE-US compared with the studies informing BSC, given the small sample size, the ERG considers that adjusting for known prognostic indicators, as well as potential confounders, could potentially reduce the effective sample size without necessarily increasing precision or accuracy of the results. Thus, the ERG considers the unadjusted results are the best available evidence to inform the decision problem, at this time.

In terms of impact of differences in outcome assessment between START Cohort 2 and STR1VE-US on the pooled analysis, a disparity between the studies applied in the pooled analysis was the time threshold for independent sitting, which was sitting alone for ≥30 seconds for STR1VE-US compared with sitting alone for ≥5 seconds for START. Applying a threshold of ≥30 seconds independent sitting in START resulted in the omission of two patients from the analysis, compared with the use of the ≥5 second threshold. The company considers the loss of two patients from the independent sitting analysis to result in a pessimistic model because the two patients, who remain in the non-sitting health state in the requested scenario, went on to [redacted]. Overall, the ERG considers the pooled analysis to be appropriate for decision-making, with consideration of the highlighted caveat around threshold for independent sitting.

To enable the comparison between onasemnogene and BSC, the company identified cohorts of patients from the SMA natural history studies PNCR and NeuroNext, for which the company has access to individual patient level data. The natural history studies all have different issues and merits in terms of their comparability with START or STR1VE-US. ENDEAR has the largest sample size (N=41), but especially survival data are limited by the relatively short follow-up in the study (13 months). NeuroNext has a small sample size (N=16) and the less stringent definition of PAV will lead to an

overestimate of EFS in NeuroNext compared with PNCR and ENDEAR, but the likely size or direction of the effect on event-free survival compared with UK clinical practice is unclear. PNCR also has a small sample size (N=23) and, in addition, the study was partly retrospective in design with a potential risk of selection bias and reliance on adequate record-keeping.

4.4.1 Clinical issues

- The sample sizes for the studies informing the efficacy of onasemnogene and BSC are small. Although results from START and STR1VE-US indicate a clear benefit of onasemnogene therapy, the small number of patients available generates some uncertainty around the true magnitude of the benefit compared with BSC; differences between studies in baseline characteristics (such as age at treatment or age at symptom onset) or single outcome events could have a large impact on the results and the small sample sizes mean that the accuracy and precision of the findings could be unstable due to chance events.

- As SPR1NT is evaluating the use of onasemnogene as a treatment before symptoms manifest, it must be borne in mind that the type of SMA a patient would have gone on to develop is unknown. To be eligible for SPR1NT, patients could have two or three copies of SMN2, and therefore a proportion, the size of which cannot be reliably predicted, is likely to develop types of SMA other than type 1.

- Partly due to the small study sample sizes, only naïve comparisons could be made between onasemnogene and BSC; that is, no adjustments were made for differences in patient's baseline characteristics or other factors that may confound the results.

- The natural history studies, PNCR, NeuroNext and ENDEAR enrolled patients either primarily or exclusively in the USA, where tracheostomy is much more commonly used than in the UK for patients with SMA type 1 who need PAV. Higher use of tracheostomy, which can extend life by several years, will lead to overestimation of OS in the natural history studies compared with UK clinical practice, where tracheostomy for children with type 1 SMA is rare.

- Considering longer-term follow-up, in LT-001, no patient has lost motor milestones achieved during START, with a follow-up of 4.4 years. However, no longer-term data is available to inform the likely trajectory of infants with SMA type 1, and so it is unknown whether they may gain further motor function as they grow older, stay at the functional level they have achieved, or if their functional ability may eventually decline.

5 COST EFFECTIVENESS

In August 2019, the company submitted clinical and cost-effectiveness evidence to support the recommendation for onasemnogene abeparvovec, hereafter referred to as onasemnogene, to be used for treatment of infants with spinal muscular atrophy (SMA) type 1. Based on the company's submission, the ERG produced an interim report which reviewed and critiqued the company's evidence and put forth recommendations for structural changes to the model and clinical data, as well as its preferred assumptions for the economic analysis.[65]

In May 2020, the company provided NICE with a supplementary appendix to their original submission and a revised cost-effectiveness analysis for the symptomatic SMA type 1 population which addressed the issues with the model and reflected the all of the ERG's preferred assumptions. As such, the ERG's summary and critique of the company's economic evaluation provided in this report reflects the company's revised base case, including the accepted ERG preferred assumptions, presented in the company's supplementary appendix. Sections 5.1 to 5.4 provides a description and critique of the company's revised evidence as well as updated company base case results. For details on the ERG's original critique and preferred assumptions, please refer to the interim ERG report.

It is important to highlight that in March 2020 the company received a positive opinion from the Committee for Medicinal Products for Human Use (CHMP) for onasemnogene and the proposed indication was widened to include:

- patients with 5q SMA with a bi-allelic mutation in the survival motor neuron (SMN) 1 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 three copies of the SMN2 gene (the pre-symptomatic population).

In the supplementary appendix, only clinical evidence was presented for the pre-symptomatic population, but no cost-effectiveness evidence was provided. In response to clarification questions, the company provided two scenarios (A and B) exploring the cost-effectiveness of onasemnogene for the pre-symptomatic population using the symptomatic SMA type 1 model. Please refer to Section 5.5 for a description, results and critique of the company's scenario analysis for the pre-symptomatic population.

5.1 Summary of the company's base case results

The deterministic and mean probabilistic incremental cost effectiveness ratios (ICERs) for the comparison of onasemnogene and best supportive care (BSC) for treating infants with symptomatic SMA type 1 are presented in Table 27 and Table 28, respectively. These results include the company's

agreed patient access scheme (PAS) for onasemnogene, which provides a discount of [redacted] on the list price.

Table 27. Company's deterministic base case results for onasemnogene versus BSC including PAS discount (adapted from Table 5 of the company PAS submission)

Treatment	Total costs	Total LYs	Total QALYs	Incremental costs	Incremental LYs	Incremental QALYs	ICER (∆£/∆QALY)
BSC	381,131	2.15	0.21	-	-	-	-
Onasemnogene + BSC	[redacted]	15.68	10.21	[redacted]	13.53	10.00	[redacted]

Abbreviations: BSC, best supportive care; ICER, incremental cost-effectiveness ratio; LYs, life years; QALY, quality-adjusted life year.

Table 28. Mean probabilisitic results for onasemnogene versus BSC (results taken by the ERG from the company's economic model)

Treatment	Total costs	Total LYs	Total QALYs	Incremental costs	Incremental LYs	Incremental QALYs	ICER (∆£/∆QALY)
BSC	378,637	2.13	0.22	-	-	-	-
Onasemnogene + BSC	[redacted]	14.44	9.38	[redacted]	12.30	9.16	[redacted]

Abbreviations: BSC, best supportive care; ICER, incremental cost-effectiveness ratio; LYs, life years; QALY, quality-adjusted life year.

5.2 ERG comment on the company's review of cost-effectiveness evidence

The company carried out systematic literature reviews (SLRs) in March 2019 to identify existing cost-effectiveness evidence and health-related quality of life (HRQoL) evidence for onasemnogene and competing interventions for the treatment of SMA types 1 to 3. Both searches included a broader SMA population than the decision problem (SMA type 1) because the motor function milestones included in the economic model rely on inputs from proxy populations (SMA types 2 and 3). As for cost and resource use evidence, the company searched the same sources identified for the cost-effectiveness evidence. A summary of the ERG's critique of the methods implemented by the company to identify relevant evidence is presented in Table 29. Due to time constraints, the ERG was unable to replicate the company's searches and appraisal of identified abstracts.

Table 29. Summary of ERG's critique of the methods implemented by the company to identify health economic evidence

Systematic review step	Section of CS in which methods are reported			ERG assessment of robustness of methods
	HRQoL evidence	Cost-effectiveness evidence	Cost and resource use evidence	
Data sources	Section 1.2 of Appendix 1	Section 1.3 of Appendix 1		Appropriate. Electronic databases included: EMBASE, Medline and EconLit. Other sources for grey literature included: HTA publications (NICE, CADTH, SMC,

				INAHTA, TLV and the Croatian Agency), conference proceedings, NHS EED and Tufts Cost-Effectiveness Analysis Registry. The reference lists of relevant SLRs identified from the reviews, as well as the US ICER's report on SMA therapies were hand-searched to identify any additionally relevant publications not identified by the database searches. Medline (R) In-Process and the Cochrane Library were not considered, but the ERG does not consider this to be an issue given the relevant evidence identified.
Search terms	Section 1.2 of Appendix 1	Section 1.3 of Appendix 1		Appropriate. Study design filters recommended by SIGN and CADTH used to capture economic evidence and HRQoL evidence, respectively.[66, 67] Comprehensive terms used to identify the generic and brand names of relevant interventions.
Inclusion criteria	Table 7 in Section 1.2 of Appendix 1	Table 11 in Section 1.3 of Appendix 1		Appropriate.
Screening	Section 1.1.7 of Appendix 1	Section 1.1.7 of Appendix 1		Appropriate.
Data extraction	Table 19 in Appendix 2	Table 20 in Appendix 2	NR	Appropriate.
QA of included studies	Section 1.2 of Appendix 4 using the Cochrane risk of bias assessment or Newcastle Ottowa QA[37, 40]	Section 1.3 of Appendix 4 using the Newcastle Ottowa QA or Drummond checklist[40, 68]	NR	Inconsistent checklists used for each SLR without justification. The Drummond checklist[68] and CASP checklist (recommended in DSU TSD 9) would be preferred for cost-effectiveness evidence and HRQoL evidence, respectively.

Abbreviations: CADTH, Canadian Agency for Drugs and Technologies in Health; CASP, Critical Appraisal Skills Programme; CS, company submission; DSU, Decision Support Unit; ERG, Evidence Review Group; HRQoL, health-related quality of life; HTA, health technology assessment; INAHTA, HTA Database of the International Network of Agencies for Health Technology Assessment; NHS EED, National Health Service Economic Evaluation Database; NR, not reported; QA, quality assessment; SIGN, Scottish Intercollegiate Guidelines Network; SLR, systematic literature review; SMC Scottish Medicines Consortium TLV, Swedish Dental and Pharmaceutical Benefits Agency; TSD, Technical Support Document

The electronic database searches for cost-effectiveness evidence (Embase, Medline and EconLit) identified a total of 1,067 citations after de-duplication. After title/abstract screening, 119 publications were selected for full-text review. Of those, a total of nine publications were identified for inclusion. An additional six HTA publications (including two non-English language publications) were identified for inclusion via hand searches of the grey literature. Of the 15 included studies, eight were partial economic evaluations (e.g. cost-of-illness analyses and budget impact analyses) and seven were full

economic evaluations (e.g. cost-effectiveness analyses and cost-utility analyses). None of the included studies were explicitly used to inform the economic model. However, the ERG considers it important to note that The US Institute for Clinical and Economic Review's (US ICER) final report, (hereafter referred to as the US ICER) [69] which assessed the comparative clinical effectiveness and value of onasemnogene and nusinersen for SMA, was not formally included, primarily because it was published after the date on which the SLRs were conducted. Moreover, as mentioned throughout Section 5.3, the US ICER's approach to modelling was considered throughout the development of the company's *de novo* economic model.

The electronic database searches for HRQoL evidence (Embase and Medline) identified a total of 395 citations after de-duplication. After title/abstract screening, 68 publications were selected for full-text review. Of those, a total of seven publications were identified for inclusion. An additional four publications were identified for inclusion via hand searches of the grey literature. As described in Section 5.3.8, the company used one of the included publications (Thompson *et al.* 2017[70]) to inform the base case analysis.

Post-submission of the company's supplementary appendix (May 2020), the company finalised the update to the SLR. For the update, the company expanded the search for natural history studies by including search terms for SMA types 1 to 3, rather than restricting to SMA type 1 only. In the updated SLR, an additional 11 natural history studies, eight utility studies, six cost studies and seven economic evaluations (including the US ICER report) were identified. However, none of the new studies were used to update the analysis as the company state insufficient detail on methods and outcomes were provided. For further detail on the updated SLR, please refer to the response to question C5 in the company clarification response (July 2020).

5.3 Summary and critique of the company's submitted economic evaluation by the ERG

5.3.1 NICE reference case checklist

Table 30 summarises the ERG's appraisal of the company's economic evaluation against the requirements set out in the NICE reference case checklist for the base case analysis, with reference to the NICE scope outlined in Section 3.

Table 30. NICE reference checklist

Attribute	Reference case	Does the *de novo* economic evaluation match the reference case?
Decision problem	The final scope developed by NICE	Yes, for the symptomatic SMA type 1 population. Pre-symptomatic population may be broader.
Comparator(s)	Alternative therapies routinely used in the NHS	Yes, the company included best supportive care.

Perspective costs	NHS and Personal Social Services	Yes.
Perspective benefits	All health effects on individuals	Yes.
Form of economic evaluation	Cost-utility analysis	Yes.
Time horizon	Sufficient to capture differences in costs and outcomes	Yes.
Synthesis of evidence on outcomes	Systematic review	Yes.
Outcome measure	Quality adjusted life years	Yes.
Health states for QALY	Described using a standardised and validated instrument	Partially. For health states D and E, utilities are based on parent-parent proxy values using the EQ-5-3L. For health states A and B, utility values are based on general population EQ-5D-3L data. For health states C, utility value is based on clinical expert opinion.
Benefit valuation	Time-trade off or standard gamble	Yes time-trade off.
Source of preference data for valuation of changes in HRQoL	Representative sample of the public	Yes.
Discount rate	An annual rate of 3.5% on both costs and health effects	Yes.
Equity	An additional QALY has the same weight regardless of the other characteristics of the individuals receiving the health benefit	Yes.
Sensitivity analysis	Probabilistic sensitivity analysis	Yes.
Abbreviations used in the table: CS, company submission; EQ-5D, EuroQoL-5 Dimensions; ERG, Evidence Review Group; HRQoL, health-related quality of life; NHS, National Health Service; NICE, National Institute for Health and Care Excellence; QALY, quality-adjusted life year.		

5.3.2 Population

The marketing authorisation for onasemnogene includes infants with symptomatic SMA type 1 and the pre-symptomatic population and reflects the updated NICE final scope (see Section 3.1 for more details).[1] However, the patient population considered in the economic model is infants with symptomatic SMA type 1. For more information on the pre-symptomatic population, please refer to Section 5.5.

Based on the patient characteristics of the main clinical trials for onasemnogene in the symptomatic SMA type 1 population (START and STR1VE-US), the modelled 5q13 SMA type 1 population is further defined to include patients with two copies of the SMN2 gene and age of six months or less at the time of gene replacement therapy.

The ERG consulted its clinical experts, who consider that the modelled population is reflective of those patients who would be eligible to receive onasemnogene in the National Health Service (NHS). Overall,

the ERG considers the modelled population to be reflective of the SMA type 1 population in the updated NICE final scope and of the symptomatic SMA type 1 population in England but does not reflect the pre-symptomatic population (see Section 5.5 for more details).[1]

5.3.3 Interventions and comparators

The intervention and comparator considered in the economic analysis is onasemnogene and BSC, respectively, in line with the NICE final scope.[1] Nusinersen was also included in the original NICE final scope, as it was approved for routine commissioning in England (July 2019) via a managed access agreement for use in all patients with 5q SMA (pre-symptomatic SMA, or SMA types 1, 2 or 3). However, nusinersen is not yet considered established standard of care and has therefore been removed from the updated NICE final scope.[1] Therefore, nusinersen is not a comparator of interest for this appraisal and any comparison with onasemnogene provided in the supplementary appendix and economic model (indirect treatment comparison and cost-effectiveness results) will not be described or critiqued further in this report by the ERG.

Onasemnogene is a one-time, single intravenous (IV) treatment. A dose of onasemnogene for the IV infusion is calculated based on patient weight and is received at a dose of 1.1 x 10^{14} vg/kg, with the infusion lasting approximately 60 minutes. This is reflective of the dose received by cohort 2 in the completed phase I/IIa single arm study of onasemnogene, START and the completed phase III single arm study of onasemnogene, STR1VE-US. In START, cohort 2 was given a therapeutic dose of onasemnogene of 2.0 x 10^{14} vg/kg. However, upon further analysis the company determined that the actual dose received by patients was 1.1 x 10^{14} vg/kg. A dose of 1.1 x 10^{14} vg/kg has been used for all phase III trials of onasemnogene.

The cost of onasemnogene is a one-off cost regardless of the size of the dose administered, thus calculation of dose size based on patient weight is not included in the model. Patient eligibility for treatment with onasemnogene is based on a patient's level of adeno-associated virus subtype 9 (AAV9) antibodies (anti-AAV9 titres ≤1:50) and was an exclusion criterion for the START and STR1VE-US trials. The company have indicated that AAV9 testing will be funded and coordinated by AveXis.

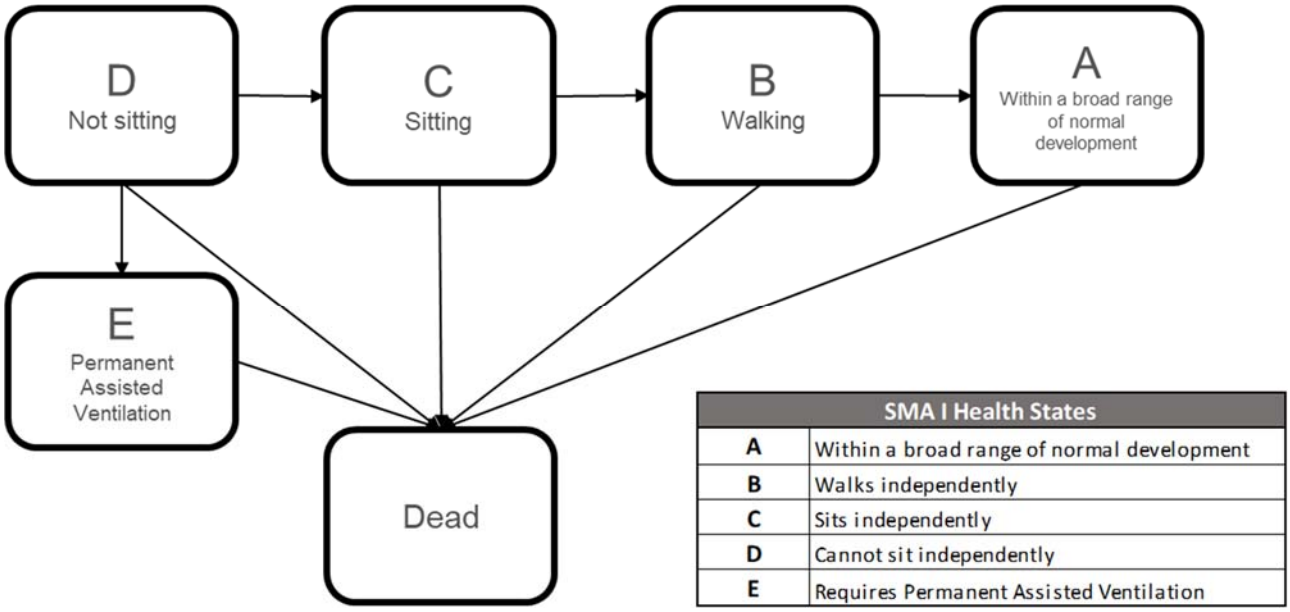
The comparator (BSC) comprises standard respiratory, gastrointestinal and nutritional care delivered by a multidisciplinary team, which the ERG considers appropriate based on consultations with clinical experts.

5.3.4 Modelling approach and model structure

A single *de novo* economic model was developed in Microsoft© Excel to assess the cost-effectiveness of onasemnogene compared with BSC for treating patients with symptomatic SMA type 1. The structure of the model is a six-state Markov chain, with the health states reflective of motor function milestones

achieved, need for permanent ventilation and death. Furthermore, the model is sub-divided into two time horizons; a short-term (three years) model informed by clinical study data and a long-term (lifetime) extrapolation model. Please refer to Section 5.3.5 for further detail on the clinical data and extrapolations informing the economic model. Figure 10 presents the model schematic.

Figure 10.Model schematic (adapted from Figure 34 in the supplementary appendix to the CS)



The health states D (not sitting) and E (permanent assisted ventilation [PAV]) reflect the natural history of patients with SMA type 1. For patients treated with onasemnogene, transitions to higher functioning health states C (sitting), B (walking) and A (within a broad range of normal development) are possible. The company have stated that within each of the health states the likely associated symptoms and complications of SMA are captured, outlined in Table 31.

Table 31. Associated symptoms and complications of SMA by model health state (Table 45 of the supplementary appendix to the CS)

Health state	Motor features	Additional features
A	Within a broad range of normal development	• Within a broad range of normal development
B	Walks unassisted	• No breathing difficulties • Number and severity of chest infections similar to a typically developing child of the same age • Does not require a feeding tube – few difficulties swallowing, is able to eat and, for instance, swallow water • Talking ability similar to that of a typically developing child of the same age
C	Sits unassisted	• May have breathing problems and sometimes require NIV • Development of chest infections more frequently than a typically developing child of the same age • Some difficulties with eating and swallowing but able to swallow thin liquids and take some food by mouth • Risk of choking

		• Temporary placement of a gastric tube may be required • Requires help moving • Can talk, but ability to speak will deteriorate over time
D	Not sitting	• Experiences breathing problems and requires regular NIV for a number of hours every night or during the day • Development of chest infections more frequently than a typically developing child of the same age • Difficulties feeding and swallowing • High risk of choking • Only able to swallow thick fluids • Fed by a feeding tube (gastrostomy) surgically placed directly into the stomach • Requires moving regularly to prevent sores • Unable to talk, but can make sounds and cry
E	Permanent assisted ventilation	• Require 24-hour non-invasive ventilation • May require a tracheostomy if NIV is not working well • Require gastrostomy to be surgically placed directly into the stomach due to difficulty feeding and swallowing • High risk of choking • Require moving regularly to prevent sores • Develop chest infections more often than healthy children of the same age • Unable to talk, but can make sounds and cry
Abbreviations: NIV, non-invasive ventilation		

All patients enter the short-term model in the D state. At the end of every model cycle (up to three years), patients can remain in their current health state, transition to higher functioning health states (C and B) if they have achieved motor function milestones or transition to the E state if their health is deteriorating. From any health state, patients can also transition to the death state. It should be noted that patients can only transition to the E state from the D state and no backward transitions from higher functioning health states are permitted. For example, if a patient is able to sit independently (thus residing in the C state), they cannot experience a decline in motor function and move to the not sitting health state (D state) or permanent assisted ventilation (E state).

In STR1VE-US, one patient went on to permanent ventilation and one patient died, thus in the short-term model for patients treated with onasemnogene, transitions from the D state to the E state and D to death were modelled. It should be noted that in START, no patients went on to permanent ventilation or died. Please refer to Section 5.3.5 and 5.3.6 for further information on clinical inputs used in the economic model.

At the end of the short-term model, if patients are in the C state, they remain there until death. For patients in the B state, it was assumed that if they are able to walk independently before the age of 2 (which 2 patients in START and 1 patient in STR1VE-US achieved), then at the age of 5 these patients transitioned to the A state. Patients in the D state could still transition to the E state, but not to any of the higher functioning health states. The company assumed for the base case, that once a patient

achieved a motor function milestone, they would not regress to lower functioning health states. However, in a scenario analysis the company explored motor function milestone loss.

Other motor function milestones such as head control, rolling, crawling and standing were considered by the company, but due to lack of data, could not be modelled as explicit health states. Interim milestones that may be achieved as a result of treatment with onasemnogene, such as improvements in motor function milestones, speech and non-verbal communication, and fine motor skills were accounted for by the company through use of on-treatment utilities applied to patients residing in the D or C health states.

The cycle length used in the short-term model is 6 months, which is reflective of the assessment timepoints in START. Follow-up assessment timepoints in STR1VE-US were monthly. Annual cycles were used for the long-term model. Half cycle correction was applied in the model. The perspective of the analysis is based on the UK national health service (NHS), with costs and benefits discounted using a rate of 3.5% as per the NICE reference case.[71]

The company state that the structure of the model was informed by consultations with clinical experts as well as drawing upon the framework used by the US ICER for the cost-effectiveness analysis of nusinersen and onasemnogene for SMA (hereafter referred to as the US ICER model).[69]

5.3.4.1 ERG critique

The ERG considers the cycle length employed in the short-term model (6 months) and long-term model (12 months), with half-cycle correction are appropriate and reflective follow up timepoints used in START, which were longer than the monthly assessments performed in STR1VE-US. Furthermore, the time horizon and structure of the company's model is appropriate and is largely similar to that employed for the US ICER model, which was developed by the University of Sheffield Modelling Group.[69] Based on discussions with clinical experts, the ERG considers the health states and transitions between health states included in the model are clinically relevant and capture the most important changes in the health state of a patient, allowing for robust estimates of costs and benefits to be calculated for each arm of the model.

In the economic model, the company have assumed no differences in costs and utilities between the A and B state. As such, the purpose of the A state is solely for the estimation of patient flow in the model, which the ERG considers appropriate.

The company acknowledge, and the ERG's clinical experts agree, that interim milestones such as head control, rolling, crawling and standing are clinically important and will have an impact on quality of life as they will allow a patient to look around and explore their environment, if achieved. As such, the ERG considers the use of on-treatment utility values to account for intra-health state benefits that cannot

be captured as explicit health states is appropriate. Please refer to Section 5.3.8 for further details of the on-treatment utilities included the economic model.

The assumption of no loss of motor function once gained (i.e. no backward transitions to lower functioning health states) was a simplifying assumption made by the company as they stated data from completed and ongoing clinical trials of onasemnogene (in particular, the interim results of the follow-up study to START, LT-001) demonstrate that treated patients suffered no loss of motor function milestones. However, long-term data are not available and as such there is uncertainty about the duration of effect of onasemnogene. Please refer to Section 5.3.5.1 for further details on this issue.

5.3.5 Treatment effectiveness

Estimates of treatment effectiveness in the short-term model are based on pooled motor milestone data from the START and STR1VE-US trials. In START and STR1VE-US, the primary efficacy endpoints were event-free survival (EFS) and overall survival (OS). Please refer to Section 5.3.6 for definitions and further information on EFS and OS used in the model. Motor milestone achievement was a secondary efficacy endpoint in START and in STR1VE-US, independent sitting for ≥30 seconds was a co-primary endpoint and other motor milestone achievements were included as exploratory efficacy endpoints.

Confirmation of motor milestone achievement in START and STR1VE-US was based on video recordings of the CHOP-INTEND, Bayley Scales, submitted home videos and physical examinations sent to an independent central reviewer. The CHOP-INTEND and Bayley Scales were assessed monthly until 12 months post-dose and then quarterly until end of study. Development Milestones/Gross Motor Skills Checklist at physical therapy assessments were assessed every six months.

Table 32 presents the proportions of patients in the pooled START and STR1VE-US dataset achieving observed motor milestones and the company's assumption of one additional independent sitter and one additional independent walker, discussed below.

Table 32. Observed motor milestones in the pooled START and STR1VE-US dataset including assumption of one additional sitter and one additional walker (adapted from Table 49, Company's supplementary appendix)

Model cycle	Age at end of cycle (months)	Not sitting (D state)		Sitting (C state)		Walking (B state)	
		n	%	n	%	n	%
1	6	34	100.0%	0	0.0%	0	0.0%
2	12	24	75.0%	8	25.0%	0	0.0%
3	18	13	40.6%	18	56.3%	1	3.1%
4	24	9	28.1%	20	62.5%	3	9.4%
5	30	6	18.8%	22	68.8%	4	12.5%

Data were pooled by summing the number of patients attaining a motor milestone in the same cycle from each trial. Due to the small patient numbers in each trial, sophisticated methods for adjusting and pooling the data were not feasible. However, a key difference between the trials is the follow-up period. In START, patients were followed up to 24 months post-dose (approximately 30 months of age), whereas in STR1VE-US, patients were followed up to 18 months of age. The company highlighted that it is clinically plausible for some patients between 18 and 30 months of age in STR1VE-US to attain higher functioning motor milestones and have assumed for the pooled dataset that there will be one additional independent sitter and one additional independent walker, added to the last cycle of the short-term model (patient age of 30-36 months).

The company verified their assumption with an internal clinical expert steering committee, who concluded that motor milestone achievement at 18 months of age in STR1VE-US is not indicative of final outcomes for these patients, though long-term follow up data is required to support this. To further validate the assumption of an additional independent sitter and independent walker in the pooled dataset, the company analysed the data of the non-sitters and non-walkers from STR1VE-US to anticipate which patients potentially could achieve a higher functioning motor milestone. The company found that one non-sitter ([redacted]) had a CHOP-INTEND score of 58, which was above the mean score of 52 for patients at the visit where they were observed to be sitting independently for more than 30 seconds. Furthermore, the same non-sitter ([redacted]) was treated with onasemnogene at less than two months of age, which the company highlight is linked to better outcomes, and achieved interim milestones of head control and rolls from back to side. One non-walker ([redacted]) was also treated with onasemnogene at less than two months of age and one non-sitter ([redacted]) achieved interim milestones of head control and rolls from back to side.

Finally, the company looked at the median age of motor milestone attainment in START to assess the likelihood that patients will achieve higher functioning motor milestones after the follow-up period in STR1VE-US. In START, two patients were independent walkers and the company state the median age for independent walking in the trial was 17.1 months (range: 8.0 - 30.8 months). The median age for independent sitting in START was 19.3 months (range: 18.9 - 19.6 months), compared with 12.6 months (range: 9.2 - 18.6 months) in STR1VE-US. However, it should be noted that the threshold for sitting unassisted in START was ≥5 seconds (item 22 on the Bayley-III scale), but in STR1VE-US, the threshold used was sitting unassisted for ≥30 seconds (item 26 on the Bayley-III scale).

The company used the pooled motor milestone data from START and STR1VE-US, including the assumed additional sitter and walker, to calculate the proportion of onasemnogene patients transitioning to higher functioning health states in the short-term model. The calculation for the proportion of patients moving to a higher functioning health state was number of new patients achieving the motor milestone at the start of each cycle divided by the number of patients in the outgoing health state in the previous

cycle. The company stated that an "offset" approach is used to calculate the percentage of patients moving into higher functioning health states, such that motor milestones achieved during a model cycle are accounted for in the following model cycle. Thus, for the first year of the short-term model, all patients in the onasemnogene arm remain in the D (not sitting) health state.

Table 33 presents the "offset" proportion of patients in each cycle achieving observed motor milestones, including the assumption of one additional independent sitter and one additional independent walker, and the proportion of patients transitioning from the D to C state and the C to B state. As mentioned previously, the company added the additional sitter and walker to the last cycle of the short-term model. Furthermore, the company assumed that at the end of the short-term model, motor milestones achieved by patients will be sustained until death. The only exception to this assumption is for patients in the B state (walking). All patients in the B state (n=4) were transitioned to the A state (within a broad range of normal development) at 5 years of age. This was because patients observed to be walking in START and STR1VE-US did so by 2 years of age, which is deemed reflective of normal development as per the World Health Organisation (WHO) reported windows of motor milestone achievement in healthy children.[72] However, the B to A transitions only affect patient flow, as costs and utilities are equal for the B and A health states.

Table 33. "Offset" motor milestones and transition proportions per cycle used in the economic model (adapted from Table 49 and 53 of the company's supplementary appendix)

Model cycle	Age at end of cycle (months)	Not sitting (D state)			Sitting (C state)			Walking (B state)	
		n	%	D to C	n	%	C to B	n	%
1	6	34	100.0%	0.00%	0	0.0%	0.00%	0	0.0%
2	12	32	100.0%	0.00%	0	0.0%	0.00%	0	0.0%
3	18	24	75.0%	25.00%	8	25.0%	0.00%	0	0.0%
4	24	13	40.6%	45.83%	18	56.3%	12.50%	1	3.1%
5	30	9	28.1%	30.77%	20	62.5%	11.11%	3	9.4%
6	36	6	18.8%	33.33%	22	68.8%	5.00%	4	12.5%

For the BSC arm of the model, no patients achieve any motor milestones based on observed data from natural history studies.[30-34] Thus, BSC patients can only transition from the D state to the E state (PAV) or death, based on EFS and OS data discussed in Section 5.3.6.

5.3.5.1 ERG critique

The ERG considers that treatment effectiveness for onasemnogene using pooled data on motor milestone achievement directly from START and STR1VE-US is appropriate and aligns with published economic models for SMA type 1.[21, 69] Furthermore, the company's "offset" approach to estimating the proportion of patients moving to higher functioning health states in the short-term model is both reasonable and conservative.

The ERG consulted its clinical experts with regards to motor milestone achievement for BSC patients, who agreed that without treatment, patients would not be expected in achieve any motor milestones, but instead will experience a decline in their health status. Thus, it is reasonable that patients in the BSC arm of the model cannot transition to higher functioning health states.

Overall, the company's approach to pooling the motor milestone data from START and STR1VE-US is reasonable. The ERG and its clinical experts consider that baseline characteristics of patients in both trials are comparable. However, there are two key differences between the trials that affect motor milestone status: the follow-up of the trials and the definition of independent sitting used in each trial. In START, follow-up was for 24 months post dose (30 months of age) and the threshold for sitting unassisted was for ≥5 seconds (item 22 on the Bayley-III scale). In contrast, follow-up in STR1VE-US was up until 18 months of age and the threshold for sitting unassisted was ≥30 seconds (item 26 on the Bayley-III scale).

As mentioned previously, the company included an assumption of one additional independent sitter and one independent walker in the pooled motor milestone data to balance the difference in follow-up between the two trials. The company based their assumption on an analysis of motor milestone data in START and STR1VE-US, as well as clinical expert opinion, described earlier. The ERG consulted its clinical experts on the company's assumption, and they considered it to be reasonable to assume that there will be additional motor milestones achieved after 18 months of age but recognise there is no robust data to confirm this. One clinical expert suggested that the assumption of an additional walker between 18 and 30 months is strong. The company provided several scenarios exploring different assumptions of additional sitters and walkers to the pooled data, as well as a scenario using only observed data, presented in Section 5.4.2. Based on the ERG's clinical experts view, the two scenarios of relevance are the assumption of only an additional sitter (no addition walker) and only observed motor milestones for the pooled dataset, these scenarios increased the base case ICER of [redacted] to [redacted] and [redacted], respectively.

The ERG considers that, even though the company has provided extensive justifications for the assumption of an additional independent sitter and independent walker to the pooled dataset, there is no evidence that this would be achieved for the STR1VE-US patients between 18 and 30 months as the study has reached the planned period of follow-up for the last patient. A conservative approach would be to considered the cost-effectiveness of onasemnogene based on the available evidence and thus the ERG prefers the removal of the additional independent sitter and independent walker to the pooled dataset and explores this in its preferred base case assumptions in Section 6.3.

The ERG was also concerned about the different definitions used for the assessment of independent sitting in the START and STR1VE-US. In particular, the definition used for sitting in START (sitting

unassisted for ≥5 seconds) was too short to be clinically different from the D state (not sitting health state). The ERG's clinical experts stated that a threshold of sitting unassisted for ≥30 seconds or more (item 26 on the Bayley-III scale) is a more clinically relevant measurement to show treatment benefit with onasemnogene.

During the clarification stage, the ERG requested the company to perform a scenario adjusting the pooled data so that patients transitioning from the D to C state are based on the definition of sitting unassisted for ≥30 seconds as per STR1VE-US and the ERG's clinical experts' opinion. The company performed the analysis but stated that the higher threshold meant two patients no longer contribute to the C state in the short-term model and remain in the D state entering the long-term model. The company considers the scenario pessimistic as data for the two patients in the follow up study to START (LT-001) demonstrate both patients achieve the milestone of sitting unassisted for ≥30 seconds or more, however this has not been video confirmed. Nonetheless, the company supplied results of the scenario, including the base case assumption of an additional sitter and walker, which increased the ICER from [redacted] to [redacted].

The ERG performed two additional scenarios around the company's scenario of using the threshold of sitting unassisted for ≥30 seconds or more for the pooled data, removing the assumption of an addition walker and using only observed motor milestones for the pooled dataset. When using only observed motor milestones and the ≥30 seconds or more threshold, the ICER increased to [redacted] and when only removing the additional walker from the company's scenario, the ICER was [redacted]. The results of these two scenarios are presented in Section 6.2. The ERG considers that amending the threshold for sitting independently to ≥30 seconds or more is more clinically meaningful, however as it has been demonstrated in the follow up study to START (LT-001) that the two patients who would have been excluded go on to achieve the higher threshold of sitting, it may be appropriate to maintain the threshold to ≥5 seconds or more, which all the sitters in STR1VE-US achieved by nature of achieving the ≥30 seconds or more threshold.

The above scenarios are important, as they relate to the company's assumption of motor milestone achievement being sustained until death. At the end of the short-term model, patients in higher function health states are assumed to remain there until death. Thus, patients cannot regress, but also cannot progress. Considering the data from START for a higher threshold of sitting unassisted for ≥30 seconds or more was not achieved for two patients until later in the LT-001 follow up study, albeit unconfirmed, and no patients have lost motor milestones, this could be considered a conservative assumption.

In the original company submission, the company performed a scenario exploring motor milestone loss, as it is recognised there are no long-term data to suggest that patients will maintain or improve their

achieved motor skills over the duration of their life. The motor milestone loss scenario resulted in an increase in the list price ICER of approximately £45,000. However, an update to this scenario based on the revised analysis submitted with the supplementary appendix was not provided. The ERG does not consider this to be a substantial omission given that there is potential for patients to continue to achieve motor milestones (whether interim or beyond defined thresholds). Furthermore, as there is no robust long-term data for the treatment effect in either direction, the ERG views exploring motor milestone loss with caution as until long-term follow up data are available, it can be considered potentially conservative and prefers the company's base case assumption of no change in milestone status in the long-term model.

5.3.6 Overall survival and event-free survival

Company's approach to survival analysis of Kaplan-Meier data for overall and ventilation-free survival

Extrapolations of the Kaplan-Meier (KM) data for OS and EFS were performed using standard parametric survival distributions (exponential, Weibull, Gompertz, log-normal, log-logistic and generalised gamma). The company used the R software package, 'flexsurv' and published methods to perform reconstructions of individual patient data (IPD) and fit parametric distributions to the KM data.[73, 74]

The process of curve selection recommended in the NICE decision support unit technical support document (DSU TSD) 14[75] was implemented by the company to select an appropriate distribution for the extrapolation of OS and EFS. The company assessed the fit of each modelled curve against the observed KM data using statistical goodness of fit statistics, including Akaike information criterion (AIC) and Bayesian information criterion (BIC) statistics and visual inspection of the distributions. Table 34 presents an overview of the base-case data sources and survival functions informing each of the health states of the model for each treatment arm.

Table 34. Summary of data sources and survival functions used in the company base-case analyses for the short and long-term model for both arms of the model

Health State	Onasemnogene		Best supportive care	
	Short-term	Long-term	Short-term	Long-term
E - OS	Extrapolation of PAV patient mortality (Gregoretti *et al*. 2013[76]) using the exponential distribution.			
D - EFS	Kaplan-Meier data from START and STR1VE-US	Extrapolation of NeuroNext data using Weibull distribution	Kaplan-Meier data from NeuroNext	Extrapolation of NeuroNext data using Weibull distribution
D - OS	Kaplan-Meier data from START and STR1VE-US	Extrapolation of Kaplan-Meier data from NeuroNext,	Kaplan-Meier data from NeuroNext	Extrapolation of NeuroNext adjusted

		adjusted to censor patients on PAV, using Weibull distribution	adjusted to censor patients on PAV	data using Weibull distribution
C - OS	Kaplan-Meier data from START and STR1VE-US	SMA type 2 mortality (Zerres *et* al. 1997[77]) extrapolated using generalised gamma distribution	No patients were assumed to achieve this motor milestone	
B & A - OS	Kaplan-Meier data from START and STR1VE-US	General population mortality (ONS life tables 2014-2016[78])	No patients were assumed to achieve this motor milestone	
Abbreviations: EFS, event-free survival; ONS, Office of National Statistics; OS, overall survival; PAV, permanent assisted ventilation.				

Health State D – Not sitting

For the short-term model EFS and OS KM data were used directly to inform the D state for both arms of the model. In the onasemnogene arm, pooled EFS and OS KM data from START and STR1VE-US were used. In START, EFS was defined as time from birth to either (a) requirement of ≥16-hour respiratory assistance per day (includes bi-level positive airway pressure [BiPAP]) continuously for ≥2 weeks in the absence of an acute reversible illness, excluding perioperative ventilation or (b) death. In STR1VE-US, EFS was defined as avoidance of either (a) death or (b) permanent ventilation, at 14 months. The definition of permanent ventilation in STR1VE-US was as follows: tracheostomy or the requirement of ≥16 hours of respiratory assistance per day (via non-invasive ventilatory support) for ≥14 consecutive days in the absence of an acute reversible illness, excluding perioperative ventilation.

The follow-up period in STR1VE-US was up to 18 months of age, which is shorter than in START (24-months follow-up post dose). As such the company censored all STR1VE-US patients from the pooled KM data after 18 months. Furthermore, in STR1VE-US, one patient died and one patient went on to received PAV and these events are captured in the pooled data.

The BSC arm was informed using EFS and OS KM data from the natural history study, NeuroNext.[30, 31] Please refer to Section 10.5.2 for further information on NeuroNext. In NeuroNext, EFS was defined as alive without tracheostomy. OS data from NeuroNext included patients who were alive and on PAV. As such, the company adjusted/disaggregated their analysis of KM OS data from NeuroNext to censor patients at the point in time which they receive PAV. The company state that this approach allows as much of the OS data as possible to be used in the calculations.

For the long-term model, EFS and OS informing the D state for both arms of the model were based on extrapolations of EFS and disaggregated OS data from NeuroNext using standard parametric survival distributions (exponential, Weibull, Gompertz, log-normal, log-logistic and generalised gamma).

None of the assessed distributions had a good fit to the observed KM data for EFS and OS. However, the generalised gamma had the best statistical fit according to AIC/BIC statistics but a clinically implausible long tail in the extrapolation. Please refer to Table 59 and Table 60 of the company supplementary appendix for AIC/BIC statistics.

In the original submission, the company selected the generalised gamma distribution for the base case but truncated the survival curve to zero at 4 years of age to avoid implausibly long survival. However, in the supplementary appendix the company revised its base case and implemented the Weibull distribution for both EFS and OS (Figure 11 and Figure 12) based on the preferred ERG analysis presented in the interim ERG report.

The Weibull distribution was considered to be a more plausible extrapolation by the ERG as it naturally declined down to the company's original truncation point of four years (~6% at year three), compared with the generalised gamma. The truncation of the EFS and OS curves to four years has been maintained for the revised base case, but by implementing the Weibull distribution the impact of the assumption has been substantially reduced, as can be seen in Figure 11 and Figure 12. It should be noted that the Weibull distribution has a unique feature, allowing it to accommodate the accelerated failure time (AFT) assumption, which means there is a multiplicative effect with respect to survival time. Given the nature of SMA type 1, this assumption can be considered appropriate.

Figure 11. Event-free survival for the D state based on NeuroNext (taken from the economic model)

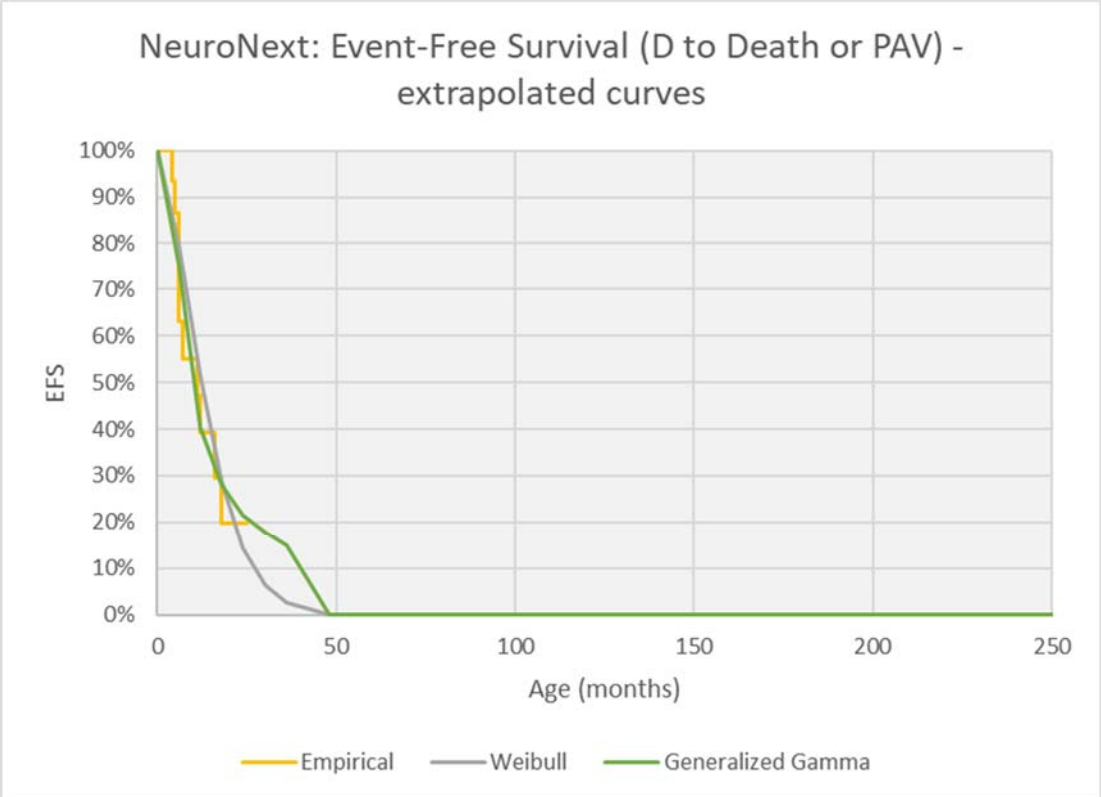
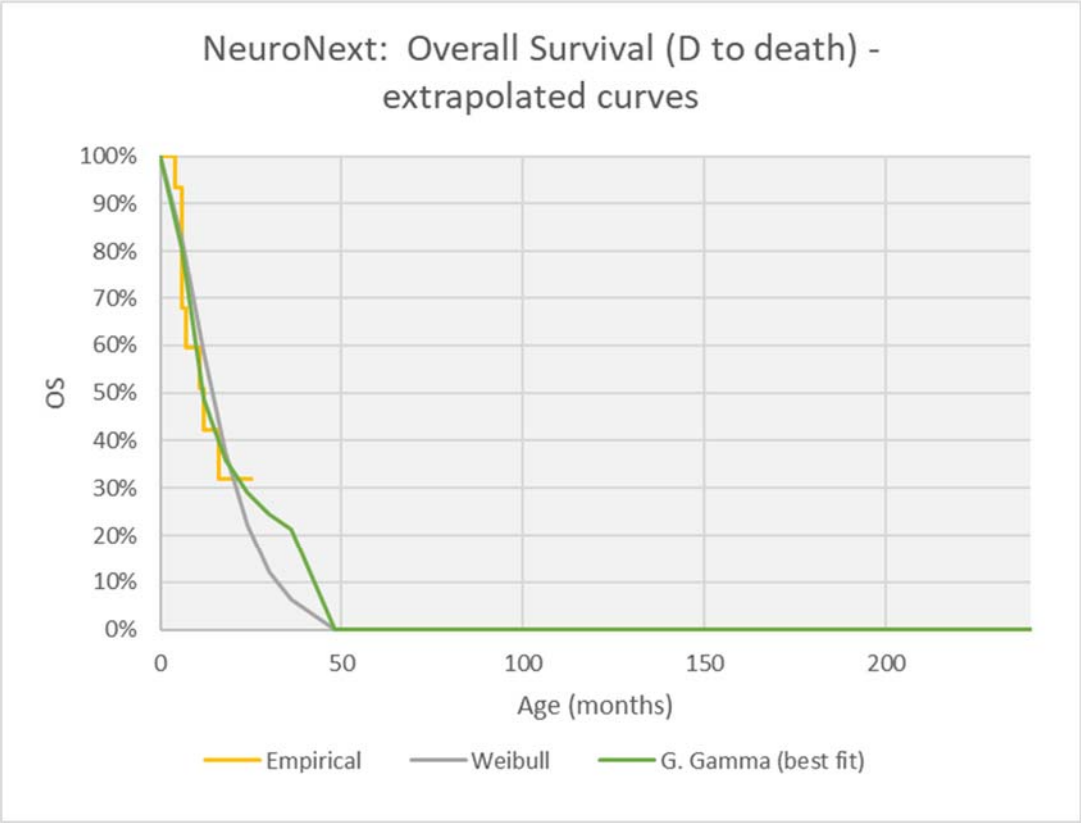


Figure 12. Adjusted overall survival for the D state based on NeuroNext (taken from the economic model)



Based on the selected survival distributions for EFS and OS, per cycle transition probabilities (most notably for the D state to the Death state) were calculated using the following, published function:[79]

$$Tp(t_u) = 1 - S(t)/S(t-u)$$

Health state E – Permanent assisted ventilation

The proportion of patients occupying the E state is calculated based on the difference between D state transitions probabilities for EFS and transition probabilities for OS based on aggregated KM data from NeuroNext, extrapolated using the Weibull distribution. Aggregated OS from NeuroNext includes all patients alive (irrespective of whether they are on PAV or not) and censoring only occurred when patients were lost to follow-up.

Per cycle transition probabilities from the D state to the E state were calculated using the following function:

$$TP_{PAV} = TP_{EFS} - TP_{OS}$$

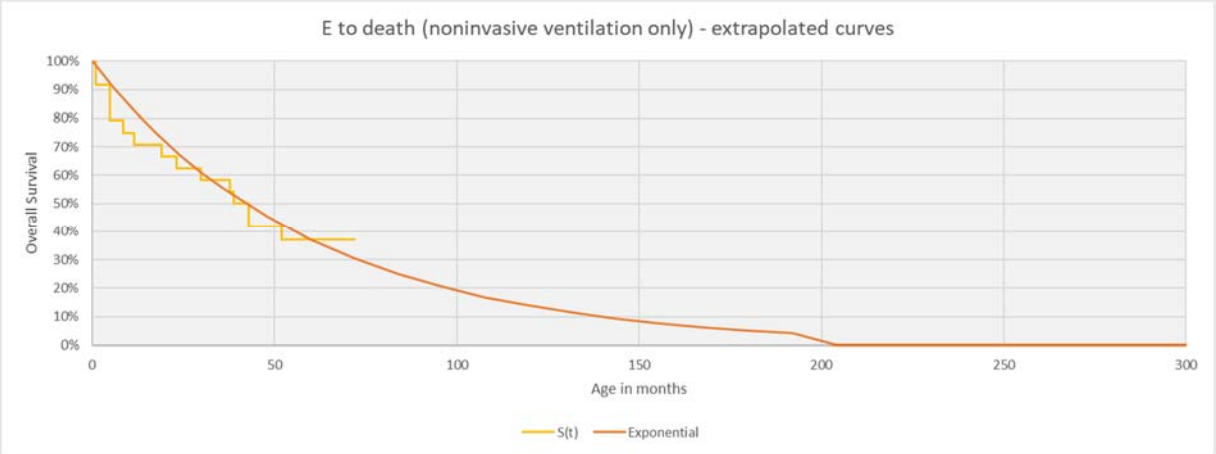
To estimate long-term survival for patients who are on PAV, OS KM data for SMA type 1 patients requiring PAV are derived from a study by Gregoretti *et al*. 2013.[76] The study was a retrospective chart

review of 194 SMA type 1 patients in Italy, which estimated long-term survival for three cohorts of patients; no treatment (NT arm, n=121), non-respiratory aid (NRA arm, n=31) or tracheostomy and invasive mechanical ventilation (TV arm, n=42).[76] In the NRA cohort, seven patients went on to receive tracheostomy, but it is not clear whether or not these patients are included in the study's survival estimates. Nonetheless, if tracheostomy patients are included in the NRA survival estimates, this would result in a proportion of 22.6% (7/31).

In line with the methodology adopted in the US ICER report and based on the preferred analysis put forth in the interim ERG report, the company used the NRA cohort to inform OS for the E state. The NRA cohort was deemed suitable for use in the model as the proportion of patients receiving tracheostomy is similar to UK clinical practice. The company state in their original clarification response that in the UK, based on published information, the proportion of patients on tracheostomy is between 13%–16%.[80, 81] Furthermore, the ERG's clinical experts explained that in the UK, clinicians tend to advise parents of patients not to opt for full time invasive ventilation and instead choose non-invasive ventilation as palliative care. This is because survival for patients with tracheostomy is substantially extended, with no change in physical symptoms nor any progression in motor milestones.

Standard parametric survival distributions (exponential, Weibull, Gompertz, log-normal, log-logistic and generalised gamma) were used to extrapolate the NRA KM OS data. Based on the AIC/BIC statistics and visual inspection of the extrapolations, the company chose the exponential distribution, presented in Figure 13. Please refer to Table 58 of the company's supplementary appendix for AIC/BIC statistics. Due to plateaus in all the extrapolations, the company truncated OS to zero at 16 years. As cycles in the long-term model are annual, the truncation to zero takes effect from year 17 onwards.

Figure 13. Overall survival for the E state based on Gregoretti *et al*. 2013[76] (taken from the economic model)



The company used the extrapolation of the NRA KM OS data for both the short and long-term model and stated this was to avoid overfitting the model to the study population observed in Gregoretti *et al*.

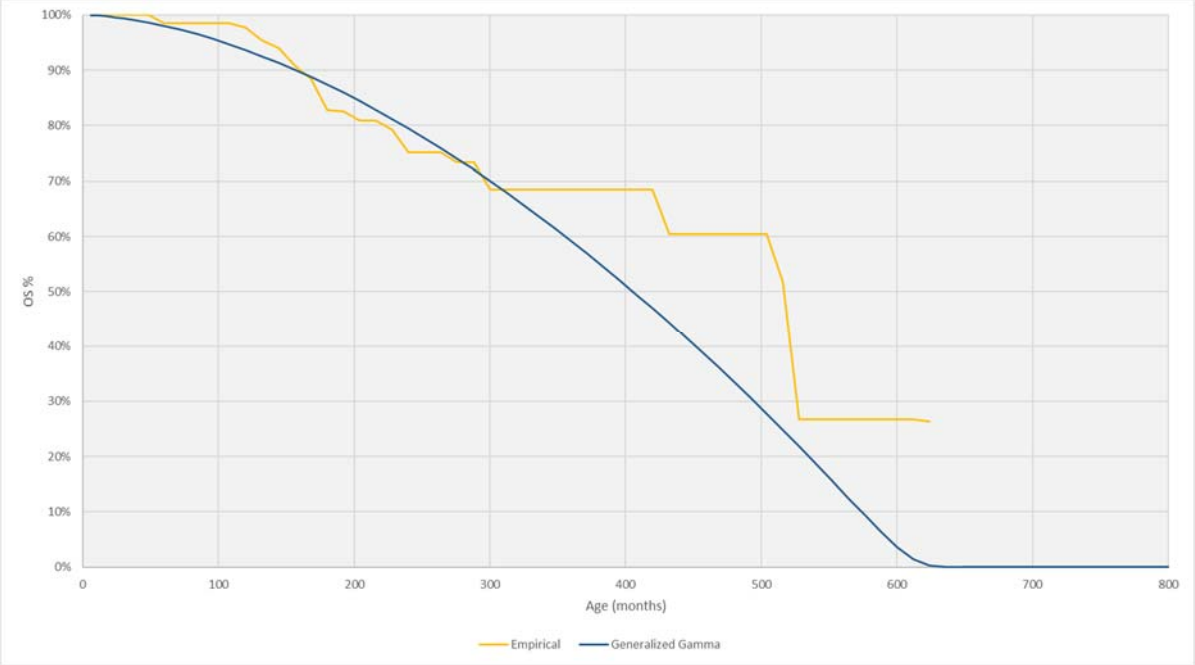
2013 and to ensure transition probabilities remained relatively constant over time. Furthermore, OS for the E state is the same for both the onasemnogene and BSC arms of the model.

Health state C – Sitting

In lieu of any long-term data for SMA type 1 patients who are able to sit unassisted for ≥ 5 seconds or more, the company assumed that OS will be similar to that of SMA type 2 patients. Long-term KM OS data for the C state was derived from Zerres *et al*. 1997,[77] which was a 52-year prospective and retrospective genetic study of SMA type 2 patients.

Standard parametric survival distributions (exponential, Weibull, Gompertz, log-normal, log-logistic and generalised gamma) were used to extrapolate the KM OS data digitised from the Zerres *et al*. 1997[77] publication. Based on the AIC/BIC statistics and visual inspection of the extrapolations, the company chose the generalised gamma distribution. Please refer to Table 61 of the company's supplementary appendix for AIC/BIC statistics. No truncation was applied to the selected survival curve. Furthermore, the extrapolated survival curve is used only for the long-term model. Based on data from START and STR1VE-US, no patients who achieved the ability to sit unassisted died and as such, 100% survival for the C stated is assumed for the short-term model. Figure 14 presents the OS curve used to model the C state.

Figure 14. Overall survival for the C state based on Zerres *et al*. 1997[77] (adapted from Figure 42 of the company's supplementary appendix)

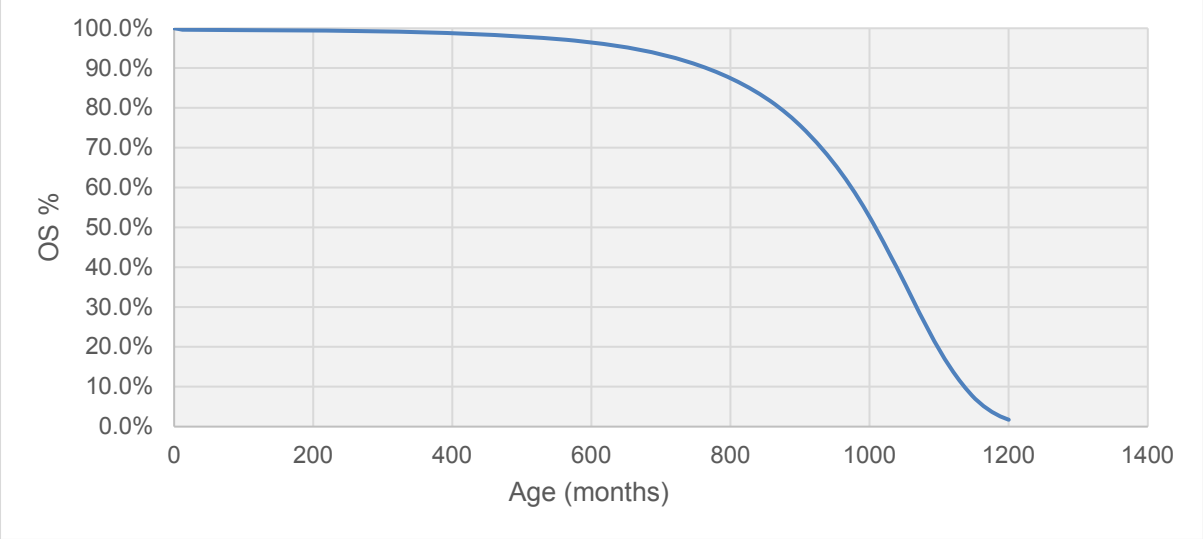


Health State B and A – Walking and within a broad range of normal development

For the base-case analysis, the company assumed that patients who could walk unassisted followed the natural history of SMA type 3 patients in terms of OS, which they state is not significantly different to that of the general population, based on a study by Zerres *et al*. 1997.[77]

As such, OS for both the A state (within a broad range of normal development) and the B state for the long-term models is based on UK life tables for 2014-16,[78] presented in Figure 15. For the short-term model, OS is 100% to reflect that no patients who are able to walk died in START or STR1VE-US.

Figure 15. Overall survival for the B and A state (Figure 44 of the company's supplementary appendix)



5.3.6.1 ERG critique

Modelling of OS for all the health states and EFS for the D state in both the short- and long-term model is considered appropriate by the ERG.

The ERG consulted its clinical experts on whether it is reasonable to assume that if a symptomatic SMA type 1 patient gains the ability to walk they would have the same mortality as healthy individual and if patients who are able to sit would have the same mortality as SMA type 2 patients. The ERG's clinical experts agreed that it is not unreasonable for SMA type 2 patients to be a proxy for SMA type 1 patients who are able to sit independently. Furthermore, the ERG's clinical experts agreed that it is reasonable to assume general population mortality for a patient who is able to walk and would develop normally. However, the clinical experts did highlight that there are no long-term data to suggest this would be the case and that these patients would still have some health problems associated with SMA.

The OS modelling used in the base case for states B and C is reflective of the approach used in the US ICER model. In the US ICER model, data from START were used directly for the short-term model as no one died in the trial, thus no patients were subject to a mortality risk. As such, the ERG preferred this assumption for the C, B and A states for the ERG analysis in the interim ERG report and this has been adopted by the company for its revised base case using the pooled data from START and STR1VE-US.

After interrogation of the various natural history datasets presented by the company for the modelling of EFS and OS for the BSC D state and the long-term modelling of the D state for the onasemnogene arm (NeuroNext, PNCR, ENDEAR sham control and De Sanctis *et al*. 2016), the ERG is satisfied with the company's choice of NeuroNext for the base-case analysis.[30, 32, 34] Ideally, the ERG would have preferred to use PNCR, as the definition of PAV more closely matches that of START and STR1VE-US and the cohort size in PNCR is larger (n=23) than NeuroNext (n=16). However, the OS data for PNCR are immature and the extrapolations produced by the company were considered clinically implausible. For example, at 30 months of age, over 60% of patients are alive and not on PAV, which is inconsistent with the ERG's clinical experts who advised that patients on BSC would be unlikely to live beyond on two years. Conversely, data for NeuroNext are mature and as such the extrapolations of the data are likely to be more robust. However, the definition of PAV in NeuroNext was intubation only, thus potentially underestimating the number of patients that go on to PAV and positively impacting the analysis of BSC. For further detail on the natural history datasets, please refer to Section 4.2.4.

Due to the way the model is constructed, changing the selection of distribution for the OS curve changes the selection of the EFS curve to match. Thus, the ERG's preference for the Weibull distribution for OS, means the same distribution is used for EFS. The ERG attempted to adjust the model to separate out the curve selections for the two parameters but found that separate selections lead to crossing of the curves and found it challenging to implement a cap on EFS based on OS as the model calls upon several worksheets and formulas, making it difficult to adjust the source data. Upon investigation of the Weibull distribution for EFS, the ERG considers that, pragmatically, it is not unreasonable to use this distribution, as it also has a natural decline to zero.

5.3.7 Adverse events

Adverse events (AEs) are not included in the economic model as the company state it is difficult to separate out AEs due to treatment from complications associated with SMA itself, which are accounted for in health state costs and utilities.

In the supplementary appendix, it is reported that in cohort 2 of START, 3 out of 12 patients (25%) experienced an AE that was related to treatment with onasemnogene. In STR1VE-US, 12 patients

(54.5%) experienced an AE that was related to treatment with onasemnogene. The most common treatment emergent adverse events (TEAEs) related to treatment with onasemnogene were increased transaminases and increased aspartate aminotransferase. Furthermore, to manage possible increases in liver transaminases, reflective of liver inflammation, all patients are required to receive prophylactic oral prednisolone 24 hours prior to treatment with onasemnogene.

The company state that in START all AEs related to treatment resolved within the study period and based on the clinical study report for STR1VE-US, AEs related to treatment also resolved within the study period. As such, the company did not include separate disutilities in the economic model. In addition, the company state that prophylactic treatment with prednisolone incurs minimal costs and are also not included in the economic model.

It should be noted that in STR1VE-US, one patient died ([redacted]) due to a TEAE of respiratory arrest and one patient ([redacted]) discontinued from the study due to a TEAE of respiratory distress.

5.3.7.1 ERG critique

Based on the company's justification, the ERG considers the exclusion of AEs from the economic model to be reasonable. The ERG expects that because AEs related to treatment resolved within the observation period, the impact on the ICER from not the modelling associated costs and utilities will be non-substantial. Furthermore, the ERG's clinical experts considered that because prophylactic prednisolone is recommended before treatment with onasemnogene, it is unlikely that AEs related to treatment observed in START will be observed in clinical practice.

5.3.8 Health-related quality of life

Health-related quality of life (HRQoL) data were not collected in any of the onasemnogene trials for SMA type 1, the nusinersen SMA type 1 trials (CS3A, ENDEAR or SHINE[32, 82, 83]) and the SMA type 1 natural history studies identified in the clinical effectiveness SLR (PNCR, NeuroNext and Finkel 2014b[31, 33, 39, 42]). As described in Section 5.3, the company also performed a SLR to identify HRQoL evidence for onasemnogene and competing interventions for the treatment of SMA types 1 to 3 and a total of 11 publications were included in this. One of these publications (Thompson *et al.* 2017[70]) was used to inform the recent US ICER assessment of SMA therapies.[69] However, the US ICER's final report itself was not formally included in the SLR as a standalone HRQoL study, primarily because it was published after the date on which the SLR was conducted.

Prior to the publication of the US ICER report, the company also undertook a *de novo* UK utilities elicitation study to capture robust utility values to populate the economic model.[84] Further details of the UK utilities elicitation report are given in Section 10.7. Nonetheless, the company chose to use health state utility values (HSUVs) derived from the US ICER report and incorporated the ERG's preferred

assumption for the E state to inform the economic model.[65, 69] A description of the utility data included in the company's economic model is provided in Table 35. Disutilities associated with adverse events were not included in the company's model or US ICER assessment and the company justified this approach stating the difficulty in separating utilities due to treatment from the complications associated with SMA, which are already accounted for in the HSUVs.

Table 35. HSUVs used in the base case cost-effectiveness analysis

Health state	Description	Utility value	Reference
E	PAV	0	Assumption based on the ERG interim report
D	Not sitting - BSC	0.19	Thompson *et al.* 2017[70]
	Not sitting - onasemnogene	0.29	Thompson et al. 2017[70] and on treatment utility of 0.1 as per US ICER report[69]
C	Sits unassisted - BSC	0.60	Tappenden *et al.* 2018[85]
	Sits unassisted - onasemnogene	0.65	Tappenden *et al.* 2018[85] and on treatment utility of 0.05 as per US ICER report[69]
B	Walks unassisted	General population	Ara and Brazier 2010[86]
A	Broad range of normal development		
Abbreviations: HSUV, health state utility value; PAV, permanent assisted ventilation			

Based on the AveXis UK utilities elicitation study, the clinical advisory board estimated that utilities for the E state (PAV) would be lower than the D state. Furthermore, the ERG's clinical experts advised that patients could have a HRQoL considered worse than death and as such, the ERG recommended utility for the E state should be set to zero, which the company implemented for its base case analysis.

To account for the impact on a patient's quality of life of achieving interim milestones, such as fine motor skills (head control, rolling, crawling and standing), speech and non-verbal communication with onasemnogene treatment, the company included on-treatment utility benefits. Additional utilities of 0.1 and 0.05 compared to BSC were included in the D state (non-sitting) and C state (sits unassisted), respectively.

For health states A (broad range of normal development) and B (walks unassisted), general population utility values were applied, and the company justified this approach because walking unassisted by 2 years of age is reflective of normal development, as per the WHO reported windows of motor milestone achievement in healthy children.[87] The company applied annual age-related utility values to health states A and B using the following equation reported by Ara and Brazier 2010:[86]

$$\text{utility (EQ-5D)} = 0.9508566 + (0.0212126 \times \text{male}) - (0.0002587 \times \text{age}) - (0.0000332 \times \text{age}^2)$$

The male coefficient (0.417) was sourced from the patients enrolled in Cohort 2 of START. The proportion of males in the pooled analysis is 44.1%. It is not clear why male coefficient for the pooled

analysis was not used in the base case analysis, but the company ran a scenario using the pooled estimate and it had minimal impact on the ICER.

The company provided several justifications for following the approach taken in the US ICER report and adopting the ERG preferred assumptions:[69]

- Firstly, they were considered most appropriate by the US ICER independent assessment group and the ERG.
- Secondly, except for health state C, HRQoL is measured using NICE's preferred measure (EQ-5D).[71]
- Thirdly, health state D uses parent-proxy assessments and the NICE reference case states when it is not possible to obtain measurements of HRQoL directly from patients, data should be obtained from the person who acts as their carer (typically parents in the case of SMA type 1).
- Finally, the utility values in the US ICER study were considered plausible by the company's UK clinical advisory board (May 2019).[88]

The company explored alterative HRQoL data and assumptions in scenario analyses, which included the following:

- AveXis UK utilities elicitation study.[84]
- Alternative values from the SLR:
    - Utility values from CHERISH: PedsQL mapped to EQ-5D-Y (Thompson et al. 2017[70]),
    - Clinician-proxy Case Vignette EQ-5D-Y (Lloyd et al. 2017[89]),
    - Parent-proxy EQ-5D-3L, UK reports only (Thompson et al. 2017[70]).
- Caregiver disutilities.

Please see Appendix 10.7 for a detailed description of each scenario.

5.3.8.1 ERG critique

The difficulties of exploring subjective HRQoL in infants with SMA type 1 means that obtaining utilities, which are truly reflective of the patient experience and aspects of the condition that most affect patients' HRQoL is problematic. However, the ERG considers that the company base case assumptions

are appropriate, and they have provided extensive scenario analyses that cover a range of plausible scenarios.

In their original evidence submission, the company presented various scenarios around utilities which are unchanged in the revised supplementary appendix. The ERG has concerns with the company's scenario which incorporates caregiver HRQoL and further critique on this issue can be found in Appendix 10.7.1.

5.3.9 Resources and costs

Onasemnogene is administered as a single, peripheral, intravenous (IV) infusion, over 60 minutes, at a dose of $1.1x10^{14}$ vg/kg. This is reflective of the dose included in the draft summary of product characteristics (SmPC) and the dose received by patients included in the STR1VE-US, STR1VE-EU, SPR1NT and START (Cohort 2) studies. The European Medicines Agency (EMA) process is ongoing at the time of writing, therefore, the final marketing authorisation is pending. However, in March 2020, onasemnogene received a positive CHMP opinion and the proposed indication includes infants with the SMA type 1 and the pre-symptomatic population.

The list price of onasemnogene is £1,795,000 per dose. The company has included a patient access scheme (PAS) simple discount on the list price for onasemnogene of [redacted]. Infants will require a test for the AAV9 antibody prior to treatment with onasemnogene, which will be funded and coordinated by AveXis at a central European lab (Viroclinics, The Netherlands). The exact requirements of AAV9 antibody testing are subject to the final SmPC.

According to the company's clinical experts', the one-time IV infusion with onasemnogene will also require one pre-infusion visit at a secondary/tertiary neuromuscular centre followed by a two-night, three-day elective stay at a highly specialised infusion centre. To capture these costs in the economic model, the company applied an administration cost of £2,803. This was based on elective inpatient costs associated with nervous system disorders in NHS Reference Costs 2018/19.[90] As a scenario analysis, the company explored using an administration cost that was ten times greater (£28,030), presented in Section 5.4.2.

The acquisition and administration costs associated with onasemnogene are summarised in Table 36.

Table 36. Costs per treatment/patient associated with onasemnogene with PAS (adapted from Table 67 of the supplementary appendix)

Items	Cost	Source
Price of the technology per treatment/patient	[redacted]	List price with PAS applied
Treatment administration cost	£2,803	NHS Schedule of Reference Costs, 2018/19[90]

		Weighted average of codes relating paediatric nervous system disorders and cerebral degenerations or miscellaneous disorders of nervous system (EL- PR01A-E and EL - AA25C-G)
Total cost per treatment/patient	[redacted]	Calculation
Abbreviations: EL, elective; GBP, Great British Pound; USD, United States Dollars		

Onasemnogene is given in addition to BSC. BSC comprises standard respiratory, gastrointestinal and nutritional care delivered by a multidisciplinary team. BSC alone is also the comparator. The costs associated with BSC are included in the economic model as health state costs.

5.3.9.1 Health state costs

This section outlines how direct health care costs for each health state in the economic model are calculated. Detailed calculations can be found in Appendix 7 of the original company submission. Aligned with the long-term survival estimates in the model, health state costs for states C and B use the estimated costs for SMA types 2 and 3 as proxies, respectively. The company also assumed that patients in the A state incur the same SMA-related health care as patients in the B state, as per the ERG preferred assumptions outlined in the interim ERG report.[65] Furthermore, the same annual costs for a given health state in cycle one persist for the life time horizon of the model. However, as described in Section 5.3.4, the model is sub-divided into two time horizons; a short-term (three years) model that employs semi-annual cycles and a long-term (lifetime) model that employs annual cycles. As such, the company halved the annual health state costs in the short-term model to account for differences in cycle length.

Table 37 provides the annual health state costs included in the company's base case analysis informed by the UK healthcare resource utilisation (HCRU) study[13] conducted by the company and data from Noyes *et al.* 2006[91]. The data obtained from each of these sources is described in turn below. The company considered several scenario analyses replacing the base case health state costs with the 'Real World Evidence (RWE)' costs presented at the third appraisal committee meeting (ACM3) for TA588.[92] The results of the company's scenario analyses are given in Section 5.4.2.

Table 37. Annual health state costs included in the economic model

Cost category	Cost source	SMA type 1		SMA type 2 as proxy	SMA type 3 as proxy
Health state		**E**	**D**	**C**	**B/ A**
Drugs	UK HCRU study [a]	£680	£919	£743	£939
Medical tests	UK HCRU study [b]	£645	£873	£651	£533
Medical visits	UK HCRU study [c]	£3,153	£4,264	£2,509	£2,217
Hospitalisations	UK HCRU study [d] and Noyes *et al.* 2006[91]	£200,247	£63,516	£37,336	£452
GP and Emergency	UK HCRU study [e]	£325	£439	£183	£73
Health material	UK HCRU study [f]	£3,172	£4,027	£2,079	£592
Social services	Noyes *et al*. 2006[91]	£49,994	£27,896	£18,598	£2,952

Total	**£258,216**	**£101,934**	**£62,099**	**£7,759**

Abbreviations: UK HCRU, United Kingdom Healthcare resource utilisation; SMA, spinal muscular atrophy.
The following worksheet references relate to the company's accompanying excel files on UK HCRU cost categories, as explained in Appendix 7 of the CS.
a results from 'pharm.ther'
b results from 'tests' section of 'tests(I)devices(I),surgery', and 'tests(II)devices(II),nutrit'
c results from 'consultations' but minus the 'GP visits' fields
d results from 'data hospitals' but minus 'a&e' field plus 'surgery' results from 'tests(I)devices(I),surgery')
e GP results only from 'consultations' plus 'a&e' field from 'data hospitals
f results from 'devices' section from 'tests(I)devices(I),surgery', and 'tests(II)devices(II),nutrit' plus 'nutrition' section of 'tests(II)devices(II),nutrit'

UK HCRU study

A *de novo* UK HCRU study with 16 UK healthcare professionals (HCPs), was conducted by the company to determine the HCRU costs associated with BSC.[13] Each of the HCPs took part in an individual, in-depth telephone interview. The HCPs were asked to report on resource use (frequency and where relevant, duration) in the 12 months prior to the survey (3 months for pharmacological therapy) for the following components of SMA care: HCP consultations; non-elective hospitalisations and visits to accident and emergency (A&E); respiratory tests and support; nutritional support; surgical interventions; laboratory tests; mobility equipment; and, devices.

The prevalence per resource use was calculated using the total number of patients seen by all interviewed HCPs, per SMA type, as a denominator [redacted] The mean prevalence was based on responses from HCPs who were considered the most likely to use or prescribe a type of resource ('Scenario 3' in the UK HCRU study).

The company used multiple UK sources to obtain the unit costs associated the aforementioned resources. For consultations, hospitalisations and visits to A&E, the main source of unit costs was NHS Reference Costs 2018/19 and the Personal Social Services Research Unit (PSSRU) 2019.[90, 93] For resources related to pharmacological therapy, Prescription Cost Analysis (PCA) England data, 2018 were used.[94] For resources related to laboratory tests, respiratory tests/evaluations, orthopaedic devices, surgeries and respiratory devices, the key additional unit cost sources included: NHS 2018/19 cost collection data, NHS England local tariffs for direct access to orthotic services, the NICE guideline on the assessment and management of motor neurone disease (NG42), published articles and NHS buyer's guides/information leaflets.[95-97]

A summary of the final cost categories reported in the UK HCRU study (consultations; data hospitals; pharmacological therapy; tests (I), devices (I), surgeries; tests (II), devices (II); and, nutrition) is given in Table 64 of the company's supplementary appendix and Table 62 in Appendix 7 of the original company submission. It should be noted that in STR1VE-US, scoliosis was captured as a treatment emergent adverse effect, with 40.9% of children in STR1VE-US developing scoliosis during follow-

up. During the clarification stage, the company confirmed that costs of scoliosis surgery were included in the model based on data obtained in the UK HCRU study. Scoliosis surgery rates of 56.67%, 19.62%, and 3.75% were applied for the D, C, and B states, respectively, according to rates reported in the HCRU study for Scenario 3.

The company removed nusinersen costs from the final estimates of pharmacological therapy because they state that these should be not treated as BSC costs in the economic model. As described in Appendix 7 of the original company submission, the company was required to convert the final UK HCRU study cost categories (used in the company's accompanying Excel files) into model cost categories presented in Table 37.

One limitation noted by the company was that the UK HCRU study did not include specialists who care for ventilator-dependent patients. To address the fact that ventilator-dependent patients are included in the company's model, the company complemented the UK HCRU study with ventilatory support costs from Noyes *et al.* 2006.[91] The types and proportions of ventilatory support considered by the company are given in the subsequent subsection.

Types and proportions of ventilatory support

The company considered three types of ventilatory support in the economic model: tracheostomy, NIV>16 hours/day and NIV<16 hours/day. Patients in the E state receive either tracheostomy or NIV>16 hours/day. To align with the OS modelling for the E state, the company used the proportion of patients on NIV>16 hours/day (77.4%) and tracheostomy (22.6%) in the NRA cohort from Gregoretti *et al*., 2013.[76] Patients in the D, C and B states receive either NIV<16 hours/day or no ventilation. Based on the UK HCRU study, the company estimated that 84%, 56% and 20% of patients in states D, C and B receive NIV<16 hours/day, respectively. As mentioned previously, cost assumptions for the B state were also assumed for the A state for the revised company base case, as the ERG clinical experts stated that there is no long term evidence to suggest that patients who achieve the ability to walk would incur no additional SMA related costs compared to a healthy individual of the same age.[65]

The company sourced the proportion of patients receiving ventilatory support in three settings: home-based; high-dependency; and intensive care, from the company's UK clinical advisory board (May 2019).[88] The proportion of patients requiring each type of ventilatory support, by healthcare setting, for each health state, is summarised in Table 38.

Table 38. Types and proportions of ventilatory support included in the economic model

Health state	Ventilation group		Setting		Weighted results	
	Type	Proportion	Type	Proportion	Ventilation group and setting	Proportion

E	NIV>16	77.4%	Home	70.0%	NIV>16 at home	54.2%
			ITU	15.0%	NIV>16 in ITU	11.6%
			HDU	15.0%	NIV>16 in HDU	11.6%
	Tracheostomy	22.6%	Home	60.0%	Tracheostomy at home	13.6%
			ITU	10.0%	Tracheostomy in ITU	2.3%
			HDU	30.0%	Tracheostomy in HDU	6.8%
D	NIV<16	84.0%	Home	90.0%	NIV<16 at home	75.6%
			ITU	5.0%	NIV<16 in ITU	4.2%
			HDU	5.0%	NIV<16 in HDU	4.2%
	Non-ventilated	16.0%	-	-	Non-ventilated	16.0%
C	NIV<16	56.0%	Home	90.0%	NIV<16 at home	50.4%
			ITU	5.0%	NIV<16 in ITU	2.8%
			HDU	5.0%	NIV<16 in HDU	2.8%
	Non-ventilated	44.0%	-	-	Non-ventilated	44.0%
B/A	NIV<16	20.0%	Home	100.0%	NIV<16 at home	20.0%
	Non-ventilated	80.0%	-	-	Non-ventilated	80.0%

Abbreviations: NIV, non-invasive ventilation; HDU, high dependency unit; ITU, intensive care unit
NIV<16 and NIV>16 = NIV<16 hours/day and NIV>16 hours/day, respectively

Adjustments to costs for ventilator-dependent patients using Noyes et al. 2006[91]

For patients receiving home-based ventilation, the company added the social service costs collected in Noyes *et al.* 2006.[91] The Noyes study reported the annual cost of social care services including NHS community services, primary care service, social services from primary care, nursing/personal care/respite care and other social services. The company inflated those costs from 2002 prices (£51,556) into 2018 prices (£73,800) using the CPI (42.4%). The company assumed tracheostomy at home and NIV >16 hours/day at home for the E state both incur 100% of social service costs while NIV <16 hours/day at home incurs 50% of those social service costs in states D and C, and 20% in state B.

For patients receiving hospital-based ventilation in the high-dependency unit (HDU) or intensive care unit (ITU), the company used hospital-based service costs reported in Noyes *et al*. 2006 to inform the 'hospitalisations' cost category in the model.[91] Once inflated to 2018 prices, the annual cost was £833,592 in the ITU and £415,808 in the HDU. The company assumed hospital-based service costs were dependent on the setting (ITU or HDU) and not the type of ventilation (NIV<16 hours/day, NIV>16 hours/day or tracheostomy).

In summary, the cost categories included in the economic model that account for ventilator-dependent patients include "hospitalisations" and "social services". The "hospitalisations" cost category includes hospitalisation data obtained from the HCRU study (for patients on home-based ventilation and no ventilation) and Noyes *et al.* 2006 study (for patients on hospital-based ventilation).[13, 91] The "social

services" cost category only includes data from Noyes *et al.* 2006 (for patients on hospital-based ventilation). The costs included in "hospitalisations" and "social services" are summarised in Table 39 for each health state.

Table 39. Ventilator-dependent costs included in the economic model

Cost category	Source	SMA type 1		SMA type 2 as proxy	SMA type 3 as proxy
Health state		**E**	**D**	**C**	**B/A**
Hospitalisations[1]	UK HCRU study[13]	NIV>16 at home (54.2% * £12,053) + tracheostomy at home (13.6% * £12,053) **= £8,165**	NIV<16 at home (75.6% * £12,053) + non-ventilated (16% * £12,053) **= £11,041**	NIV<16 at home (50.4% * £2,493) + non-ventilated (44% * £2,493) **= £2,353**	NIV<16 at home (20% * £452) + non-ventilated (80% * £452) **= £452**
	Noyes *et al.* 2006[91]	NIV>16 in ITU (£833,592 * 11.6%) + NIV>16 in HDU (£415,808 * 11.6%) + tracheostomy in ITU (£833,592 * 2.3%) + tracheostomy in HDU (£415,808 * 6.8%) **= £192,082**	NIV<16 in ITU (£833,598 * 4.2%) + NIV<16 in HDU (£415,808 * 4.2%) **= £52,475**	NIV<16 in ITU (£833,598 * 2.8%) + NIV<16 in HDU (£415,808 * 2.8%) **= £34,983**	NA
	UK HCRU study[13] + Noyes *et al*. 2006[91]	**£200,247**	**£63,516**	**£37,336**	**£452**
Social services	Noyes *et al.* 2006[91]	NIV>16 at home (54.2%*£73,800) + tracheostomy at home (13.6*£73,800) **= £49,994**	NIV<16 at home 75.6% * (50%*£73,800) **= £27,896**	NIV<16 at home 50.4% * (50%*£73,800) **= £18,598**	NIV<16 at home 20% * (20% * £73,800) **= £2,952**

Abbreviations: HDU, high dependency unit; ITU, intensive care unit; NA, not applicable; NIV, non-invasive ventilation; SMA, spinal muscular atrophy
NIV<16 and NIV>16 = NIV<16 hours/day and NIV>16 hours/day, respectively
1 Hospitalisation data obtained from the HCRU study includes results from 'data hospitals' but minus 'a&e' field plus 'surgery' results from 'tests(I)devices(I),surgery'.

'Home-based' patient costs

Patients who receive no ventilation incur the costs of care collected in the UK HCRU study alone.[13] The cost categories in the model informed by the UK HCRU study include: drugs; medical tests; medical visits; GP and emergency, health material; and, hospitalisations. Patients who receive home-based ventilation incur the costs of care collected in the UK HCRU study in the aforementioned cost categories, plus the costs of social care collected in Noyes *et al.* 2006.[91] The company weighted the cost categories informed by the UK HCRU study in the model by the proportion of patients who receive home-based ventilation or no ventilation in each health state. For example, in state E, the "medical visits" cost is £3,153. This is from the HCRU cost for medical visits (£4,655) weighted by the proportion of patients in state E who receive home-based ventilation or no ventilation. So, for medical visits, NIV

>16 hours at home equals 54.2% of all E state patients * £4,655 (=£2,523), while tracheostomy at home equals 13.6% of all E state patients * £4,655 (=£630): £2,523 + £630 = £3,153. Zero patients in state E received no ventilation. The company used the same method to calculate the cost for every other cost category and health state.

5.3.9.2 ERG critique

The ERG considers the company's approach to estimate health state costs was overly complex. The company took too many steps to convert resource use in the UK HCRU study into model cost categories.[13] To start with, the company converted the resource use components in the UK HCRU study into UK HCRU study cost categories and then into model cost categories, but this conversion required disaggregating the UK HCRU cost categories into the original resource use components. Therefore, the need for the second step (the UK HCRU cost categories) is questionable. Although the company provided detailed appendices and supporting information on how the conversions were made, the ERG considers that a simpler approach, such as omitting the second conversion step, would increase transparency and the ERG's confidence in manipulations to the data.

Furthermore, with regards to the company's UK HCRU study itself, the company could have designed the study with the model cost categories at the forefront. In addition, instead of considering the granularity from every HCP, the company could have elicited HCP opinion using the SHELF methodology to aggregate judgements on resource use. In short, SHELF requires experts to come together to agree on plausible ranges and come to a 'consensus' judgement on the true value which reduces the impact of outliers.[98]

When the ERG sought clinical expert opinion to verify the company's assumptions, there was a consensus among the experts that it is unreasonable to assume all health state costs are constant (i.e. the same annual costs for a given health state in cycle one persist for the life time horizon of the model). According to the ERG's clinical experts, SMA-related health care would increase with age as the patient's mobility deteriorates. Clinical advisors to the ERG for TA588 also noted that the costs of managing SMA are likely to be dependent on age (this was not captured in the company's models for TA588).[92] In response to the ERG's first round clarification question the company stated their assumption was based on the absence of any evidence that these costs would vary substantially (either up or down) by age. Even so, the company noted that this assumption was important for health states associated with higher life expectancy, such as the C state. Health state C is largely made-up of NIV-related costs and therefore the company acknowledged that changes in the treatment setting (ITU versus HDU versus home-based) of patients receiving NIV over time is likely to be a driver of age-related health state cost variation but concluded that the direction and magnitude of these changes is unknown. Overall, the ERG agrees with the company's rationale and is therefore unable to define and explore a

more plausible scenario. However, any changes that increase the costs of the health states associated with motor milestone achievement, will cause the ICER to increase.

The ERG also sought clinical expert opinion on the patient pathway following onasemnogene. In particular, if they would offer nusinersen as a subsequent treatment to SMA type 1 patients who have received onasemnogene, assuming both treatments are approved for those corresponding indications. Clinical experts advised the ERG that without long-term evidence on subsequent nusinersen use after onasemnogene, they would not consider offering it to treated patients in the NHS. Nonetheless, [redacted] patients started nusinersen in the follow up study to START (LT-001 described in Section 4.3.1.2) and [redacted]. Thus, the potential impact of nusinersen on motor function milestone achievements is partially incorporated in the assumption that there is no motor function milestone loss and therefore costing subsequent nusinersen should be explored. The ERG ran a scenario analysis applying the subsequent nusinersen costs to [redacted] However, the ERG considers it important to caveat this analysis with the fact that LT-001 was conducted in the USA which may overestimate the number of clinical decisions for subsequent nusinersen in the UK. In addition, the calculations do not account for any discontinuation of nusinersen (i.e. received until death) which may not be realistic in clinical practice. The results of this analysis using the list price for nusinersen are presented in Section 6.2. The impact of the subsequent nusinersen scenario on the ICER was large (increasing the base case from [redacted] to [redacted]).

As touched upon in Section 5.3.9.1, the company considered several scenario analyses replacing the health state costs with the RWE costs presented at the third and final ACM for TA588. The costs were assumed as follows: £148,214, £68,322 and £21,765 for type 1, 2 and 3 SMA patients, respectively. For completeness, the ERG also compared the health states costs and sources included in the original CS with the US ICER report and explored these costs in a scenario analysis.[69] The health state costs included in this scenario are presented in Table 40 while the results of the scenario analysis are presented in Section 6.2. A narrative description of the different approaches used to estimate the health state costs is also below.

Table 40. Total health state cost comparison with US ICER

Source	Frequency	Currency	PAV	Not Sitting	Sitting	Walking
Table 4.10 in the US ICER report	Monthly	2017 $	$28,218	$25,517	$6,357	$2,499
	Annual	2017 $	$338,616	$306,204	$76,284	$29,988
	Annual	2017 £*	£266,829	£241,289	£60,112	£23,631

Table 66 of the supplementary appendix	Annual	2018/19 £	£258,216	£101,934	£62,099	£7,759
Abbreviations: PAV, permanent assisted ventilation *A Bank of England exchange rate of 0.788 GBP to the USD (11 June 2019 rate)						

In the US ICER report, the costs specific to PAV were obtained from Noyes *et al.* 2006, which is consistent with the source used to inform PAV-related costs in the company's economic model, but the data taken from Noyes *et al.* 2006 were considerably different.[91] Unfortunately, the ERG was unable to replicate the calculations used to obtain the costs applied in the US ICER report, and in response to the ERG's clarification question, the company was also unable to determine which costs were obtained from Noyes *et al.* 2006 given the limited narrative in the US ICER report. Despite this, the total health state costs associated with the 'PAV' health state are similar in the two assessments and, therefore, the ERG does not consider the different approaches to estimate those costs to be a major issue.

The remaining health state costs in the US ICER report were sourced from a claims analysis of commercial health plans and the ERG considers that the setting and perspective in this source is inappropriate for decision making in a publicly funded health care system and, therefore, agrees with the company's use of alternative sources. Following this, the 'not sitting' health state is associated with a much higher cost in the US ICER report (£241,289) compared to the CS (£101,934). Moreover, the difference in cost between the 'PAV' and 'not sitting' health states was considerably different between the two approaches. The company estimated a health state cost for 'PAV' that was two and a half times greater than 'not sitting', whereas there was a negligible difference in those health state costs in the US ICER report. As such, the ERG sought clinical expert opinion to validate the difference in cost between 'PAV' and 'not sitting'. The ERG's clinical experts noted that it would reasonable to have a 'PAV' cost that is at least two times greater than a 'not sitting' cost due to the high additional costs of 'PAV'. Furthermore, TA588 aggregated 'PAV' and 'not sitting' into an overall SMA type 1 cost and that cost presented in ACM3 for TA588 (£148,214) is a lot closer to the company's estimates than US ICER.[92]

Another discrepancy between the assessments relates to the 'walking' (SMA type 3) health state. The company employed a much lower cost (£7,759) than the ACM3 for TA588 (£21,765) and the US ICER report (£23,631). When the company explored a scenario using the SMA type 3 cost presented at the ACM3 for TA588, the base case ICER increased from [redacted] to [redacted].[92]

Overall, the impact of using US ICER health state costs on the ICER was notable, increasing from [redacted] to [redacted] (see Section 6.2) and this result is similar to the company's scenario using all ACM3 health state costs for TA588 ([redacted]) (see Section 5.4.2).[92]

Aside from the aforementioned key areas of uncertainty, the ERG identified several issues with how costs and resources were implemented in the model that were explored during the first clarification

stage based on the original company submission. These included a justification for why SMA type 2 and 3 patients incur 50% and 20% of the social care costs received by patients with SMA type 1 and an explanation for why nusinersen-specific resource use estimates were taken from the HCRU study. In response to the ERG's clarification questions for the assumption on social care costs, the company confirmed that these estimates were not externally validated and, therefore, the company provided an extreme scenario where all ventilated patients in any health state receive 100% of social care costs. This scenario increased the base case ICER from [redacted] to [redacted]. To address the ERG's concerns that the company included nusinersen-specific resource use estimates from the UK HCRU study (nusinersen was received by 37 of the 49 patients with SMA type 1) in health states E and D, the company provided scenarios where nusinersen-naïve patients incurred costs that were 48.6% greater than nusinersen treated patients, based on the findings by Droege *et al.* 2019.[99] Following this, the ICER decreased from [redacted] to [redacted] or marginally increased to [redacted] depending on the number of cost categories that were adjusted by Droege *et al.* 2019.

5.4 Results included in company's submission

5.4.1 Base case results – symptomatic SMA Type 1 population

The results of the company's base-case analysis for onasemnogene versus BSC are provided in Table 41. These results include the company's agreed patient access scheme (PAS) for onasemnogene, which provides a discount of [redacted] on the list price. According to the company's analysis, onasemnogene is expected to extend patients' lives by around 13 years compared to BSC. This translates to an incremental quality-adjusted life year (QALY) gain for onasemnogene of 10 QALYs, and an incremental cost-effectiveness ratio (ICER) of [redacted] per QALY gained.

Table 41. Company's deterministic base case results for onasemnogene versus BSC including PAS discount (adapted from Table 5 of the company PAS submission)

Treatment	Total costs (£)	Total LYs	Total QALYs	Incremental costs	Incremental LYs	Incremental QALYs	ICER (∆£/∆QALY)
BSC	381,131	2.15	0.21	-	-	-	-
Onasemnogene + BSC	[redacted]	15.68	10.21	[redacted]	13.53	10.00	[redacted]
Abbreviations: BSC, best supportive care; ICER, incremental cost-effectiveness ratio; LYs, life years; QALY, quality-adjusted life year.							

Table 42 and Table 43 show the total QALYs and costs for onasemnogene by health state versus BSC, respectively. Over 90% of the QALY gains for onasemnogene compared with BSC are due to gains in the C and A states. As for costs, the company did not provide a breakdown of cost burden by health state in the supplementary appendix and due to the complexity of the model and paucity of time, the ERG could not produce these results. However, in the company's original submission, the cost burden by health state was provided and is presented in Table 43 and shows the only cost saving health state

for onasemnogene compared with BSC is the E state. Over 70% of the additional costs for onasemnogene compared with BSC are due to patients residing in the C and A states. For the current analysis, the ERG considers the cost burden trends would be the same as the previous analysis.

Table 42. Total QALYs of onasemnogene and BSC by health state (taken from the economic model)

Health state	QALYs onasemnogene	QALYs BSC	Increment
E	0.00	0.00	0.00
D	0.55	0.21	0.34
C	6.99	0.00	6.99
B	0.30	0.00	0.30
A	2.37	0.00	2.37
Total	10.21	0.21	10.0
Abbreviations: BSC, best supportive care; QALYs, quality-adjusted life years			

Table 43. Cost burden of onasemnogene and BSC by health state (discounted at 3.5%) (adapted from Table 92 of the CS, Appendix B)

Health state	Cost burden (%) onasemnogene*	Cost burden (%) BSC	% difference
E	2%	76%	-634%
D	15%	24%	67%
C	68%	0%	100%
B	2%	0%	100%
A	13%	0%	100%
Total	100%	100%	-
Abbreviations: BSC, best supportive care *Since onasemnogene is a one-time, single IV treatment the company allocated the discounted cost of onasemnogene and administration between the health states by the proportion of the total (discounted) life years gained by health state. **percentage difference is based on a comparison of the costs in each health state for onasemnogene vs BSC			

It should be noted that according to the NICE methods guide, "*In cases when treatment restores people who would otherwise die or have a very severely impaired life to full or near full health, and when this is sustained over a very long period (normally at least 30 years), cost-effectiveness analyses are very sensitive to the discount rate used. In this circumstance, analyses that use a non-reference-case discount rate for costs and outcomes may be considered. A discount rate of 1.5% for costs and benefits may be considered by the Appraisal Committee if it is highly likely that, on the basis of the evidence presented, the long-term health benefits are likely to be achieved*". While onasemnogene doesn't restore the majority of treated symptomatic SMA type 1 patients to full or near full health, data from START demonstrates a substantial survival benefit for patients who would have otherwise died. As such, the ERG presents the company base case results using a 1.5% discount rate for costs (including PAS discount) and QALYs for committee consideration in Table 44.

Table 44. Company's base case results for onasemnogene versus BSC with PAS (discounted at 1.5%) (taken from the economic model)

Treatment	Total costs (£)	Total LYs	Total QALYs	Incremental costs (£)	Incremental LYs	Incremental QALYs	ICER (∆£/∆QALY)
BSC	413,269	2.28	0.21	-	-	-	-
Onasemnogene + BSC	[redacted]	22.14	14.88	[redacted]	19.86	14.67	[redacted]

Abbreviations: BSC, best supportive care; ICER, incremental cost-effectiveness ratio; LYs, life years; QALY, quality-adjusted life year.

5.4.2 Sensitivity analysis

One-way sensitivity analysis

The values used in the one-way sensitivity analysis (OWSA) are given in Table 69 of the company's supplementary appendix. All variables were varied by +/- 20% or natural limits if these were within the +/- 20% range. The impact on the ICER is given below in Table 45 for the 20 parameters that had the largest impact on the ICER. The company also presented these results in a tornado diagram in Figure 45 of the company's supplementary appendix.

Table 45. Results of OWSA for onasemnogene versus BSC (adapated from Table 6 of the the company's PAS submission)

Parameter Description		ICER (∆£/∆QALY)		% change from baseline	
		Low	High	Low	High
1	Onasemnogene drug costs	[redacted]	[redacted]	15%	15%
2	C state utility value	[redacted]	[redacted]	15%	11%
3	Cost of hospitalisations for the C state	[redacted]	[redacted]	4%	4%
4	Cost of hospitalisations for the E state	[redacted]	[redacted]	2%	2%
5	Survival limit for the E state	[redacted]	[redacted]	2%	2%
6	Cost of social services for the C state	[redacted]	[redacted]	1%	1%
7	Cost of social services for the E state	[redacted]	[redacted]	0%	1%
8	E state utility value	[redacted]	[redacted]	0%	0%
9	Cost of hospitalisations for the D state	[redacted]	[redacted]	0%	0%
10	Survival limit for the D state	[redacted]	[redacted]	0%	0%
11	D state utility value	[redacted]	[redacted]	1%	0%
12	Cost of medical visits for the C state	[redacted]	[redacted]	0%	0%
13	Cost of health material for the C state	[redacted]	[redacted]	0%	0%
14	Cost of social services for the D state	[redacted]	[redacted]	0%	0%

Parameter Description		ICER (Δ£/ΔQALY)		% change from baseline	
		Low	High	Low	High
15	Cost of drugs for the C state	[redacted]	[redacted]	0%	0%
16	Cost of health material for the E state	[redacted]	[redacted]	0%	0%
17	Cost of medical visits for the E state	[redacted]	[redacted]	0%	0%
18	Cost of medical tests for the C state	[redacted]	[redacted]	0%	0%
19	Cost of health material for the D state	[redacted]	[redacted]	0%	0%
20	Cost of medical visits for the D state	[redacted]	[redacted]	0%	0%
Abbreviations: ICER, incremental cost-effectiveness ratio; OWSA, one-way sensitivity analysis					

According to the OWSA, results were most sensitive to the cost of onasemnogene, the patient utility value attached to the C state and the cost of hospitalisations for C state patients. However, the ERG has two issues with the company's approach to OWSA. Firstly, the hospitalisations cost category is influenced by many variables including the proportion of patients receiving tracheostomy versus NIV>16 hours, the proportion of different healthcare settings (home-based, high-dependency and intensive care) by ventilation status and the proportion of non-ventilated patients. Secondly, the company restricted the uncertainty reported in the literature to be within the +/- 20% range. For these reasons, the ERG considers that the company has not identified the true key drivers in the model.

In response to the ERG's concerns during the original clarification stage, the company provided OWSA results for each hospitalisation variable included in health states E, D and C (please refer to Table 46 in the ERG's interim report).[65] Based on this analysis, the proportion of patients in different healthcare settings by ventilation status was a key driver. However, an updated version of the hospitalisation variables analysis was requested based on the company's revised analysis, which looked at changes in each variable separately, with a 20% variance around the point estimated, which showed the ICER was not sensitive to changes in the variables used to calculate the hospitalisation costs for the E, D and C health states (Table 46). The ERG considers the analysis presented in the first round of clarification response was more informative to demonstrate the impact on the ICER due to combined changes in the underlying variables used to calculate the cost of hospitalisations.

Table 46. Results of OWSA on hospitalsation parameters including PAS (Taken from the company's economic model)

Variable	Default value	Low variation	High variation	Results with low value			Results with high value		
				Cost-AVXS	Cost-BSC	ICER vs BSC (£/QALY)	Cost-AVXS	Cost-BSC	ICER vs BSC (£/QALY)
ITU_trach	10%	8%	12%	[redacted]	£377,676	[redacted]	[redacted]	£384,586	[redacted]
ITU_NIV>16hpd	15%	12%	18%	[redacted]	£363,360	[redacted]	[redacted]	£398,902	[redacted]
ITU_NIV<16hpd_D	5%	4%	6%	[redacted]	£373,954	[redacted]	[redacted]	£388,308	[redacted]
ITU_NIV<16hpd_C	5%	4%	6%	[redacted]	£381,131	[redacted]	[redacted]	£381,131	[redacted]
high_dep_trach	30%	24%	36%	[redacted]	£376,650	[redacted]	[redacted]	£385,613	[redacted]
high_dep_NIV>16hpd	15%	12%	18%	[redacted]	£373,448	[redacted]	[redacted]	£388,814	[redacted]
high_dep_NIV<16hpd_D	5%	4%	6%	[redacted]	£377,834	[redacted]	[redacted]	£384,428	[redacted]
high_dep_NIV<16hpd_C	5%	4%	6%	[redacted]	£381,131	[redacted]	[redacted]	£381,131	[redacted]
Noyes_cost_high_dep	£415,808	£332,646	£498,970	[redacted]	£361,373	[redacted]	[redacted]	£400,889	[redacted]
Noyes_cost_ITU	£833,592	£666,874	£1,000,310	[redacted]	£349,349	[redacted]	[redacted]	£412,914	[redacted]
c_NIV>16hpd_high_dep	£48,288	£38,630	£57,945	[redacted]	£371,091	[redacted]	[redacted]	£391,171	[redacted]
c_NIV>16hpd_ITU	£96,805	£77,444	£116,166	[redacted]	£361,003	[redacted]	[redacted]	£401,259	[redacted]
c_trach_high_dep	£28,167	£22,533	£33,800	[redacted]	£375,275	[redacted]	[redacted]	£386,988	[redacted]
c_trach_ITU	£18,823	£15,058	£22,587	[redacted]	£377,217	[redacted]	[redacted]	£385,045	[redacted]
c_NIV<16hpd_high_dep_D	£17,464	£13,971	£20,957	[redacted]	£377,270	[redacted]	[redacted]	£384,992	[redacted]
c_NIV<16hpd_ITU_D	£35,011	£28,009	£42,013	[redacted]	£373,390	[redacted]	[redacted]	£388,872	[redacted]
c_NIV<16hpd_high_dep_C	£11,643	£9,314	£13,971	[redacted]	£381,131	[redacted]	[redacted]	£381,131	[redacted]
c_NIV<16hpd_ITU_C	£23,341	£18,672	£28,009	[redacted]	£381,131	[redacted]	[redacted]	£381,131	[redacted]

Multi-way sensitivity analysis

For the multi-way sensitivity analysis, the three variables with the largest impact on the results (excluding the cost of onasemnogene) in the OWSA were combined. From the onasemnogene versus BSC analysis these are: the cost of social services in the C state; the cost of hospitalisations for C state patients; and, the patient utility value of the C state. The mean values associated with each of those three variables was varied by +/- 20%. As noted previously, the hospitalisation cost category aggregates a number of variables. Nonetheless, the results of the company's multi-way sensitivity analysis are given in Table 47.

The results ranged from a low of [redacted] (20% reduction in C state hospitalisation costs, 20% reduction in C state social services costs and 20% increase in the C state utility value) to a high of [redacted] (20% increase in C state hospitalisation costs, 20% increase in C state social services costs and 20% reduction in the C state utility value). Compared with the base case ICER, these are a decrease of 16.5% and an increase of 21.5%, respectively.

Table 47. ICER results of multi-way analysis of three variables for onasemnogene versus BSC with PAS discount (taken from Table 7 of the company PAS submission)

	Hospitalisation cost in C state = base case	**Hospitalisation cost in C state = base case * 0.8**	**Hospitalisation cost in C state = base case * 1.2**
Social services cost in C state = base case	[redacted]	[redacted]	[redacted]
Social services cost in C state = base case * 0.8	[redacted]	[redacted]	[redacted]
Social services cost in C state = base case * 1.2	[redacted]	[redacted]	[redacted]

Abbreviations: BSC, best supportive care; ICER, incremental cost effectiveness ratio.
Note: U1 = base case utility value; U2 = base case utility value * 0.8; U3 = base case utility value * 1.2.

Scenario analysis

The impact of changing assumptions on discount rates, cost assumptions, utility values, alternative natural history sources and other exploratory scenarios are given in Table 48. The scenarios that led to the largest increases in the ICER included:

- Exploring utility values from the Lloyd *et al.* 2017[89] clinician-proxy vignette study ([redacted]);
- A discount rate of 0% for costs and 5% for effects ([redacted]); and
- Utility values from the AveXis UK utilities elicitation study[84] ([redacted]).

Table 48. Results of scenario analysis for onasemnogene versus BSC (Table 8 of the company PAS submission)

Scenario	ICER (∆£/∆QALY)	% change from baseline
Base case results	[redacted]	-
DISCOUNT RATES		
Costs and effects at 0%	[redacted]	-40%
Costs and effects at 5%	[redacted]	+19%
Costs at 0%, effects at 5%	[redacted]	+60%
Costs at 5%, effects at 0%	[redacted]	-55%
Costs and effects at 1.5%	[redacted]	-24%
COST ASSUMPTIONS		
Use of RWE costs (scenario with SMA type 1 costs doubled) presented at the nusinersen NICE ACM3	[redacted]	+12%
SMA type 3 costs from RWE presented at nusinersen ACM3 applied to the A state and B state patients, other health state costs remain as base case	[redacted]	+2%
Cost of onasemnogene abeparvovec administration 10x higher than base case	[redacted]	+1%
US ICER approach to the costing of ventilatory support (ERG question 2019, **B16**)	[redacted]	-22%
Increase of total D state and E state costs explorative scenario 1 (ERG question 2019, **B20**)	[redacted]	-2%
Increase of HCRU in the D state and E state costs explorative scenario 2 (ERG question 2019, **B20**)	[redacted]	0%
Extreme scenario where all non-permanent ventilated patients (84% in state D, 56% in state C, 20% in state B/A) in whatever health state receive 100% of the Noyes social care/ social services costs (ERG question 2019, **B23**)	[redacted]	+12%
UTILITY VALUES		
On-treatment utility using lower values than US ICER (0.05 for D state; 0.025 for C state)	[redacted]	+4%
On-treatment utility using higher values than US ICER (0.15 for D state; 0.075 for C state)	[redacted]	-4%
The base case values for the C, D and E states were substituted with the utility values derived from the mapping of the PedsQL score in the CHERISH nusinersen study to EQ-5D-Y. Values for these states were 0.878 (B state), 0.764 (C state), 0.756 (D state) and 0.730 (E state	[redacted]	-13%
The base case values for the C, D and E states were substituted with the utility values derived from the Lloyd et al 2017 Clinician-proxy Case Vignette. Values for these states were 0.710 (B state), -0.04 (C state), -0.12 (D state) and -0.33 (E state)	[redacted]	+223%
The base case values for the B, C, D and E states were substituted with the utility values derived from the exploratory AveXis UK utilities elicitation study using the TTO results from the 'parent vignettes'. Values for these states were 0.7898 (B state), 0.2628 (C state), -0.2367 (D state) and -0.2634 (E state);	[redacted]	+61%
No utility weights (cost per life year gained)	[redacted]	-26%
ALTERNATIVE NATURAL HISTORY SOURCE		
Use of AveXis external PNCR control dataset: fitted curve kept as Weibull, survival maximum equals 4 years	[redacted]	-15%
Use of Finkel et al. 2017a (ENDEAR sham control): fitted curve kept as Weibull, survival maximum equals 4 years	[redacted]	-13%

Scenario	ICER (∆£/∆QALY)	% change from baseline
Use of De Sanctis et al. 2016 (PNCR, US and Italy study): fitted curve kept as Weibull, survival maximum equals 4 years	[redacted]	-15%
EXPLORATORY SCENARIOS		
Patients in the C state (sits unassisted) have a life expectancy the same as the general population: applied to onasemnogene abeparvovec arm only	[redacted]	-14%
Use of POOLED dataset, but with only one additional sitter compared to empirical data in STR1VE-US after 18 months of age. The additional sitter sits between 24–30 months of age and therefore moves to sitting in cycle ending 36 months	[redacted]	+5%
Use of POOLED dataset, but with only one additional walker compared to empirical data in STR1VE-US after 18 months of age. The additional walker walks between 24–30 months of age and therefore moves to walking in cycle ending 36 months	[redacted]	+2%
Use of POOLED dataset but use of the empirical data only from STR1VE-US. i.e. no additional patients who can sit or walk unassisted in STR1VE-US after 18 months of age.	[redacted]	+7%
Use of POOLED dataset but with four new sitters and four new walkers in STR1VE-US after 18 months of age. Half move in cycle ending 30 months and half move in cycle ending 36 months	[redacted]	-16%
E state overall survival based on the 'pooled' Gregoretti cohort, i.e. patients with tracheostomy (n=42) or NIV (n=31) with proportions adjusted accordingly in medical cost calculator; curve = exponential, survival limit = 16 years	[redacted]	-13%
Caregiver disutility scores included	[redacted]	+3%
Milestones, overall survival and event-free survival is based on those treated at ≤3.5 months of age in START and STR1VE-US (n=17)	[redacted]	-13%
Milestones, overall survival and event-free survival are based on those treated in START only (n=12)	[redacted]	-14%
Milestones are not 'offset' by a model cycle (i.e. not 'offset' by 6 months)	[redacted]	-2%
Proxy pre-symptomatic scenario A: Assumes age-appropriate milestones (sitting and walking) are observed for all patients, but with conservative one cycle motor milestone offset still applied. Assumes overall survival and event-free survival is 100% in the D state for the short-term model for onasemnogene abeparvovec.	[redacted]	-69%
Proxy pre-symptomatic scenario B: Assumes sitting is observed in all patients, of which 50% attain age-appropriate sitting and 50% achieve delayed sitting. Assumes walking is observed for 82% of patients; of which 50% attain age-appropriate walking and 50% achieve delayed walking. The conservative one cycle motor milestone offset still applied to all milestones. Assumes overall survival and event-free survival is 100% in the D state for the short-term model for onasemnogene abeparvovec.	[redacted]	-62%
30 second threshold for sitting independently: Use of the POOLED dataset in which sitting independently is defined as 'sitting alone for ≥30 seconds' for both the START and STR1VE-US trials. All other base case assumptions regarding motor milestones (e.g. application of the conservative one model cycle offset and the assumption of one additional sitter and walker in STR1VE-US between 24 and 30 months of age) remain in place for this scenario. (ERG clarification questions 2020, **A3/B2**)	[redacted]	+4%

Abbreviations: ACM3, third appraisal committee meeting; BSC, best supportive care; EFS, event-free survival; HCRU, healthcare resource use; ICER, incremental cost effectiveness ratio; OS, overall survival; PNCR, Pediatric Neuromuscular Clinical Research; QALY, quality-adjusted life-year; RWE, real-world evidence; TTO, time trade-off; UK, United Kingdom; US, United States; vs. versus.

Probabilistic Sensitivity Analysis

Variables included in the Probabilistic Sensitivity Analysis (PSA) are given in Table 71 of the company's supplementary appendix. Details of how the best fitting survival curve parameters, and associated transition probabilities, are incorporated into the PSA are given in Appendix 8 of the original company submission. The ERG considers the distributions chosen for PSA to be generally sound. In the original model, the company applied arbitrary measures of uncertainty (standard errors) of 5% to utilities and 20% to costs and survival limit, without justification. However, during the clarification stage, the company stated that the standard error for utilities was assumed to be 5% of the mean due to the small variation in these values published in previous studies, but updated the model to include standard error for utilities to be 20%.

Figure 16 illustrates the 1,000 simulations on the cost-effectiveness plane comparing the incremental cost-effectiveness of onasemnogene over BSC. Those results produced a mean ICER of [redacted] per QALY gained for onasemnogene compared to BSC (Table 49), which is 5.8% larger than the deterministic base-case result. In addition, the minimum and maximum ICERs were [redacted] and [redacted] with a 95% credible interval of between [redacted] and [redacted]. As illustrated in Figure 17 onasemnogene has a 0% chance of being cost-effective at a willingness-to-pay threshold of £100,000.

The ERG could produce very similar PSA results when replicating the analysis.

Table 49. Mean probabilisitic results for onasemnogene versus BSC (results taken by the ERG from the company's economic model)

Treatment	Total costs (£)	Total LYs	Total QALYs	Incremental costs (£)	Incremental LYs	Incremental QALYs	ICER (∆£/∆QALY)
BSC	378,637	2.13	0.22	-	-	-	-
Onasemnogene + BSC	[redacted]	14.44	9.38	[redacted]	12.30	9.16	[redacted]

Abbreviations: BSC, best supportive care; ICER, incremental cost-effectiveness ratio; LYs, life years; QALY, quality-adjusted life year.

Figure 16. Cost-effectiveness plane of 1,000 simulations for onasemnogene versus BSC (reproduced from Figure 2 of the company's PAS submission)

Figure 17. Cost Effectiveness Acceptability Curve for onasemnogene versus BSC (reproduced from Figure 3 of the company's PAS submission)

5.4.3 Model validation

The company report that clinical expert engagement via a UK advisory board was obtained to validate the conceptual economic model, including modelling technique, structure, health states, key sources of model input data and model outcomes. Quality assurance of the economic model was assessed by investigation of Markov traces and by comparing modelled mortality and disease progression probabilities with the populated data. Furthermore, the robustness of the model was investigated through extreme value testing of parameters.

The ERG highlights that the submitted economic model contained over 60 worksheets of data and calculations, making it extremely difficult to validate the model had no undiscovered errors. Many of the final data used in the model link back through several calculations in several different worksheets and as such it was problematic to navigate to the source data. The ERG is not confident that all errors

have been identified, but the results pass face and clinical validity. Therefore, it is unlikely that there are substantial errors in the economic model that would make the ICERs unreliable.

5.5 Cost effectiveness analysis for the pre-symptomatic population

In March 2020 the company received a positive CHMP opinion for onasemnogene and the proposed indication was widened to include:

- patients with 5q SMA with a bi-allelic mutation in the survival motor neuron (SMN) 1 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 three copies of the SMN2 gene (the pre-symptomatic population).

The main cost-effectiveness analysis presented by the company and discussed in the ERG report was focussed on the symptomatic SMA type 1 population. The economic model submitted by the company was entirely constructed to reflect the treatment pathway for the symptomatic SMA type 1 population, with comparator, parameters and assumptions aligned to analyse the costs and benefits of onasemnogene in this population. However, the company would like the HST committee to consider onasemnogene for the pre-symptomatic population and has presented two scenarios (A and B) using the economic model for the symptomatic SMA type 1 population. A key assumption made by the company is that the pre-symptomatic patient population (up to three copies of the SMN2 gene) covers a genotype that is predictive of SMA type 1.

The main trial assessing onasemnogene in the pre-symptomatic population is SPR1NT. SPR1NT recruited infants who had genetically determined SMA, defined by bi-allelic deletion of SMN1 with two or three copies of SMN2, were asymptomatic and were less than six weeks of age at the time of treatment. Cohort 1 of the trial consisted of patients with two copies of SMN2 and cohort 2 comprised of patients with three copies of SMN2. Enrolment was completed in November 2019 and the company provided an interim data cut dated 31 December 2019. Please refer to Section 4.3.2 for more details on SPR1NT. The company stated that data from SPR1NT are not sufficiently mature to inform a full cost-effectiveness analysis but have based the assumptions used for the scenarios on the interim results from the trial.

For Scenarios A and B, the only changes made by the company to adapt the symptomatic SMA type 1 economic model for the pre-symptomatic population relate to motor milestone achievements, EFS and OS in the short-term model. All other parameters and assumptions described in the previous sections for the SMA type 1 analysis hold for the scenarios. The company acknowledged that the patient pathway, and in particular costs for the pre-symptomatic population are different compared to the

symptomatic SMA type 1 patient pathway but consider that costs would be overestimated for the scenarios.

For Scenario A, the company has assumed the following for pre-symptomatic patients treated with onasemnogene:

- 100% of patients achieve age appropriate milestones of sitting independently and walking independently in the short-term model. Table 50 presents the proportion of patients achieving motor milestones by model cycle (including the company's "offset" assumption).
- No patients receive PAV.
- EFS and OS is 100% in the short-term model for patients in the D state.
- The comparator analysis remains the same as for the symptomatic SMA type 1 population.

Table 50. Proportion of patients assumed to achieve motor milestones, offset by one cycle – Scenario A (taken from the company's economic model)

Model cycle	Age at end of cycle (months)	Not sitting (D state)		Sitting (C state)		Walking (B state)	
		n	%	n	%	n	%
1	6	34	100%	0	0%	0	0.0%
2	12	34	100%	0	0%	0	0.0%
3	18	0	0%	34	100%	0	0%
4	24	0	0%	0	0%	34	100%
5	30	0	0%	0	0%	34	100%
6	36	0	0%	0	0%	34	100%

Relative to Scenario A, Scenario B is a less optimistic analysis where the company has assumed the following for pre-symptomatic patients treated with onasemnogene:

- 100% of patients achieve the motor milestone of sitting independently, with 50% assumed to sit independently by 9.2 months of age (which is the 99th percentile of the WHO window for sitting independently in normal childhood) and the remaining 50% experiencing a delay in sitting independently, achieving the motor milestone by 18 months of age. Table 51 presents the proportion of patients achieving motor milestones by model cycle (including the company's "offset" assumption.
- 82% of patients achieve the motor milestone of walking independently, with 50% assumed to walk independently by 17.6 months of age (which is the 99th percentile of the WHO window for sitting independently in normal childhood) and the remaining 50% experiencing a delay in walking independently, achieving the motor milestone by 30 months of age, presented in Table

51. It should be noted that the company has not explained why 82% was assumed for the proportion of patients achieving the motor milestone of walking independently.

- No patients receive PAV.
- EFS and OS is 100% in the short-term model for patients in the D state.
- The comparator analysis remains the same as for the symptomatic SMA type 1 population.

Table 51. Proportion of patients assumed to achieve motor milestones, offset by one cycle – Scenario B (taken from the company's economic model)

Model cycle	Age at end of cycle (months)	Not sitting (D state)		Sitting (C state)		Walking (B state)	
		n	%	n	%	n	%
1	6	34	100%	0	0%	0	0.0%
2	12	34	100%	0	0%	0	0.0%
3	18	17	50%	17	50%	0	0%
4	24	0	0%	20	59%	14	41%
5	30	0	0%	20	59%	14	41%
6	36	0	0%	6	18%	28	82%

The cost-effectiveness results for Scenarios A and B are presented in Table 52 and Table 53, respectively.

Table 52. Deterministic cost-effectiveness results for Scenario A - onasemnogene versus BSC including PAS discount (taken from the company's economic model)

Treatment	Total costs	Total LYs	Total QALYs	Incremental costs	Incremental LYs	Incremental QALYs	ICER (∆£/∆QALY)
BSC	381,131	2.15	0.21	-	-	-	-
Onasemnogene + BSC	[redacted]	26.79	23.80	[redacted]	24.65	23.59	[redacted]

Abbreviations: BSC, best supportive care; ICER, incremental cost-effectiveness ratio; LYs, life years; QALY, quality-adjusted life year.

Table 53. Deterministic cost-effectiveness results for Scenario B - onasemnogene versus BSC including PAS discount (taken from the company's economic model)

Treatment	Total costs	Total LYs	Total QALYs	Incremental costs	Incremental LYs	Incremental QALYs	ICER (∆£/∆QALY)
BSC	381,131	2.15	0.21	-	-	-	-
Onasemnogene + BSC	[redacted]	25.29	21.41	[redacted]	23.14	21.20	[redacted]

Abbreviations: BSC, best supportive care; ICER, incremental cost-effectiveness ratio; LYs, life years; QALY, quality-adjusted life year.

5.5.1 ERG critique

The scenarios presented by the company to demonstrate the cost-effectiveness of onasemnogene in the pre-symptomatic population are based on a key assumption that the population (up to three copies of the SMN2 gene) covers a genotype that is predictive of SMA type 1. However, the ERG's clinical

experts stated that pre-symptomatic patients with up to three copies of the SMN2 gene can potentially develop symptomatic SMA type 1, 2 or 3 and the proportions vary by SMN copy number. Studies have estimated that approximately 70-80% of SMA type 1 patients have two copies of SMN2, 70-80% of SMA type 2 patients and approximately 50% of SMA type 3 patients have three copies of SMN2.[16, 100] Thus, if a large proportion of the pre-symptomatic population with three copies of SMN2 are likely to develop SMA type 2 or 3, then the age at which patients will develop symptoms, the comparators and the treatment pathways can be quite different. Please see Section 4.3.2 for more information on the pre-symptomatic population.

For the scenarios, the company rely heavily on the interim data from SPR1NT demonstrating attainment of age appropriate milestones for patients to inform their assumptions of 100% of treated patients achieving age appropriate milestones (Scenario A) or 100% of treated patients achieving the ability to sit independently and 82% achieving the ability to walk independently (Scenario B). However, as a proportion of these patients may have developed symptomatic SMA type 2 or 3, these patients are more likely be able to sit independently (type 2 and 3) and walk independently (type 3 only) irrespective of being treated with onasemnogene.[101] Therefore, different outcomes may be appropriate to use to demonstrate treatment effectiveness for the SMA type 2 and 3 analyses.

The ERG considers that assuming all pre-symptomatic patients would have developed symptomatic SMA type 1 is flawed. However, the evidence base to understand what type of SMA pre-symptomatic patients might go on to develop is limited. Furthermore, the company has acknowledged the challenges and limitations in developing robust cost-effectiveness analysis for the pre-symptomatic population before the SPR1NT trial is completed. In addition, the ERG agrees with the company that using the symptomatic SMA type 1 economic model for the scenarios may not accurately reflect costs for the proportion of patients treated with onasemnogene who may have developed symptomatic SMA type 1. However, in the absence of data, the ERG cannot predict if the company's assumption that costs would be lower for pre-symptomatic patients with a genotype predictive of SMA type 1 is true.

Given the issues and substantial uncertainty with the scenarios for the pre-symptomatic population, the ERG considers the cost-effectiveness results presented by the company are not robust for decision making. Mature data from SPR1NT will aid robust cost-effectiveness analysis for the pre-symptomatic population, but any economic model built for this population will need to:

- Model SMA type 1 appropriately for patients with a genotype predictive of SMA type 1. As mentioned by the company, costs are anticipated to be lower for treated patients, but no analyses have been provided to demonstrate this.

- For patients with a genotype predictive of SMA type 2 or 3, appropriately capture the right comparators, likely motor milestone achievement in the comparator arm, as well as other clinical outcomes that may be more appropriate for this population and the timing of treatment for patients (as symptoms develop later than for patients with symptomatic SMA type 1).

- Use natural history data to weight the analyses by the proportions of patients with two or three copies of SMN2 that have SMA type 1, 2 and 3.[16, 100]

The ERG recognises that while the data may not be available and assumptions will need to be made, that this is no different to how the company has developed its current analysis. However, as with the analysis for symptomatic SMA type 1, it would go further to give a more robust representation of the cost-effectiveness of onasemnogene than is currently available using the scenarios supplied by the company.

As a secondary issue, new-born screening for SMA in the UK is not currently available and the ERG's clinical experts stated that this would be needed to identify eligible patients. Currently in the UK, pre-symptomatic patients are only identified if there is familial history of SMA. In their clarification response, the company estimated that one to three pre-symptomatic patients per year will be identified as a result of family history of SMA. However, as there is no treatment for pre-symptomatic SMA, the need for new-born screening for SMA is limited and as such the company would need to put in place measures to provide free testing to identify infants or include the cost of testing within its cost-effectiveness analysis for the pre-symptomatic population.

6 ADDITIONAL WORK UNDERTAKEN BY THE ERG

6.1 Model corrections

No model corrections were made by the evidence review group (ERG).

6.2 ERG scenario analysis

Throughout Section 5 the ERG has described several scenarios that warrant further exploration in addition to the company's sensitivity analyses to ascertain the impact of these changes on the incremental cost effectiveness ratio (ICER). The scenarios that the ERG have produced are applied to the company base case and are as follows:

- Implementing the threshold of sitting independently of ≥30 seconds for the pooled dataset and removing the company's base case assumption of one additional sitter and one additional walker (observed motor milestones only);
- Implementing the threshold of sitting independently of ≥30 seconds for the pooled dataset and removing the company's base case assumption of one additional walker;
- Use of US ICER model costs for health states included in the model. As most of the modelling approach and assumptions are based on the US ICER model, the ERG presents a scenario using the same costs as a comparison;
- Use of subsequent nusinersen costs.

Table 54 presents the results of the ERG's scenario analysis, including the company's patient access scheme (PAS) simple discount of [redacted].

Table 54. Results of the ERG's scenario analysis

	Results per patient	Onasemnogene	Best supportive care	Incremental value
0	**Company's Base case**			
	Total Costs (£)	[redacted]	£381,131	[redacted]
	QALYs	10.21	0.21	10.00
	ICER (£/QALY)			[redacted]
1	**Threshold for sitting independently of ≥30 seconds for the pooled dataset (observed motor milestones only)**			
	Total Costs (£)	[redacted]	£381,131	[redacted]
	QALYs	8.96	0.21	8.75
	ICER (£/QALY)			[redacted]
2	**Threshold for sitting independently of ≥30 seconds for the pooled dataset (no additional walker)**			
	Total Costs (£)	[redacted]	£381,131	[redacted]
	QALYs	9.26	0.21	9.05

	ICER (£/QALY)			[redacted]
3	**US ICER model report costs**			
	Total Costs (£)	[redacted]	£544,139	[redacted]
	QALYs	10.21	0.21	10.00
	ICER (£/QALY)			[redacted]
4	**Subsequent nusinersen treatment costs**			
	Total Costs (£)	[redacted]	£381,131	[redacted]
	QALYs	10.21	0.21	10.00
	ICER (£/QALY)			[redacted]

Abbreviations: ERG, evidence review group; HSUVs, health state utility values; ICER, incremental cost effectiveness ratio; KM, Kaplan Meier; NRA; non-respiratory aid; OS, overall survival; QALYs, quality adjusted life years, US, united states.

6.3 ERG base case ICER

In this section the ERG presents its preferred ICER for the symptomatic SMA type 1 population, including the company's PAS simple discount of [redacted]. Based on the ERG's interim report, the company accepted all the ERG's original preferred assumptions for their revised base case analysis.[65] Thus, the main change the ERG has made to the company's base case is around the removal of the company's assumption of an additional independent sitter and independent walker in the pooled dataset for motor milestone achievement, as discussed in Section 5.3.5.1

The ERG could not present probabilistic sensitivity analysis (PSA) results, as the economic model is set up so that when PSA is run, the parameters default back to the company's base case preferences. Based on a comparison of the company's base case deterministic and PSA ICERs, which showed an upward increase in the ICER of approximately £12,000 (5.8%), the ERG's preferred ICER based on the PSA is likely to be larger than the [redacted].

Table 55. ERG base case ICER

Results per patient	**Onasemnogene**	**Best supportive care**	**Incremental value**
Company's base case			
Total Costs (£)	[redacted]	£381,131	[redacted]
QALYs	10.21	0.21	10.00
ICER (£/QALY)			[redacted]
Removal of the assumption of an additional independent sitter and independent walker from pooled dataset			
Total costs (£)	[redacted]	381,131	[redacted]
QALYs	9.56	0.21	8.29
ICER (£/QALY)			[redacted]
ERG's preferred base case ICER (£/QALY)			[redacted]

Abbreviations: ERG, evidence review group; HSUVs, health state utility values; ICER, incremental cost effectiveness ratio; KM, Kaplan Meier; NRA; non-respiratory aid; OS, overall survival; QALYs, quality adjusted life years, US, united states.

As mentioned in Section 5.3.5.1, the ERG's clinical experts stated that sitting independently for ≥30 seconds or more was a more meaningful threshold than ≥5 seconds, which was used for the START dataset. However, by adjusting the threshold for START, two patients no longer contribute to the C state, but evidence from the follow-up study, LT-001, demonstrates that these two patients do go on to achieve sitting independently for ≥30 seconds. Nevertheless, it is important to consider the ERG's preferred base-case ICER in the context of the clinical expert view and as such, Table 56 presents the ERG's preferred base case, including the threshold of ≥30 seconds for sitting independently.

Table 56. ERG's base case results for onasemnogene versus BSC including threshold for sitting independently of ≥30 seconds

Treatment	Total costs	Total LYs	Total QALYs	Incremental costs	Incremental LYs	Incremental QALYs	ICER (£/QALY)
BSC	381,131	2.15	0.21	-	-	-	-
Onasemnogene + BSC	[redacted]	14.08	8.96	[redacted]	11.94	8.75	[redacted]

Abbreviations: BSC, best supportive care; ICER, incremental cost-effectiveness ratio; LYs, life years; QALY, quality-adjusted life year.

While onasemnogene doesn't restore the majority of treated symptomatic SMA type 1 patients to full or near full health, data from START demonstrates a substantial survival benefit for patients who would have otherwise died, discussed in Section 5.4.1. As such, the ERG presents the company's revised base case results and the ERG's preferred base case using a 1.5% discount rate for costs and quality adjusted life years (QALYs) for committee consideration in Table 57 and Table 58, respectively.

Table 57. Company's base case results for onasemnogene versus BSC (discounted at 1.5%)

Treatment	Total costs	Total LYs	Total QALYs	Incremental costs	Incremental LYs	Incremental QALYs	ICER (£/QALY)
BSC	413,269	2.28	0.21	-	-	-	-
Onasemnogene + BSC	[redacted]	22.14	14.89	[redacted]	19.86	14.67	[redacted]

Abbreviations: BSC, best supportive care; ICER, incremental cost-effectiveness ratio; LYs, life years; QALY, quality-adjusted life year.

Table 58. ERG's base case results for onasemnogene versus BSC (discounted at 1.5%)

Treatment	Total costs	Total LYs	Total QALYs	Incremental costs	Incremental LYs	Incremental QALYs	ICER (£/QALY)
BSC	413,269	2.28	0.21	-	-	-	-
Onasemnogene + BSC	[redacted]	20.87	13.74	[redacted]	18.58	13.52	[redacted]

Abbreviations: BSC, best supportive care; ICER, incremental cost-effectiveness ratio; LYs, life years; QALY, quality-adjusted life year.

7 BUDGET IMPACT ANALYSIS

7.1 Costs to the NHS and PSS - eligible population and net budget impact

The company state that onasemnogene is expected to be used only in newly diagnosed patients, limiting the eligible population to incident patients. The budget impact model assumes that 34 patients per year will be diagnosed with spinal muscular atrophy (SMA) type 1. This was estimated using an annual incidence for all SMA types of 9.4:100,000 live births, as reported by Lally *et al*. 2017.[8] The incidence was then applied to the 2018 live births data for England, reported as 625,651, thus estimating the annual incidence for all SMA types as 59 patients.[102] To estimate the proportion of patients that will have SMA type 1, the company obtained data from published literature and assumed that 58% of SMA patients will have type 1, resulting in an incident population of 34 patients per year, over the forthcoming five years.[9] Table 59 summarises the population inputs used in the budget impact model.

Table 59. Eligible population for onasemnogene

Parameter	Value	Source
Live births in England	625,651	Office of National Statistics 2018[102]
SMA (all types) incidence	9.4:100,000	Lally *et al*. 2017[8]
Proportion of SMA type 1 patients	58%	Verhaart *et al*. 2017[9]
Annual incident population	34	Calculation: incidence per 100,000*annual live births*proportion SMA type 1
Abbreviations: SMA, spinal muscular atrophy		

Based on real world evidence from the nusinersen early access programme obtained from the company's personal communication with [redacted] (paediatric neurologist), 32 patients in England were treated with nusinersen in the last 12 months of operation. Based on this, the company assumed that two out of the estimated 34 incident SMA type 1 patients (5.9%) did not present for pharmacotherapy. Furthermore, high anti-adeno-associated virus subtype 9 (AAV9) antibody titre (above 1 in 50) is an exclusion criterion for treatment with onasemnogene. In STR1VE-EU trial, five out of 41 patients (12.2%) were found to have high anti-AAV9 antibody titre and were thus ineligible for treatment with onasemnogene.

Therefore, in the budget impact model 32 of 34 patients (94%) are assumed to present for treatment with onasemnogene and of those, 12.2% are assumed to not be eligible for treatment with onasemnogene. Thus, 17.4% (5.9% + (12.2% * 94%)) are assumed to be on best supportive care (BSC). Table 60 presents the distribution of SMA type 1 patients between onasemnogene and BSC for the company's budget impact analysis and Table 61 presents the budget impact results, including the company PAS simple discount of [redacted].

Table 60. Distibution of SMA type 1 patients between treatments in the company's budget impact analysis (adapted from Table 88 of the company's supplementary appendix)

Intervention	Year 1		Year 2		Year 3		Year 4		Year 5	
	%	n*	%	n*	%	n*	%	n*	%	n*
Onasemnogene	82.6%	26	82.6%	26	82.6%	26	82.6%	26	82.6%	26
Best supportive care	17.4%	6	17.4%	6	17.4%	6	17.4%	6	17.4%	6
*note – numbers have been rounded to the nearest whole number										

Table 61. Budget impact of onasemnogene replacing BSC for 34 incident cases of SMA type 1 (adapted from Table 93 of the company's supplementary appendix)

Annual cost outcomes	Year 1	Year 2	Year 3	Year 4	Year 5
Best supportive care					
Total drugs cost	£0	£0	£0	£0	£0
Total SMA care cost	£2,965,884	£4,975,476	£6,849,276	£8,266,569	£9,428,935
Total costs	**£2,965,884**	**£4,975,476**	**£6,849,276**	**£8,266,569**	**£9,428,935**
Onasemnogene					
Total drugs cost	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total SMA care cost	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total budget impact	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Abbreviations: BSC, best supportive care; SMA, spinal muscular atrophy					

The evidence review group (ERG) considers that the estimate of 34 patients for the incident population is reasonable and was verified by its clinical experts. However, the ERG's clinical experts were not able to validate the percentage of patients who would not present for pharmacotherapy and were of the view that the baseline assumption should be all symptomatic SMA type 1 patients will present for treatment with onasemnogene. Applying the 12.2% proportion that would not be eligible for onasemnogene due to high anti-AAV9 antibody titre, the ERG preferred estimate for the eligible population is 30 patients (~88%), with 4 patients (~12%) on BSC. Note that figures have been rounded up to account for whole patients. Table 62 presents the ERG's preferred distribution of symptomatic SMA type 1 patients between onasemnogene and BSC for the budget impact analysis and Table 63 presents the ERG's budget impact results, with the preferred assumptions for the ERG base case and company PAS simple discount of [redacted] incorporated. Please refer to Section 6.3 for the ERG base case assumptions.

Table 62. ERG preferred distibution of SMA type 1 patients between treatments for the budget impact analysis

Intervention	Year 1		Year 2		Year 3		Year 4		Year 5	
	%	n*	%	n*	%	n*	%	n*	%	n*
Onasemnogene	88%	30	88%	30	88%	30	88%	30	88%	30

Best supportive care	12%	4	12%	4	12%	4	12%	4	12%	4
*note – numbers have been rounded to the nearest whole number										

Table 63. ERG Budget impact of onasemnogene replacing BSC for 34 incident cases of SMA type 1

Annual cost outcomes	Year 1	Year 2	Year 3	Year 4	Year 5
Best supportive care					
Total drugs cost	0	0	0	0	0
Total SMA care cost	£2,965,884	£4,975,476	£6,849,276	£8,266,569	£9,428,935
Total costs	**£2,965,884**	**£4,975,476**	**£6,849,276**	**£8,266,569**	**£9,428,935**
Onasemnogene					
Total drugs cost	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total SMA care cost	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total budget impact	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Abbreviations: BSC, best supportive care; SMA, spinal muscular atrophy					

7.2 Potential wider costs and benefits not included in the company's economic analysis

The company has indicated that in addition to the health benefits gained, if a patient is able to achieve and retain mobility, they will be able to go to school and gain and education and eventually participate in the workforce, driving economic productivity. Furthermore, if a patient gains any degree of independence this may alleviate burden on the caregiver, potentially allowing them to return to work and make up for otherwise lost income.

8 OVERALL CONCLUSIONS

8.1 Conclusions on the clinical effectiveness

SMA type 1 is a rare condition with an annual incidence of approximately 1:10,000 live births. It is a disease with a poor prognosis, and it is the most common genetic cause of death in infants. There is currently no effective therapy for SMA type 1 available in UK as part of established clinical practice. The main evidence of the clinical efficacy and safety of onasemnogene for the treatment of patients with a clinical diagnosis of SMA type 1 is derived from the completed START and STR1VE-US studies. Evidence on the potential benefit of treatment with onasemnogene before symptoms manifest in those identified as likely to develop SMA type 1 is being assessed in the ongoing SPR1NT study.

Results for the 12 patients in START Cohort 2 who received the therapeutic dose of onasemnogene show an impressive efficacy of onasemnogene therapy for children with SMA type 1; 75.0% of patients were able to sit unassisted for ≥ 30 seconds, 16.7% able to stand and walk without support, and all patients were alive and without the need for permanent assisted ventilation (PAV) two years after treatment. In STR1VE-US, at 18 months of age, 20 out of 22 infants (90.9%) were alive without the need for permanent ventilation, and 86.4% of patients achieved motor milestone(s), confirmed by independent central video review. In contrast to START and STR1VE-US, no patient in any of the identified SMA type 1 natural history studies achieved a significant motor milestone, and 50 to 70% of those assessed had reached the composite outcome of PAV or death at 13–14 months follow up.

Considering the pre-symptomatic population, as of December 2019, all patients involved in SPR1NT, were alive and free of permanent ventilation at their last study visit prior to the 31 December 2019 data cut. Despite the short follow up and immature data in SPR1NT, motor milestone achievements seem consistent with normal, age-appropriate development, potentially demonstrating the benefit of early treatment, but longer term data will be required to substantiate the promise of early treatment. Additionally, because SPR1NT enrolled patients before symptoms manifested, it must be borne in mind that the type of SMA a patient would have gone on to develop is unknown. To be eligible for SPR1NT, patients could have two or three copies of SMN2, and therefore a proportion, the size of which cannot be reliably predicted, is likely to develop types of SMA other than type 1.

Evidence presented from START and STR1VE-US indicates increased efficacy of onasemnogene compared with patients treated with BSC. However, the sample sizes of the onasemnogene studies and the SMA type 1 natural history studies informing results for BSC are small. As a result of the small sample sizes across the studies, although START and STR1VE-US indicate a clinical benefit of onasemnogene therapy, there is considerable uncertainty around the true magnitude of the benefit associated with onasemnogene; differences between studies in baseline characteristics (such as age at treatment or age at symptom onset) or single outcome events are likely to impact on the absolute results

and the small sample sizes mean that the accuracy and precision of the findings could be unstable due to chance events. In addition, partly due to the small sample sizes, only naïve comparisons could be made between onasemnogene and BSC, meaning no adjustments were made for differences in patients' baseline characteristics or other factors which may confound the results.

The SMA type 1 natural history studies enrolled patients either primarily or exclusively in the USA where tracheostomy, which can keep patients alive for several years, is more commonly used for patients with SMA type 1 who need PAV than in the UK, where it is rare. Thus, OS for BSC is likely to be overestimated in the natural history studies compared with UK clinical practice. Consequently, the cost-effectiveness of onasemnogene relies heavily on the choice of natural history study chosen to model OS.

Although no patient has lost any milestones from the end of START to the latest data cut in the follow-up study LT-001, the data are limited to a follow-up of 4.4 years. Data are not available to inform longer-term outcomes of patients, who may gain further motor function as they grow older, stay at the functional level they have achieved at around 4 years of age, or eventually decline. Without long-term follow-up data there is nothing to inform the likely trajectory of these children.

8.2 Conclusions on the cost-effectiveness analysis

Symptomatic SMA type 1

For the cost-effectiveness analysis, the company based most of their approach on a published economic model of nusinersen and onasemnogene produced by the US Institute for Clinical and Economic Review (US ICER) in collaboration with the University of Sheffield's School of Health and Related Research (ScHARR) and accepted all of the ERG's preferred assumptions from its interim report.[69] As such most of the assumptions used have been thoroughly explored and independently reviewed.

The main update the company made to the economic model, from their original submission, was the inclusion of pooled data from START and STR1VE-US. The ERG considers that pooling the data from the two trials of onasemnogene is reasonable, but that the differences in trial follow-up and thresholds for determining sitting independently and the company's approach to account for the differences introduces additional uncertainty into the analysis.

To overcome the shorter follow-up (18 months of age) in STR1VE-US compared with 30 months of follow-up in START and the potential underestimation of motor milestone achievement from the trial, the company assumed that between 18 to 30 months of age, there will be one additional independent sitter and one independent walker and this was included in the last cycle of the short-term model. The ERG's clinical experts considered that it might reasonable to assume there could be an additional independent sitter but were cautious about assuming an additional independent walker and caveated

their opinion by stating that none of the assumptions are founded in evidence. Thus, the ERG's preference was to use only the observed motor milestones in START and STR1VE-US to produce a conservative estimation of the cost-effectiveness of onasemnogene for symptomatic SMA type 1.

The different definition of patients achieving the ability to sit independently in the pooled analysis (sitting unassisted for ≥5 seconds in START and ≥30 seconds in STR1VE-US) was a concern for the ERG. In the interim ERG report, sitting unassisted for ≥5 seconds in START was accepted despite the ERG's clinical experts stating that the threshold was not clinically relevant and preferred the threshold of sitting unassisted for ≥30 seconds. The ERG considered that the loss of two patients from the data set who did achieve the milestone of sitting unassisted for ≥30 seconds or more (albeit not video confirmed) in the follow-up study to START (LT-001) was overly conservative and still maintains this view. Furthermore, as the threshold in STR1VE-US was longer, all patients who are included in the C state (sitting independently) implicitly meet the ≥5 seconds threshold. Nonetheless, the ERG explored the use of the ≥30 seconds threshold in its preferred assumptions and this had a substantial upward impact on the ICER.

Overall, the company's updated cost-effectiveness analysis is another step towards reducing the uncertainty around the cost-effectiveness of onasemnogene, but additional data from the going STR1VE-EU and SPR1NT trials will further mitigate the uncertainty around the proportions of patients achieving higher functioning motor milestones, as well overall and event-free survival.

Pre-symptomatic population

In March 2020 the company received a positive CHMP opinion for onasemnogene and the proposed indication was widened to include the pre-symptomatic population (patients with 5q SMA with a bi-allelic mutation in the SMN1 gene and up to three copies of the SMN2 gene). The main trial assessing onasemnogene in the pre-symptomatic population is SPR1NT. The company stated that data from SPR1NT are not sufficiently mature to inform a full cost-effectiveness analysis. Instead, the company provided two scenarios using the economic model for the symptomatic SMA type 1 population. The economic model submitted by the company was entirely constructed to reflect the treatment pathway for the symptomatic SMA type 1 population, with comparator, parameters and assumptions aligned to analyse the costs and benefits of onasemnogene in this population. A key assumption made by the company for the scenarios is that the pre-symptomatic patient population (up to three copies of the SMN2 gene) covers a genotype that is predictive of SMA type 1.

For the scenarios, the only changes made by the company to adapt the symptomatic SMA type 1 economic model for the pre-symptomatic population relate to improvements in motor milestone achievements, EFS and OS in the short-term model. All other parameters and assumptions for the SMA

type 1 analysis hold for the scenarios. The company acknowledged that the patient pathway, and in particular costs for the pre-symptomatic population are different compared to the symptomatic SMA type 1 patient pathway but consider that costs would be overestimated for the scenarios.

The ERG's clinical experts stated that pre-symptomatic patients with up to three copies of the SMN2 gene can potentially develop symptomatic SMA type 1, 2 or 3 and the proportions vary by SMN copy number. For the scenarios, the company rely heavily on the interim data from SPR1NT demonstrating attainment of age appropriate milestones for patients to inform their assumptions, but a proportion of these patients may have developed symptomatic SMA type 2 or 3 and these patients are more likely be able to sit independently (type 2 and 3) and walk independently (type 3 only) irrespective of being treated with onasemnogene.[101] Therefore, different comparators, outcomes, costs and benefits may be appropriate to use to demonstrate cost-effectiveness for the SMA type 2 and 3 analyses.

The ERG considers that assuming all pre-symptomatic patients would have developed symptomatic SMA type 1 is flawed. However, the evidence base to understand what type of SMA pre-symptomatic patients might go on to develop is unavailable. Furthermore, the company has acknowledged the challenges and limitations in developing robust cost-effectiveness analysis for the pre-symptomatic population before the SPR1NT trial is completed. In addition, the ERG agrees with the company that using the symptomatic SMA type 1 economic model for the scenarios may not accurately reflect costs for the proportion of patients treated with onasemnogene who may have developed symptomatic SMA type 1. However, in the absence of data, the ERG cannot predict if the company's assumption that costs would be lower for pre-symptomatic patients with a genotype predictive of SMA type 1 is true.

Given the issues and substantial uncertainty with the scenarios for the pre-symptomatic population, the ERG considers the cost-effectiveness results presented by the company are not robust for decision making. Mature data from SPR1NT will aid robust cost-effectiveness analysis for the pre-symptomatic population.

8.3 Implications for research

The uncertainty around the short-term and long-term outcomes of patients treated with onasemnogene is likely to be reduced as the as the ongoing onasemnogene studies, LT-001 LT-002, STR1VE-EU, and SPR1NT report more mature data.

9 REFERENCES

1. National Institute for Health and Care Excellence. Highly Specialised Technologies Evaluation. Onasemnogene abeparvovec for treating spinal muscular atrophy. Final scope., 2020. Available from: https://www.nice.org.uk/guidance/gid-hst10026/documents/final-scope. Date accessed: 28 Aug 2020.

2. Kolb SJ, Kissel JT. Spinal muscular atrophy: a timely review. *Arch Neurol* 2011; **68**: 979-84.

3. Kolb SJ, Kissel JT. Spinal Muscular Atrophy. *Neurologic clinics* 2015; **33**: 831-46.

4. Feldkotter M, Schwarzer V, Wirth R, Wienker TF, Wirth B. Quantitative analyses of SMN1 and SMN2 based on real-time lightCycler PCR: fast and highly reliable carrier testing and prediction of severity of spinal muscular atrophy. *Am J Hum Genet* 2002; **70**: 358-68.

5. Wirth B, Brichta L, Schrank B, Lochmuller H, Blick S, Baasner A, et al. Mildly affected patients with spinal muscular atrophy are partially protected by an increased SMN2 copy number. *Hum Genet* 2006; **119**: 422-8.

6. Prior TW, Krainer AR, Hua Y, Swoboda KJ, Snyder PC, Bridgeman SJ, et al. A positive modifier of spinal muscular atrophy in the SMN2 gene. *Am J Hum Genet* 2009; **85**: 408-13.

7. Darras BT. Spinal muscular atrophies. *Pediatr Clin North Am* 2015; **62**: 743-66.

8. Lally C, Jones C, Farwell W, Reyna SP, Cook SF, Flanders WD. Indirect estimation of the prevalence of spinal muscular atrophy Type I, II, and III in the United States. *Orphanet Journal of Rare Diseases* 2017; **12**: 175.

9. Verhaart IEC, Robertson A, Wilson IJ, Aartsma-Rus A, Cameron S, Jones CC, et al. Prevalence, incidence and carrier frequency of 5q-linked spinal muscular atrophy - a literature review. *Orphanet J Rare Dis* 2017; **12**: 124.

10. Farrar MA, Park SB, Vucic S, Carey KA, Turner BJ, Gillingwater TH, et al. Emerging therapies and challenges in spinal muscular atrophy. *Ann Neurol* 2017; **81**: 355-68.

11. Spinal Muscular Atrophy UK. Looking after your baby with spinal muscular atrophy type 1. *Available at https://smaukorguk/looking-after-your-baby (accessed March 2019)* 2019.

12. Arnold WD, Kassar D, Kissel JT. Spinal muscular atrophy: diagnosis and management in a new therapeutic era. *Muscle Nerve* 2015; **51**: 157-67.

13. AveXis. Date on file: UK Healthcare Resource Use Study Report. 14 June 2019. 2019.

14. 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* 2018a; **28**: 103-15.

15. Prior TW FE. Spinal muscular atrophy. Last updated: December 22, 2016. In: Pagon RA, Adam MP, Ardinger HH, et al, eds. GeneReviews® [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2017. 2016.

16. Calucho M, Bernal S, Alias L, March F, Vencesla A, Rodriguez-Alvarez FJ, et al. Correlation between SMA type and SMN2 copy number revisited: An analysis of 625 unrelated Spanish patients and a compilation of 2834 reported cases. *Neuromuscular disorders : NMD* 2018; **28**: 208-15.

17. Qian Y, McGraw S, Henne J, Jarecki J, Hobby K, Yeh WS. Understanding the experiences and needs of individuals with Spinal Muscular Atrophy and their parents: a qualitative study. *BMC Neurol* 2015; **15**: 217.

18. Lopez-Bastida J, Pena-Longobardo LM, Aranda-Reneo I, Tizzano E, Sefton M, Oliva-Moreno J. Social/economic costs and health-related quality of life in patients with spinal muscular atrophy (SMA) in Spain. *Orphanet J Rare Dis* 2017; **12**: 141.

19. 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**: 197-207.

20. National Institute for Health and Care Excellence. Managed Access Agreement - Nusinersen for treating spinal muscular atrophy. Published date: 24 July 2019. 2019.

21. National Institute for Health and Care Excellence. Technology appraisal guidance [TA588] - Nusinersen for treating spinal muscular atrophy. Published date: 24 July 2019. 2019.

22. European Medicine Agency (EMA). Zolgensma: assessment report, 2020. Available from: https://www.ema.europa.eu/en/documents/assessment-report/zolgensma-epar-public-assessment-report_en.pdf. Date accessed: 9 Jul 2020.

23. National Institute for Health and Care Excellence. Highly Specialised Technologies Evaluation. Onasemnogene abeparvovec for treating spinal muscular atrophy. Original scope., 2020. Available from: https://www.nice.org.uk/guidance/gid-hst10026/documents/draft-scope-pre-referral. Date accessed: 28 Aug 2020.

24. Avexis. Data on file. Clinical Study Report (CSR). START (CL-101). 2018.

25. AveXis. Data on File: Draft SmPC onasemnogene abeparvovec. 2019.

26. Al-Zaidy S, Pickard AS, Kotha K, Alfano LN, Lowes L, Paul G, et al. Health outcomes in spinal muscular atrophy type 1 following AVXS-101 gene replacement therapy. *Pediatr Pulmonol* 2019; **54**: 179-85.

27. AveXis. Data on file. STR1VE-US (CL-303) Protocol. Version 4.0, 4 Oct 2018. 2018.

28. AveXis. Data on file. STR1VE-EU (CL-302) Protocol. Version 4.0, 17 May 2019. 2019.

29. AveXis. AveXis. Data on file. SPR1NT (CL-304) Protocol. Version 4.0, 30 May 2019. 2019.

30. AveXis. Data on file. PNCR and NeuroNext database report. 2018.

31. Kolb SJ, Coffey CS, Yankey JW, Krosschell K, Arnold WD, Rutkove SB, et al. Natural history of infantile-onset spinal muscular atrophy. *Ann Neurol* 2017; **82**: 883-91.

32. Finkel RS, Mercuri E, Darras BT, Connolly AM, Kuntz NL, Kirschner J, et al. Nusinersen versus Sham Control in Infantile-Onset Spinal Muscular Atrophy. *N Engl J Med* 2017a; **377**: 1723-32.

33. Finkel RS, McDermott MP, Kaufmann P, Darras BT, Chung WK, Sproule DM, et al. Observational study of spinal muscular atrophy type I and implications for clinical trials. *Neurology* 2014a; **83**: 810-7.

34. De Sanctis R, Coratti G, Pasternak A, Montes J, Pane M, S. Mazzone E, et al. *Developmental milestones in type I spinal muscular atrophy*2016.

35. Alanizi A, A., D'Argenzio, L,D., Hacohan, Y,H., Edel, L,E., Wallis, C,W., Chan, E,C., Abel, F,A., Munot, P,M., Robb, S,R., Craig, F,C., Muntoni, F,M., Manzur, A,M. Spinal Motor Atrophy Type 1: clinical outcome and evolution of care of SMA1 at a single neuromuscular centre in the decade 2007-2017. Abstract presented on the 4th January 2018 at the Developmental medicine and child neurology conference. 2018.

36. AveXis. Data on file. Systematic literature review of clinical and economic evidence for interventions for spinal muscular atrophy. Technical Report. Version 6. 20 May 2019. 2019.

37. Higgins JP, Altman DG, Gotzsche PC, Juni P, Moher D, Oxman AD, et al. The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. *Bmj* 2011; **343**: d5928.

38. CASP. 2018. Available from: https://casp-uk.net/casp-tools-checklists/. Date accessed: 07/01/2020.

39. Kolb SJ, Coffey CS, Yankey JW, Krosschell K, Arnold WD, Rutkove SB, et al. Baseline results of the NeuroNEXT spinal muscular atrophy infant biomarker study. *Annals of clinical and translational neurology* 2016; **3**: 132-45.

40. Wells G, Shea B, O'Connell J. The Newcastle-Ottawa Scale (NOS) for Assessing The Quality of Nonrandomised Studies in Meta-analyses. 2013 [updated 2013; cited 2016 October 1]; Available from: http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp.2013.

41. AveXis. Data on file. LT-001 Protocol. Version 4.0. 5 Oct 2018. 2018.

42. Finkel RS, Weiner DJ, Mayer OH, McDonough JM, Panitch HB. Respiratory muscle function in infants with spinal muscular atrophy type I. *Pediatr Pulmonol* 2014b; **49**: 1234-42.

43. AveXis. Data on file. LT-002 Protocol. Version 3.0, 17 Jun 2019. 2019.

44. 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. *N Engl J Med* 2017; **377**: 1713-22.

45. AveXis. Data on file. Clinical Overview. onasemnogene abeparvovec [data_cut_08Mar2019]. 2019.

46. Mendell JR, Shell R., Lehman, K.J., McColly, M., Lowes, L.P., Alfano, L.N., Miller, N.F., Iammarino, M.A., Church, K., Ogrinc, F.G., Ouyang, H., Kernbauer, E., Shah, S., L'Italien, J., Sproule, D.M., Feltner, D.E., Al-Zaidy, S. AVXS-101 Gene-Replacement Therapy in Spinal Muscular Atrophy Type 1: Long-Term Follow-Up From the Phase 1/2a Clinical Trial. Poster presented at AAN 2019. Data on file. 2019.

47. AveXis. Data on file. LT-001 Protocol. Version 5.0. 13 Jan 2020. 2020.

48. AveXis. Data on file. Clinical overview onasemnogene abeparvovec [data cut 31 December 2019]. 2020.

49. AveXis. Data on file. Efficacy Update onasemnogene abeparvovec [data cut 31 December 2019]. 2020.

50. AveXis. Data on file. Safety Update onasemnogene abeparvovec [data cut 31 December 2019]. 2020.

51. AveXis. Data on file. Clinical Study Report (CSR). STR1VE-US. 2020.

52. AveXis. Data on file. STR1VE-EU (CL-302) Protocol. Version 6.0, 26 November 2019. 2019.

53. AveXis. Data on file. SPR1NT (CL-304) Protocol. Version 5.0, 26 November 2019. 2019.

54. Wijnhoven TM, de Onis M, Onyango AW, Wang T, Bjoerneboe GE, Bhandari N. Assessment of gross motor development in the WHO Multicentre Growth Reference Study. *Food and nutrition bulletin* 2004; **25 (1 Suppl)**: S37-45.

55. Jedrzejowska M, Borkowska J, Zimowski J, Kostera-Pruszczyk A, Milewski M, Jurek M, et al. Unaffected patients with a homozygous absence of the SMN1 gene. *Eur J Hum Genet* 2008; **16**: 930-4.

56. Prior TW, Swoboda KJ, Scott HD, Hejmanowski AQ. Homozygous SMN1 deletions in unaffected family members and modification of the phenotype by SMN2. *Am J Med Genet A* 2004; **130A**: 307-10.

57. Glanzman AM, Mazzone E, Main M, Pelliccioni M, Wood J, Swoboda KJ, et al. The Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders (CHOP INTEND): test development and reliability. *Neuromuscular disorders : NMD* 2010; **20**: 155-61.

58. Glanzman AM, McDermott MP, Montes J, Martens WB, Flickinger J, Riley S, et al. Validation of the Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders (CHOP INTEND). *Pediatric physical therapy : the official publication of the Section on Pediatrics of the American Physical Therapy Association* 2011; **23**: 322-6.

59. Bayley N. Bayley scales of infant and toddler development: Bayley-III: Harcourt Assessment, Psych. Corporation. 2006.

60. AveXis. Data on File: Draft SmPC onasemnogene abeparvovec. 2020.

61. Lowes LPA, L.N.; Miller, N.f.; Iammarino, M.; Dugan, M.; Berry, K.; Al-Zaidy, S.; Mendell J.R. Gene replacement therapy study for spinal muscular atrophy type 1: patients demonstrate cognitive, fine motor and language abilities within the normal range [poster]. Presented at the International Scientific Congress on Spinal Muscular Atrophy; January 25-27, 2018b; Krakow, Poland. 2018.

62. AveXis. Data on file. Safety Update onasemnogene abeparvovec [data cut 31 December 2019]. 2020.

63. Shieh P, Chen, E., Punekar, RS., Tan, H. . Treatment patterns and cost of care among patients with spinal muscular atrophy. CureSMA Annual Meeting; 2017; Orlando, FL. 2017.

64. Chatwin M, Bush A, Simonds AK. Outcome of goal-directed non-invasive ventilation and mechanical insufflation/exsufflation in spinal muscular atrophy type I. *Arch Dis Child* 2011; **96**: 426-32.

65. S.J E, C K, T J, K K, G M. Onasemnogene abeparvovec for treating spinal muscular atrophy type 1: A Highly Specialised Technology Appraisal. BMJ Technology Assessment Group, 2020.

66. Canadian Agency for Drugs and Technologies in Health. CADTH resources. https://www.cadth.ca/resources. 2019.

67. Scottish Intercollegiate Guidelines Network. SIGN Search filters. https://www.sign.ac.uk/search-filters.html. 2019.

68. Drummond MF, Jefferson TO. Guidelines for authors and peer reviewers of economic submissions to the BMJ. The BMJ Economic Evaluation Working Party. *Bmj* 1996; **313**: 275-83.

69. US Institute for Clinical and Economic Review. Spinraza® and Zolgensma® for Spinal Muscular Atrophy: Effectiveness and Value. Final Evidence Report. April 3, 2019. (Updated May 24, 2019). 2019.

70. Thompson R, Vaidya S, Teynor M. The Utility of Different Approachs to Developing Health Utilities Data in Childhood Rare Diseases; A Case Study in Spinal Muscular Atrophy (SMA). *Value in Health* 2017; **20**: A725-A6.

71. National Institute for Health and Care Excellence (NICE). Guide to the methods of technology appraisal. 2013. Available from: https://www.nice.org.uk/process/pmg9/resources/guide-to-the-methods-of-technology-appraisal-2013-pdf-2007975843781. Date accessed: Feb 2019.

72. World Health Organization. WHO Motor Development Study: windows of achievement for six gross motor development milestones. *Acta Paediatr Suppl* 2006a; **450**: 86-95.

73. Hoyle MW, Henley W. Improved curve fits to summary survival data: application to economic evaluation of health technologies. *BMC Med Res Methodol* 2011; **11**: 139.

74. Tierney JF, Stewart LA, Ghersi D, Burdett S, Sydes MR. Practical methods for incorporating summary time-to-event data into meta-analysis. *Trials* 2007; **8**: 16.

75. National Institute for Health and Care Excellence Decision Support Unit (NICE DSU). TSD 14: Survival analysis for economic evaluations alongside clinical trials – extrapolation with patient-level data. Accessed 17th June 2019. Available at: http://nicedsu.org.uk/technical-support-documents/survival-analysis-tsd/.

76. Gregoretti C, Ottonello G, Chiarini Testa MB, Mastella C, Rava L, Bignamini E, et al. Survival of patients with spinal muscular atrophy type 1. *Pediatrics* 2013; **131**: e1509-14.

77. Zerres K, Rudnik-Schoneborn S, Forrest E, Lusakowska A, Borkowska J, Hausmanowa-Petrusewicz I. A collaborative study on the natural history of childhood and juvenile onset

proximal spinal muscular atrophy (type II and III SMA): 569 patients. *J Neurol Sci* 1997; **146**: 67-72.

78. Office for national statistics. National Life Tables. United Kingdom. Based on data from the years 2014-2016. Published September 2018. Available at: https://www.ons.gov.uk/file?uri=/peoplepopulationandcommunity/birthsdeathsandmarriages/lifeexpectancies/datasets/nationallifetablesunitedkingdomreferencetables/current/nltuk1517reg.xls.

79. Briggs AH, Claxton K, Sculpher MJ. *Decision modelling for health economic evaluation*. Oxford: Oxford University Press; 2006.

80. Bladen CL, Thompson R, Jackson JM, Garland C, Wegel C, Ambrosini A, et al. Mapping the differences in care for 5,000 spinal muscular atrophy patients, a survey of 24 national registries in North America, Australasia and Europe. *J Neurol* 2014; **261**: 152-63.

81. London UC, editor Nusinersen EAP UK. BPNA congress; 2019.

82. Finkel R, Castro, D., Farrar, M.A., Tulinius, M., Krosschell, K.J., Saito, K., Zhang, Y., Bhan, I., Farwell, W., Reyna, S.P. Longer-term assessment of nusinersen safety/efficacy in infantile-onset spinal muscular atrophy: interim analysis of SHINE. *Journal of Neuromuscular Diseases* 2018.

83. Finkel RS, Chiriboga CA, Vajsar J, Day JW, Montes J, De Vivo DC, et al. Treatment of infantile-onset spinal muscular atrophy with nusinersen: a phase 2, open-label, dose-escalation study. *Lancet* 2016; **388**: 3017-26.

84. AveXis. Data on file. UK Health State Utilities Elicitation for Spinal Muscular Atrophy - Report. 01 August 2019. 2019. 2019.

85. Tappenden P HJ, Kaltenthaler E, Hock E, Rawdin A, Mukuria C, Clowes M, Simonds A, Childs A. . Nusinersen for treating spinal muscular atrophy: A Single Technology Appraisal. School of Health and Related Research (ScHARR). 2018.

86. Ara R, Brazier JE. Populating an economic model with health state utility values: moving toward better practice. *Value Health* 2010; **13**: 509-18.

87. World Health Organization. WHO Multicentre Growth Reference Study Group: WHO Child Growth Standards based on length/height, weight and age. *Acta Paediatr Suppl* 2006b; **450**: 76-85.

88. AveXis. Data on file: UK Clinical Advisory Board: Summary Report. 28 May 2019. 2019.

89. Lloyd AJGK, Thompson, R., Vaidya, S., Teynor, M. . Estimation of the health-related quality of life benefits of treatment for spinal muscular atrophy (SMA). ISPOR 20th Annual European Congress; 2017; Glasgow, Scotland.

90. NHS Improvement. NHS Reference Costs 2018/19, 2019. Available from: https://improvement.nhs.uk/resources/national-cost-collection/. Date accessed: July 2020.

91. Noyes J, Godfrey C, Beecham J. Resource use and service costs for ventilator-dependent children and young people in the UK. *Health Soc Care Community* 2006; **14**: 508-22.

92. National Institute for Health and Care Excellence. Nusinersen for treating spinal muscular atrophy: technology appraisal guidance [TA588]. 2019.

93. Curtis LAaB, Amanda. Unit Costs of Health and Social Care 2019. . 2019.

94. NHS Digital. Prescription Cost Analysis, England. 18 March 2018. https://data.gov.uk/dataset/3eecf351-fca5-4f00-87b8-6a2282fa0d13/prescription-cost-analysis-england.

95. Department of Health and Social Care (NHS Improvement). NHS National Schedule of reference costs. National cost collection data 2018/2019.

96. National Institute for Health and Care Excellence. NICE, Motor neurone disease: assessment and management, 24 Feb 2016. Available at: https://www.nice.org.uk/guidance/ng42/resources/motor-neurone-disease-assessment-and-management-pdf-1837449470149. 2016.

97. NHS England. NHS Commissioning: Orthotic services; Local tariffs for direct access. Available at:, https://www.england.nhs.uk/wp-content/uploads/2015/11/orthcs-rep-attach-5.pdf.

98. O'Hagan T. The SHeffield ELicitation Framework (SHELF). Available from: http://www.tonyohagan.co.uk/shelf/. Date accessed: Oct 2019.

99. Droege M, Sproule D, Arjunji R, Gauthier-Loiselle M, Cloutier M, Dabbous O. Economic burden of spinal muscular atrophy in the United States: a contemporary assessment. *J Med Econ* 2019: 1-10.

100. Crawford TO, Paushkin SV, Kobayashi DT, Forrest SJ, Joyce CL, Finkel RS, et al. Evaluation of SMN protein, transcript, and copy number in the biomarkers for spinal muscular atrophy (BforSMA) clinical study. *PLoS ONE* 2012; **7**: e33572.

101. Service NH. Spinal Muscular Atrophy - Types. 2020. Available from: https://www.nhs.uk/conditions/spinal-muscular-atrophy-sma/types/. Date accessed: 14/07/2020.

102. Office for National Statistics. Birth Summary Tables, England and Wales 2017, 18 Jul 2018. Available at: https://www.ons.gov.uk/peoplepopulationandcommunity/birthsdeathsandmarriages/livebirths/bulletins/birthsummarytablesenglandandwales/2017/relateddata.

103. Wijnhoven TM, de Onis M, Onyango AW, Wang T, Bjoerneboe GE, Bhandari N, et al. Assessment of gross motor development in the WHO Multicentre Growth Reference Study. *Food and nutrition bulletin* 2004; **25**: S37-45.

104. AveXis. Data on file: Day 120 efficacy data update (31 Dec 2018). 2019.

105. de Onis M, Garza, C., Victora, C.G., Bhan, M.K., Norum, K.R. The WHO multicentre growth reference study (MGRS): Rationale, planning, and implementation. Food and Nutrition Bulletin. 2004;25(1 supplement 1).

106. Wang CH, Finkel RS, Bertini ES, Schroth M, Simonds A, Wong B, et al. Consensus statement for standard of care in spinal muscular atrophy. *J Child Neurol* 2007; **22**: 1027-49.

107. Main M, Kairon H, Mercuri E, Muntoni F. The Hammersmith functional motor scale for children with spinal muscular atrophy: a scale to test ability and monitor progress in children with limited ambulation. *Eur J Paediatr Neurol* 2003; **7**: 155-9.

108. Tilford JM, Grosse SD, Robbins JM, Pyne JM, Cleves MA, Hobbs CA. Health state preference scores of children with spina bifida and their caregivers. *Qual Life Res* 2005; **14**: 1087-98.

109. Higgs EJ, McClaren BJ, Sahhar MA, Ryan MM, Forbes R. 'A short time but a lovely little short time': Bereaved parents' experiences of having a child with spinal muscular atrophy type 1. *Journal of Paediatrics and Child Health* 2016; **52**: 40-6.

110. Kirschner J, Butoianu N, Goemans N, Haberlova J, Kostera-Pruszczyk A, Mercuri E, et al. European ad-hoc consensus statement on gene replacement therapyfor spinal muscular atrophy. *Eur J Paediatric Neurol* 2020 (in press). Availble from: https://www.ejpn-journal.com/article/S1090-3798(20)30142-2/pdf (last accessed 16 Sep 2020).

10 APPENDICES

10.1 Inclusion criteria

Table 64. Selection criteria used for review of clinical efficacy and safety studies (reproduced from CS, Table 9)

Inclusion criteria	
Population	SMA (type 1, type 2, and type 3; pre-symptomatic and symptomatic)
Interventions	Any of the following interventions used in the treatment of SMA: • Nusinersen • Onasemnogene abeparvovec (ZOLGENSMA; AVXS-101) • Branaplam • CK-2127107 • RO7034067/RG7916 • RO6885247 • Olesoxime • Proactive ventilator use and insufflator/exsufflator use (“cough assist”) • 4-aminopyridine • Anti-cholinesterase therapy/pyridostigmine bromide • Celecoxib • Hydroxyurea • Leuprolide and testosterone • Pyridostigmine • Riluzole • Sodium phenylbutyrate • Somatotropin • Valproic acid • Valproic acid and levocarnitine • Air stacking technique • Assisted standing treatment programme • Exercise • Palliation • Whole body vibration therapy
Comparators	No restrictions

Outcomes	**SMA type 1** • Efficacy outcomes: o Overall survival o Mortality (time-to-event) o Event-free survival o Achievement of motor milestones o CHOP-INTEND response o Time from treatment onset until full-time ventilation (≥16 out of 24 hours, regardless of ventilation type) • Safety outcomes: o Any adverse events o Treatment-related adverse events	**SMA type 2 and 3** • Efficacy outcomes: o Disability score (e.g. Hammersmith Functional Motor Score, Upper Limb Module, Hammersmith Functional Motor Scale Expanded, Motor Function Measure, Gross Motor Function Measure), where possible transformed to Modified Rankin Scale o Muscle strength (e.g. dynamometry, isometric strength testing, manual muscle testing), where possible transformed to Medical Research Council Sum score o Ambulatory status o Forced vital capacity • Safety outcomes: o Any adverse events o Treatment-related adverse events
Study design	• Randomised controlled trials • Single-arm or non-randomised controlled trials	
Language restrictions	Unrestricted	
Search dates	Unrestricted	

Abbreviations: CHOP-INTEND, The Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders; SMA, spinal muscular atrophy.

Table 65. Selection criteria used for review of natural history studies (reproduced CS, Table 10)

Inclusion criteria	
Population	SMA (type 1, type 2, and type 3; pre-symptomatic and symptomatic)†
Interventions	No intervention or best supportive care (natural history)
Comparators	No intervention or best supportive care (natural history)
Outcomes	• Overall survival • Event-free survival • Achievement or deterioration of motor milestones (e.g. CHOP-INTEND) • Ventilation support • Nutritional support
Study design	• Prospective cohort studies with ≥12 months of follow-up • Randomised controlled trials
Language restrictions	Unrestricted
Search dates	Unrestricted

Abbreviations: CHOP-INTEND, The Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders; PICOS, Population, intervention, comparators, outcomes, and study design; SMA, spinal muscular atrophy.
† The search and PICOS criteria allow for the inclusion of all SMA types. While publications describing SMA types 1-3will be flagged separately, ultimately only SMA type 1 will be included in this review

10.2 SLR PRISMA diagrams

Figure 18. Study selection flow diagram for clinical review (reproduced from CS, Figure 5)

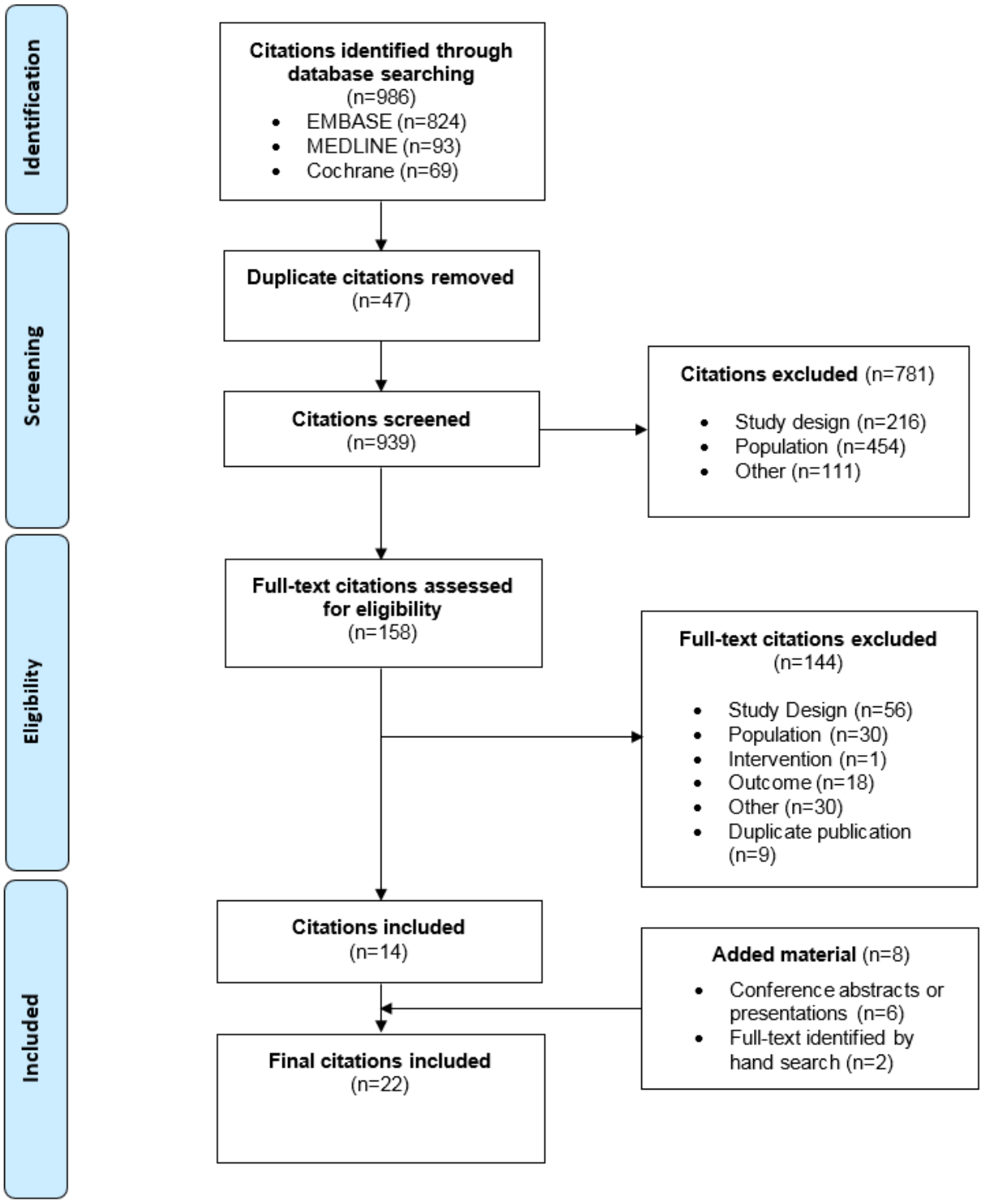
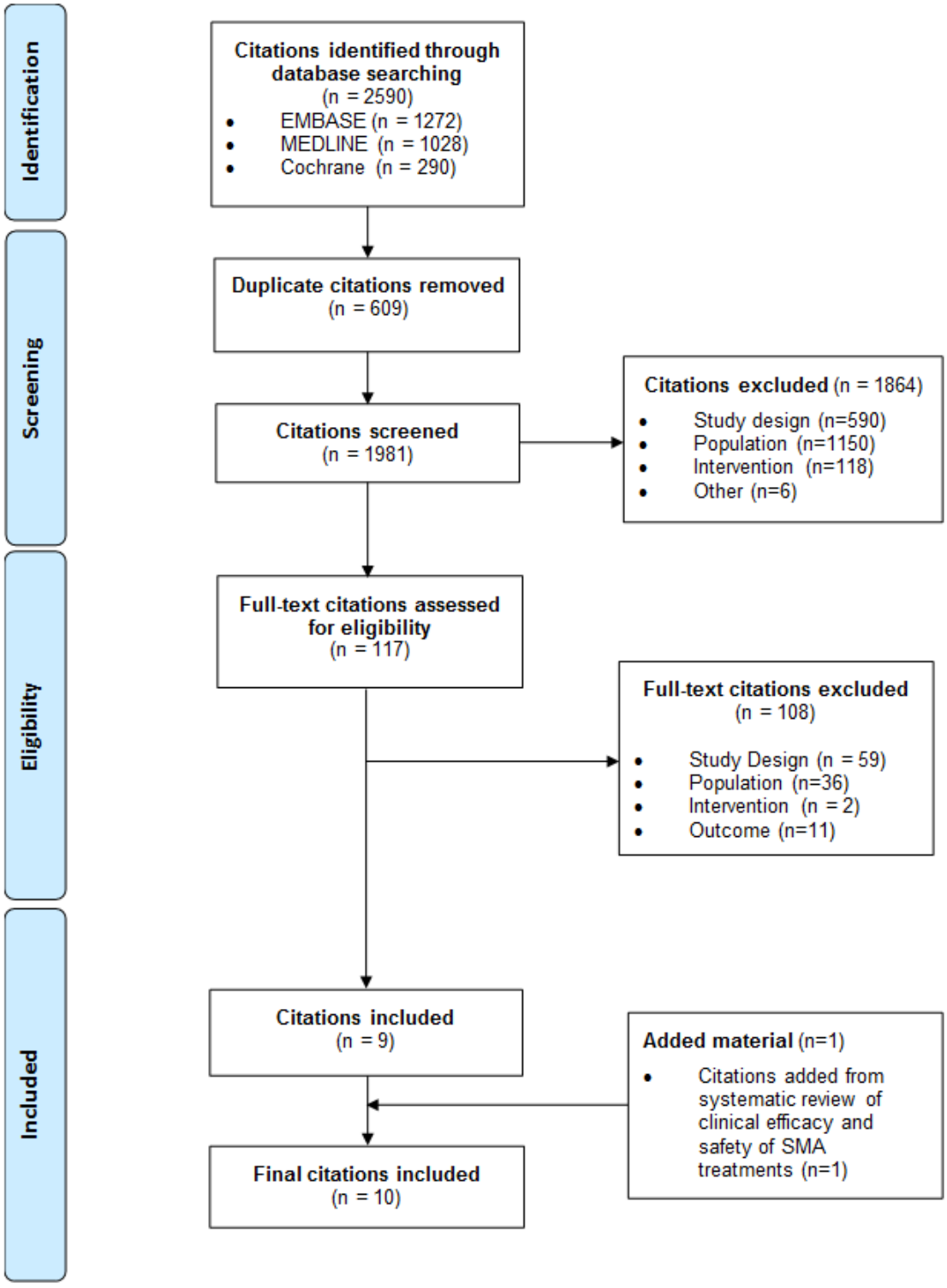


Figure 19. Study selection flow diagram for natural history review of SMA type 1 (reproduced from CS, Figure 6)



10.3 Methods of studies evaluating onasemnogene

Table 66. Summary of methodology for START (AVXS-1010-CL-101) (reproduced from CS Table 15)

Study name	Phase I gene transfer clinical trial for spinal muscular atrophy type 1 delivering AVXS-101
Objective	To assess the safety of onasemnogene abeparvovec
Location	US
Design	Phase I, open-label, one-time infusion, ascending-dose, single-centre study
Duration of study	Start date: 5 May 2014 Date of completion: 15 December 2017
Patient population	Patients with SMA type 1 possessing 2 copies of *SMN2* without c.859G>c modification in exon 7
Sample size	15 patients
Inclusion criteria	Six months of age† and younger at day of vector infusion with SMA type 1 as defined by the following features: Bi-allelic *SMN1* gene mutations (deletion or point mutation) with 2 copies of *SMN2* (no more and no fewer) Patients 6 months of age and younger with disease onset up to 6 months of age Hypotonia by clinical evaluation with delay in motor skills, poor head control, round shoulder posture, and hypermobility of joints
Exclusion criteria	Active viral infection (included HIV or serology positive for hepatitis B or C) Use of invasive ventilatory support (tracheostomy with positive pressure) or pulse oximetry <95% saturation at the screening visit Non-invasive ventilator support (e.g. BiPAP) for >16 hours/day Concomitant illness that in the opinion of the Investigator created unnecessary risks for gene transfer Concomitant use of: drugs for treatment of myopathy or neuropathy, agents used to treat diabetes mellitus, or ongoing immunosuppressive therapy or immunosuppressive therapy within 3 months of starting the study (e.g. corticosteroids, cyclosporine, tacrolimus, methotrexate, cyclophosphamide, IV immunoglobulin, rituximab) Antibody to anti-AAV9 titres >1:50 Abnormal laboratory values considered clinically significant (GGT >3 × ULN, bilirubin ≥3.0 mg/dL, creatinine ≥1.8 mg/dL, haemoglobin <8 or >18 g/dL; white blood cells >20,000/mm^3) Participation in a recent SMA treatment clinical trial or receipt of an investigational or commercial compound, product or therapy administered with the intention to treat SMA (e.g. nusinersen, valproic acid) that in the opinion of the Investigator created unnecessary risks for gene transfer Patient with signs of aspiration based on a swallowing test and unwilling to use an alternative method to oral feeding Patients with c.859G>C modification in exon 7, based on predicted mild phenotype
Intervention(s) (n =) and comparator(s) (n =)	Onasemnogene abeparvovec (IV) Cohort 1 received a low dose 6.7×10^{13} vg/kg (n=3) Cohort 2 received a therapeutic dose 2.0×10^{14} vg/kg‡ (n=12) Comparator: natural history cohort§

Baseline differences	See full details of baseline characteristics in Section 4.2.1
Duration of follow-up, participants lost to follow-up information	During the first year of the 2-year safety follow-up period, patients returned for post-dose follow-up visits on Days 7, 14, 21, and 30, followed by monthly visits through Month 12 During the second year, patients with CHOP-INTEND scores ≥62 were assessed with the Bayley Scales and completed visits every 3 months; all other patients completed monthly visits (subsequently changed to quarterly visits)
Statistical tests	Efficacy analyses conducted for START were considered descriptive by agreement with FDA and were performed without a statistical analysis plan The following analysis sets were used for the statistical analyses: SAS, ITT, FAS, EES, mITT, per protocol set, and ability to thrive ITT population Changes from baseline to each study visit were analysed with the use of a mixed-effects model for repeated measurements. The mixed model included the fixed effects of cohort and visit and a covariate of baseline score. Statistical analyses were performed with the use of SAS software, version 9.4. All hypothesis testing was conducted at the 0.05 level of significance except for the endpoint of survival, which was conducted at the 0.025 level of significance. Tests were 1-sided or 2-sided, as appropriate, and were considered descriptive. Categorical measures, such as percent surviving event-free, were summarised using counts and percentages.
Primary outcomes (including scoring methods and timings of assessments)	Primary Objective: Safety (AEs, laboratory evaluations, DILI, vital signs, ECGs, physical examinations, and immunologic response) Primary efficacy endpoint: Survival, defined as time from birth to either (a) requirement of ≥16-hour respiratory assistance per day (includes BiPAP) continuously for ≥2 weeks in the absence of an acute reversible illness, excluding perioperative ventilation or (b) death Efficacy analyses were conducted at the following time points: The date at which all patients had completed a study visit after reaching 13.6 months of age When the last enrolled patient had a study visit after reaching 20 months of age When all patients completed 24 months of post-dose follow-up
Secondary outcomes (including scoring methods and timings of assessments)	Secondary efficacy endpoints Change in CHOP-INTEND from baseline score Demonstration of improvement of motor function and muscle strength as determined by achievement of significant development milestones including but not limited to the ability to sit alone and roll over unassisted
Exploratory efficacy endpoints	Maintain ability to thrive defined as meeting the following criteria at the each of the 3 efficacy data time points: The ability to tolerate thin liquids as demonstrated through a formal swallowing test Did not receive nutrition through mechanical support (e.g. feeding tube) Maintained weight (>3rd percentile for age and gender as defined by WHO guidelines) at the time of the primary efficacy data cut-off A patient was defined as not requiring non-oral nutrition at baseline if the patient 1) did not use non-oral nutrition of any kind and 2) demonstrated intact swallowing at the baseline assessment such that the patient did not receive a recommendation for non-oral nutrition prior to onasemnogene abeparvovec administration Independence from ventilatory support defined as requiring no daily ventilator support/usage at the 3 efficacy analysis time points, in the absence of acute reversible illness and excluding perioperative ventilation Achievement of CHOP-INTEND threshold scores of ≥40, ≥50, and ≥60 by the time of the primary efficacy data cut-off and at 24 months post-infusion

	Development of significant motor function milestones per gross motor skills checklist Achievement of functional independent sitting (≥30 seconds) based on video reviews by an external expert Change from baseline in fine and gross motor components of the Bayley Scales of Infant and Toddler Development Motor neurone function assessed through CMAP and MUNE The proportion of patients who used non-oral feeding (gastrostomy with Nissen fundoplication, gastrostomy without Nissen fundoplication, nasogastric, or nasojejunal) The types of and reasons for invasive ventilatory support required by patients Hospitalisations during the study

† This inclusion criterion was revised to allow enrolment of patients 6 months of age or younger. The first 9 patients were enrolled under previous version(s) of the protocol, which allowed an age range of 9 months or younger.
‡ Direct testing of the actual lot of IMP used in START by an improved and more fully qualified analytical method has determined the actual dose received by Cohort 2 to be 1.1 x 1014 vg/kg. The same method has been used to establish an equivalent dose for the IMP in all Phase III trials.
§ Well characterised external datasets from SMA natural history studies (PNCR and NeuroNext [30]) are used to provide an external control comparator.
Abbreviations: AAV9, adeno-associated virus serotype 9; AE, adverse event; BiPAP, bi-level positive airway pressure; CHOP-INTEND, Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders; CMAP, compound motor action potential; DILI, drug-induced liver injury; ECG, electrocardiogram; EES, efficacy evaluable set; FAS, full analysis set; GGT, gamma-glutamyl transferase; HIV, human immunodeficiency virus; IMP, investigational medicinal product; ITT, intention-to treat; IV, intravenous; MUNE, motor unit number estimation; mITT, modified ITT; PNCR, Pediatric Neuromuscular Clinical Research database; SAS, safety analysis set; SMA, spinal muscular atrophy; SMN, survival motor neurone; ULN, upper limit of normal; WHO, World Health Organization.

Table 67. Summary of methodology for STR1VE-US (AVXS-101-CL-303) (reproduced from CS Table 17)

Study name	Phase III, open-label, single-arm, single-dose gene replacement therapy clinical trial for patients with spinal muscular atrophy type 1 with one or two *SMN2* copies delivering onasemnogene abeparvovec by intravenous infusion
Objective	To determine the efficacy of onasemnogene abeparvovec
Location	US
Design	Phase III, open-label, single-arm, one-time infusion gene replacement study
Duration of study	Start date: Q2 2017 Completion date: Q4 2019
Patient population	Patients with SMA type 1 with 1 or 2 copies of *SMN2* <6 months of age at the time of gene replacement therapy
Sample size	21 (enrolled n=22†)
Inclusion criteria	• Diagnosis of SMA based on gene mutation analysis with bi-allelic *SMN1* mutations (deletion or point mutations) and 1 or 2 copies of *SMN2* (inclusive of the known *SMN2* gene modifier mutation [c.859G>C]) • Patients must be <6 months (<180 days) of age at the time of onasemnogene abeparvovec infusion • Patients must have a swallowing evaluation test performed prior to administration of gene replacement therapy • Up-to-date on childhood vaccinations

Exclusion criteria	• Previous, planned or expected scoliosis repair surgery/procedure during the study assessment period • Pulse oximetry <96% saturation at screening while the patient is awake or asleep without any supplemental oxygen or respiratory support, or for altitudes >1,000 m, oxygen saturation <92% awake or asleep without any supplemental oxygen or respiratory support. Pulse oximetry saturation may decrease to <96% after screening provided that the saturation does not decrease by ≥4 percentage points • Tracheostomy or current use or requirement of non-invasive ventilatory support averaging ≥6 hours daily over the 7 days prior to the screening visit; or ≥6 hours/day on average during the screening period or requiring ventilatory support while awake over the 7 days prior to screening or at any point during the screening period prior to dosing • Patients with signs of aspiration/inability to tolerate non-thickened liquids based on a formal swallowing test performed as part of screening. Patients with a gastrostomy tube who pass the swallowing test will be allowed to enrol in the study • Patients whose weight-for-age is below the third percentile based on WHO Child Growth Standards [87] • Active viral infection (includes HIV or positive serology for hepatitis B or C, or Zika virus) • Serious non-respiratory tract illness requiring systemic treatment and/or hospitalisation within 2 weeks prior to screening • Upper or lower respiratory infection requiring medical attention, medical intervention, or increase in supportive care of any manner within 4 weeks prior to screening • Severe non-pulmonary/respiratory tract infection (e.g. pyelonephritis, or meningitis) within 4 weeks before administration of gene replacement therapy or concomitant illness that, in the opinion of the Principal Investigator, creates unnecessary risks for gene replacement therapy • Known allergy or hypersensitivity to prednisolone or other glucocorticosteroids or their excipients • Concomitant use of any of the following: drugs for treatment of myopathy or neuropathy, agents used to treat diabetes mellitus, or ongoing immunosuppressive therapy, plasmapheresis, immunomodulators such as adalimumab, immunosuppressive therapy within 3 months prior to gene replacement therapy (e.g. corticosteroids, cyclosporine, tacrolimus, methotrexate, cyclophosphamide, IV immunoglobulin, rituximab) • Anti-AAV9 antibody titre >1:50. Should a potential patient demonstrate anti-AAV9 antibody titer >1:50, he or she may receive retesting within 30 days of the screening period and will be eligible to participate if the anti-AAV9 antibody titer upon retesting is ≤1:50 o The mothers of enrolled patients were also screened for anti-AAV9 antibodies. Mothers who tested positive for antibodies to AAV9 were be asked to refrain from further feedings with breast milk. If AAV9 antibodies were identified, the patient stopped consuming breast milk from the biological mother. Patients consuming banked breast milk from donor sources that could not be test for anti-AAV9 antibodies were transitioned to formula prior to participation • Clinically significant abnormal laboratory values (GGT, ALT, and AST >3 × ULN, bilirubin ≥3.0 mg/dL, creatinine ≥1.0 mg/dL, Hgb <8 or >18 g/dL, WBC >20,000/cmm) prior to gene replacement therapy • Participation in recent SMA treatment clinical study (with the exception of observational cohort studies or non-interventional studies) or receipt of an investigational or commercial compound, product, or therapy administered with the intention to treat SMA (e.g.

	nusinersen, valproic acid) at any time prior to screening for this study. Oral β-agonists must be discontinued at least 30 days before gene replacement therapy dosing. Inhaled albuterol specifically prescribed for the purposes of respiratory (bronchodilator) management is acceptable and not a contraindication at any time prior to screening for this study • Expectation of major surgical procedures during the study assessment period (e.g. spinal surgery or tracheostomy) • Gestational age at birth <35 weeks (245 days)
Intervention(s) (n =) and comparator(s) (n =)	Onasemnogene abeparvovec at 1.1 X 10^{14} vg/kg[‡] will be administered as a one-time peripheral IV infusion over approximately 30–60 minutes (enrolled n=22[†]) Comparator: natural history cohort[§]
Baseline differences	See full details of baseline characteristics in Section 4.2.2.
Duration of follow-up, participants lost to follow-up information	During the outpatient follow-up period (Day 4 to End of Study at 18 months of age), patients returned at regularly scheduled intervals for efficacy and safety assessments. Missed visits were rescheduled as soon as possible, but within 7 days and still within the required visit window. For the 14 and 18 months of age visits, the patient will return within 0 to 14 days after the date on which the patient reaches 14 and 18 months of age, respectively. The 18 months of age visit will also serve as the End of Study visit. After the End of Study visit, eligible patients may roll over into the long-term follow-up study
Statistical tests	<u>Primary efficacy endpoints:</u> The number and percent of patients whom, through video evidence, exhibit the milestone achievement of sitting without support at any visit up to and including 18 months of age study visit will be summarised for the ITT population. A one-sided Exact Binomial Test will be used to test the null hypothesis of p=0.1% at significance level of 0.025. Furthermore, the corresponding 95% confidence intervals will be estimated by the exact method for binomial proportions. The observed proportion surviving in the current study was compared with the natural history data of the matching cohort using a two-sample Fisher's exact test, along with the corresponding 95% confidence intervals
Primary outcomes (including scoring methods and timings of assessments)	<u>Co-primary outcomes:</u> • Proportion of patients who achieved functional independent sitting for ≥30 seconds at the 18 months of age study visit • Survival, defined as avoidance of either (a) death or (b) permanent ventilation, at 14 months of age. Permanent ventilation is defined by tracheostomy or by the requirement of ≥ 16 hours of respiratory assistance per day (via non-invasive ventilatory support) for ≥ 14 consecutive days in the absence of an acute reversible illness, excluding perioperative ventilation.

Secondary outcomes (including scoring methods and timings of assessments)	Co-secondary outcomes: • Proportion of patients maintaining the ability to thrive, defined as the ability to tolerate thin liquids (as demonstrated through a formal swallowing test) and to maintain weight (>3rd percentile based on WHO Child Growth Standards [87] for age and gender) without need of gastrostomy or other mechanical or non-oral nutritional support at 18 months of age • Proportion of patients who are independent of ventilatory support, defined as requiring no daily ventilator support/usage at 18 months of age, excluding acute reversible illness and perioperative ventilation, as defined above through assessment of actual usage data captured from the device (Phillips Trilogy)
Exploratory efficacy endpoints	• Achievement of the ability to: o hold head erect without support o roll from back to both sides o sit with support o sit independently (>10 seconds; WHO Motor Developmental Milestones [103]) o crawl o pull to stand o stand with assistance o stand alone o walk with assistance o walk alone • Change from baseline in fine and gross motor components of the Bayley Scales of Infant and Toddler Development • Change from baseline in gross motor function as determined by improvement CHOP-INTEND score • Proportion of patients achieving CHOP-INTEND score ≥40 • Proportion of patients achieving CHOP-INTEND score ≥50 • Proportion of patients achieving CHOP-INTEND score ≥58 • Improvement in peroneal nerve CMAP amplitude • Age at which independent sitting (30 seconds) is first achieved

† As of 31 December 2018 data cut[104] 22 patients enrolled; 1/22 patients was initially enrolled as a pre-symptomatic SMA patient, however this patient was reclassified as symptomatic by the Investigator after 31 December 2018.
‡ Equivalent to the dose received by the Cohort 2 in START as determined by direct product testing with improved analytical methods. Direct testing of the actual lot of IMP used in START by an improved and more fully qualified analytical method has determined the actual dose received by Cohort 2 to be 1.1×10^{14} vg/kg. The same method has been used to establish an equivalent dose for the IMP in all Phase III trials.
§ Well characterised external datasets from SMA natural history studies (PNCR and NeuroNext [30]) are used to provide an external control comparator.
Abbreviations: AAV9, adeno-associated virus serotype 9; CMAP, compound motor action potential; GGT, gamma glutamyl- transpeptidase; Hgb, haemoglobin; HIV, human immunodeficiency virus; IMP, investigational medicinal product; ITT, intention-to-treat; IV, intravenous; PNCR, Pediatric Neuromuscular Clinical Research database; SMA, spinal muscular atrophy; *SMN*, survival motor neurone; US, United States; WBC, white blood cell; WHO, World Health Organization.

Table 68. Summary of methodology for STR1VE-EU (AVXS-101-CL-302) (reproduced from CS, Table 16)

Study name	Phase III, open-label, single-arm, single-dose gene replacement therapy clinical trial for patients with spinal muscular atrophy type 1 with one or two *SMN2* copies delivering AVXS-101 by intravenous infusion
Objective	To assess the efficacy of onasemnogene abeparvovec
Location	12−16 European investigative sites located in the following countries: Belgium, France, Germany, Italy, Netherlands, Spain, UK (2 sites), Sweden
Design	Phase III open-label, single-arm, one-time infusion trial investigating the efficacy and safety of onasemnogene abeparvovec in patients with SMA type 1
Duration of study	Estimated start date: Q2 2018. Estimated date of completion: Q4 2020 (amended from Q3 to Q4 during assessment of supplementary appendix)
Patient population	Symptomatic SMA type 1 patients genetically defined by no functional *SMN1* as well as 1 or 2 copies of *SMN2* who are ≤6 months of age at time of gene replacement therapy infusion
Sample size	Planned: up to 30 patients (enrolled n=33[†])
Inclusion criteria	• Patients with SMA type 1 as determined by diagnosis of SMA based on gene mutation analysis with biallelic *SMN1* mutations (deletion or point mutations) and one or two copies of *SMN2* (inclusive of the known *SMN2* gene modifier mutation [c.859G>C]) • Aged <6 months (<180 days) at the time of onasemnogene abeparvovec infusion • Patients must have a swallowing evaluation test performed prior to administration of gene replacement therapy • Up-to-date on childhood vaccinations
Exclusion criteria	• Previous, planned or expected scoliosis repair surgery/procedure prior to 18 months of age • Use of invasive ventilatory support (tracheostomy with positive pressure) or pulse oximetry <95% saturation at screening (saturation must not decrease ≥4 percentage points between screening and dosing with confirmatory oximetry reading), patients may be put on non-invasive ventilatory support for <12 hours per day at the discretion of their physician or trial staff) • Use or requirement of non-invasive ventilatory support for ≥12 hours daily in the 2 weeks prior to dosing • Patient with signs of aspiration based on a swallowing test or whose weight-for-age falls below the third percentile based on WHO Child Growth Standards, and unwilling to use an alternative method to oral feeding • Active viral infection (includes HIV or positive serology for hepatitis B or C, or known Zika virus infection) • Serious non-respiratory tract illness requiring systemic treatment and/or hospitalization within 2 weeks prior to screening • Upper or lower respiratory infection requiring medical attention, medical intervention, or increase in supportive care of any manner within 4 weeks prior to screening.

	• Severe non-pulmonary/respiratory tract infection (e.g. pyelonephritis, or meningitis) within 4 weeks before administration of gene replacement therapy or concomitant illness that, in the opinion of the Investigator, creates unnecessary risks for gene replacement • Known allergy or hypersensitivity to prednisolone or other glucocorticosteroids or their excipients • Concomitant use of any of the following: drugs for treatment of myopathy or neuropathy, agents used to treat diabetes mellitus, or ongoing immunosuppressive therapy, plasmapheresis, immunomodulators such as adalimumab, or immunosuppressive therapy within 3 months prior to gene replacement therapy • Anti-AAV9 antibody titre >1:50. Should a potential patient demonstrate anti-AAV9 antibody titer >1:50, he or she may receive retesting within 30 days of the screening period and will be eligible to participate if the anti-AAV9 antibody titer upon retesting is ≤1:50 • Biological mother refuses anti-AAV9 antibody testing prior to dosing o The mothers of enrolled patients were also screened for anti-AAV9 antibodies. If AAV9 antibodies were identified, the investigator discussed with the mother whether to continue or to stop breastfeeding. Biological mothers who tested positive for antibodies to AAV9 were asked to refrain from further feedings with breast milk until at least 1 month after the onasemnogene abeparvovec administration. Patients consuming banked breast milk from donor sources that could not be tested for anti-AAV9 antibodies were transitioned to formula prior to participation • Clinically significant abnormal laboratory values prior to gene replacement therapy (GGT, ALT, and AST >3x ULN; bilirubin ≥3.0 mg/dL; creatinine ≥1.0 mg/dL; Hgb <8 or >18 g/dL; WBC >20,000/cmm) • Participation in recent SMA treatment clinical trial (with the exception of observational cohort studies or non-interventional studies) or receipt of an investigational or commercial compound, product or therapy administered with the intention to treat SMA (e.g. nusinersen, valproic acid) at any time prior to screening for this trial. Oral beta-agonists must be discontinued ≥30 days prior to dosing • Expectation of major surgical procedures during the trial assessment period (e.g. spinal surgery or tracheostomy) • Patients <35 weeks gestational age at time of birth
Intervention(s) (n =) and comparator(s) (n =)	Intervention: peripheral IV infusion of 1.1 X 10^{14} vg/kg‡ onasemnogene abeparvovec (enrolled n=33†) Comparator: natural history cohort§
Baseline differences	See full details of baseline characteristics in Section 4.2.2.

Duration of follow-up, participants lost to follow-up information	Patients will return for follow-up visits on Days 7, 14, 21, and 30. Patients will return monthly thereafter, following the Day 30 visit, for 18 months from dose administration.
Statistical tests	Primary efficacy endpoint: The number and percent of patients whom, through video evidence, exhibit the milestone achievement of sitting without support at any visit up to and including 18 months of age study visit will be summarised for the ITT population. A one-sided Exact Binomial Test will be used to test the null hypothesis of p=0.1% at significance level of 0.025. Furthermore, the corresponding 95% confidence intervals will be estimated by the exact method for binomial proportions. Secondary efficacy endpoint: The observed proportion surviving in the current study was compared with the natural history data of the matching cohort using a two-sample Fisher's exact test, along with the corresponding 95% confidence intervals.
Primary outcomes (including scoring methods and timings of assessments)	The primary objective was to demonstrate efficacy by achievement of the developmental milestone of sitting without support for at least 10 seconds up to 18 months of age (as assessed by WHO Motor Development Milestones)
Secondary outcomes (including scoring methods and timings of assessments)	To determine efficacy based on survival at 14 months of age, defined by the avoidance of combined endpoint of either (a) death or (b) permanent ventilation (defined by tracheostomy or by the requirement of ≥16 hours of respiratory assistance per day [via non-invasive ventilatory support] for ≥14 consecutive days in the absence of an acute reversible illness, excluding perioperative ventilation)

Exploratory efficacy endpoints	• Achievement of the ability to: o hold head erect without support o roll over o sit with support [58] o achieve functional independent sitting for at least 30 seconds [58] o crawl as defined by WHO Motor Developmental Milestones [103] o pull to stand o stand with assistance as defined by WHO Motor Developmental Milestones [103] o stand alone as defined by WHO Motor Developmental Milestones [103] o walk with assistance as defined by WHO Motor Developmental Milestones [103] o walk alone as defined by WHO Motor Developmental Milestones [103] • Change from baseline in fine and gross motor components of the Bayley Scales of Infant and Toddler Development • Change from baseline in gross motor function as determined by improvement CHOP-INTEND score • Ability to remain independent of ventilator support, defined as requiring no daily ventilator support/usage at 18 months of age • Maintain ability to thrive defined as meeting the following criteria at the each of the 3 efficacy data time points: o The ability to tolerate thin liquids as demonstrated through a formal swallowing test o Did not receive nutrition through mechanical support (e.g. feeding tube) o Maintained weight (>3rd percentile for age and gender as defined by WHO guidelines) at the time of the primary efficacy data cut-off

† Enrolment to STR1VE-EU completed in May 2019 (N=33). At the 8 March 2019 data cut [45], 23/33 infants with SMA type 1 were enrolled in STR1VE-EU.
‡ Equivalent to the dose received by the Cohort 2 in START as determined by direct product testing with improved analytical methods. Direct testing of the actual lot of IMP used in START by an improved and more fully qualified analytical method has determined the actual dose received by Cohort 2 to be 1.1×10^{14} vg/kg. The same method has been used to establish an equivalent dose for the IMP in all Phase III trials.
§ Well characterised external datasets from SMA natural history studies (PNCR and NeuroNext [30]) are used to provide an external control comparator.
Abbreviations: AAV9, adeno-associated virus serotype 9; ALT, alanine aminotransferase; AST, aspartate aminotransferase; CHOP-INTEND, Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders ; GGT, gamma-glutamyl transpeptidase; Hgb, haemoglobin; HIV, human immunodeficiency virus; IMP, investigational medicinal product; ITT, intention-to-treat; IV, intravenous; PNCR, Pediatric Neuromuscular Clinical Research database; SMA, spinal muscular atrophy; *SMN*, survival motor neurone; UK, United Kingdom; ULN, upper limit of normal; WBC, white blood cell; WHO, World Health Organization.

Table 69. Summary of methodology for LT-001 (extension of START) (reproduced from CS Table 19)

Study name	A long-term follow-up safety study of patients in the AVXS-101-CL-101 gene replacement therapy clinical trial for spinal muscular atrophy type 1 delivering AVXS-101
Objective	To collect long-term follow-up safety data of patients with SMA type 1 who were treated with onasemnogene abeparvovec in START
Location	US
Design	Long-term, safety follow-up study
Duration of study	Estimated start date: Q2 2017 Estimated date of completion: Q4 2033
Patient population	Patients with SMA type 1 who were treated with onasemnogene abeparvovec in START
Sample size	Planned: up to 15 (enrolled n=13[†])
Inclusion criteria	• Patient who received onasemnogene abeparvovec in the START gene replacement therapy clinical trial for SMA type 1 • Parent/legal guardian willing and able to complete the informed consent process and comply with study procedures and visit schedule
Exclusion criteria	• Parent/legal guardian unable or unwilling to participate in the long-term follow-up safety study
Intervention(s) (n =) and comparator(s) (n =)	Study drug was not administered in LT-001 they were dosed in START
Baseline differences	See full details of baseline characteristics in Section 4.2.2.
Duration of follow-up, participants lost to follow-up information	The study will consist of an initial 5-year phase, during which subjects will be seen annually for evaluation of long-term safety, followed by a 10-year observational phase. Upon completion of the initial five years of follow-up visits, patients will be contacted via phone annually for the remaining 10-year follow-up period. During the 10-year observational phase, caregivers and patients will be contacted at least once a year and site staff will review a yearly questionnaire designed to elicit information regarding medical history, adverse events, and other clinical conditions. Additionally, patient record transfers from their local physician and/or neurologist will be requested in conjunction with the annual phone contacts for review by the investigator
Statistical tests	This is a long-term follow-up study with safety as the primary measure. Sample size was not determined through statistical justification

Primary outcomes (including scoring methods and timings of assessments)	<u>Safety assessments:</u> • Medical history and record review • Physical examinations, including height, weight, vital signs, ventilation, nutritional support, and developmental milestone assessments • Clinical laboratory evaluations • Pulmonary assessments • Echocardiograms, holter monitoring, electrocardiograms <u>Efficacy assessments:</u> • Physical examinations to assess developmental milestones o New milestones demonstrated by patients which were not documented during START must be supported by video evidence
Secondary outcomes (including scoring methods and timings of assessments)	N/A

† Number of patients enrolled as of 31 December 2018 data cut.[104]
Abbreviations: N/A, not applicable; SMA, spinal muscular atrophy.

Table 70. Summary of methodology for LT-002 (long-term extension study) (reproduced from CS Table 20)

Study name	A long-term follow-up study of patients in the clinical trials for spinal muscular atrophy receiving AVXS-101
Objective	To collect long-term follow-up safety and efficacy data of patients with SMA type 1, 2, or 3 who were treated with onasemnogene abeparvovec in an onasemnogene abeparvovec clinical trial, including but not limited AVXS-101-CL-302 (Phase III), AVXS-101-CL-303 (Phase III), and AVXS-101-CL-304 (Phase III) In addition, patients treated with onasemnogene abeparvovec (intravenous or intrathecal) in future parent studies may be enrolled
Location	Studies may be conducted in any location worldwide
Design	Long-term, safety and efficacy follow-up study
Duration of study	Estimated start date: Q4 2019 Estimated date of completion: Q4 2034
Patient population	Patients participating in clinical trials for SMA type 1, 2, or 3 who were treated with onasemnogene abeparvovec
Sample size	Planned: approximately 308 • Cohort 1 (patients dosed IV): approximately 83 • Cohort 2 (patients dosed IT): approximately 225
Inclusion criteria	• Patients with SMA (with 1, 2 or 3 copies of survival motor neuron gene 2) who received onasemnogene abeparvovec gene replacement therapy in an AveXis clinical study • Patient/parent/legal guardian willing and able to complete the informed consent process and comply with study procedures and visit schedule
Exclusion criteria	• Patient/parent/legal guardian unable or unwilling to participate in the long-term follow-up study
Intervention(s) (n =) and comparator(s) (n =)	Study drug was not administered in LT-002
Baseline differences	N/A

Duration of follow-up, participants lost to follow-up information	Monitoring will continue for up to 15 years from the date of onasemnogene abeparvovec dosing. The number of study visits required in LT-002 will depend on the length of participation in the parent study. For example, patients followed 1 year in the parent study will participate in LT-002 for 14 years, patients followed 2 years in the parent study will participate for 13 years, and patients followed for 3 years in the parent study will participate for 12 years. If the HFMSE was performed during the parent study, within 6 months of the baseline visit in LT-002, it does not need to be repeated (parent study HMFSE may serve as the baseline for LT-002). If not done as part of the last visit in the parent study, or if the last HMFSE was conducted >6 months prior to the initial visit in LT-002, the HMFSE evaluation may be performed at the initial visit of LT-002. Patients will then return bi-annually for follow-up study visits for 2 years. Thereafter, in-person annual follow-up visits will be conducted for years 3 to 5. Patients will then be contacted via phone annually for the remainder of the study, until 15 years from the date of onasemnogene abeparvovec dosing
Statistical tests	The primary analysis of evaluating safety and efficacy data will be conducted when the last patient has completed the initial 5-year phase annual safety follow-up study visit or has discontinued study follow-up. Since less data will be collected during the 10-year observational phase which is based on annual telephone contact, analyses on serious adverse events, adverse events of special interest and pulmonary assessment will be implemented at the end of study using data collected during the 10-year observational phase Descriptive statistical methods will be used to summarise the data from this study. Continuous data, such as lab values, will be summarised using count, mean, median, standard deviation, minimum, and maximum. For continuous data specified to be analysed using parametric procedures, non-parametric procedures will be used if the parametric procedure is felt to be inappropriate
Primary outcomes (including scoring methods and timings of assessments)	<u>Safety assessments:</u> • Medical history and record review • Physical examinations, including height, weight, vital signs, ventilatory and nutritional support • Clinical laboratory evaluations • Pulmonary assessments • Cardiac assessments • Observational phase questionnaire <u>Efficacy assessments:</u> • Physical examinations to assess developmental milestones • New milestones demonstrated by patients which were not documented during onasemnogene abeparvovec study must be supported by video evidence • HFMSE to be performed during first 2 years of study in all patients • Pulmonary assessments • Swallowing questionnaire
Secondary outcomes (including	N/A

scoring methods and timings of assessments)	

Abbreviations: HFMSE, Hammersmith Functional Motor Scale - Expanded; N/A, not applicable; SMA, spinal muscular atrophy.

Table 71. Summary of methodology for SPR1NT (AVXS-101-CL-304) (reproduced from CS Table 18)

Study name	A global study of a single, one-time dose of AVXS-101 delivered to infants with genetically diagnosed and pre-symptomatic spinal muscular atrophy with multiple copies of *SMN2*
Objective	To evaluate the safety and efficacy of onasemnogene abeparvovec in infants with genetically diagnosed and pre-symptomatic spinal muscular atrophy
Location	15–25 global centres in the US, Australia, Belgium, Canada, Germany, Israel, Japan, Spain, Taiwan, and the UK (1 site)
Design	Phase III, open-label, single-arm study of a one-time infusion of onasemnogene abeparvovec in patients with spinal muscular atrophy
Duration of study	Estimated start date: Q1 2018 Estimated date of completion: *SMN2* 2 copies: Q4 2020; *SMN2* 3 copies: Q2 2021
Patient population	Pre-symptomatic patients with type 1 or 2 SMA genetically defined by bi-allelic deletion of *SMN1* with 2 or 3 copies of *SMN2* and ≤6 weeks of age at the time of gene replacement therapy who meet enrolment criteria
Sample size	Planned: ≥27 (enrolled n=29[†])
Inclusion criteria	**All patients** • Age ≤6 weeks (≤42 days) at time of dose • Ability to tolerate thin liquids as demonstrated through a formal bedside swallowing test • CMAP ≥2 mV at baseline; centralised review of CMAP data will be conducted • Gestational age of 35 to 42 weeks • Genetic diagnosis as described below, obtained from an acceptable newborn or pre-natal screening test method **Patients with 2 copies of *SMN2* (n≥15)** • Patients with pre-symptomatic SMA type 1 as determined by 2 copies of *SMN2* **Patients with 3 copies of *SMN2* (n≥12)** • Patients with pre-symptomatic SMA type 2 as determined by 3 copies of *SMN2*
Exclusion criteria	• Weight at screening visit <2 kg

	• Hypoxaemia (oxygen saturation <96% awake or asleep without any supplemental oxygen or respiratory support) at the screening visit or for altitudes >1,000 m, oxygen saturation <92% awake or asleep without any supplemental oxygen or respiratory support at the screening visit • Any clinical signs or symptoms at screening or immediately prior to dosing that are, in the opinion of the Investigator, strongly suggestive of SMA (e.g. tongue fasciculation, hypotonia, areflexia) • Tracheostomy or current prophylactic use or requirement of non-invasive ventilatory support at any time and for any duration prior to screening or during the screening period • Patients with signs of aspiration/inability to tolerate non-thickened liquids based on a formal swallowing test performed as part of screening or patients receiving any non-oral feeding method • Clinically significant abnormalities in haematology or clinical chemistry parameters as determined by the investigator or medical monitor • Treatment with an investigational or commercial product, including nusinersen, given for the treatment of SMA. This includes any history of gene replacement therapy, prior antisense oligonucleotide treatment, or cell transplantation. • Patients whose weight-for-age is below the third percentile based on WHO Child Growth Standards [87] • Biological mother with active viral infection as determined by screening laboratory samples (includes HIV or positive serology for hepatitis B or C) • Serious non-respiratory tract illness requiring systemic treatment and/or hospitalisation within 2 weeks prior to screening • Upper or lower respiratory infection requiring medical attention, medical intervention, or increase in supportive care of any manner within 4 weeks prior to dosing • Severe non-pulmonary/respiratory tract infection (e.g. pyelonephritis, or meningitis) within 4 weeks before administration of gene replacement therapy or concomitant illness that, in the opinion of the Investigator or Sponsor medical monitor, creates unnecessary risks for gene replacement therapy • Known allergy or hypersensitivity to prednisolone or other glucocorticosteroids or their excipients • Previous, planned or expected major surgical procedure including scoliosis repair surgery/procedure during the study assessment period • Concomitant use of any of the following: drugs for treatment of myopathy or neuropathy, agents used to treat diabetes mellitus, or ongoing immunosuppressive therapy, plasmapheresis, immunomodulators such as adalimumab, immunosuppressive therapy within 4 weeks prior to gene replacement therapy (e.g. corticosteroids, cyclosporine, tacrolimus, methotrexate, cyclophosphamide, IV immunoglobulin, rituximab) • Anti-AAV9 antibody titre >1:50

	• Biological mother refuses anti-AAV9 antibody testing prior to dosing o The mothers of potential participants were screened for anti-AAV9 antibodies. Patient samples for anti-AAV9 screening were collected if biological mother's titer result was positive. If AAV9 antibodies were identified, the investigator discussed with the mother whether to continue or to stop breastfeeding. Patients consuming banked breast milk from donor sources that could not be tested for anti-AAV9 antibodies were transitioned to formula prior to participation. Patients who do not have a biological mother available to screen for antibodies to AAV9 will have blood drawn for screening of anti-AAV9 antibodies.
Intervention(s) (n =) and comparator(s) (n =)	Onasemnogene abeparvovec at 1.1 X 10^{14} vg/kg‡ will be administered as a one-time peripheral IV infusion over approximately 60 minutes (planned n=30, enrolled n=29†) Comparator: natural history cohort§
Baseline differences	See full details of baseline characteristics in Section 4.2.2.
Duration of follow-up, participants lost to follow-up information	During the outpatient follow-up period (Days 3 to End of Study at 18 or 24 months of age, dependent upon respective *SMN2* copy number), patients will return at regularly scheduled intervals for efficacy and safety assessments until the End of Study when the patient reaches 18 months of age (*SMN2* = 2), 24 months of age (*SMN2* = 3)
Statistical tests	Primary efficacy endpoint in patients with 2 copies of *SMN2*: The proportion of patients who exhibit the milestone achievement of sitting without support for at least 30 seconds up to 18 months of age will be summarised for the ITT population. A one-sided Exact Binomial Test will be used to test the null hypothesis of p=0.1% at significance level of 0.025 Primary efficacy endpoint in patients with 3 copies of *SMN2*: The proportion of patients who achieve the ability to stand without support for at least three seconds up to 24 months of age will be compared with the natural history data of the matching cohort using a two sample 2-sided superiority Fisher exact test with a significance level of 0.05
Primary outcomes (including scoring methods and timings of assessments)	Safety: • Incidence of AEs and/or serious AEs • Change from baseline in clinical laboratory parameters Primary efficacy: • **2 copies of *SMN2*:** Proportion of patients achieving the ability of functional independent sitting for at least 30 seconds up to 18 months of age • **3 copies of *SMN2*:** Proportion of patients achieving the ability to stand without support for at least 3 seconds up to 24 months of age

Secondary outcomes (including scoring methods and timings of assessments)	<u>Secondary efficacy:</u> **2 copies of *SMN2*:** • Proportion of patients that have survived and have not required permanent ventilation in the absence of acute illness and perioperatively, assessed at 14 months of age. Permanent ventilation is defined as tracheostomy or the requirement of ≥16 hours of respiratory assistance per day (via non-invasive ventilatory support) for ≥14 consecutive days in the absence of an acute reversible illness, excluding perioperative ventilation • Proportion of patients that have achieved the ability to maintain weight at or above the third percentile without need for non-oral/mechanical feeding support at any visit up to 18 months of age **3 copies of *SMN2*:** • Proportion of patients demonstrating the ability to walk alone defined as the ability to take at least five steps independently displaying coordination and balance at any visit up to 24 months of age
Exploratory efficacy endpoints	**2 copies of *SMN2*:** • Achievement of motor milestones as assessed by WHO Multicentre Growth Reference Study [103] criteria at any visit up to 18 months of age: o Sitting without support o Hands and knees crawling o Standing with assistance o Walking with assistance o Standing alone o Walking alone • Time to respiratory intervention • Requirement for respiratory intervention at 18 months of age • Avoidance of death or the requirement of permanent ventilation in the absence of acute illness or perioperatively as assessed at 18 months of age • Proportion of patients alive and without tracheostomy at 18 months of age • Proportion of patients achieving an improvement over baseline of ≥15 points on Bayley V.3 Gross and Fine Motor Subsets (raw score) at any visit up to 18 months of age • Ability to achieve a scaled score on Bayley V.3 Gross and Fine Motor Subtests within 1.5 standard deviations of a chronological development reference standard at any visit up to 18 months of age • Achievement of a CHOP-INTEND motor function scale score ≥40 at any visit up to 18 months of age • Achievement of CHOP-INTEND score >50 at any visit up to 18 months of age

	• Achievement of CHOP-INTEND score ≥58 at any visit up to 18 months of age • Maintenance of achieved milestones at visits up to 18 months of age in the absence of acute illness or perioperatively **3 copies of *SMN2*:** • Achievement of motor milestones as assessed by WHO Multicentre Growth Reference Study [103] criteria at any visit up to 24 months of age: o Standing with assistance o Walking with assistance • Time to respiratory intervention • Proportion of patients requiring respiratory intervention at 24 months of age • Survival, defined as avoidance of death or the requirement of permanent ventilation in the absence of acute illness or perioperatively as assessed at 24 months of age • Improvement over baseline of ≥15 points on Bayley V.3 Gross and Fine Motor Subsets (raw score) at any visit up to 24 months of age • Achievement of a scaled score on Bayley V.3 Gross and Fine Motor Subtests within 1.5 standard deviations of a chronological development reference standard as assessed at any visit up to 24 months of age • Ability to maintain weight at or above the third percentile without need for non-oral/mechanical feeding support at any visit up to 24 months of age • Maintenance of achieved milestones at visits up to 24 months of age in the absence of acute illness or perioperatively

† As of July 2019, 29 patients were enrolled in SPR1NT. At the 8 March 2019 efficacy data cut, 17 patients were enrolled in SPR1NT (4).
‡ Equivalent to the dose received by the Cohort 2 in START as determined by direct product testing with improved analytical methods. Direct testing of the actual lot of IMP used in START by an improved and more fully qualified analytical method has determined the actual dose received by Cohort 2 to be 1.1 x 1014 vg/kg. The same method has been used to establish an equivalent dose for the IMP in all Phase III trials.
§ Well characterised external datasets from SMA natural history studies (PNCR and NeuroNext [30]) are used to provide an external control comparator.
Abbreviations: AAV9, adeno-associated virus serotype 9; AE, adverse event; CMAP, compound muscle action potential; HIV, human immunodeficiency virus; IMP, investigational medicinal product; IV, intravenous; ITT, intention-to-treat; PNCR, Pediatric Neuromuscular Clinical Research database; SMA, spinal muscular atrophy; SMN, survival motor neurone; UK, United Kingdom; US, United States; WHO, World Health Organization.

10.4 Quality assessment of SMA type 1 natural history studies

The company assessed the quality of the RCT ENDEAR using the Cochrane risk of bias tool,[37] whereas NeuroNext and PNCR were assessed using the Newcastle-Ottawa scale.[40] The ERG agrees with the tools used when assessing the internal validity of each study. However, as only one arm of each study is of interest for the comparison with START, the ERG considers it more appropriate to assess the studies using the same tool and treating them all as single arm observational studies. In addition, the company's quality assessments of PNCR and NeuroNext are based on the populations reported in Finkel *et al*. 2014a (PNCR) and Kolb *et al*. 2016 and Kolb *et al*. 2017 (NeuroNext) and not the IPD cohorts that inform the comparison with START.

The ERG's independent quality assessment of the relevant population in the three SMA type 1 natural history studies is provided together with the company's original assessments are available below. The quality of the three studies is similar when assessed as single arm studies using the Newcastle-Ottawa scale; the relevant cohorts are representative of SMA type 1 patients, all patients receive BSC and follow-up is complete. However, ENDEAR has a shorter maximum follow-up compared with PNCR and NeuroNext, which means that although the length of follow up is enough to assess motor milestones it gives less mature event-free and overall survival data, than the other studies. The comparability and quality of the studies is discussed in Section 4.2.4.1.

Table 72: Cochrane risk of bias assessment - ENDEAR Finkel et al. 2017a[32] (reproduced from CS Table 19)

Cochrane risk of bias item	Judgment	Support
Random sequence	Unclear risk	Procedure not described
Allocation concealment	Unclear risk	Procedure not described
Blinding of participants	Low risk	To maintain blinding, nusinersen was administered or the sham procedure was performed by dedicated trial personnel who were aware of the group assignments, whereas the infant's parents and key trial personnel were unaware of the group assignments
Blinding of outcomes	Low risk	To maintain blinding, nusinersen was administered or the sham procedure was performed by dedicated trial personnel who were aware of the group assignments, whereas the infant's parents and key trial personnel were unaware of the group assignments
Attrition	Low risk	Patient ineligibility and discontinuation were explained in the text
Selective reporting	Low risk	All predefined outcomes reported
Other sources	Low risk	No indication there are other sources of bias.

Table 73. ERG Newcastle Ottowa quality assessment of ENDEAR

Newcastle Ottowa item	Score	Support
Selection: Representativeness of exposed cohort	*	Somewhat representative of the average SMA patient in the community
Selection: Selection of non-exposed cohort	NA	Only control arm is of interest
Selection: Ascertainment of exposure	*	Secure record

Newcastle Ottowa item	Score	Support
Selection: Outcome not present at start of study	*	Assumed that patients requiring PAV were excluded from the study
Comparability: Comparability of cohorts	NA	Only control arm is of interest
Outcomes: Assessment of outcome	*	independent blind assessment
Outcomes: Follow-up length		Maximum follow-up 13 months
Outcomes: Follow-up cohort	*	Assumed complete follow up
Overall quality	5	

Table 74. Newcastle Ottowa quality assessment - PNCR (adapted from CS Table 20)

	Company assessment of Finkel et al. 2014a[33]		ERG assessment of Avexis PNCR database report[30]	
Newcastle Ottowa item	**Score**	**Support**	**Score**	**Support**
Selection: Representativeness of exposed cohort	*	Somewhat representative of the average SMA patient in the community	*	Somewhat representative of the average SMA patient in the community
Selection: Selection of non-exposed cohort	NA	Single-arm study	NA	Single-arm study
Selection: Ascertainment of exposure	*	Secure record	*	Secure record
Selection: Outcome not present at start of study		Respiratory support present in some patients at enrolment	*	Assumed that patients requiring PAV were excluded from the study
Comparability: Comparability of cohorts	NA	Single-arm study	NA	Single-arm study
Outcomes: Assessment of outcome	*	Record linkage	*	Record linkage
Outcomes: Follow-up length		Only 50% of subjects completed at least 12 months of follow up	*	Maximum follow-up around 2.5 years
Outcomes: Follow-up cohort		Only 50% of subjects completed at least 12 months of follow up	*	Assumed complete follow up
Overall quality	3		6	

Table 75. Newcastle Ottowa quality assessment - NeuroNext (adapted from CS Table 20)

	Company assessment of Kolb *et al.* 2016, 2017[31, 39]		ERG assessment of Avexis NeuroNext database report[30]	
Newcastle Ottowa item	**Score**	**Support**	**Score**	**Support**
Selection: Representativeness of exposed cohort	*	Somewhat representative of the average SMA patient in the community	*	Somewhat representative of the average SMA patient in the community
Selection: Selection of non-exposed cohort	*	Control arm of healthy infants	NA	Only control arm is of interest
Selection: Ascertainment of exposure	*	Secure record	*	Secure record
Selection: Outcome not present at start of study	*	Outcome not present at start of study	*	Patients requiring PAV were excluded from the study
Comparability: Comparability of cohorts	**	Comparative arm of healthy infants controlled for age, gestational week, genetic testing, etc.	NA	Only control arm is of interest

	Company assessment of Kolb *et al.* 2016, 2017[31, 39]		ERG assessment of Avexis NeuroNext database report[30]	
Newcastle Ottowa item	**Score**	**Support**	**Score**	**Support**
Outcomes: Assessment of outcome	*	Record linkage	*	Record linkage
Outcomes: Follow-up length	*	24 months follow-up	*	Maximum follow-up around 24 months
Outcomes: Follow-up cohort		7 out of 26 infants completed the study. There were 12 deaths in the SMA cohort and 7 infants withdrew from the study before the 24-month visit.	*	Assumed complete follow up
Overall quality	8		6	

10.5 SMA type 1 natural history studies

10.5.1 PNCR

The PNCR cohort,[30] identified as a comparator and external control group to START, was drawn from a natural history study (The Pediatric Neuromuscular Clinical Research network natural history study [PNCR]) of 337 infants with SMA type 1, 2 or 3, at three medical centres in the USA. Individual patient level data (IPD) from the full PNCR study were available to the company, and what is hereafter referred to as the PNCR cohort consists of the subgroup of infants with age of onset ≤6 months, bi-allelic deletion of SMN1 (exon 7/8 common homozygous deletion) and two copies of SMN2.

The full PNCR study enrolled infants that were previously identified at PNCR site clinics as well as newly diagnosed infants, that is, the study included a prospective and a retrospective component. Infants who were, at any point, unable to sit independently for >10 seconds (the World Health Organization-Multicentre Growth Reference Study criteria[105]) were classified as SMA type 1. The SMN2 modifier mutation c.859G>C was not assessed in the PNCR study. Study visits were scheduled at Baseline, 2, 4, 6, 9, and 12 months, and every 6 months thereafter. The International Standard of Care Committee for Spinal Muscular Atrophy's guidelines[106] were used as a basis for providing uniform care among the study sites.

Survival of SMA patients was defined by the avoidance of the combined endpoint of either death or permanent ventilation, defined as tracheostomy or the requirement of ≥16 hours of respiratory assistance per day (via non-invasive ventilatory support) for ≥14 consecutive days in the absence of an acute reversible illness, excluding perioperative ventilation.

10.5.1.1 Finkel et al. 2014a

The company presents an alternative reference for the PNCR cohort as an external control group to START, Finkel *et al.* 2014a[33], which was also selected from the full PNCR natural history database for SMA. Both Finkel *et al* 2014a and the PNCR cohort[30] described above assessed 23 infants with SMA

type 1 and two copies of SMN2, but one infant differs between the cohorts (Table 76). Finkel *et al*. 2014a selected infants enrolled from May 2005 until April 2009 in the PNCR database, while the PNCR cohort was selected using the entire PNCR database. In addition, Finkel *et al.* 2014a did not limit inclusion to age of SMA onset to ≤6 months, as in the PNCR cohort. The difference in between studies in one infant in the cohort leads to disparity in the number of events reported by each study, with Finkel *et al.* 2014a reporting 19 events (death or permanent ventilation) compared with 18 events (death or permanent ventilation) reported for the START PNCR control group. Although the company has referred to both references in the CS, the ERG focuses on the PNCR cohort in this report and so does not discuss Finkel *et al* 2014a further.

Table 76. Individual patient status in PNCR control group and Finkel *et al* 2014a (reproduced from CS, Table 26)

Patient ID	Status for Finkel et al. 2014a PNCR control group	Status for START PNCR control group	Patient status for composite event
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: CS, company's submission; CHOP-INTEND, Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders; PNCR, Pediatric Neuromuscular Clinical Research database; SD, standard deviation.

10.5.1.2 De Sanctis et al. 2016

The company does not use the PNCR cohort or Finkel *et al.* 2014a described above to inform the natural history of SMA type 1 in the health economic modelling, instead choosing to incorporate the cohort described by De Sanctis *et al*. 2016[34] in scenario analysis. De Sanctis *et al*. 2016, which is described as a retrospective study, includes the PNCR dataset and also a dataset from Italy.

Although all infants in the cohort were reported to have a clinical diagnosis of SMA type 1, only 24 out of a total of 33 had symptom onset between 1 week and 5–6 months of age. Few baseline characteristics are reported in the publication and none are available for the subgroup of infants with symptom onset before 6 months of age. It is unclear what number of copies of SMN2 the infants had and how this cohort compares with START, NeuroNext or the PNCR cohort for any other baseline characteristic. In addition, no survival data, in terms of Kaplan-Meier (KM) curves, were reported in the full publication. The origin of the De Sanctis *et al*. 2016 data used in the economic model is therefore unclear.

The company's choice of using De Sanctis *et al.* 2016 rather than the PNCR cohort was based on:

- a larger sample size (De Sanctis n=26, PNCR n=23) – De Sanctis *et al.* 2016 did not limit inclusion based on SMN2 copy number (in contrast to START, ENDEAR, NeuroNext and the PNCR cohort);

- more recent data – De Sanctis *et al.* 2016 enrolled patients between 2010 and 2014, Finkel *et al.* 2014a enrolment patients between 2005 and 2009, and for the PNCR cohort enrolment dates were not reported.

The company states that a more recent enrolment would better reflect current standard of care with a higher reported use of ventilatory support. The ERG notes that it is not able to assess the appropriateness of De Sanctis *et al* 2016 as data are not available on baseline characteristics of the relevant subgroup. The choice of data informing the clinical efficacy in the economic model is discussed in Section 5.3.6.

10.5.2 NeuroNext

The Network for Excellence in Neuroscience Clinical Trials (NeuroNext) natural history study[31, 39] was a longitudinal, multicentre, prospective, natural history study that enrolled 26 SMA infants (and 27 healthy control infants) at 14 centres within the National Institute of Neurological Disorders and Stroke (NINDS)-sponsored NeuroNext Network in the USA. NeuroNext was designed to mimic the inclusion and timing of future SMA clinical trials targeting treatment to infants with SMA, and IPD for the study were available to the company.

Enrolment was restricted to infants who were 6 months of age or younger and born between 36 and 42 weeks of gestation. The diagnosis of SMA was made by the study investigators or community neurologists and was confirmed with clinical genetic testing prior to enrolment. All patients had bi-allelic deletions of SMN1 exon 7. Asymptomatic (pre-symptomatic) patients who had been genetically tested prior to the enrolment were also permitted entry into the study. SMN2 copy number was measured in all patients except for four who died before confirmation samples were obtained but who were presumed to have two copies of SMN2 based on disease course. Sixteen infants from the full NeuroNext study with two copies of SMN2 were included in the external control group for START, hereafter referred to as the NeuroNext cohort.[30] Exclusion of the SMN2 gene modifier mutation c.859G>C was confirmed in all but the four patients who died. Patients were also excluded if they required non-invasive ventilatory support (i.e., bi-level positive airway pressure [BiPAP]) for ≥12 hours/day, had a comorbid illness or were enrolled in an SMA therapeutic clinical trial. The study excluded SMA infants taking any therapies thought to increase SMN expression, such as valproic acid. Survival within the NeuroNext study was defined as alive without tracheostomy, a less stringent definition than that used in the PNCR study and the onasemnogene clinical trials (event defined by death, tracheostomy or requirement of ≥16 hours of ventilatory support for ≥2 weeks, excepting acute reversible illness or perioperative use). Infant motor function as measured by the CHOP-INTEND was assessed prior to 6 months of age and at 6, 9, 12, 18, and 24 months of age.

10.5.3 ENDEAR

ENDEAR is an international, randomised, multicentre, sham-controlled, Phase III trial that assesses the clinical efficacy and safety of nusinersen in infants with SMA. Infants in the control arm of ENDEAR received a sham procedure similar to administration of nusinersen, as well as standard care. The sham arm of ENDEAR was therefore identified as a relevant source of SMA type 1 natural history data by the company and used in a scenario analysis in the health economic model. However, the trial was not described and its comparability to NeuroNext, PNCR and START was not discussed in the CS. For clarity, the ERG has provided a summary of ENDEAR below.

ENDEAR was carried out at 36 study centres worldwide. Infants enrolled were those with a genetic diagnosis of SMA, with two copies of SMN2, and with onset of symptoms at ≤6 months of age. At baseline, all infants were symptomatic, hypotonic and weak; features consistent with a phenotype that is most likely to be classified as SMA type 1. Infants were randomly assigned to intrathecal administration of nusinersen or a sham procedure (control group). Forty-one infants were randomised to the control group. Efficacy end points were assessed around 2, 6, 10, and 13 months and safety visits occurred on day 16 and thereafter at 1, 2, 6 and 10 months.

An interim analysis in ENDEAR, showing a benefit–risk assessment in favour of nusinersen, prompted early termination of the trial. Infants who completed the ENDEAR trial were invited to enrol in the open-label extension study, SHINE (ClinicalTrials.gov number, NCT02594124). Data are presented both for the interim and the final analysis, which was based on data collected up to the date of the last visit by the last infant at 13 months of follow-up.

The trial had two primary efficacy endpoints. The first was a motor-milestone response, which was defined according to results on the Hammersmith Infant Neurological Examination (HINE-2).[107] The HINE is a three-section, 37-item, quantifiable assessment of overall neurologic function in infants. The second primary efficacy endpoint was event-free survival, defined as the time to death or the use of permanent assisted ventilation (tracheostomy or ventilatory support for ≥16 hours per day for >21 continuous days in the absence of an acute reversible vent). Secondary outcomes included CHOP-INTEND response and motor milestones achieved, which were reported at the last available assessment for each patient. However, CHOP-INTEND response was reported for only 37 infants in the control group, who had been enrolled for ≥6 months.

10.5.4 Baseline characteristics and quality assessments of SMA type 1 natural history studies

Baseline characteristics of the patients in START, STR1VE-US, NeuroNext, PNCR and ENDEAR are reported in Table 77 and differences in baseline characteristics between the studies are discussed in Section 4.2.4.1.

Table 77. Demographic and baseline characteristics START, NeuroNext and PNCR (adapted from CS Table 27 and clarification response A5 Table 2)

Characteristic	START Cohort 2 (N=12)	STR1VE-US (N=22)	NeuroNext control (N=16)	PNCR control (N=23)	ENDEAR sham arm (N=41)
Age at enrolment,[a] months • Mean (SD) • Min, Max	3.5 (2.1) 0.9, 7.9	NR	4.1 (1.7) 0, 6	29.0 (41.7) 2, 171	5.4[b] 0.7, 6.9
Mean age at first dose, months (range)	3.4 (0.9, 7.9)	NR	NA	NA	5.9 (1, 8.6)[f]
Mean age at diagnosis, months (range)	2.0 (0, 4.5)	2.6 (0, 5.4)	NR	5 (1, 12)	3.9 (0.2, 4.6)[f]
Sex, % • Female • Male	 58.3 41.7	 54.5 45.5	 50.0 50.0	 52.2 47.8	 59 41
Race, % • White • Other	 91.7 8.3	 50.0 27.3	 93.8 6.2	 69.6 30.4	 NR NR
Ethnicity, % • Not Hispanic or Latino • Hispanic or Latino	 83.3 16.7	 81.8 18.2	 68.7 31.3	 87.0 13.0	 NR NR
Mean age at symptom onset, months (SD)	1.4 (1.0)	1.9 (1.2)	NR	3.0 (1.6)	2.2 (0.2, 4.6)
Mean birth weight (SD), kg	3.39 (0.71)[c]	NR	NR	11.8 (7.8)[d]	3.48 (0.74)
CHOP-INTEND scale, score[e] Mean (SD) Min, Max	 28 (12.3) 12, 50	 32.0 (NR) 18, 52	 20.3 (7.3) 10, 33	 24.6 (11.6) 5, 40	 26.7 (8.1) NR
Did not require support of, n (%): • Nutrition • Ventilation • Both nutrition and ventilation	 7 (58.3) 10 (83.3) 10 (83.3)	 22 (100) 22 (100) 22 (100)	 9 (56.3) 10 (62.5) 14 (87.5)	 5 (21.7) 11 (47.8) 11 (47.8)	 36 (88) 35 (85) NR
• Ventilation before 6 months of age	10 (83.3)	NR	10 (62.5)	21 (91.3)	NR

[a] At baseline (START and NeuroNext), at enrolment (PNCR), or at screening (ENDEAR).
[b] Value reported in days and converted to months by dividing by 30.417.
[c] Data reported for 11/12 patients in Cohort 2 of START.
[d] Average (mean) weight at study enrolment rather than birth weight.
[e] Scores on the CHOP-INTEND scale of motor function range from 0 to 64, with higher scores indicating better function.
[f] Value reported in weeks and converted to months by dividing by 4.345.
Abbreviations: CHOP-INTEND, Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders; NA, not applicable; NR, not reported; PNCR, Pediatric Neuromuscular Clinical Research database; SD, standard deviation.

10.6 Comparison of definitions of outcomes for START and STR1VE-US

Table 78. Definitions of clinical outcomes in START and STR1VE-US (reproduced from CQ response 02 July 2020, Table 3)

Outcome	**Definition**	
	START (Cohort 2)	**STR1VE-US**
Survived without permanent ventilation	Patients alive and free of permanent ventilation (defined as tracheostomy or the requirement of ≥16 hours of respiratory assistance per day via non-invasive ventilatory support for ≥14 consecutive days in the absence of an acute reversible illness, excluding perioperative ventilation) **at 24 months post-dose (approximately 30 months of age)**	Patients alive and free of permanent ventilation (defined as tracheostomy or the requirement of ≥16 hours of respiratory assistance per day via non-invasive ventilatory support for ≥14 consecutive days in the absence of an acute reversible illness, excluding perioperative ventilation) **at 18 months of age[a]**
Proportion of patients who achieved CHOP-INTEND scores of:[b] • ≥40 • ≥50 • ≥60	Proportion of patients who achieved scores of ≥40, ≥50, and ≥60 in the CHOP-INTEND motor function scale, administered by a qualified clinical evaluator **by 24 months post-dose (approximately 30 months of age)**[c]	Proportion of patients who achieved scores of ≥40, ≥50, and ≥60 in the CHOP-INTEND motor function scale, administered by a qualified clinical evaluator **by 18 months of age[d]**
Change from baseline in Bayley Scales score: • Gross motor subtest • Fine motor subtest	Change from baseline score in the Bayley Scales of Infant and Toddler Development (Version 3), administered by a physical therapist. **Bayley Scales were not a mandatory assessment in START[e] and are not available for all patients**	Change from baseline score in the Bayley Scales of Infant and Toddler Development (Version 3), administered by a physical therapist. **The gross and fine motor subtests of the motor domain were administered at screening and at each monthly visit, up to 18 months of age**
Developed significant motor milestones‡‡	Attainment of the following centrally reviewed/video-confirmed motor milestones **by 24 months post-dose (approximately 30 months of age):**	Attainment of the following centrally reviewed/video-confirmed motor milestones, unless otherwise stated, **by 18 months of age:**
Sits alone ≥5 seconds	Attainment of Bayley Scales gross motor subtest item #22: Child sits alone without support for at least 5 seconds	Attainment of Bayley Scales gross motor subtest item #22: Child sits alone without support for at least 5 seconds **(*NB:* not centrally reviewed/video-confirmed – the source of this information is the Bayley individual item scores, as assessed during study visits)**
Sits alone ≥10 seconds	Child sits up straight with head erect for at least 10 seconds and does not use arms or hands to balance body or support position, as defined by WHO MGRS	Child sits up straight with head erect for at least 10 seconds and does not use arms or hands to balance body or support position, as defined by WHO MGRS

Sits alone ≥30 seconds	Attainment of Bayley Scales gross motor subtest item #26: Child sits alone without support for at least 30 seconds	Attainment of Bayley Scales gross motor subtest item #26: Child sits alone without support for at least 30 seconds
Stands with assistance	Attainment of Bayley Scales gross motor subtest item #33: Child supports his or her own weight for at least 2 seconds, using your hands for balance only	Attainment of Bayley Scales gross motor subtest item #33: Child supports his or her own weight for at least 2 seconds, using your hands for balance only
Stands alone	Attainment of Bayley Scales gross motor subtest item #40: Child stands alone for at least 3 seconds after you release his or her hands	Attainment of Bayley Scales gross motor subtest item #40: Child stands alone for at least 3 seconds after you release his or her hands
Walks with assistance[f]	Attainment of Bayley Scales gross motor subtest item #37: Child walks by making coordinated, alternated stepping movements	Attainment of Bayley Scales gross motor subtest item #37: Child walks by making coordinated, alternated stepping movements
Walks alone[g]	**Attainment of Gross Motor Checklist: 'takes independent steps' or the Motor Milestone Development Survey: 'walks independently'**	**Attainment of Bayley Scales gross motor subtest item #43: Child takes at least 5 steps independently, displaying coordination and balance**
Independent of ventilatory support	Independent of ventilatory support **at 24 months post-dose (approximately 30 months of age)**	Independent of ventilatory support **at 18 months of age**
Maintained the ability to thrive	Patient met all of the following criteria **at 24 months post-dose (approximately 30 months of age)**:[§§] The ability to tolerate thin liquids as demonstrated through a formal swallowing test Not requiring nutrition through mechanical support such as a feeding tube Maintained weight >3rd percentile based on WHO Child Growth Standards for age and gender	Patient met all of the following criteria **at 18 months of age**: The ability to tolerate thin liquids as demonstrated through a formal swallowing test Not requiring nutrition through mechanical support such as a feeding tube Maintained weight >3rd percentile based on WHO Child Growth Standards for age and gender
Proportion of patients in the SAS receiving non-oral feeding support	The proportion of patients who used non-oral feeding at any time from baseline to **24 months post-dose (approximately 30 months of age)**	The proportion of patients who used non-oral feeding at any time from baseline to **18 months of age**

[a] It should be noted that the co-primary endpoint for STR1VE-US survival, was defined as avoidance of either (a) death or (b) permanent ventilation, at 14 months of age.
[b] Based on maximum post-Baseline CHOP-INTEND score achieved.
[c] If a patient achieved 2 consecutive CHOP-INTEND scores of ≥62, a teleconference was conducted between the principal investigator, the physical therapist, and the sponsor to review the patient status and determine whether or not continued CHOP-INTEND assessments were necessary. If it was decided that no further assessments were necessary, the physical therapist ceased completion of the CHOP-INTEND assessment at subsequent visits; otherwise, CHOP-INTEND assessments continued monthly during Year 1 and quarterly during Year 2.
[d] Patients who achieved three consecutive CHOP-INTEND scores ≥58 did not undergo any additional CHOP-INTEND examinations.
[e] The Bayley gross and fine motor subtests were only to be administered if a patient reached or exceeded a score of 60 out of 64 on the CHOP-INTEND. If so, Bayley subtests were conducted monthly through the time point that the patient reached 15 months of age or 12 months post-dose, whichever was later, and then every 3 months except for subjects still being seen monthly for CHOP-INTEND assessments, up to 24 months post-dose (approximately 30 months of age).

[f] Physical therapy assessments and physical examinations conducted at each study visit will were video recorded in an effort to produce compelling, demonstrable, documented evidence of efficacy, as determined by changes in functional abilities. Videos were provided to an independent, centralized reviewer for unbiased assessment of developmental milestone achievement. Additionally, the Parent(s)/legal guardian(s) were able to submit additional videos demonstrating achievement of developmental milestones at any time during the study. These videos were handled in the same manner in which the study-derived videos are handled.
[g] Only 7 patients were able to be assessed for the maintenance of the ability to thrive as only 7 patients in Cohort 2 did not require non-oral nutrition at baseline.
Abbreviations: CHOP-INTEND, Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders; SAS, safety analysis set; WHO, World Health Organization; MGRS, Multicentre Growth Reference Trial.

10.7 Health-related quality of life data used in scenario analysis

The company explored alternative sources of utility data and caregiver disutilities in scenario analyses. Each of these scenarios is described in turn below. In addition, the company also explored the impact on the ICERs by removing all utility weightings from all health states (i.e. results are 'cost per life year gained') and substituting the B state utility value (age-adjusted, general population utility) with the C state utility value (0.6). The results of the company's scenario analyses are given in Section 5.4.2.

AveXis UK utilities elicitation study[84]

Four health state vignettes were developed, which reflected the health states in the company's economic model. To value these vignettes, the company recruited 100 adults aged 18 to 86 from the general UK population. Participants were asked to complete the visual analogue scale (VAS), then the time trade-off (TTO), under two different scenarios:

1. "Parent vignettes" – Imagining being a parent valuing the state of their child with SMA;
2. "Adult vignettes" – Imagining themselves as an adult with SMA.

The summary statistics obtained from the scenarios are given in Table 79 and Table 80 for "Parent vignettes" and "Adult vignettes", respectively. Both scenarios showed an improvement (increase) in the mean health values moving from the lowest (PAV) to the highest functioning state (walking unassisted). These differences were also observed for both elicitation methods and were statistically significant. Moreover, both scenarios and elicitation methods produced negative values for the two worst states (PAV and non-sitting).

Table 79. Results of "Parent vignettes" taken from Table 50 of the original CS, Appendix B

Statistic	PAV	Non-sitting	Sitting Unassisted	Walking Unassisted
TTO				
Mean	[redacted]	[redacted]	[redacted]	[redacted]
SD	[redacted]	[redacted]	[redacted]	[redacted]
SE	[redacted]	[redacted]	[redacted]	[redacted]
95%CIL	[redacted]	[redacted]	[redacted]	[redacted]
95%CIH	[redacted]	[redacted]	[redacted]	[redacted]
VAS				

Mean	[redacted]	[redacted]	[redacted]	[redacted]
SD	[redacted]	[redacted]	[redacted]	[redacted]
SE	[redacted]	[redacted]	[redacted]	[redacted]
95%CIL	[redacted]	[redacted]	[redacted]	[redacted]
95%CIH	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: CIL, confidence interval lower; CIH, confidence interval higher; PAV, permanent assisted ventilation; SE, standard error; SD, standard deviation, TTO, time trade off; VAS, visual analogue scale.

Table 80. Results of "Adult vignettes" taken from Table 51 of the original CS, Appendix B

Statistic	PAV	Non-sitting	Sitting Unassisted	Walking Unassisted
TTO				
Mean	[redacted]	[redacted]	[redacted]	[redacted]
SD	[redacted]	[redacted]	[redacted]	[redacted]
SE	[redacted]	[redacted]	[redacted]	[redacted]
95%CIL	[redacted]	[redacted]	[redacted]	[redacted]
95%CIH	[redacted]	[redacted]	[redacted]	[redacted]
VAS				
Mean	[redacted]	[redacted]	[redacted]	[redacted]
SD	[redacted]	[redacted]	[redacted]	[redacted]
SE	[redacted]	[redacted]	[redacted]	[redacted]
95%CIL	[redacted]	[redacted]	[redacted]	[redacted]
95%CIH	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: CIL, confidence interval lower; CIH, confidence interval higher; PAV, permanent assisted ventilation; SE, standard error; SD, standard deviation, TTO, time trade off; VAS, visual analogue scale.

The mean health values for the "Adult vignettes" were consistently lower than those of the "Parent vignettes" using the TTO and generally lower using the VAS. The company considered that "Adult vignettes" entailed a lower quality of life than "Parent vignettes" because some participants struggled to imagine themselves as having SMA, or because they valued the SMA state from the point of view of an adult who was previously healthy and lost function rather than a person who had never achieved significant motor milestones in their earlier life. In addition, the company noted that VAS scores do not include a trade-off element or produce "utilities". As such, the company considered the "Parent vignettes" valued using the TTO, to be the most appropriate results obtained from the study. Even so, these values were only employed in scenario analysis by the company because they produced an overall negative QALY in the standard care arm, which may be considered to lack face validity.

Other alternative sources

Utilities from three alternative studies identified as part of the HRQoL SLR were assessed for incorporation as scenario analyses. Further details of each study and a justification for why these were not use in the base case are provided in Table 81.

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Table 81. Summary of alernative HRQoL sources identified in the SLR (adapted from Table 42 of the Supplementary Appendix)

Health state†	**CHERISH: PedsQL mapped to EQ-5D-Y (Thompson et al. 2017[70])**		**Lloyd: Clinician-proxy Case Vignette EQ-5D-Y (Lloyd et al. 2017[89])**		**European study: Parent-proxy EQ-5D-3L, UK reports only (Thompson et al. 2017[70])**	
	Health state	**Utility value**	**Health state**	**Utility value**	**Health state**	**Utility value**
E	SMA type 2: Worsened (from baseline)	0.730	SMA type 1: Requires ventilation	-0.33	SMA type 1	0.190
D	SMA type 2: Stabilisation of baseline function	0.756	SMA type 1: Baseline	-0.12	SMA type 1	0.190
C	SMA type 2: Moderate improvement	0.764	SMA type 1: Reclassified as SMA type 2†	-0.04	SMA type 2	0.100
B	SMA type 2: Walks unaided	0.878	SMA type 1: Reclassified as SMA type 3‡	0.71	SMA type 3	0.540
A	Identified studies did not included an A state. The A state (within broad range of normal development) is assumed to have HRQoL equivalent to the UK general population					
Justification for exclusion from the base case	The mapping described by Kahn et al 2014 has several methodological limitations: for example, it was conducted in a population that differed considerably (school children aged of 11 to 15 years) to SMA type 1 babies. In addition, the values seem implausibly high; for example, it seems unlikely that for an individual who requires PAV would be considered as being three quarters of that of an individual in perfect health		The study uses clinician-proxy assessment, which is less preferred to parent-proxy assessments, as per the NICE reference case. In addition, the study reported a negative utility (a health state worse than death) for 'reclassified SMA type 2'. A negative utility value for the C state (sits unassisted) lacks face validity and was deemed implausible by UK clinical experts (UK advisory board, May 2019)[88]		Whilst this study uses parent-proxy assessment, which is preferred to clinician-proxy assessments, the results for the SMA type 2 group (used as proxy for the C state [sit unassisted]) lack face validity, as they are lower than the utility value reported for SMA type 1 patients who fail to achieve any milestones. Due to this lack of face validity, a scenario using values reported for SMA type 2 and 3 groups from this study is also not formally modelled	

Abbreviations: BSC, best supportive care; EQ-5D-3L, 3-level EuroQol-Five Dimension; EQ-5D-Y, EuroQol-Five Dimension youth; N/A, not applicable; NICE, National Institute of Health and Care Excellence; PAV: permanent assisted ventilation; pop., population; QALY, quality-adjusted life-year; SMA, spinal muscular atrophy; TTO, ; UK, United Kingdom.
† Where possible, it was decided to use available utility data of type 1 patients behaving as type 2, rather than type 2 as a proxy. These are patients that have been treated, so type 1 patients who can sit, which is similar to our model.
‡ Where possible, it was decided to use available utility data of type 1 patients behaving as type 3, rather than type 2 proxy walkers. These are patients that have been treated, so type 1 patients who can walk, which is similar to our model. Baseline is D state and they can transition to B state.

Caregiver disutilities

The company explained that although it is well accepted that caregivers of infants with SMA type 1 face a constant physical and emotional burden, the incorporation of caregiver HRQoL into economic evaluations is lacking. Recent economic evaluations of SMA therapies including the US ICER report[69] and the NICE technology appraisal assessment of nusinersen for treating SMA (TA588)[92] did not include the burden associated with caregivers in their base case analyses due to extreme difficulties in quantifying those effects. However, given that Committee discussions for TA588 concluded that caregiver utility should be considered in decision making, the company explored the impact of caregiver HRQoL as a scenario analysis.

The company choose spina bifida as an appropriate proxy disease as it shares several characteristics with infants and children with SMA. A study by Tilford *et al.* 2005 who collected Quality of Well-Being (QWB) data from primary caregivers of children aged 0 to 17 years with (case) and without (control) spina bifida was chosen to inform the company's analysis.[108] Children with Spina bifida were categorised into three disability levels according to the location of their lesion. Then, for each lesion, the company compared the QWB preference scores between the control caregivers (n=49) and case caregivers (n=98) and allocated them to health states E, D and C, as shown in Table 82.

Table 82 Caregiver disutilties

Health state	Location of lesion	Caregiver disutility
E and D	Thoracic	0.80 – 0.72 = -0.08
C	Lower lumbar	0.80 – 0.77 = -0.03
C	Sacral	0.80 – 0.77 = -0.03

10.7.1 ERG critique of the Caregiver HRQoL scenario analysis

Clinical expert opinion provided to the ERG was consistent in reporting that SMA type 1 has a much higher caregiver burden than spina bifida because spina bifida is not associated with breathing or feeding difficulties. One of the experts also questioned the assumption that caregivers of patients with SMA type 1 with and without PAV incur the same caregiver burden, while another considered that the company's attempts to link the location of the child's spina bifida lesion with motor function milestones was potentially unreliable.

For completeness, the ERG searched the company's reference list for studies providing relevant caregiver HRQoL data. The ERG subsequently identified a study by Lopez-Bastia *et al.* 2017 who assessed the HRQoL of SMA caregivers in Spain, using the EQ-5D.[18] The average age of study participants with SMA was 7.2 years and 10% of those had type 1, 74% had type 2 and 16% had type 3. The average age of caregivers was 40.3 years and the majority were female (9% male, 44% female,

47% missing). The mean EQ-5D utility score of all caregivers was 0.484 (n=81) and when considering SMA type 2 alone, the mean EQ-5D utility score decreased to 0.472 (n=60). Separate utility scores for caregivers of SMA type 1 and 3 were not provided.

During the clarification stage, the ERG asked the company why the study by Lopez-Bastia *et al.* 2017 was not considered for scenario analysis and they stated that there were several limitations with the study, including the small sample size, lack of utility by health state and no control group analysis and as such was not appropriate for use in an exploratory scenario.

Nonetheless, the ERG explored a scenario using the data from Lopez-Bastia *et al.* 2017 to provide an alternative disutility for caregivers, by estimating the utility of "non-caregivers" to compare to the utility of caregivers. Using the formula by Ara and Brazier 2010 to calculate general population utility values, the ERG calculated a utility of 0.891 for "non-caregivers" using the age and gender (assuming 9 of 53 caregivers are male) characteristics collected in Lopez-Bastida *et al*. 2017.[18, 86] Then, comparing the utility of all SMA caregivers in Lopez-Bastida *et al.* 2017 (0.484) with the utility of the general population (0.891), the caregiver disutility is -0.407.

The ERG's estimation of caregiver disutility (-0.407) is substantially larger than the company's estimations (-0.08 and -0.03) and may lack face validity. Moreover, the ERG's estimation must be interpreted with caution as the general population utilities estimated using the methodology reported in Ara and Brazier 2010 may not be representative of a control population for the Lopez-Bastida *et al.* 2017 study.[18, 86] Nonetheless, the ERG explored the impact of incorporating a caregiver disutility of -0.407 in health states E, D and C. A caregiver disutility was not incorporated into health state B (SMA type 3) based on clinical expert advice to the ERG that caregivers of patients with SMA type 3 do not face a constant physical and emotional burden. The impact of the ERG's scenario on the ICER was large ([redacted] to [redacted]) due to the large reduction in incremental QALYs (10.00 to 5.68). This scenario also led to an overall negative QALY value for BSC which may lack face validity. Results of the ERG's scenario analyses are presented in Table 83.

Table 83. Results of the ERG's caregiver disutility scenario (inlcuding PAS)

Results per patient	Onasemnogene	Best supportive care	Incremental value
Company's Base case			
Total Costs (£)	[redacted]	£381,131	[redacted]
QALYs	10.21	0.21	10.00
ICER			[redacted]
Caregiver disutility based on Lopez-Bastida et al. 2017[18]			
Total Costs (£)	[redacted]	£381,131	[redacted]
QALYs	5.01	-0.76	5.68
ICER			[redacted]

Abbreviations: ERG, evidence review group; HSUVs, health state utility values; ICER, incremental cost effectiveness ratio; KM, Kaplan Meier; NRA; non-respiratory aid; OS, overall survival; QALYs, quality adjusted life years, US, united states.

Finally, in the CS, the company highlighted that the emotional burden of caregivers continues with bereavement as patients succumb to the disease (Higgs *et al.* 2016).[109] However, the company did not attempt to quantify caregiver bereavements. In response to the ERG's clarification question, the company provided a comprehensive explanation on the methodological challenges in evaluating the emotional impact on the caregiver losing a child, and the opposing perspectives the caregiver could have following a bereavement. As such, the company concluded that approaches to calculating disutility due to caregiver bereavement are not sufficiently advanced to include in current health technology assessments which the ERG agrees with.

Onasemnogene abeparvovec for treating spinal muscular atrophy

ERG report addendum

September 2020

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1 Introduction

After submission of the Evidence Review Group (ERG) report for onasemnogene abeparvovec (hereafter referred to as onasemnogene) for treating spinal muscular atrophy (SMA), the National Institute for Health and Care Excellence (NICE) requested additional information on the estimated undiscounted QALYs for the company and ERG analyses and scenarios exploring a 1.5% discount rate for costs and QALYs, to help with committee decision making.

Table 1 to Table 5 presents the company's undiscounted QALYs by health state and the ERG's scenarios, ERG preferred analyses and a utility scenario requested by NICE including undiscounted QALYs. Table 6 to Table 9 presents the ERG's scenarios, ERG preferred analyses and the utility scenario requested by NICE using a 1.5% discount rate for costs and QALYs.

Table 1. Total undiscounted QALYs of onasemnogene and BSC by health state (taken from the economic model)

Health state	QALYs onasemnogene (undiscounted)	QALYs BSC (undiscounted)	Increment
E	0.00	0.00	0.00
D	0.58	0.22	0.36
C	12.76	0.00	12.76
B	0.34	0.00	0.34
A	7.73	0.00	7.73
Total	21.41	0.22	21.19
Abbreviations: BSC, best supportive care; QALYs, quality-adjusted life years			

Table 2. Results of the ERG's scenario analysis (costs and QALYs discounted at 3.5%)

	Results per patient	Onasemnogene	Best supportive care	Incremental value
0	**Company's Base case**			
	Total Costs (£)	[redacted]	381,131	[redacted]
	QALYs	10.21	0.21	10.00
	Undiscounted QALYs	21.41	0.22	21.19
	ICER (£/QALY)			[redacted]
1	**Threshold for sitting independently of ≥30 seconds for the pooled dataset (observed motor milestones only)**			
	Total Costs (£)	[redacted]	£381,131	[redacted]
	QALYs	8.96	0.21	8.75
	Undiscounted QALYs	18.28	0.22	18.07
	ICER (£/QALY)			[redacted]
2	**Threshold for sitting independently of ≥30 seconds for the pooled dataset (no additional walker)**			

	Total Costs (£)	[redacted]	£381,131	[redacted]
	QALYs	9.26	0.21	9.05
	Undiscounted QALYs	18.84	0.22	18.62
	ICER (£/QALY)			[redacted]
3	**US ICER model report costs**			
	Total Costs (£)	[redacted]	£544,139	[redacted]
	QALYs	10.21	0.21	10.00
	Undiscounted QALYs	21.41	0.22	21.19
	ICER (£/QALY)			[redacted]
4	**Subsequent nusinersen treatment costs**			
	Total Costs (£)	[redacted]	£381,131	[redacted]
	QALYs	10.21	0.21	10.00
	Undiscounted QALYs	21.41	0.22	21.19
	ICER (£/QALY)			[redacted]

Abbreviations: ERG, evidence review group; ICER, incremental cost effectiveness ratio; QALYs, quality adjusted life years, US, united states.

Table 3. ERG base case ICER (costs and QALYs discounted at 3.5%)

Results per patient	Onasemnogene	Best supportive care	Incremental value
Company's base case			
Total Costs (£)	[redacted]	381,131	[redacted]
QALYs	10.21	0.21	10.00
Undiscounted QALYs	21.41	0.22	21.19
ICER (£/QALY)			[redacted]
Removal of the assumption of an additional independent sitter and independent walker from pooled dataset			
Total costs (£)	[redacted]	381,131	[redacted]
QALYs	9.56	0.21	8.29
Undiscounted QALYs	19.41	0.22	19.19
ICER (£/QALY)			[redacted]
ERG's preferred base case ICER (£/QALY)			[redacted]

Abbreviations: ERG, evidence review group; ICER, incremental cost effectiveness ratio; QALYs, quality adjusted life years.

Table 4. ERG's base case results for onasemnogene versus BSC including threshold for sitting independently of ≥30 seconds (costs and QALYs discounted at 3.5%)

Results per patient	Onasemnogene	Best supportive care	Incremental value
Total Costs (£)	[redacted]	£381,131	[redacted]
QALYs	8.96	0.21	8.75
Undiscounted QALYs	18.28	0.22	18.07
ICER (£/QALY)			[redacted]

Abbreviations: ICER, incremental cost effectiveness ratio; QALYs, quality adjusted life years.

Table 5. Scenario 2 from Table 45 of the ERG report (costs and QALYs discounted at 3.5%)

Results per patient	Onasemnogene	Best supportive care	Incremental value
Company's base case			
Total Costs (£)	[redacted]	381,131	[redacted]
QALYs	10.21	0.21	10.00
Undiscounted QALYs	21.41	0.22	21.19
ICER (£/QALY)			[redacted]
C state utility – 20% increase from baseline value (0.72)			
Total costs (£)	[redacted]	381,131	[redacted]
QALYs	11.51	0.21	11.30
Undiscounted QALYs	23.76	0.22	23.54
ICER (£/QALY)			[redacted]
C state utility – 20% decrease from baseline value (0.48)			
Total costs (£)	[redacted]	381,131	[redacted]
QALYs	8.92	0.21	8.71
Undiscounted QALYs	19.05	0.22	18.83
ICER (£/QALY)			[redacted]

Abbreviations: ICER, incremental cost effectiveness ratio; QALYs, quality adjusted life years.

1.1 Scenarios using 1.5% discount rate for costs and QALYs

As mentioned in the ERG report, onasemnogene doesn't restore the majority of treated symptomatic SMA type 1 patients to full or near full health. Based on data from START and STR1VE-US, the majority of patients treated with onasemnogene achieve the ability to sit unassisted, but the ERG's clinical experts stated that these patients will still require a substantial amount of medical care over their lifetimes. Nonetheless, data from START and STR1VE-US demonstrates a substantial survival benefit for patients who would have otherwise died. As such, the ERG presents the company's revised base case results, ERG scenarios, ERG preferred analyses and a utility scenario requested by NICE using a 1.5% discount rate for costs and quality adjusted life years (QALYs) for committee consideration in Table 6 to Table 9.

Table 6. Results of the ERG's scenario analysis (costs and QALYs discounted at 1.5%)

	Results per patient	Onasemnogene	Best supportive care	Incremental value
0	**Company's Base case**			
	Total Costs (£)	[redacted]	413,269	[redacted]
	QALYs	14.89	0.21	14.67
	Undiscounted QALYs	21.41	0.22	21.19
	ICER (£/QALY)			[redacted]
1	**Threshold for sitting independently of ≥30 seconds for the pooled dataset (observed motor milestones only)**			

	Total Costs (£)	[redacted]	413,269	[redacted]
	QALYs	12.90	0.21	12.68
	Undiscounted QALYs	18.28	0.22	18.07
	ICER (£/QALY)			[redacted]
2	**Threshold for sitting independently of ≥30 seconds for the pooled dataset (no additional walker)**			
	Total Costs (£)	[redacted]	413,269	[redacted]
	QALYs	13.31	0.21	13.10
	Undiscounted QALYs	18.84	0.22	18.62
	ICER (£/QALY)			[redacted]
3	**US ICER model report costs**			
	Total Costs (£)	[redacted]	580,341	[redacted]
	QALYs	14.89	0.21	14.67
	Undiscounted QALYs	21.41	0.22	21.19
	ICER (£/QALY)			[redacted]
4	**Subsequent nusinersen treatment costs**			
	Total Costs (£)	[redacted]	413,269	[redacted]
	QALYs	14.89	0.21	14.67
	Undiscounted QALYs	21.41	0.22	21.19
	ICER (£/QALY)			[redacted]

Abbreviations: ERG, evidence review group; ICER, incremental cost effectiveness ratio; QALYs, quality adjusted life years, US, united states.

Table 7. ERG base case ICER (costs and QALYs discounted at 1.5%)

Results per patient	Onasemnogene	Best supportive care	Incremental value
Company's base case			
Total Costs (£)	[redacted]	413,269	[redacted]
QALYs	14.89	0.21	14.67
Undiscounted QALYs	21.41	0.22	21.19
ICER (£/QALY)			[redacted]
Removal of the assumption of an additional independent sitter and independent walker from pooled dataset			
Total costs (£)	[redacted]	413,269	[redacted]
QALYs	13.74	0.21	13.52
Undiscounted QALYs	19.41	0.22	19.19
ICER (£/QALY)			[redacted]
ERG's preferred base case ICER (£/QALY)			[redacted]

Abbreviations: ERG, evidence review group; ICER, incremental cost effectiveness ratio; QALYs, quality adjusted life years.

Table 8. ERG's base case results for onasemnogene versus BSC including threshold for sitting independently of ≥30 seconds (costs and QALYs discounted at 1.5%)

Results per patient	Onasemnogene	Best supportive care	Incremental value

Total Costs (£)	[redacted]	413,269	[redacted]
QALYs	12.90	0.21	12.68
Undiscounted QALYs	18.28	0.22	18.07
ICER (£/QALY)			[redacted]
Abbreviations: ICER, incremental cost effectiveness ratio; QALYs, quality adjusted life years.			

Table 9. Scenario 2 from Table 45 of the ERG report (costs and QALYs discounted at 1.5%)

Results per patient	Onasemnogene	Best supportive care	Incremental value
Company's base case			
Total Costs (£)	[redacted]	413,269	[redacted]
QALYs	14.89	0.21	14.67
Undiscounted QALYs	21.41	0.22	21.19
ICER (£/QALY)			[redacted]
C state utility – 20% increase from baseline value (0.72)			
Total costs (£)	[redacted]	413,269	[redacted]
QALYs	16.67	0.21	16.46
Undiscounted QALYs	23.76	0.22	23.54
ICER (£/QALY)			[redacted]
C state utility – 20% decrease from baseline value (0.48)			
Total costs (£)	[redacted]	413,269	[redacted]
QALYs	13.11	0.21	12.89
Undiscounted QALYs	19.05	0.22	18.83
ICER (£/QALY)			[redacted]
Abbreviations: ICER, incremental cost effectiveness ratio; QALYs, quality adjusted life years.			

National Institute for Health and Care Excellence
Centre for Health Technology Evaluation

Pro-forma Response

ERG report

Onasemnogene abeparvovec for treating type 1 spinal muscular atrophy [ID1473]

You are asked to check the ERG report from BMJ-TAG to ensure there are no factual inaccuracies contained within it.

If you do identify any factual inaccuracies you must inform NICE by **5pm** on **Wednesday 9 September 2020** using the below proforma comments table. All factual errors will be highlighted in a report and presented to the Evaluation Committee and will subsequently be published on the NICE website with the Evaluation report.

The proforma document should act as a method of detailing any inaccuracies found and how and why they should be corrected.

Issue 1 Description of the population of interest

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 15. The report states "Given that the updated scope limits the population of interest for a genetic diagnosis of SMA to those with three copies of the SMN2 gene…" This is incorrect and should state "with up to three copies."	Text should be amended to read: Given that the updated scope limits the population of interest for a genetic diagnosis of SMA to those with up to three copies of the SMN2 gene	To correctly describe the population of interest.	The ERG thanks the company for highlighting the error. The text has been amended in line with the company's suggestion.
Page 15. The report states "In March 2020, onasemnogene was granted a conditional marketing authorisation by the European Medicines Agency (EMA) that encompassed those with a clinical diagnosis of SMA type 1 and children with no symptoms of SMA but with a genotype indicative of SMA type 1." Whist the sentence is correct in terms of the company's proposed positioning, it is not fully reflective of the EMA indication statement.	Text should be updated to reflect the EMA indication and the company's positioning within this licensed indication.	To correctly describe the EMA indication and the company's positioning.	The ERG has amended the text on page 15 to read: "and children with no symptoms of SMA but identified as having a genotype indicative of development of SMA".
Page 34. The report states "with no symptoms of SMA (hereafter referred to as pre-symptomatic) but identified as having a genotype indicative of development of SMA" The company's positioning is in	Text should be updated to: with no symptoms of SMA (hereafter referred to as pre-symptomatic) but identified as having a genotype indicative of development of SMA type 1	To correctly describe the company's positioning.	No change required. The paragraph immediately after the bullet point highlighted by the company clarifies the company's positioning of

pre-symptomatic infants with a genotype predictive of SMA type 1 (i.e. those with up to three copies of the SMN2 gene).			onasemnogene. Additionally, although the company is positioning onasemnogene as a treatment for SMA type 1 with or without symptoms, the ERG highlights that those who are pre-symptomatic and with up to three copies of the SMN2 gene could potentially develop SMA type 2 or SMA type 3. Although there is consensus that, in pre-symptomatic patients, SMN2 copy number is the best available predictor of clinical severity, it is also acknowledged that there are limitations in the predictive value of SMN2 copy number.[(1)] 1. Kirschner et al. European ad-hoc consensus statement on gene replacement therapy for spinal muscular atrophy. *Eur J Paediatric Neurol* 2020 (in press): https://www.ejpn-journal.com/article/S1090-3798(20)30142-2/pdf

Issue 2 Description of complications data

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 16 and page 45. Report states "Data are not available for complications of SMA. However, many complications of SMA type 1 will be captured within the adverse events experienced during the studies, for example, occurrence of scoliosis" This is an inaccurate description given that complications are captured in the adverse event data.	Amend this section to: Many complications of SMA type 1 will be captured within the adverse events experienced during the studies, for example, occurrence of scoliosis"	Accurate description of the data included in the submission.	The ERG has amended the text to read: "Data are not presented for the specified outcome of complications of SMA. However, …"

Issue 3 Nusinersen commissioning

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 16, 44 and 126. Report states: "Nusinersen was approved in July 2019 for routine commissioning in England for use in all patients with 5q SMA (pre-symptomatic SMA, or SMA types 1, 2 or 3) but is not yet considered established standard of care" This description states that	Please amend the wording to match previous reporting from NICE on this topic, for example: As nusinersen is available via a managed access agreement, in accordance with the final scope for this appraisal, its use is not considered to be embedded in NHS clinical practice because its availability to patients is contingent on further evidence generation and re-appraisal by NICE. Additionally, the significant uncertainties identified prevented NICE's committee from making a positive	Accurate framing of nusinersen commissioning.	The ERG has amended the text in line with the NICE scope and has clarified that nusinersen is available through a managed access agreement.

nusinersen is routinely commissioned, which does not align with the previous position of NICE on this topic, including the information provided in the updated, final scope for this appraisal that states: "However, as nusinersen is available via a managed access agreement, its use is not considered to be embedded in NHS clinical practice because its availability to patients is contingent on further evidence generation and re-appraisal by NICE. Additionally, the significant uncertainties identified prevented NICE's committee from making a positive recommendation during its appraisal, so it cannot be considered to be routinely commissioned."	recommendation during its appraisal, hence it was not considered to be routinely commissioned. Therefore, for the purposes of this highly specialised technology evaluation, nusinersen is not included as a relevant comparator.		

Issue 4 Follow-up periods

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 17. Page 58. Page 67. Page 76. Report states an 18-month follow-up period is used in STR1VE US	Replace "18-month" with "18 months of age" on pages 17, 67 and 76. Substitute the following on page 58: "Follow-up is planned up to 18 months of age in patients administered onasemnogene."	Accurately represent follow-up period.	The ERG has amended the text as highlighted by the company on pages 17, 67, and 76. The ERG has not made the change to text on page 57. The text reads "End of study visit

and STR1VE-EU. Follow-up for STR1VE-US and STR1VE-EU is 18 months of age.			was planned for when the patient reached 18 months of age".
Page 17, 18 and 115 The report states: 'In Cohort 2 of START, 91.7% of patients were able to hold their head erect without support for ≥3 seconds and sit with support, 75% were able to sit alone for ≥30 seconds, 16.7% of were able to walk alone' This statement is correct, but please add in the follow-up period for context.	Amendment of statement to "In Cohort 2 of START, 91.7% of patients were able to hold their head erect without support for ≥3 seconds and sit with support, 75% were able to sit alone for ≥30 seconds, 16.7% of were able to walk alone by the end of the study (24 months post-dose).	Accurately represent follow-up period.	No change required. The ERG considers that, when taken in the context of the full ERG report, it is clear that results are presented for the planned follow-up of START as it is stated that the study is complete.
Page 120: report states: "Considering longer-term follow-up, in LT-001, no patient has lost motor milestones achieved during START, with a follow-up of 4.4 years." Page 177: "the data are limited to a follow-up of 4.4 years" For clarity, specify that this is median follow-up in Cohort 2.	Substitute the following in each case: "a median follow-up period of 4.4 years in Cohort 2 (range 4.1–5.0)".	Accurately represent follow-up period.	No change required. When taken in the context of the full report, the ERG considers that it is clear that data are reported for only those from Cohort 2, which is specified to be the subgroup of interest from START.

Issue 5 START objectives and endpoints

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 17. Report states: "The primary objective of the START study was to evaluate the safety of onasemnogene whereas efficacy (achieved motor milestones and time to death or PAV) was a secondary objective." Although the statement is correct, it should be noted that time to death or PAV was the primary efficacy endpoint, whereas as achievement of motor milestones was a secondary efficacy endpoint.	Amendment of sentence to: "The primary objective of the START study was to evaluate the safety of onasemnogene whereas efficacy (time to death or PAV [primary efficacy endpoint] and achieved motor milestones) was a secondary objective.	Accurate description of START objectives and endpoints	No change required. The ERG considers that the text as it stands is accurate, in that the primary objective of START was safety, with any efficacy endpoint being a secondary endpoint.

Issue 6 Sitting thresholds

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 22. Report states: "In the pooled dataset, three patients were observed to be walking by 2 years of age, 20 patients were observed to be sitting unassisted and nine patients remained in the not-sitting state." It should be clarified in this	Substitute the following text: "In the pooled dataset, three patients were observed to be walking by 2 years of age, 22 patients were observed to be sitting unassisted and seven patients remained in the not-sitting state, when using a ≥5 second threshold for sitting in START and a ≥30 second threshold for sitting in STR1VE-US. In the pooled dataset, three patients were observed to be walking by 2	To clarify the thresholds used for sitting unassisted in STRIVE-US and START	The ERG thanks the company for highlighting the error. The text has been amended in the ERG report.

paragraph that these numbers are based on using a ≥30 second threshold for sitting independently in START (i.e. as per item 26 of the Bayley-III Scales gross motor subtest).	years of age, 20 patients were observed to be sitting unassisted and nine patients remained in the not-sitting state, when using a ≥30 second threshold for sitting in START and STR1VE-US.”		

Issue 7 Description of SMN2 copy number/SMA type evidence

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 28. The report states "The ERG considers that assuming all pre-symptomatic patients would have developed symptomatic SMA type 1 is flawed but the evidence base to understand what type of SMA pre-symptomatic patients might go on to develop is unavailable." There is evidence base available describing the breakdown of SMA type by SMN2 copy number, and the risk of developing different SMA types depending on SMN2 copy number. A number of these papers are referred to in the company submission and ERG report (for example, Calucho et al 2018 and Feldkotter et al 2002). To say that the evidence base is completely "unavailable" is misleading.	Update sentence to reflect that some data are available to describe SMN2 copy number correlation with SMA type	To provide a more balanced description of the evidence base available related to SMN2 copy number and SMA type	The ERG has updated the sentence in the ERG report to state that the evidence base is limited.
Page 32. The report states: "Although the number of copies a person has of the SMN2 gene is linked with severity of symptoms, there is an overlap and continuum between SMN2 copy number and SMA type, which means that copy	Update sentence to: "Although the number of copies a person has of the SMN2 gene is linked with severity of symptoms, there is an overlap and continuum between SMN2 copy number and SMA type, which means that copy number is considered not to fully predict the age of onset of	To provide a more balanced description of the evidence base available related to SMN2 copy number and SMA type	The ERG has amended the wording in line with the consensus statement available in the reference provided in the ERG's response to Issue 1.

number is considered not to be a reliable predictor of the age of onset of symptoms, and therefore SMA type." SMN2 copy number is known to correlate with SMA severity and SMA type. The use of the language "not to be a reliable predictor" is misleading.	symptoms, and therefore SMA type."""		

Issue 8 Description of SMA

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 31. The report states: "The diagnosis is confirmed by genetic testing of SMN1, with the absence of a functional SMN1 copy providing a diagnosis of SMA.[14] " This is incorrect. The sentence should state "…absence of a functional SMN1 gene ……" not copy	Update sentence to: "The diagnosis is confirmed by genetic testing of SMN1, with the absence of a functional SMN1 gene providing a diagnosis of SMA.[14] "	Correct description of the SMA	The ERG thanks the company for highlighting this error. The text has been amended in line with the company's suggestion.

Issue 9 Description of nusinersen mechanism of action

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 33. The report states: "Nusinersen modulates alternate splicing of the SMN2 gene, functionally converting it into SMN1 gene, thus increasing the level of SMN protein in the central nervous system (CNS)." This description of the mechanism of action of nusinersen is misleading and does not correspond to how the mechanism of action is described in the nusinersen SmPC.	Delete the phrase: "functionally converting it into SMN1 gene" Rephrase the mechanism of action, as per the SmPC for nusinersen: "Nusinersen is an antisense oligonucleotide (ASO) which increases the proportion of exon 7 inclusion in survival motor neuron 2 (SMN2) messenger ribonucleic acid (mRNA) transcripts which leads to retention of exon 7 in the SMN2 mRNA and hence when SMN2 mRNA is produced, it can be translated into the functional full length SMN protein."	Accurate description of the mechanism of action, as per the SmPC for nusinersen.	Text amended to state the mode of action of Nusinersen more accurately. Text now reads: Nusinersen increases the proportion of exon 7 (critical for production of fully functional SMN protein) inclusion in SMN2 messenger ribonucleic acid (mRNA) transcripts, which leads to retention of exon 7 in the SMN2 mRNA. Thus, when SMN2 mRNA is produced, the mRNA can be translated into functional full length SMN protein, thereby increasing the level of SMN protein in the central nervous system (CNS)."

Issue 10 Nusinersen in clinical practice

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 33, the report states: "Nusinersen is anticipated to become part of established clinical practice for the management of SMA in England and Wales."	Delete the sentence.	There is no justification currently provided in the report for the claim.	The ERG has amended the text in line with earlier comments and the NICE scope. The text now reads, "At the time of writing, nusinersen is

The references given to substantiate this claim do not back it up. Reference 20 only states that it is a possibility; Reference 21 is to NICE guidance.			not considered established clinical practice in England for the management of SMA, but, should more robust evidence on the effectiveness of nusinersen become available, use of nusinersen could become routine in the management of SMA.”

Issue 11 Description of prednisolone

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 35. The report states: "To manage a possible increase in liver transaminases, all patients should receive oral prednisolone 24 hours prior to onasemnogene administration, with continued administration of prednisolone for 30 days after treatment." Whilst this is correct, further information is required to be consistent with the SmPC. This sentence should have the following added "followed by a period of steroid tapering according to the patient's clinical findings".	Update sentence to: "To manage a possible increase in liver transaminases, all patients should receive oral prednisolone 24 hours prior to onasemnogene administration, with continued administration of prednisolone for 30 days after treatment. This is followed by a tapering of prednisolone depending on the patient's clinical findings"	Consistency with the SmPC.	Text amended in line with the company's suggestion.

Issue 12 Natural history data sources in the economic model

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 42. Report states: "For the purposes of the economic model, the PNCR cohort is combined with a second cohort of patients that included additional SMN2 gene copy numbers (De	Substitute the following text: "For the purposes of the economic model, the PNCR cohort is incorporated into the economic model in two separate scenarios: One scenario (PNCR cohort only) includes individuals with 2 *SMN2* copies and SMA type 1 only (n=23) from	Precise account of the economic model and scenario analyses submitted.	Text amended in line with the suggestion from the company. Text now reads, "For the purposes of the economic model, the PNCR cohort is implemented in two scenarios. One scenario involves the

Sanctis et al. 2016[34]).” This is incorrect. It should be stated that the company presented both the PNCR dataset and the De Sanctis 2016 dataset (which is a combined cohort of PNCR [US] and Italy patients) as two separate scenario analyses in the economic model. These scenarios are presented in the company submission (May 2020) as scenario analysis #19 and #21 and can be seen in the economic model in the worksheet ‘Result5’. The PNCR cohort only dataset can be selected by setting cell Q12=4 on the worksheet ‘D_Survival_BSC’ in the economic model. The De Sanctis 2016 dataset can be selected by setting cell Q12=3 on the worksheet ‘D_Survival_BSC’ in the economic model.	the PNCR database. A second scenario includes patients described in De Sanctis et al. (2016) (which is a combined cohort of PNCR [US] and Italy patients) with SMA type 1, where *SMN2* copy number is not defined (n=26).”		PNCR cohort alone and comprises patients with 2 copies of SMN2 gene and SMA type 1 (n=23). A second scenario involves a cohort (n=26) combining patients from Italy, where SMN2 copy number is not available, as described in De Sanctis et al.34, with the PNCR database. The population in the combined cohort applied in scenario analysis in the economic model is in line with the NICE final scope1 but a mismatch compared with the more specific population enrolled in START (limited to two copies of the SMN2 gene), which is informing the efficacy and safety data for onasemnogene.”
Page 68. Page 77. Report states: “Instead of the identified PNCR cohort, the company used another natural history data source in scenario analyses in the health economic model.”	Reword as follows in each case.: “In addition to the identified PNCR cohort, the company used…”	Precise account of the economic model and scenario analyses submitted	Text amended as per company’s suggestion. Text now reads: “The company implemented the PNCR cohort in two scenario analyses. One scenario involves the PNCR cohort alone and comprises

This is incorrect. It should be stated that the company presented both the PNCR dataset and the De Sanctis 2016 dataset (which is a combined cohort of PNCR [US] and Italy patients) as two separate scenario analyses in the economic model. These scenarios are presented in the company submission (May 2020) as scenario analysis #19 and #21 and can be seen in the economic model in the worksheet 'Result5'. The PNCR cohort only dataset can be selected by setting cell Q12=4 on the worksheet 'D_Survival_BSC' in the economic model. The De Sanctis 2016 dataset can be selected by setting cell Q12=3 on the worksheet 'D_Survival_BSC' in the economic model.			patients with 2 copies of SMN2 gene and SMA type 1 (n=23). A second scenario involves a cohort (n=26) combining patients from Italy, where SMN2 copy number is not available, as described in De Sanctis et al.34, with patients from the PNCR database."

Issue 13 Description of the technology

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 44. The report states "The ERG considers that only comparator of relevance is BSC, irrespective of whether onasemnogene has been given as a prophylaxis with the goal of preventing development of symptoms in patients identified as having a genotype associated with SMA type 1 or as a treatment in those with a clinical diagnosis of SMA type 1." Onasemnogene abeparvovec is not prophylaxis, it is disease-modifying by addressing the genetic root cause of SMA.	Update sentence to: "The ERG considers that the only comparator of relevance is BSC, irrespective of whether onasemnogene has been given pre-symptomatically with the goal of preventing development of symptoms in patients identified as having a genotype associated with SMA type 1 or as a treatment in those with a clinical diagnosis of SMA type 1."	Correct description of the technology	"Prophylaxis" has been removed.

Issue 14 Motor function and motor milestone assessments

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 45. The report states: "Motor function, measured as achieving motor milestones, were mainly assessed using Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders, CHOP-INTEND, a scale developed and validated for use specifically to monitor motor	Amends paragraph to: "Motor function and the achievement of motor milestones, were assessed using a number of assessment tools, including the Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders (CHOP-INTEND), a scale developed and validated for use specifically to monitor motor function status amongst children with SMA type 1, and by the	Correct representation of the assessments used to assess motor milestone achievements.	No change required, not a factual inaccuracy. The text does not indicate that CHOP-INTEND was the sole tool used to assess motor function and achievement of motor milestones. The ERG considers that the points highlighted by the company are

function status amongst children with SMA type 1." This description is not fully correct. Other scales were used, in addition to the CHOP INTEND, to assess motor milestones. It should also be clarified that these different assessments were video-recorded and centrally reviewed, in order to identify motor milestone achievements.	Bayley Scales of Infant and Toddler Development (Version 3), a standard instrument for assessing the development of infants. Compiled video recordings of the CHOP-INTEND, Bayley Scales, submitted home videos, and physical examinations were sent to a central reviewer for independent confirmation of motor milestones."		made in the ERG report.
Page 56. Report states: "the ERG considers that bias in assessment of motor milestone outcomes is minimised by recording children during assessment of motor skills." The exact recording procedure should be clarified, as above.	Add the following: "Compiled video recordings of the CHOP-INTEND, Bayley Scales, submitted home videos, and physical examinations were sent to a central reviewer for independent confirmation of development milestones."	Correct representation of the assessments used to assess motor milestone achievements.	No change required, not a factual inaccuracy. The ERG considers that the points highlighted by the company are made in the ERG report.
Page 89. Report states: "The company reports that the mean Bayley fine motor subset scores increased from [redacted] between the first and final visit. Mean gross motor subset raw scores also increased between the first and final visit from [redacted]. The increases in Bayley Scale scores reflect gains in motor function"	Substitute the following: "The company reports that the mean Bayley fine motor subset scores increased from [redacted] between the first when Bayley scores were assessed and the final visit. Mean gross motor subset raw scores also increased between the first visit when Bayley scores were assessed and the final visit from [redacted]. The increases in Bayley Scale scores reflect gains in motor function. Bayley Scales were not a mandatory assessment in START and were only	Correct representation of the Bayley Scales data in START.	The ERG has added, "when Bayley scores were assessed" to the text. CiC marking for gross motor subset scores has been applied. That the assessment of Bayley Score was only carried out for those with a CHOP-INTEND score of 62 or more in START is reported on page 57 of the ERG report.

This paragraph is unclear, as the Bayley scores weren't always recorded at the first visit. Bayley Scales were not a mandatory assessment in START and were only administered if a child reached or exceeded a score of 60 out of 64 on the CHOP-INTEND. A baseline assessment for all patients was not collected as a result of the study protocol terms described. The figures quoted represent the change from the first visit when Bayley scores were assessed and the final visit.	administered if a child reached or exceeded a score of 60 out of 64 on the CHOP-INTEND. Therefore, a baseline assessment for all patients was not collected as a result of the study protocol terms described" Please ensure CIC marking for this paragraph is applied as per this pro forma response. Currently, in the ERG report, the gross motor subset raw scores are not CIC marked, but they should be.		

Issue 15 STR1VE-EU completion date

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 59 and page 202. Report states the estimated completion date for STR1VE-EU is Q3 2020. This is incorrect, as the database lock/completion date is provisionally scheduled for 28 October 2020.	Update to "Q4 2020"	Accurate completion date of STR1VE-EU	Both instances of Q3 amended to Q4.

Issue 16 SMN2 copy number of enrolled cohorts

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 63. Table 8. The *SMN2* copy number is missing for the STR1VE-EU and LT-001 columns in Table 8. These data are available: all patients enrolled in STR1VE-EU and LT-001 have 2 copies of the *SMN2* gene.	*SMN2* copy number for enrolled patients should be updated to "2" for STR1VE-EU and LT-001.	To correctly represent the enrolled study populations.	The ERG thanks the company for highlighting this oversight. Entries for SMN2 copy number for STR1VE-EU and LT-001 have been updated.

Issue 17 Incorrect CIC marking

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 65. Table 8. Information in the 'familial history of SMA including affected siblings or parent carriers' row is incorrectly marked with CIC marking.	The 'familial history of SMA including affected siblings or parent carriers' row should be marked as CIC for both STR1VE-US and STR1VE-US columns in Table 8.	Correct description of the SPR1NT study.	The ERG apologises for this oversight. CiC marking applied for STR1VE-US as highlighted by the company.

Issue 18 START Cohort 2 population number

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 82, Table 15 Page 87, Table 17	Change table headings to read "N=12" for START, Cohort 2.	To correctly represent the START cohort.	Column headings corrected as per company's comment.

Table headings state “N=13” for START, Cohort 2. The correct sample size is N=12.			

Issue 19 CHOP INTEND data for START

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 87. Table 17. Currently ‘NR’ is reported for mean change from baseline in CHOP-INTEND score at Month 1, 3 and 6 for the START trial. Some of these data were shared in the company submission appendix (May 2020), on page 83: Mean increases from baseline of 9.8 and 15.4, were reported at 1 and 3 months post gene therapy, respectively (n=12, both p<0.001).	Update Table 17, START (Cohort 2), with the data shared in the company submission (May 2020) on page 83: Mean increases from baseline of 9.8 and 15.4, were reported at 1 and 3 months post gene therapy, respectively (n=12, both p<0.001)	Complete description of the START data submitted.	The ERG thanks the company for providing the data. Table entries updated accordingly.

Issue 20 Description of the pre-symptomatic study, SPR1NT

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 118. The report states: "One ongoing study evaluates the use of onasemnogene as a prophylactic treatment in patients with no symptoms of SMA but identified as having a genetic profile indicative of likely development of SMA type 1 (SPR1NT)." The term 'prophylactic' is incorrect.	Update sentence to: One ongoing study evaluates the use of onasemnogene as a treatment in pre-symptomatic infants with no symptoms of SMA but identified as having a genetic profile indicative of likely development of SMA type 1 (SPR1NT).	Correct description of the SPR1NT study	"Prophylactic" removed from the text
Page 120. The report states: "As SPR1NT is evaluating the use of onasemnogene as a prophylactic treatment, it must be borne in mind that the type of SMA a patient would have gone on to develop is unknown" The term 'prophylactic' is incorrect.	Update sentence to: As SPR1NT is evaluating the use of onasemnogene in pre-symptomatic infants, it must be borne in mind that the type of SMA a patient would have gone on to develop is unknown	Correct description of the SPR1NT study	"Prophylactic" removed and "before symptoms manifest" added.
Page 176. The report states: "Evidence on the potential benefit of prophylactic treatment with onasemnogene in those identified as likely to develop SMA type 1 is being assessed in the ongoing	Update sentence to: Evidence on the potential benefit of treatment with onasemnogene in pre-symptomatic infants identified as likely to develop SMA type 1 is being assessed in the ongoing SPR1NT study	Correct description of the SPR1NT study.	"Prophylactic" removed and "before symptoms manifest" added.

SPR1NT study" The term 'prophylactic' is incorrect.			

Issue 21 Referencing of supplementary table

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 157. Report references Table 9 of the supplementary appendix as the source for the values used in the one-way sensitivity analysis. Reference should be to Table 69.	Update reference to refer to Table 69.	Correct referencing to company submission.	The ERG thanks the company for highlighting this error. Table reference has been updated in the ERG report.

Issue 22 Results of OWSA on hospitalisation parameters

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 159. It should be clarified that the results in Table 46 are based on the list price of onasemnogene abeparvovec.	Update table heading as follows: "Results of OWSA on hospitalisation parameters, conducted at list price."	Improved clarity regarding OWSA results.	The ERG thanks the company for highlighting this issue. Table 46 has been updated to reflect the OWSA inclusive of the company's PAS.

Issue 23 Explanation of results

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 156 and 172. The report states: "While onasemnogene doesn't restore the majority of treated patients to full or near full health…" This statement is referring to treatment of symptomatic SMA type 1 patients, therefore, this information should be added.	Update sentence to: While onasemnogene does not restore the majority of treated symptomatic SMA type 1 patients to full or near full health, data from START and STR1VE-US demonstrates a substantial survival benefit for patients who would have otherwise died	Context of statement	The ERG has amended the statement in the ERG report to specify symptomatic SMA type 1 patients.

Issue 24 ERG's scenario 1 results

<table>
<tr><th>Description of problem</th><th>Description of proposed amendment</th><th>Justification for amendment</th><th>ERG response</th></tr>
<tr>
<td>Page 170. Table 54. Scenario 1 ('Threshold for sitting independently of ≥30 seconds for the pooled dataset (observed motor milestones only)')
The same scenario is also presented in the document in various pages and tables: Table 56 on page 172, Table B on page 29 and text on page 134.
Results for scenario 1 appear to be incorrect. It is believed that the milestone data used for this scenario was incorrect.</td>
<td>In texts, substitute £[redacted] with £[redacted].
In tables, substitute values with the values in the table below.
<table>
<tr><th>Treatment</th><th>Total costs</th><th>Total LYs</th><th>Total QALYs</th><th>Incr. costs</th><th>Incr. LYs</th><th>Incr. QALYs</th><th>ICER (£/QALY)</th></tr>
<tr><td>BSC</td><td>381,131</td><td>2.15</td><td>0.21</td><td>-</td><td>-</td><td>-</td><td>-</td></tr>
<tr><td>Onasemnogene + BSC</td><td>[redacted]</td><td>14.08</td><td>8.96</td><td>[redacted]</td><td>11.94</td><td>8.75</td><td>[redacted]</td></tr>
<tr><td colspan="8">Abbreviations: BSC, best supportive care; ICER, incremental cost-effectiveness ratio; Incr., Incremental; LYs, life years; QALY, quality-adjusted life year.</td></tr>
</table>
</td>
<td>Inaccurate results are presented in the report</td>
<td>The ERG thanks the company for providing the correct milestone data for the scenario. The ERG report has</td>
</tr>
</table>

The table below includes the correct milestone data showing the number of patients in each health state based on observed milestones from the pooled dataset and ≥30 seconds threshold applied for independent sitting (offset by one cycle). **age at end of cycle (month) / Not sitting / Sitting but not walking / Walking / Dead or PAV** 6 / 34 / 0 / 0 / 0 12 / 32 / 0 / 0 / 2 18 / 24 / 8 / 0 / 2 24 / 14 / 17 / 1 / 2 30 / 10 / 19 / 3 / 2 36 / 9 / 20 / 3 / 2 48 / 9 / 20 / 3 / 2 60 / 9 / 20 / 3 / 2			been updated to present the correct results.

Issue 25 ERG's scenario 2 results

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 170/171. Table 54. Scenario 2 ('Threshold for sitting independently of ≥30 seconds for the pooled dataset (no additional walker)') The same scenario is also presented in	In the text, substitute £[redacted] with £[redacted]. In the table, substitute values with the values in the table below. **Treatment / Total costs / Total LYs / Total QALYs / Incr. costs / Incr. LYs / Incr. QALYs / ICER (£/QALY)** BSC / 381,131 / 2.15 / 0.21 / - / - / - / -	Inaccurate results are presented in the report	The ERG thanks the company for providing the correct

the text on page 134.

Results for scenario 2 appear to be incorrect. It is believed that the milestone data used for this scenario was incorrect.

The table below includes the correct milestone data showing the number of patients in each health state based on observed milestones from the pooled dataset with an additional sitter (but no additional walker) between the age of 30-36 months and ≥30 seconds threshold applied for independent sitting (offset by one cycle).

age at end of cycle (month)	Not sitting	Sitting but not walking	Walking	Dead or PAV
6	34	0	0	0
12	32	0	0	2
18	24	8	0	2
24	14	17	1	2
30	10	19	3	2
36	8	21	3	2
48	8	21	3	2
60	8	21	3	2

Onasemnogene + BSC	[redacted]	14.53	9.26	[redacted]	12.38	9.05	[redacted]

Abbreviations: BSC, best supportive care; ICER, incremental cost-effectiveness ratio; Incr., Incremental; LYs, life years; QALY, quality-adjusted life year.

milestone data for the scenario. The ERG report has been updated to present the correct results.

Issue 26 ERG's scenario 3 results

<table>
<tr><th>Description of problem</th><th>Description of proposed amendment</th><th>Justification for amendment</th><th>ERG response</th></tr>
<tr>
<td>
Page 171. Table 54. Scenario 3 ('US ICER model report costs')

The same scenario is also presented in the text on page 154.

Results for scenario 3 appear to be incorrect, as the company cannot replicate the ICER described by the ERG. The company believes using the 2017 GBP values of the US ICER report from Table 40 in the ERG report to replace the health state costs in the model gives different results. For this scenario, it is believed that only the following values are changed in the company's base case model:
<table>
<tr><th></th><th>E state</th><th>D state</th><th>C state</th><th>B state</th><th>A st</th></tr>
<tr><td>US ICER report – annual health state costs converted to 2017 GBP values</td><td>£266,829</td><td>£241,289</td><td>£60,112</td><td>£23,631</td><td>£23</td></tr>
</table>
</td>
<td>
In the text, substitute £[redacted] with £[redacted].

In the table, substitute values with the values in the table below.
<table>
<tr><th>Treatment</th><th>Total costs</th><th>Total LYs</th><th>Total QALYs</th><th>Incr. costs</th><th>Incr. LYs</th><th>Incr. QALYs</th><th>IC (£</th></tr>
<tr><td>BSC</td><td>544,139</td><td>2.15</td><td>0.21</td><td></td><td></td><td></td><td></td></tr>
<tr><td>Onasemnogene + BSC</td><td>[redacted]</td><td>15.68</td><td>10.21</td><td>[redacted]</td><td>13.53</td><td>10.00</td><td>[redacted]</td></tr>
</table>
Abbreviations: BSC, best supportive care; ICER, incremental cost-effectiveness ratio; Incr., Incremental; LYs, life years; QALY, quality-adjusted life year.
</td>
<td>Inaccurate results are presented in the report</td>
<td>The ERG thanks the company for highlighting this issue. The ERG found an error with the formula used for the scenario related to the cost of the E state. This has been correct and the ERG report updated accordingl</td>
</tr>
</table>

			y.

Issue 27 ERG's scenario 4 results

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 171. Table 54. Scenario 4 ('Subsequent nusinersen treatment costs') The same scenario is also presented in the text on page 153. The company cannot replicate this scenario, due to the following omission of information: • It is not clear how loading versus maintenance doses have been accounted for • It is not clear how/if the ERG has correctly adjusted for 6-month versus annual cycles • It is not clear if administration costs for nusinersen have been calculated/amended based on the age of the cohort The company considers this analysis to be incorrect and inappropriate due to the following reasons: • From the scenario description in the ERG report (page 153), it is assumed that nusinersen costs were applied from cycle 1 onwards (including the START trial period), which does not correspond to what was observed in the trials. Only during the follow up study to START, i.e. in LT-001 after 30 months of age, a minority of patients received	Removal of the scenario in which nusinersen costs have been added to the onasemnogene abeparvovec arm.	An inappropriate scenario analysis is being presented	No change required, not a factual inaccuracy. The implementation of this scenario was based on the instructions provided by the company in their response to clarification questions for the original company submission (2019), question B19.

nusinersen in the US. • As per the expert clinical advice sought by the ERG, the clinical experts advised that without long-term evidence on subsequent nusinersen use after onasemnogene abeparvovec, they would not consider offering it to treated patients in the NHS. Thus, the inclusion of this scenario is not valid for an England perspective. • The calculations do not account for any discontinuation of nusinersen (i.e. received until death) which may not be realistic in clinical practice. • The results of this analysis use the list price for nusinersen. However, a confidential PAS for nusinersen is available. • The company has been informed by NICE that nusinersen is not part of routine commissioning/clinical practice in England and not a comparator for this appraisal. Therefore, the request to add in nusinersen usage seems to oppose this premise – as it requires/implies nusinersen is not only part of routine commissioning/clinical practice in England, but part of routine commissioning as a second line intervention, which is a positioning with no formal clinical trial evidence or NICE or other guidance to support this use. • A recent consensus publication from EU clinicians (Kirschner et al 2020) does not recommend combination use stating that combination treatment has not been studied systematically and warrants further investigation			

• In a hypothetical scenario where nusinersen were to be routinely available, the company considers the use of LT-001 data as a basis for estimating the proportion of patients that would receive nusinersen following treatment onasemnogene abeparvovec to be flawed. This is because LT-001 was conducted in a US payer health-care, clinical trial setting prior to the regulatory approval of onasemnogene abeparvovec and therefore the clinical decision making to provide nusinersen would differ from that in an England payer healthcare setting following regulatory approval of onasemnogene abeparvovec for use in routine clinical practice • There is no formal risk/benefit assessment of the ERG-proposed positioning of nusinersen usage; thus, AveXis considers it inappropriate for NICE to consider such a treatment approach in their assessment of onasemnogene abeparvovec			

National Institute for Health and Care Excellence
Centre for Health Technology Evaluation

Pro-forma Response

ERG report

Onasemnogene abeparvovec for treating type 1 spinal muscular atrophy [ID1473]

You are asked to check the ERG report from BMJ-TAG to ensure there are no factual inaccuracies contained within it.

If you do identify any factual inaccuracies you must inform NICE by **5pm** on **Tuesday 15 September 2020** using the below proforma comments table. All factual errors will be highlighted in a report and presented to the Evaluation Committee and will subsequently be published on the NICE website with the Evaluation report.

The proforma document should act as a method of detailing any inaccuracies found and how and why they should be corrected.

Issue 1 ERG's scenario 1 results

<table>
<tr><th>Description of problem</th><th>Description of proposed amendment</th><th>Justification for amendment</th><th>ERG response</th></tr>
<tr>
<td>
Page 2. Table 2. Scenario 1 ('Threshold for sitting independently of ≥30 seconds for the pooled dataset (observed motor milestones only)') at a 3.5% discount rate. These results are also presented in Table 4 on page 3.

Page 5. Table 6. Scenario 1 ('Threshold for sitting independently of ≥30 seconds for the pooled dataset (observed motor milestones only)') at a 1.5% discount rate. These results are also presented in Table 8 on page 6.

Results for scenario 1 appear to be incorrect. It is believed that the milestone data used for this scenario was incorrect.

The table below includes the correct milestone data showing the number of patients in each health state based on observed milestones from the pooled dataset and ≥30 seconds threshold applied for independent sitting (offset by one cycle).
<table>
<tr><th>age at end of cycle (month)</th><th>Not sitting</th><th>Sitting but not walking</th><th>Walking</th><th>Dead or PAV</th></tr>
<tr><td>6</td><td>34</td><td>0</td><td>0</td><td>0</td></tr>
<tr><td>12</td><td>32</td><td>0</td><td>0</td><td>2</td></tr>
<tr><td>18</td><td>24</td><td>8</td><td>0</td><td>2</td></tr>
</table>
</td>
<td>
For the results run at a 3.5% discount rate, substitute £[redacted] with £[redacted].

In tables, substitute values with the values in the table below.
<table>
<tr><th>Results per patient</th><th>Onasemnogene</th><th>Best supportive care</th><th>Incremental value</th></tr>
<tr><td colspan="4">Threshold for sitting independently of ≥30 seconds for the pooled dataset (observed motor milestones only)</td></tr>
<tr><td>Total Costs (£)</td><td>[redacted]</td><td>381,131</td><td>[redacted]</td></tr>
<tr><td>QALYs</td><td>8.96</td><td>0.21</td><td>8.75</td></tr>
<tr><td>Undiscounted QALYs</td><td>18.28</td><td>0.22</td><td>18.07</td></tr>
<tr><td>ICER (£/QALY)</td><td></td><td></td><td>[redacted]</td></tr>
</table>
For the results run at a 1.5% discount rate, substitute £[redacted] with £[redacted].

In tables, substitute values with the values in the table below.
<table>
<tr><th>Results per patient</th><th>Onasemnogene</th><th>Best supportive care</th><th>Incremental value</th></tr>
<tr><td colspan="4">Threshold for sitting independently of ≥30 seconds for the pooled dataset (observed motor milestones only)</td></tr>
<tr><td>Total Costs (£)</td><td>[redacted]</td><td>413,269</td><td>[redacted]</td></tr>
<tr><td>QALYs</td><td>12.90</td><td>0.21</td><td>12.68</td></tr>
<tr><td>Undiscounted</td><td>18.28</td><td>0.22</td><td>18.07</td></tr>
</table>
</td>
<td>Inaccurate results are presented in the addendum</td>
<td>The ERG thanks the company for providing the correct milestone data for the scenario. The ERG report addendum has been updated to present the correct results.</td>
</tr>
</table>

24	14	17	1	2
30	10	19	3	2
36	9	20	3	2
48	9	20	3	2
60	9	20	3	2

QALYs			
ICER (£/QALY)			[redacted]

Issue 2 ERG's scenario 2 results

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 3. Table 2. Scenario 2 ('Threshold for sitting independently of ≥30 seconds for the pooled dataset (no additional walker)') at a 3.5% discount rate. Page 5. Table 6. Scenario 2 ('Threshold for sitting independently of ≥30 seconds for the pooled dataset (no additional walker)') at a 1.5% discount rate. Results for scenario 2 appear to be incorrect. It is believed that the milestone data used for this scenario was incorrect. The table below includes the correct milestone data showing the number of patients in each health state based on	For the results run at a 3.5% discount rate, substitute £[redacted] with £[redacted]. In tables, substitute values with the values in the table below.	Inaccurate results are presented in the report	The ERG thanks the company for providing the correct milestone data for the scenario. The ERG report addendum has been updated to present the correct results.

Results per patient	Onasemnogene	Best supportive care	Incremental value
Threshold for sitting independently of ≥30 seconds for the pooled dataset (no additional walker)			
Total Costs (£)	[redacted]	381,131	[redacted]
QALYs	9.26	0.21	9.05
Undiscounted QALYs	18.84	0.22	18.62
ICER (£/QALY)			[redacted]

observed milestones from the pooled dataset with an additional sitter (but no additional walker) in the cycle 30-36 months and ≥30 seconds threshold applied for independent sitting (offset by one cycle).

age at end of cycle (month)	Not sitting	Sitting but not walking	Walking	Dead or PAV
6	34	0	0	0
12	32	0	0	2
18	24	8	0	2
24	14	17	1	2
30	10	19	3	2
36	8	21	3	2
48	8	21	3	2
60	8	21	3	2

For the results run at a 1.5% discount rate, substitute £[redacted] with £[redacted].

In tables, substitute values with the values in the table below.

Results per patient	Onasemnogene	Best supportive care	Incremental value
Threshold for sitting independently of ≥30 seconds for the pooled dataset (no additional walker)			
Total Costs (£)	[redacted]	413,269	[redacted]
QALYs	13.31	0.21	13.10
Undiscounted QALYs	18.84	0.22	18.62
ICER (£/QALY)			[redacted]

Issue 3 ERG's scenario 3 results

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 3. Table 2. Scenario 3 ('US ICER model report costs') at a 3.5% discount rate. Page 5. Table 6. Scenario 3 ('US ICER model report costs') at a 1.5% discount	For the results run at a 3.5% discount rate, substitute £[redacted] with £[redacted]. In tables, substitute values with the values in the table below. Results per patient | Onasemnogene | Best supportive care | Incremental value	Inaccurate results are presented in the report	The ERG thanks the company for highlighting this issue. The ERG found an error with the formula

rate

Results for scenario 3 appear to be incorrect, as the company cannot replicate the ICER described by the ERG. The company believes using the 2017 GBP values of the US ICER report from Table 40 in the ERG report to replace the health state costs in the model gives different results. For this scenario, it is believed that only the following values are changed in the company's base case model:

	E state	D state	C state	B s
US ICER report – annual health state costs converted to 2017 GBP values	£266,829	£241,289	£60,112	£23

US ICER model report costs			
Total Costs (£)	[redacted]	544,139	[redacted]
QALYs	10.21	0.21	10.00
Undiscounted QALYs	21.41	0.22	21.19
ICER (£/QALY)			[redacted]

For the results run at a 1.5% discount rate, substitute £[redacted] with £[redacted].

In tables, substitute values with the values in the table below.

Results per patient	Onasemnogene	Best supportive care	Incremental value
US ICER model report costs			
Total Costs (£)	[redacted]	580,341	[redacted]
QALYs	14.89	0.21	14.67
Undiscounted QALYs	21.41	0.22	21.19
ICER (£/QALY)			[redacted]

used for the scenario related to the cost of the E state. This has been corrected and the ERG report addendum updated accordingly.

Issue 4 ERG's scenario 4 results

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 3. Table 2. Scenario 4 ('Subsequent nusinersen treatment costs') at a 3.5% discount rate. Page 5. Table 6. Scenario 4 ('Subsequent	Removal of the scenario in which nusinersen costs have been added to the onasemnogene abeparvovec	An inappropriate scenario analysis is being presented	No change required, not a factual inaccuracy. The implementation of this scenario was based on the instructions provided by the company in their response to clarification questions for the

nusinersen treatment costs') at a 1.5% discount rate. The company cannot replicate this scenario, due to the following omission of information: • It is not clear how loading versus maintenance doses have been accounted for • It is not clear how/if the ERG has correctly adjusted for 6-month versus annual cycles • It is not clear if administration costs for nusinersen have been calculated/amended based on the age of the cohort The company considers this analysis to be incorrect and inappropriate due to the following reasons: • From the scenario description in the ERG report (page 153), it is assumed that nusinersen costs were applied from cycle 1 onwards (including the START trial period), which does not correspond to what was observed in the trials. Only during the follow up study to START, i.e. in LT-001 after 30 months of age, a minority of patients received nusinersen in the US. • As per the expert clinical advice sought by the ERG, the clinical experts advised that without long-term evidence on subsequent nusinersen use after onasemnogene abeparvovec, they	arm.		original company submission (2019), question B19.

would not consider offering it to treated patients in the NHS. Thus, the inclusion of this scenario is not valid for an England perspective. • The calculations do not account for any discontinuation of nusinersen (i.e. received until death) which may not be realistic in clinical practice. • The results of this analysis use the list price for nusinersen. However, a confidential PAS for nusinersen is available. • The company has been informed by NICE that nusinersen is not part of routine commissioning/clinical practice in England and not a comparator for this appraisal. Therefore, the request to add in nusinersen usage seems to oppose this premise – as it requires/implies nusinersen is not only part of routine commissioning/clinical practice in England, but part of routine commissioning as a second line intervention, which is a positioning with no formal clinical trial evidence or NICE or other guidance to support this use. • A recent consensus publication from EU clinicians (Kirschner et al 2020) does not recommend combination use stating that combination treatment has not been studied systematically and warrants further investigation • In a hypothetical scenario where			

nusinersen were to be routinely available, the company considers the use of LT-001 data as a basis for estimating the proportion of patients that would receive nusinersen following treatment onasemnogene abeparvovec to be flawed. This is because LT-001 was conducted in a US payer health-care, clinical trial setting prior to the regulatory approval of onasemnogene abeparvovec and therefore the clinical decision making to provide nusinersen would differ from that in an England payer healthcare setting following regulatory approval of onasemnogene abeparvovec for use in routine clinical practice • There is no formal risk/benefit assessment of the ERG-proposed positioning of nusinersen usage; thus, AveXis considers it inappropriate for NICE to consider such a treatment approach in their assessment of onasemnogene abeparvovec			

Issue 5 Explanation of results

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 4. The addendum states: "As mentioned in the ERG report, onasemnogene doesn't restore the majority of treated patients to full or near full health …" This statement is referring to treatment of symptomatic SMA type 1 patients, therefore, this information should be added.	Update sentence to: While onasemnogene does not restore the majority of treated symptomatic SMA type 1 patients to full or near full health, data from START and STR1VE-US demonstrates a substantial survival benefit for patients who would have otherwise died	Context of statement	The ERG has amended the statement in the ERG report addendum to specify symptomatic SMA type 1 patients.

Onasemnogene abeparvovec for treating spinal muscular atrophy

NICE requested scenarios

February 2021

Source of funding

This report was commissioned by the National Institute for Health Research Evidence Synthesis Programme as project number as project number 128205T.

1 Introduction

For the evaluation committee meeting for onasemnogene abeparvovec (hereafter referred to as onasemnogene) for treating spinal muscular atrophy (SMA) on the 10th of February 2021, the National Institute for Health and Care Excellence (NICE) requested additional information and scenarios to be provided which explore treatment with onasemnogene for babies aged 6 months and older and motor milestone achievement.

All analyses presented in this document include the company's revised patient access scheme (PAS) discount of [redacted] to the committee's preferred assumptions for the symptomatic SMA type 1 population, which are as follows:

- using the independent sitting threshold of 30 seconds or more;
- assuming 1 additional sitter to the observed data from STR1VE US;
- applying a 1.5% discount rate for costs and utilities;
- assuming that motor milestones gained in the first 3 years in the economic model are maintained in the long term – this assumption is no different from the company or ERG base case assumptions and therefore no changes are required.

Table 1 presents an overview of the company's base case ICER and the committee's preferred ICER for the symptomatic SMA type 1 population.

Table 1. Cost-effectiveness results – committee's preferred assumptions (costs and QALYs discounted at 1.5%)

	Results per patient	Onasemnogene	Best supportive care	Incremental value
0	**Company's Base case**			
	Total Costs (£)	[redacted]	413,269	[redacted]
	QALYs	14.89	0.21	14.67
	Undiscounted QALYs	21.41	0.22	21.19
	ICER (£/QALY)			[redacted]
2	**Threshold for sitting independently of ≥30 seconds for the pooled dataset (one additional sitter, no additional walker)**			
	Total Costs (£)	[redacted]	413,269	[redacted]
	QALYs	13.31	0.21	13.10
	Undiscounted QALYs	18.84	0.22	18.62
	ICER (£/QALY)			[redacted]

Abbreviations: ICER, incremental cost effectiveness ratio; QALYs, quality adjusted life years.

2 ERG additional information and scenarios

In preparation for the evaluation committee meeting on the 10th of February 2021, at the request of the National Institute for Health and Care Excellence (NICE), the Evidence Review Group (ERG) attempted to explore further whether the potential benefit of onasemnogene reported from clinical trials enrolling infants with symptom onset before 6 months would be similar or reduced in infants diagnosed with SMA type at 6 months or older. Trial data for children initiating treatment at older than 6 months are not available.

The ERG's clinical experts fed back that they considered that between 30% and 40% of infants could be diagnosed with SMA type 1 after 6 months of age. However, trial data are not available for treatment with onasemnogene in infants aged 6 months and older. Experts considered that children aged 6 months and over with SMA type 1 could potentially receive clinical benefit from treatment with onasemnogene, but the level of benefit would be dependent on symptom severity at the start of treatment, which, in turn, is influenced by the extent of loss of the units responsible for motor function. Experts considered that there is a critical threshold for loss of motor units, after which treatment with onasemnogene might not be as effective and, as a consequence, early treatment with onasemnogene is key.

To explore the potential impact on the ICER if patients older than 6 months of age are treated with onasemnogene, NICE and the committee requested the following analyses:

- Reduction in the numbers of patients achieving the milestones of sitting independently for ≥30 seconds and walking, based on pooled data from START and STR1VE-US regardless of age at treatment.
- Motor milestone achievement based on pooled data from START and STR1VE-US for babies treated older than 3.5 months of age.
- 25% of babies treated at age 3.5 months and older achieving the motor milestone of sitting independently for ≥30 seconds. NICE and the committee requested that a scenario of 25% of babies treated at age 3.5 months and older achieving the motor milestone of walking, but the ERG notes that no babies treated older than 3.5 months of age in the pooled START and STR1VE-US trials achieved the milestone of walking. Please refer to Table 26 of the ERG report for data on motor milestones by age at dosing in Cohort 2 in START, STR1VE-US, and the POOLED dataset.

The ERG notes that the 3.5-month age threshold for the analysis is solely based on median age at treatment in START and STR1VE-US and there is no clinical rationale or evidence to support the use of 3.5 months as a threshold for treatment with onasemnogene.

The first of the scenarios requested by NICE was to explore the impact on the committee's preferred ICER when motor milestone achievement is reduced, using a range of 1 to 3 patients not achieving the milestone of sitting or walking. As a reminder, the committee preferred the use of pooled data from START and STR1VE-US (n=34) using a threshold for sitting of ≥30 seconds and including the company's assumption of an additional sitter to account for additional milestones that maybe achieved post-follow up in STR1VE-US (follow-up of 18 months of age in STR1VE-US versus 30 months of age follow-up in START).

Table 2 presents the motor milestone data preferred by the committee (including the company's assumption of motor milestone achievement "offset" by one cycle) and used as the basis for the data range analysis.

Table 2. Observed motor milestone achievement including an additional sitter and a threshold of >30 seconds (reproduced from the company's factual accuracy check response)

Age at end of cycle	Not sitting	Sitting but not walking	Walking	Dead or PAV
6	34	0	0	0
12	32	0	0	2
18	24	8	0	2
24	14	17	1	2
30	10	19	3	2
36	8	21	3	2
48	8	21	3	2

The ERG explored three assumptions for the data range analysis where a range of 1 to 3 patients do not achieve motor milestones, which are as follows:

1. Reducing the number of sitters and transitioning these patients to the non-sitting health state from age 18 months onwards.
2. Reducing the number of walkers and transitioning these patients to the sitting health state from age 24 months onwards.
3. Simultaneously reducing the number of sitters and walkers and transitioning these patients to the non-sitting health state from age 24 months onwards.

The results of the data range analysis are presented in Table 3. The ERG notes that for the assumptions of reducing the number of walkers by 3 effectively assumes that no patients achieve the ability to walk. Given that clinical experts consulted have agreed that babies treated earlier with

onasemnogene have better outcomes as they haven't lost significant function, it may not be entirely clinically implausible that patients who are treated older than 6 months of age may not achieve the ability to walk. However, the ERG urges caution around the assumptions of lack of motor milestone achievement for babies treated with onasemnogene older than 6 months of age, as there are currently no data to support them.

Table 3. ERG data range analysis – impact on the incremental cost-effectiveness ratio due to reduction in motor milestone achievement

Reduction in patients achieving motor milestones	Sitters → non-sitters	Walkers → sitters	Sitters & walkers → non-sitters
Committee preferred base case		[redacted]	
-1	[redacted]	[redacted]	[redacted]
-2	[redacted]	[redacted]	[redacted]
-3	[redacted]	[redacted]	[redacted]

For the scenarios exploring motor milestone achievement for babies treated with onasemnogene aged 3.5 months and older, the company supplied a scenario implementing pooled data from START and STR1VE-US for this group. Table 4 presents the pooled observed data for babies treated with onasemnogene aged 3.5 months and older by cycle used for the scenario. The ERG notes that the company's scenario does not include the committee's preferred assumption of an additional sitter, but as the scenario explores reduction in motor milestones, using the observed pooled data is appropriate.

Table 4. Observed motor milestone achievement for babies treated with onasemnogene aged 3.5 months and older

Age at end of cycle	Not sitting	Sitting but not walking	Walking	Dead or PAV
6	[redacted]	[redacted]	[redacted]	[redacted]
12	[redacted]	[redacted]	[redacted]	[redacted]
18	[redacted]	[redacted]	[redacted]	[redacted]
24	[redacted]	[redacted]	[redacted]	[redacted]
30	[redacted]	[redacted]	[redacted]	[redacted]
36	[redacted]	[redacted]	[redacted]	[redacted]
48	[redacted]	[redacted]	[redacted]	[redacted]

Results of the company's scenario using pooled motor milestone achievement data, as well as updated overall and event-free survival for babies treated with onasemnogene aged 3.5 months and older, as well as the company's original scenario for babies treated aged ≤3.5 months are presented in Table 5.

Table 5. Treatment age sensitivity analysis (discounted at 1.5%)

Treatment	Total costs	Total LYs	Total QALYs	Incremental costs	Incremental LYs	Incremental QALYs	ICER (£/QALY)
Committee preferred base case							
BSC	413,269	2.28	0.21	-	-	-	-
Onasemnogene + BSC	[redacted]	20.24	13.31	[redacted]	17.95	13.10	[redacted]
Dosing at ≤3.5 months of age (n=17), sitting threshold of ≥30 seconds							
BSC	413,269	2.28	0.21	-	-	-	-
Onasemnogene + BSC	[redacted]	24.55	17.24	[redacted]	22.27	17.03	[redacted]
Dosing at >3.5 months of age (n=17), sitting threshold of ≥30 seconds							
BSC	413,269	2.28	0.21	-	-	-	-
Onasemnogene + BSC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: BSC, best supportive care; ICER, incremental cost-effectiveness ratio; LYs, life years; QALY, quality-adjusted life year.

The ERG also performed a scenario, requested by NICE, where the number of babies treated with onasemnogene aged 3.5 months and older achieved the motor milestone of sitting independently for ≥30 seconds is reduced to 25% of the value obtained from the pooled trial data (rounded up to the closest whole number) in every cycle of the short-term model and the remainder stay in the non-sitting health state from age 18 months, presented in Table 6.

Table 6. ERG scenario exploring 25% achievement of motor milestone of sitting independently for ≥30 seconds for babies treated older than 3.5 months

Treatment	Total costs	Total LYs	Total QALYs	Incremental costs	Incremental LYs	Incremental QALYs	ICER (£/QALY)
BSC	413,269	2.28	0.21	-	-	-	-
Onasemnogene + BSC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: BSC, best supportive care; ICER, incremental cost-effectiveness ratio; LYs, life years; QALY, quality-adjusted life year.

The company states the analyses exploring treatment age is not reflective of current clinical practice, it is arbitrary in nature and does not consider the ability of SMA type 1 patients to achieve relevant milestones despite the age at treatment. Furthermore, the company explains that their base case analysis was illustrative of a trend towards greater benefits of earlier treatment with gene therapy, based on the available clinical trial data and that stratifying the patient population by treatment age results in a smaller sample size and as such are not intended to imply that age at treatment would reliably predict motor neuron preservation or final outcomes for all patients.

As mentioned previously, there are no data on motor milestone achievement for babies treated aged 6 months and older and the analyses requested by NICE and the committee are intended to explore the impact on the ICER if there is a reduction in motor milestones achieved for this cohort.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

ZOLGENSMA® (onasemnogene abeparvovec) for treating spinal muscular atrophy type 1 [ID1473]

Response to ERG analysis

17 Feb 2021

Key:

'Commercial in confidence' in turquoise

'Academic in confidence' in yellow

'Depersonalised data' in pink

‘Model 1’: 25% sitting achievement for babies treated >3.5 months

Response

The current description for this scenario provided in the ERG ECM2 report (‘*The ERG also performed a scenario, requested by NICE, where only 25% of babies treated with onasemnogene aged 3.5 months and older achieved the motor milestone of sitting independently for ≥30 seconds in every cycle of the short-term model (the remainder stay in the non-sitting health state) from age 18 months*,..’) is difficult to interpret and can mean different approaches.

In the model provided by the ERG (‘Model 1’, received on 15 February 2021) the scenario implemented takes 25% of sitters (i.e. the ones achieving sitting in the trials for this subgroup) and rounds that figure up and then moves the rest (after taking into account the rounding) to the non-sitters. Thus, the way this scenario is currently implemented in ‘Model 1’ does not mean that 25% of all infants in this subgroup in the trials (i.e. 25% of n=17 if including those PAV/dead or 25% of n=16 if including only patients alive and not on PAV) would achieve sitting.

The company proposes one of two options:

Option 1: Clarify and update the description in the ERG ECM2 report and keep the implementation as described in ‘Model 1’. For example, to clarify the description the wording could be changed to: ‘The ERG also performed a scenario, requested by NICE, where the number of babies treated with onasemnogene abeparvovec aged 3.5 months and older achieved the motor milestone of sitting independently for ≥30 seconds is reduced to 25% of the value obtained from the trial and rounded up to the closest whole number in every cycle of the short-term model (the remainder of babies who achieved independent sitting in the trial are now removed from that group and stay in the non-sitting health state) from age 18 months,..’

Option 2: Update the description in the ERG ECM2 report and the implementation in ‘Model 1’ to calculate the ICER where 25% of babies (alive and not on PAV, i.e. 25% of n=16) treated with onasemnogene abeparvovec aged 3.5 months and older achieved the motor milestone of sitting independently for ≥30 seconds in every cycle of the short-term model (the remainder of babies who achieved independent sitting in the trial are now removed from that group and stay in the non-sitting health state) from age 18 months,…’. The company has completed this alternative approach to the analysis, and provides the results in Table 3 below, and has also provided the model via NICE docs (Titled: ID1473_onasemnogene PAS_MODEL ERG analysis_ACM2 25% scenario CIC_17022021).

The company notes that there is no clinical justification for this speculative scenario analysis.

ERG Response

The ERG thanks the company for highlighting where additional clarity is needed for the description of the ERG scenario where 25% of babies treated older than 3.5 months

achieve the milestone of sitting. The ERG has amended its ECM2 analysis document to reflect the company's suggested changes outlined in option 1.

The ERG also considered the company's alternative approach to the scenario but notes that it assumed a fixed number of sitters in each cycle (25% of 16 patients), which is more optimistic than the ERG's approach. Table 1 presents the number of sitters assumed in the company's and ERG's scenario compared with the observed pooled data.

Table 1. Motor milestone achievement of sitting independently for ≥30 seconds for babies treated with onasemnogene aged 3.5 months and older

Cycle	Observed pooled data	ERG scenario	Company scenario
6	[redacted]	[redacted]	[redacted]
12	[redacted]	[redacted]	[redacted]
18	[redacted]	[redacted]	[redacted]
24	[redacted]	[redacted]	[redacted]
30	[redacted]	[redacted]	[redacted]
36	[redacted]	[redacted]	[redacted]
48	[redacted]	[redacted]	[redacted]

The ERG validated the company's results for their alternative scenario for 25% milestone achievement for babies treated older than 3.5 months of age (presented in Table 3 and was able to replicate the results.

'Model 2': Walker to non-sitter scenario

Response

The current description for this scenario provided in the ERG ECM2 report ('Reducing the number of walkers and transitioning these patients to the non-sitting health state from age 24 months onwards') is misleading.

In the model provided by the ERG ('Model 2', received on 15 February 2021) the scenario implemented removes patients from both sitters and walkers (and not just the walkers, as suggested by the current description) and adds them to the non-sitters. When 2 or 3 patients are removed, they are only removed from the 30 months of age onwards (i.e. only 1 patient is removed from the age 24 months cycle in all three scenarios).

The company proposes one of two options:

Option 1: Clarify and update the description in the ERG ECM2 report and keep the implementation as described in 'Model 2'. For example, to clarify the description the wording could be changed to: 'Scenario when 1 patient is removed: Reducing the number of walkers

and the number sitters simultaneously by 1 and transitioning these patients to the non-sitting health state from age 24 months onwards. For the scenarios when 2 or 3 patients are removed: Reducing the number of walkers and sitters simultaneously by 1 and transitioning these patients to the non-sitting health state for the cycle when patients reach 24 months of age and reducing the number of walkers and sitters simultaneously by 2 or 3 and transitioning these patients to the non-sitting health state for the cycles when patients reach 30 months of age and onwards'. The scenario title should be amended to 'Moving walkers and sitters to non-sitters'

Option 2: Keep the current description in the ERG ECM2 report for this scenario and update the implementation in 'Model 2'. The company has completed this alternative approach to the analysis based on the current description, and provides the results in Table 4 to Table 6 below, and has also provided the model via NICE docs which contains these revised motor milestone grids in the 'ERG milestones scenarios' worksheet (Titled: ID1473_onasemnogene PAS_MODEL ERG analysis_ACM2 walker scenario CIC_17022021).

The company notes that there is no clinical justification for this speculative scenario analysis.

ERG Response

The ERG considered the company's feedback on the data range analysis and agrees that the scenario exploring reducing the number of walkers and transitioning these patients to the non-sitting health state from age 24 months onwards is a more conservative scenario that also combines reducing the number of sitters simultaneously. As such, the ERG has amended its ECM2 analysis document to correct the description of the scenario.

The ERG validated the company's scenario of transitioning walkers to the non-sitting health state and has included the results in the data range analysis, presented in Table 2.

Table 2. ERG and company data range analysis – impact on the incremental cost-effectiveness ratio due to reduction in motor milestone achievement

Reduction in patients achieving motor milestones	Sitters → non-sitters	Walkers → sitters	Walkers → non-sitters (company scenario)	Sitters & walkers → non-sitters
Committee preferred base case			[redacted]	
-1	[redacted]	[redacted]	[redacted]	[redacted]
-2	[redacted]	[redacted]	[redacted]	[redacted]
-3	[redacted]	[redacted]	[redacted]	[redacted]

Table 3: Ad hoc sensitivity analyses: 25% sitting achievement for babies treated >3.5 months

Technologies	Total			Incremental			ICER vs BSC (£/QALY)
	Costs (£)	LYG	QALYs	Costs (£)	LYG	QALYs	
BSC	413,269	2.28	0.21	-	-	-	-
OA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: BSC, best supportive care; ICER, incremental cost-effectiveness ratio; LYG, life years gained; OA, Onasemnogene abeparvovec; QALY, quality adjusted life years.

Table 4: Ad hoc sensitivity analyses: Walker to non-sitter scenario (1 walker removed to non-sitters)

Technologies	Total			Incremental			ICER vs BSC (£/QALY)
	Costs (£)	LYG	QALYs	Costs (£)	LYG	QALYs	
BSC	413,269	2.28	0.21	-	-	-	-
OA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: BSC, best supportive care; ICER, incremental cost-effectiveness ratio; LYG, life years gained; OA, Onasemnogene abeparvovec; QALY, quality adjusted life years.

Table 5: Ad hoc sensitivity analyses: Walker to non-sitter scenario (2 walkers removed to non-sitters)

Technologies	Total			Incremental			ICER vs BSC (£/QALY)
	Costs (£)	LYG	QALYs	Costs (£)	LYG	QALYs	
BSC	413,269	2.28	0.21	-	-	-	-
OA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: BSC, best supportive care; ICER, incremental cost-effectiveness ratio; LYG, life years gained; OA, Onasemnogene abeparvovec; QALY, quality adjusted life years.

Table 6: Ad hoc sensitivity analyses: Walker to non-sitter scenario (3 walkers removed to non-sitters)

Technologies	Total			Incremental			ICER vs BSC (£/QALY)
	Costs (£)	LYG	QALYs	Costs (£)	LYG	QALYs	
BSC	413,269	2.28	0.21	-	-	-	-
OA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: BSC, best supportive care; ICER, incremental cost-effectiveness ratio; LYG, life years gained; OA, Onasemnogene abeparvovec; QALY, quality adjusted life years.