NICE National Institute for Health and Care Excellence

Highly Specialised Technology

Onasemnogene abeparvovec for treating pre-symptomatic spinal muscular atrophy (MAA partial review of HST 15) [ID4051]

Committee Papers

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Contents:

The following documents are made available to stakeholders:

Access the **final scope and final stakeholder list** on the NICE website.

1. **Company submission** from Novartis Gene Therapies:
   a. Full submission
   b. Summary of Information for Patients (SIP)

2. **Clarification questions and company responses**

3. **Patient group, professional group, and NHS organisation submissions** from:
   a. MDUK and SMA UK submission
   b. NHS England

4. **Clinical expert responses to questions from NICE technical team** from:
   a. Dr Elizabeth Wraige, Consultant Paediatric Neurologist – clinical expert, nominated by Novartis Gene Therapies
      i. Main response
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   b. Professor Laurent Servais, Professor of Paediatric Neuromuscular Diseases – clinical expert, nominated by Novartis Gene Therapies
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5. **Expert personal perspectives** from:
   a. Ben Williams – patient expert, nominated by MDUK and SMA UK
   b. Portia Thorman, Advocacy Lead – patient expert, nominated by MDUK and SMA UK
   c. Dr Elizabeth Wraige, Consultant Paediatric Neurologist – clinical expert, nominated by Novartis Gene Therapies
   d. Professor Laurent Servais, Professor of Paediatric Neuromuscular Diseases – clinical expert, nominated by Novartis Gene Therapies

6. **External Assessment Report** prepared by Liverpool Reviews and Implementation Group (LRiG)

7. **External Assessment Report – factual accuracy check**

8. **Company additional evidence submission** from Novartis Gene Therapies

9. External Assessment Group critique of company additional evidence submission prepared by Liverpool Reviews and Implementation Group (LRiG)

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 technology evaluation

Onasemnogene abeparvovec for treating pre-symptomatic spinal muscular atrophy (MAA partial review of HST 15) [ID4051]

Document B

Company evidence submission

August 2022

File name	Version	Contains confidential information	Date
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Abbreviations

A&E	Accident and emergency
AAV9	Adeno-associated virus 9
AE	Adverse event
AESI	Adverse event of special interest
AIC	Akaike information criterion
ALT	Alanine transaminase
AST	Aspartate transaminase
BIC	Bayesian information criterion
BRND	Broad range of normal development
BSC	Best supportive care
BSID	Bayley Scales of Toddler and Infant Development version 3
CI	Confidence interval
CHOP-INTEND	Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders
CPAP	Continuous positive airway pressure
EC	Efficacy completer
ERG	Evidence Review Group
FM	Fine motor
GI	Gastrointestinal
GM	Gross motor
HCRU	Healthcare resource use
HFMSE	Hammersmith Functional Motor Scale Expanded
HRQoL	Health-related quality of life
HST	Highly specialised technology
ICER	Incremental cost-effectiveness ratio
ITT	Intent-to-treat
IT	Intrathecal
IV	Intravenous
KOL	Key opinion leader
LYG	Life years gained
MAA	Managed access agreement
MAH	Marketing authorisation holder
MDT	Multidisciplinary team

MHRA	Medicines and Healthcare products Regulatory Agency
NBS	Newborn blood spot
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
NSC	National Screening Committee
PAS	Patient access scheme
PAV	Permanent assisted ventilation
PCR	Polymerase chain reaction
PNCR	Pediatric Neuromuscular Research Network
PSS	Personal Social Services
QALY(s)	Quality adjusted life year(s)
QoL	Quality of life
SAP	Statistical analysis plan
SLR	Systematic literature review
SMA	Spinal muscular atrophy
SMN	Survival motor neuron
SPC	Summary of product characteristics
TEAE	Treatment-emergent adverse event
UK	United Kingdom

B.1. Decision problem, description of the technology and clinical care pathway

The National Institute for Health and Care Excellence (NICE) issued highly specialised technologies (HST) guidance (HST15) in July 2021, which made the following recommendations on the use of onasemnogene abeparvovec for treating spinal muscular atrophy (SMA):

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

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

It is only recommended in these groups if:

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

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

1.3. Onasemnogene abeparvovec is recommended as an option for treating pre-symptomatic 5q SMA with a bi-allelic mutation in the *SMN1* gene and up to three copies of the *SMN2* gene in babies. It is recommended only if the conditions in the managed access agreement (MAA) are followed.

This HST evaluation is a partial review of HST15, which relates to recommendation 1.3 only, assessing the clinical and cost effectiveness of onasemnogene abeparvovec within its marketing authorisation for treating pre-symptomatic SMA.

Table 1: The decision problem

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
Population	People with pre-symptomatic 5q SMA and up to three copies of the *SMN2* gene	As per scope, but for clarity this population is newborns (as highlighted in point 1.3 above)	N/A
Intervention	Onasemnogene abeparvovec	As per scope, but for clarity the intervention is: onasemnogene abeparvovec delivered via a single-dose IV infusion	N/A
Comparator(s)	Best supportive care	As per scope. For clarity, best supportive care is the only routinely commissioned treatment available for pre-symptomatic patients at the time of appraisal.	N/A

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
Outcomes	The outcome measures to be considered include: • Motor function (including, where applicable, age-appropriate motor milestones such as sitting, standing, walking) • Bulbar function (including, for example, swallowing and ability to communicate) • Frequency and duration of hospitalisation • Speech and communication • Respiratory function • Complications of spinal muscular atrophy (including, for example, scoliosis and muscle contractures) • Need for non-invasive or invasive ventilation • Stamina and fatigue • Mortality • Adverse effects of treatment • Health-related quality of life (for patients and carers)	As per scope, and a composite endpoint of permanent ventilation-free survival (often termed as event-free survival in the assessment of SMA) is also assessed. Carer HRQoL will be considered qualitatively in this submission, as previous NICE submissions for SMA treatments have highlighted the paucity of data and lack of robust methods when accounting for carer HRQoL and bereavement disutility in economic modelling.	N/A

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
Economic analysis	The reference case stipulates that the cost effectiveness of treatments should be expressed in terms of incremental cost per quality-adjusted life year. The reference case stipulates that the time horizon for estimating clinical and cost effectiveness should be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared. Costs will be considered from an NHS and Personal Social Services perspective. The availability of any commercial arrangements for the intervention, comparator and subsequent treatment technologies will be taken into account.	As per scope	N/A

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
Subgroups to be considered	If the evidence allows, the following subgroups will be considered: Number of *SMN2* gene copies	The SPR1NT trial was designed with two cohorts of patients with two or three copies of *SMN2* that represent the population in the MAA (1). The *SMN2* two-copy and *SMN2* three-copy cohorts have different primary and secondary efficacy outcomes and length of follow-up in the trial. Results for the two- and three-copy cohorts are included separately in the submission. In the cost-effectiveness analysis, the base case analysis is weighted based on proportions of patients expected to have two or three copies of the *SMN2* gene based on natural history data (2, 3).	SMA represents a broad spectrum of clinical manifestations, and, although patients with different *SMN2* copy numbers are genetically distinct, there is an overlap in clinical manifestations and disease severity. For example, although in general, fewer copies of *SMN2* may result in a more severe disease phenotype, some patients with three copies of *SMN2* will develop a severe form of SMA (i.e. will be non-sitters) (4). Clinical trial data are not available for patients with one copy of the *SMN2* gene, and few patients with one copy are expected to be identified pre-symptomatically as they typically experience early onset of severe symptoms. These patients will be described qualitatively in the submission (Section B.1.2.1.2).

Abbreviations: AAV, adeno-associated virus; BSC, best supportive care; HRQoL, health-related quality of life; MAA, managed access agreement; N/A, not applicable; NBS, newborn blood spot; NHS, National Health Service; NICE, National Institute for Health and Care Excellence; SMA, spinal muscular atrophy; SMN, survival motor neuron; SmPC, summary of product characteristics; TBC, to be confirmed.

B.1.1 *Description of the technology being appraised*

Table 2: Technology being appraised

UK approved name and brand name	UK approved name: Onasemnogene abeparvovec Brand name: Zolgensma®
Mechanism of action	Onasemnogene abeparvovec is a one-time, single-dose gene replacement therapy that addresses the underlying genetic cause of SMA. It is a non-replicating recombinant adeno-associated virus serotype 9 (AAV9) based vector containing the cDNA of the human SMN gene. The functional SMN gene provides continuous SMN protein expression, thus preventing motor neuron loss (5).
Marketing authorisation/CE mark status	Onasemnogene abeparvovec was recommended by EMA for conditional marketing authorisation in the EU on 18th May 2020. A positive opinion from the Committee for Medicinal Products for Human Use (CHMP) was received on 11th July 2022 for full marketing authorisation. Onasemnogene abeparvovec (EMEA/H/C/004750) is indicated for the treatment of (5): • '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' For transparency, Novartis Gene Therapies would like to note that the Great Britain Marketing Authorisation renewal application has been submitted, and it is anticipated that the conditions of marketing authorisation will be removed from the licence following Medicines and Healthcare products Regulatory Agency (MHRA) approval, which is expected in September 2022. In addition, a marketing authorisation holder (MAH) transfer is currently underway. However, the MAH will remain within the Novartis group.
Indications and any restriction(s) as described in the summary of product characteristics (SmPC)	As per the SmPC, onasemnogene abeparvovec is indicated for the treatment of: patients with 5q spinal muscular atrophy (SMA) with a bi-allelic mutation in the *SMN1* gene and a clinical diagnosis of SMA Type 1, or patients with 5q SMA with a bi-allelic mutation in the *SMN1* gene and up to 3 copies of the *SMN2* gene (5). Onasemnogene abeparvovec is contraindicated in patients with hypersensitivity to the active substance or any of the excipients (5).
Method of administration and dosage	Patients will receive a one-time treatment of onasemnogene abeparvovec, administered via a syringe pump as a single-dose IV infusion over approximately 60 minutes. Patients will receive onasemnogene abeparvovec at a dose of 1.1×10^{14} vg/kg, with the total volume being determined by patient body weight.

	An immunomodulation regimen with corticosteroids is recommended.
Additional tests or investigations	Prior to initiation of the immunomodulatory regimen and prior to administration of onasemnogene abeparvovec, the patient must be checked for symptoms of active infectious disease of any nature. Before administration of onasemnogene abeparvovec, baseline laboratory testing is required, including:(5) • AAV9 antibody testing using an appropriately validated assay • Liver function: alanine aminotransferase (ALT), aspartate aminotransferase (AST), and total bilirubin, creatinine • Complete blood count (including haemoglobin and platelet count) • Troponin-I The need for close monitoring of liver function, platelet count and troponin-I after administration and the need for corticosteroid treatment are to be considered when establishing the timing of onasemnogene abeparvovec treatment.
List price and average cost of a course of treatment	The list price for a one-time treatment is £1,795,000 (excluding VAT). Onasemnogene abeparvovec is dosed based on body weight, with the same cost of one-time treatment regardless of patient weight. Onasemnogene abeparvovec is a one-time treatment and, therefore, the average cost of a course of treatment will be the same as the cost of the drug.
Patient access scheme (if applicable)	The company has an existing commercial agreement that makes onasemnogene abeparvovec available to the NHS with a simple discount for HST15. [redacted]

Abbreviations: AAV9, adeno-associated virus 9; IV, intravenous; MAA, managed access agreement; MAH, marketing authorisation holder; NHS, National health Service; PAS, patient access scheme; SMA, spinal muscular atrophy; SMN, Survival motor neuron; SPC, summary of product characteristics.

B.1.2 *Health condition and position of the technology in the treatment pathway*

- The scope of this HST appraisal is the clinical and cost effectiveness of onasemnogene abeparvovec within its marketing authorisation for treating people with pre-symptomatic 5q SMA and up to three copies of the *SMN2* gene
- SMA is a very rare, genetic, neuromuscular disease with an estimated prevalence of approximately 1–2 per 100,000 people
    - The annual incidence of SMA is approximately 1:10,000 live births, and approximately 60 infants per year are born with SMA in England (6, 7)
    - There is currently no national population-based NBS screening programme for SMA in the UK, and it is estimated that two pre-symptomatic patients per year may be identified as being eligible for treatment with onasemnogene abeparvovec through genetic testing referrals due to sibling history of SMA or a parent with confirmed carrier status (family screening) (1). In a UK advisory board, clinical experts agreed that one additional patient per year may be identified through the UK population-based NBS screening programme pilot study (8, 9)
- SMA is one of the most common genetic causes of infant mortality and is associated with progressive, irreversible motor neuron loss that leads to muscle atrophy. The progressive muscle weakness and paralysis, and impairment of swallowing and breathing, results in premature death in more severe forms of SMA
    - SMA is devastating, significantly affecting survival and substantially impairing quality of life for patients and their caregivers.
    - Without treatment, all infants born with a biallelic deletion of the *SMN1* gene will develop SMA. Life expectancy and physical function are severely limited by severe forms of SMA. While *SMN2* copy number is one of several factors that can predict SMA phenotype, prior to observation of symptoms, there is no definitive way to determine the severity of disease in a pre-symptomatic individual.
- Rapid, progressive, and irreversible motor neuron loss can begin prenatally and continues after birth. Early diagnosis and intervention with therapies that rapidly restore SMN protein expression is critical to prevent the motor neuron loss due to SMA, avoid the typical course of disease, and improve prognosis
    - There is a need to treat infants with SMA identified through screening as soon as possible in order to avoid the clinical manifestations of the disease
- An unmet need remains for a disease-modifying therapy that addresses the underlying genetic cause of SMA in a pre-symptomatic population, in whom symptoms of SMA have not yet been observed, but will go on to develop SMA if they do not receive a disease-modifying therapy
    - There are currently no treatments routinely commissioned for patients identified through screening

Onasemnogene abeparvovec is a one-time gene therapy that addresses unmet need by providing a functional copy of the *SMN* gene, minimising the progression of SMA through rapid, continuous, and sustained SMN protein expression

B.1.2.1 *Disease overview*

SMA is a very rare, genetic, neuromuscular disease associated with progressive, irreversible motor neuron loss that leads to muscle atrophy. It is one of the most common genetic causes of infant mortality and is characterised by significant or profound physical disability and/or premature death as a result of progressive muscle weakness that causes paralysis and impairment of swallowing and breathing in the most severely affected patients (10, 11).

SMA is caused by a homozygous loss of function or absence of the survival motor neuron gene 1 (*SMN1*), resulting in a lack of survival motor neuron (SMN) protein (10, 11). Rapid and progressive motor neuron loss can begin prenatally and continues after birth, and by the time that symptoms are overtly present, significant, irreversible motor neuron loss has already occurred (12, 13). Expert recommendations and consensus statements recognise that the early initiation of disease-modifying treatment for SMA, ideally before symptoms become apparent, can halt this irreversible motor neuron loss, improve neuromuscular function, and prevent disease progression (14-19). Therefore, they support immediate treatment following genetic diagnosis (14-19).

All patients with bi-allelic loss of function mutation, most commonly deletion, of the *SMN1* gene will develop SMA, and, prior to observation of symptoms, there is no definitive way to determine the severity of disease or to predict survival. One factor that may help to predict the prognosis of patients with SMA is the number of copies of the *SMN2* gene. In general, fewer copies of *SMN2* result in a more severe disease phenotype (4, 20, 21). However, some patients with three copies of *SMN2* will develop a severe form of SMA in the absence of treatment (Section B.1.2.1.2). Without disease-modifying treatment, SMA significantly affects survival and substantially impairs quality of life (22-24).

B.1.2.1.1 Epidemiology

Although SMA is a very rare disease, it is one of the most common genetic causes of infant mortality. The estimated prevalence of SMA is approximately 1–2 per 100,000 people globally (25). Annual incidence of SMA is approximately 1:10,000 live births (6). These epidemiological data applied to the number of live births (595,239) reported in England in 2021 (7) indicate that approximately 60 infants per year are born with an SMA genotype that, if treated with BSC only, will become symptomatic SMA.

Genetic testing soon after birth allows early identification of SMA before symptoms are observed. There is currently no national population-based NBS screening programme for SMA in the UK. In routine clinical practice, infants are currently identified through genetic testing referrals due to a sibling history of SMA or a parent with confirmed carrier status (family screening). A UK population-based pilot study is also being conducted to

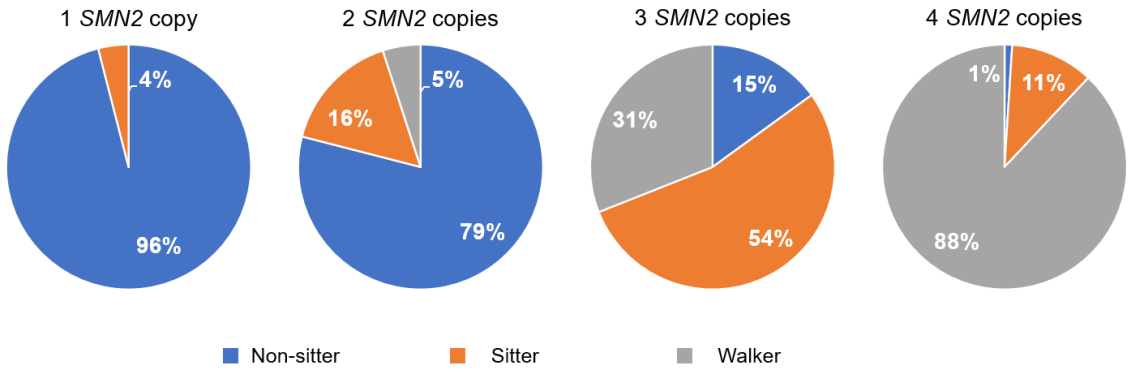
evaluate the feasibility of conducting national population-based NBS screening[a] for SMA. It is estimated by the NICE Resource Impact Assessment team that approximately two pre-symptomatic infants may be identified each year as being eligible for treatment with onasemnogene abeparvovec through genetic testing referrals due to sibling history of SMA (1). Novartis Gene Therapies conducted a UK advisory board in Q1 2022, in which clinical experts agreed that one additional patient per year may be identified through the UK population-based NBS screening programme pilot study (population-based NBS screening of SMA to evaluate the uptake and feasibility in the UK context) (8, 9). Therefore, it is anticipated that 2–3 pre-symptomatic patients eligible for treatment with onasemnogene abeparvovec will be identified within the UK population each year.

Infants identified through any national population-based NBS screening programme using dried blood spots to detect the *SMN1* deletion would be eligible for a quantitative genetic testing of *SMN1/SMN2* (Section B.1.2.2.1). Screening programmes will not increase the total number of patients eligible for SMA treatment(s) but will allow for earlier identification of infants with SMA, allowing earlier treatment and improved prognosis.

B.1.2.1.2 Clinical burden

SMA is caused by loss of function mutation, most commonly deletion, of both copies of the *SMN1* gene, which is responsible for production of the full-length SMN protein. The *SMN2* gene also encodes the SMN protein but is unable to completely compensate for the absence of *SMN1* as a large proportion of the SMN protein produced is a truncated, non-functional variant (4). As the *SMN2* gene results in production of some functional SMN protein, *SMN2* gene copy number is one of several factors that can predict SMA phenotype (4, 20, 21). A higher number of *SMN2* copies is associated with less severe disease as the absolute amount of SMN protein produced is higher (26, 27). The relationship between *SMN2* copy number and disease severity is illustrated in Figure 1 (4). However, it should be noted that, prior to observation of symptoms, there is no definitive way to determine the severity of disease or to predict survival.

Figure 1: *SMN2* copy number and severity of disease



[a] Using spare capacity from a newborn's Guthrie card (dried blood spot sample).

Non-sitter, sitter and walker are referred to as SMA types 1, 2, and 3 in source publication.
Source: Adapted from Calucho et al, 2018 (4).

Before disease-modifying therapy became available, SMA was classified as five discrete clinical types (0 through 4) based on the age at symptom onset and motor milestone achievement (10). Although this classification is widely used, particularly in studies on the natural history of SMA, it has now been unequivocally shown that 5q SMA is one disease, with a single underlying cause and a broad spectrum of clinical severity (28, 29). Clinicians are moving away from describing SMA as specific 'types' and instead describing patients according to their functional ability: non-sitter, sitter, and walker (19, 30-32). The clinical burden of SMA in these groups is described in the following sections.

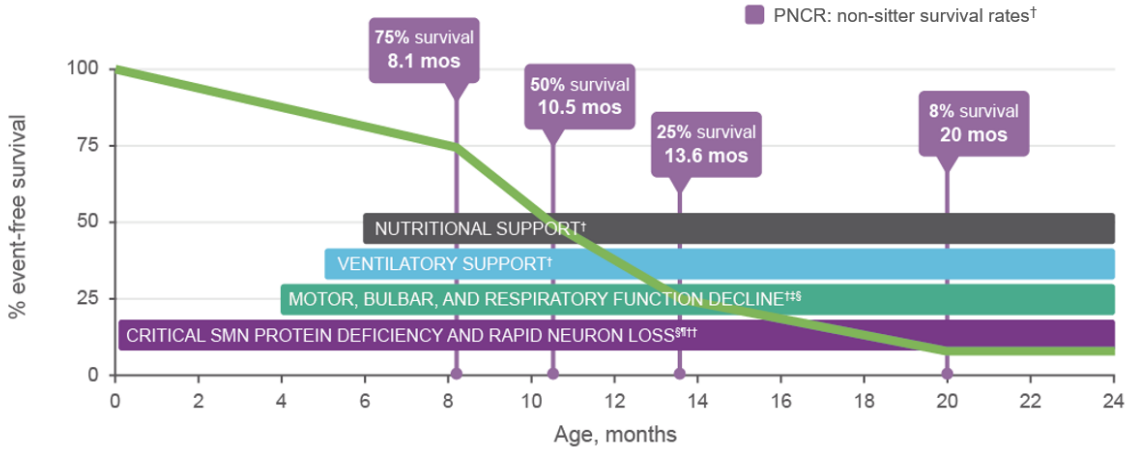
Prenatal/neonatal onset

Some infants show symptoms of SMA prenatally or neonatally. The majority of these patients have only one copy of *SMN2* and do not survive past 1 month of age (10). These patients are out of the scope of this appraisal for pre-symptomatic patients with SMA as they will have observable symptoms ahead of screening and treatment.

Non-sitters

The majority of infants with two copies (79%) of *SMN2*, and 15% of those with three copies, will be non-sitters (4), with symptom onset before 6 months of age and failure to ever achieve a sitting position when managed with best supportive care (BSC) only. Non-sitters lose the ability to swallow and safely feed by mouth, never gain developmental milestones after initial presentation, and suffer from chronic ventilatory failure, the main cause of mortality in these infants (33, 34). Without intensive respiratory and nutritional intervention and disease-modifying treatment, infants experience rapid, significant, and progressive muscle weakness, leading to the inability to breathe or swallow, and ultimate death, typically following severe respiratory complications (27). As a result, without intervention, only 25% of non-sitters receiving BSC are alive and free of permanent ventilation at 13.6 months of age, and less than 20% survive without permanent ventilation to 2 years of age (35), as illustrated in Figure 2.

Figure 2: Survival* of non-sitters in the PNCR natural history study



Abbreviations: mos, months; PNCR, Pediatric Neuromuscular Clinical Research database; SMA, spinal muscular atrophy.
*Note: Survival was defined as event-free survival (no death, or no need for ≥16-hr/day ventilation continuously for ≥2 weeks), in the absence of an acute reversible illness; n=23 (two copies of *SMN2*). Non-sitter is referred to as SMA type 1 in source publication.
† Source: Finkel et al, 2014a (27).
‡ Source: Kolb et al, 2015 (11).
§ Source: Finkel et al, 2013 (36).
¶ Source: Govoni et al, 2018 (37).
†† Source: Swoboda et al, 2005 (38).

Sitters

Infants with two or three copies of *SMN2* who do achieve sitting will never walk unaided and eventually become wheelchair bound (4, 39-41). For infants who achieve sitting unsupported as their highest milestone, symptom onset is typically at 6–12 months of age, and, on average, sitting unsupported is achieved at 1 year of age (39). This is beyond the normal developmental window for sitting without support (99th percentile ≤279 days [approximately 9.2 months] of age (42)). Highest milestone achieved varies between individuals, with some infants able to crawl and stand without support for a period of time. However, sitters never achieve independent walking (39, 41). In addition, infants commonly suffer from severe musculoskeletal symptoms and orthopaedic complications such as scoliosis and fractures, as well as pulmonary and feeding complications (31, 40, 43-45). As the disease progresses, patients can lose motor milestones that they have previously achieved. The life expectancy of sitters receiving BSC is not widely reported and, although patients usually survive into adulthood, survival is limited compared with the healthy population, with 74.2% of patients surviving to age 40 years, and 61.5% of patients surviving to age 60 years (3).

Walkers

Infants achieving walking as their highest milestone do so at approximately 7 years of age (39, 44), which is far beyond the normal developmental window for walking independently (99th percentile ≤534 days [approximately 1.5 years] of age (42)). Although their life expectancy is comparable with the normal population (39), loss of abilities can occur from 0.7–29.1 years of age (46).

Categories used for the classification of SMA based on disease onset and motor milestone achievement are summarised in Table 3.

Table 3: SMA classification based on age of disease onset and highest motor milestone achievement

SMN2 copy number	Age at symptom onset	Highest motor milestone achievable	Life expectancy	SMA type	Description used in this submission
1	Pre-natal	Nil, require respiratory support from birth	Days–Weeks	0	N/A
1, **2**, 3	<6 months	Unable to sit	<2 years	1	Non-sitter
2, **3**, 4	6–18 months	Sits, but never achieves independent walking	20–60 years	2	Sitter
3, **4**, 5	1.5–10 years	Able to walk, regression	Normal	3	Walker
4, 5	>35 years	Slow decline	Normal	4	N/A

SMN2 = survival motor neuron 2 gene.
Bold indicates the most common copy number for each SMA type.
Source: Adapted from Kolb et al, 2011 (10); Lin et al, 2015 (47); Prior et al, 2019 (40); Wijngaarde et al, 2020 (3).

B.1.2.1.3 Quality of life

Without treatment, infants with SMA and their caregivers face considerable humanistic burden as the disease progresses (48), with patients facing a substantial impairment in quality of life.

Although non-sitters are alert and aware, it is not possible to obtain self-reported health-related quality of life (HRQoL) information from infants due to their young age. Non-sitters will often have short lives, which are often spent in hospital and under 24-hour care. The majority of non-sitters will require respiratory support (non-invasive ventilation and/or required cough assist) on a daily basis (49). Infants' respiratory function can decline further requiring permanent invasive ventilation via tracheostomy (27, 35, 50). Non-sitters are unable to swallow or feed, and nutritional support, either via a nasogastric, nasojejunal, or gastrostomy tube, may be required (31). While this medical support helps to keep infants alive, the procedures are often traumatic and invasive, particularly for infants who cannot understand what is happening to them.

Sitters also have a substantial impairment in quality of life (22, 23, 39, 41, 44). In addition to not meeting developmental milestones, infants commonly suffer from severe musculoskeletal symptoms, including contractures, and orthopaedic complications such as scoliosis and fractures (31, 40, 43-45). Patients can also develop feeding complications, including difficulty in feeding and swallowing, which can result in undernutrition and dehydration, and a need for gastrostomy (43). Feeding complications can also cause patients to aspirate, leading to respiratory infections, which can be fatal (43).

Walkers also have a substantial impairment in quality of life (22-24). While they may achieve the ability to walk unassisted, they may never be able to run, jump, or climb stairs independently (43). A wheelchair may be needed for long distances, and patients may experience frequent falls (31, 40, 51).

Caregiver burden

SMA has a profound effect on families and caregivers, including the impact of caring for the patient, the need for specialist equipment and ongoing emotional, financial and social impacts. More than half of caregivers of infants with SMA report feeling that their lives were “hard,” and that they often felt “tied down” (52). The burden of caregiving can extend to multiple family members and affect those without caring responsibilities, with grandparents, siblings and family friends often severely affected (48, 53, 54).

For caregivers of infants who are never able to sit, after the initial worry and stress of their child’s symptoms, diagnosis 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 that may worsen their quality of life (48, 53). Caregivers may also feel anticipatory grief, feel helpless and at fault, and endure the loss of the typical joys of having a newborn, loss of the future imagined with the affected child, and loss of sibling relationships (28, 55). The emotional burden of caregivers continues with bereavement as patients succumb to the disease (55).

Voluntary caregivers of non-sitters in the UK report a substantial burden on their time, with feeding support, physical therapy, and cough assist as their most time-consuming activities (56). Caregivers report a substantial burden on employment status and income, with a majority of caregivers changing work hours or stopping work entirely. Caregivers also report monthly out-of-pocket expenses for home adaptations, home health care, and other ongoing expenses.

B.1.2.2 *Clinical pathway of care*

B.1.2.2.1 Diagnosis

Infants with pre-symptomatic SMA have no distinguishing clinical presentation, as symptoms of SMA have not yet been observed. NBS screening can be conducted using a real-time polymerase chain reaction (PCR) test using dried blood spots to detect the *SMN1* deletion (40). Diagnosis is then confirmed by the application of quantitative genetic testing of *SMN1/SMN2*, with the bi-allelic deletion of *SMN1* providing a diagnosis of SMA (31). NBS screening can lead to early diagnosis and provides an opportunity for early treatment intervention, prior to observation of symptoms (37, 57). Testing for *SMN1*

gene deletions and mutations enables the prospective identification at birth of infants who will go on to develop SMA, and testing for *SMN2* gene copy number allows for prediction of the expected course of disease (20, 58).

However, there is currently no national population-based NBS screening programme for SMA in the UK. In routine clinical practice, infants are currently identified through genetic testing referrals due to a sibling history of SMA or a parent with confirmed carrier status (family screening). In addition, a UK population-based pilot study is being conducted to evaluate the feasibility of conducting national population-based NBS screening for SMA, using spare capacity from a newborn's Guthrie card (dried blood spot sample) (9).

B.1.2.2.2 Management

There are currently no disease-modifying treatments routinely commissioned for the treatment of pre-symptomatic patients with SMA. Without disease-modifying treatment for pre-symptomatic patients, no treatment will be given until these patients develop symptoms of SMA. Once symptoms develop, all patients will receive BSC to manage their symptoms, and non-sitters may also receive onasemnogene abeparvovec, which is routinely commissioned for the treatment of symptomatic SMA type 1 (59). However, comparison of onasemnogene abeparvovec in pre-symptomatic vs symptomatic patients does not fall within the scope of this assessment (as detailed in Section B.1). In line with NICE processes and the scope of this assessment, BSC (described below) is considered the only relevant comparator for this appraisal.

For completeness, details of disease-modifying therapies currently available via MAA, but not routinely commissioned for pre-symptomatic patients, are also provided below.

BSC

Although BSC has an impact on the life expectancy of infants with SMA, it does not halt or delay disease progression or prevent the premature death of infants, nor does it improve motor function or the attainment of motor developmental milestones, and infants continue to have poor quality of life. In general, the goal of BSC is to reduce the burden of illness on the patient and family (33, 45). BSC for SMA uses a multidisciplinary approach that focuses on several areas, such as pulmonary care, gastrointestinal (GI) and nutritional support, orthopaedic care and rehabilitation, and palliative care (31, 33, 45).

- **Nutritional support**
  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, 27, 60). The optimal long-term method for enteral tube feeding is a gastrostomy tube (31, 33). The goals of GI and nutritional support are to reduce the risk of aspiration during swallowing, optimise the efficiency of feeding, maintain adequate calorific intake, hydration, and follow established growth curves. Sitters require nutritional assessment and glucose levels should be regularly monitored. A nasogatric feeding tube may be required if a failure to swallow develops (45).
- **Rehabilitative care**
  The goals of orthopaedic care and rehabilitation depend on the patient's functional

level and their family's wishes. In non-sitters, the main objectives are optimisation of function, minimisation of impairment, and optimising tolerance to various positions, contracture and pain management (31, 33). Non-sitters can develop scoliosis and may require spinal fusion surgery (61). In sitters, contractures are common due to decreased range of motion and can lead to pain. Rehabilitation includes active and passive stretching, splints and the use of orthoses for range of movement and to maintain function. Thoracic bracing can support posture and cervical bracing may be used for head support during transportation. Seating and postural supports can be used to support positioning and include devices for wheelchairs and sleeping. Sitters should be monitored for scoliosis. Spinal orthoses may be used and, in some cases, surgical intervention may be required, particularly if respiratory function is affected (31). Walkers should participate in aerobic and general conditioning exercise programmes designed and monitored by physical and occupational therapists familiar with SMA. Active assisted stretching should also be used to maintain flexibility, with some form of balance exercise also recommended. Lower limb orthoses and thoracic bracing may be used for posture and function (31).

- **Pulmonary care**
  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 (45). Deteriorating 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, 27, 60). Non-sitters also need assistance to maintain airway clearance and to cough and may benefit from interventions such as oral suctioning or physiotherapy (31, 45). Although not standard of care in England, tracheostomy is an option in selected infants in whom non-invasive ventilator support is insufficient or fails (45). Guidelines recommend respiratory assessment at a clinic every 6 months for sitters. Pulmonary interventions may be required including those that support airway clearance, such as cough assist and physiotherapy, including manual chest physiotherapy. In symptomatic patients NIV may be required, however continuous positive airway pressure (CPAP) is not recommended for sitters (45).
- **Palliative care**
  BSC does not halt disease progression and is primarily palliative. Management of these infants with ongoing intensive supportive care can result in children surviving for years (29), however, this is associated with significant morbidity and diminished patient and caregiver quality of life (QoL). Palliative care at the end of life is intended to allow infants to die comfortably while surrounded by loved ones, often at home (62). In general, palliative care addresses issues related to terminal care, grief, and bereavement support.

Disease-modifying therapies

The focus of this appraisal (Section B.1) is pre-symptomatic patients only. In England, there are three treatments (including onasemnogene abeparvovec), which are not routinely commissioned, but are currently available in clinical practice via MAA. Therefore, these treatments are not considered standard of care by NICE for the pre-

symptomatic population of patients with SMA at the time of this submission (see Section B.1):

- **Onasemnogene abeparvovec:** the one-time gene replacement therapy being appraised for pre-symptomatic SMA in the current partial review of HST15 assessment, relating to recommendation 1.3 only (see Section B.1). It is delivered by single-dose intravenous (IV) infusion is currently available through a MAA. Onasemnogene abeparvovec addresses the genetic root cause of SMA by delivering a stable, functional human *SMN* gene that rapidly restores continuous SMN protein expression, thus promoting the survival and function of transduced motor neurons in the screened population genetically diagnosed with SMA (5). In HST15, onasemnogene abeparvovec is recommended as an option for treating pre-symptomatic 5q SMA with a bi-allelic mutation in the *SMN1* gene and up to three copies of the *SMN2* gene in infants. It is recommended only if the conditions in the MAA are followed.
- **Nusinersen:** an antisense oligonucleotide that targets the low-functioning *SMN2* back-up gene, modulating its expression and thereby increasing production of full-length SMN protein (63). As nusinersen only temporarily increases SMN protein expression, it requires repeated and lifelong intrathecal (IT) administration via lumbar puncture (64, 65). A nusinersen treatment regimen incurs associated ongoing healthcare costs and represents a burden to patients, caregivers, and payers (64-66). In addition, as infants with SMA can develop scoliosis and may require spinal fusion surgery, long-term administration of nusinersen may not be feasible in all patients. In NICE technology appraisal guidance (TA588), nusinersen is recommended as an option for treating pre-symptomatic 5q SMA only if the conditions in the MAA are followed.
- **Risdiplam:** a small molecule, which is administered orally, once daily, corrects the splicing of *SMN2* to shift the balance from exon 7 exclusion to exon 7 inclusion into the mRNA transcript, leading to increased production of functional and stable SMN protein (67). Risdiplam is not currently indicated for infants younger than 2 months in England and is therefore not currently used in the pre-symptomatic population. In NICE technology appraisal guidance (TA755), risdiplam is recommended as an option for treating pre-symptomatic 5q SMA in people 2 months and older with one to four *SMN2* copies only if the conditions of the MAA are followed.

B.1.2.3 *Onasemnogene abeparvovec place in therapy*

As discussed in Section B.1.2.2, there are currently no disease-modifying therapies routinely commissioned for patients with pre-symptomatic SMA, making BSC the only option available for the management of pre-symptomatic patients with SMA in England. This highlights an unmet need for a routinely available disease-modifying therapy that can halt the progression of disease in those with pre-symptomatic SMA. Onasemnogene abeparvovec is a one-time disease-modifying therapy that delivers a stable, functional human *SMN* gene that replaces the missing or non-functional *SMN1* gene, thus promoting the survival and function of transduced motor neurons (5). The results of the clinical trial for onasemnogene abeparvovec in the pre-symptomatic population (SPR1NT) show that motor milestones that would never be achieved in patients receiving BSC only, can be achieved by infants with genetically confirmed SMA who are

treated before symptoms are observed (68). Furthermore, the majority of these milestones are achieved within windows of normal development (42, 68). The clinical data are presented in full in Section B.2.

In May 2021, onasemnogene abeparvovec was introduced in England, and four infusion centres have been established. In accordance with NICE recommendations (HST15; Section B.1), one-time treatment with onasemnogene abeparvovec gene therapy is available within the NHS for patients with 5q SMA with a bi-allelic mutation in the *SMN1* gene and a clinical diagnosis of SMA type 1 (non-sitters). Onasemnogene abeparvovec is currently provided with support of a national multidisciplinary team. Therefore, the infrastructure to deliver onasemnogene abeparvovec is already in place in England, and no additional infrastructure requirements are anticipated for the population under review.

The pre-symptomatic population would be identified through genetic testing soon after birth and treated with onasemnogene abeparvovec before SMA symptoms are observed, halting the course of the disease. If left on BSC alone, all infants genetically diagnosed with SMA will go on to develop symptomatic SMA. While there is currently no national population-based screening programme in England, if an infant were identified through population-based NBS screening (e.g. in a pilot study for NBS screening (9) or in any future national screening programmes), they would be eligible for a genetic test to confirm SMA diagnosis. Screening programmes will not increase the total number of patients eligible for SMA treatment(s), but will allow for earlier identification of infants with SMA, allowing earlier treatment and improved prognosis.

B.1.2.4 *Issues relating to current clinical practice*

Expert recommendations and consensus statements recognise that the early initiation of disease-modifying treatment for SMA, ideally before symptoms become apparent, can halt irreversible motor neuron loss, improve neuromuscular function, and prevent disease progression (14-19). Therefore, they support immediate treatment following genetic diagnosis (14-19). There is currently no national population-based NBS screening programme for SMA in England. The last review of SMA by the UK National Screening Committee (NSC) was completed in October 2018, prior to marketing authorisation being granted for onasemnogene abeparvovec (69). Based on this review, screening for SMA was not recommended in the UK, partially due to a lack of evidence for effective treatments for people with SMA without observed symptoms. National population-based NBS screening for SMA is urgent for those who do not know that they are carriers of the *SMN1* gene deletion (6). It should be noted that, if each parent is a carrier, there is a 25% chance that their child with have SMA. The NSC is due to start its 3-year review this year. It is essential that a treatment has been assessed by NICE and recommended for routine commissioning within the NHS as this is one of the NSC's key criteria for consideration for SMA screening.

Currently, in routine clinical practice in England, infants are identified through genetic testing referrals due to a sibling history of SMA or a parent with confirmed carrier status (family screening). A UK population-based pilot study is also being conducted to evaluate the feasibility of conducting national population-based NBS screening for SMA, using spare capacity from a newborn's Guthrie card (dried blood spot sample) (9).

Based on current clinical practice, it is estimated by the NICE Resource Impact Assessment team that approximately two pre-symptomatic infants may be identified each year as being eligible for treatment with onasemnogene abeparvovec through genetic testing referrals due to sibling history of SMA (1). Novartis Gene Therapies conducted a UK advisory board in Q1 2022, in which clinical experts agreed that one additional patient per year may be identified through the UK population-based NBS screening programme pilot study (population-based NBS screening of SMA to evaluate the uptake and feasibility in the UK context) (8, 9). As discussed in Section B.1.2.2, if a national screening programme were to be introduced, this would not increase the total number of patients eligible for SMA treatment(s), but would allow for earlier identification of infants with SMA, allowing earlier treatment and improved prognosis.

B.1.3 *Equality considerations*

There are no special equality considerations in the treatment of the pre-symptomatic population with a genetic diagnosis of SMA with onasemnogene abeparvovec.

B.2. Clinical effectiveness

- The clinical effectiveness of onasemnogene abeparvovec in infants with pre-symptomatic SMA has been evaluated in a Phase III clinical trial (SPR1NT), with ongoing long-term data collection in the long-term follow up study, LT002
- The Phase III SPR1NT trial evaluated the safety and efficacy of a one-time infusion of onasemnogene abeparvovec in pre-symptomatic infants with genetically diagnosed 5q SMA with a bi-allelic mutation in the SMN1 gene and two or three copies of the SMN2 gene. Treated infants demonstrated an ability to achieve age-appropriate motor milestones within normal World Health Organization (WHO) developmental windows, suggesting that onasemnogene abeparvovec may alter the clinical course of SMA in infants who are treated before SMA clinical symptoms are observed (68, 70, 71)
  - All (100%) 29 patients survived free of ventilatory and nutritional support at the end of the trial
  - No patients required ventilatory support of any kind (including cough assist) during the study and no patients required mechanical or non-oral support with feeding
  - Patients achieved age-appropriate milestones that would never be achieved in patients treated with BSC only, and may not have been achieved if treatment had been delayed until symptoms developed
  - In *SMN2* two-copy cohort:
    - All (100%) 14 patients achieved the primary efficacy endpoint of sitting without support for at least 30 seconds as defined by Bayley Scales of Infant and Toddler Development (Version 3) Gross Motor subtest (BSID GM) item #26 at any visit up to the 18 months of age study visit ($p<0.0001$), with 11 (78.6%) of these patients achieving this motor milestone within the normal developmental window. All (100%) 14 patients also achieved independent sitting as per the WHO definition
    - The highest developmental milestone of walking alone at any visit up to 18 months of age was achieved by nine patients (64.3%) as assessed by BSID GM item #43, and 10 patients (71.4%) as assessed by WHO definition
    - Thirteen of 14 (92.9%) patients maintained weight at or above the third percentile without the need for non-oral or mechanical feeding support at all visits up to 18 months of age ($p<0.0001$)
  - In *SMN2* three-copy cohort:
    - All (100%) 15 patients achieved the primary efficacy endpoint of standing alone (as assessed by BSID GM Subtest item #40) at any visit up to 24 months of age ($p<0.0001$). All (100%) 15 patients also achieved standing alone as per the WHO definition
    - Fourteen patients (93.3%) achieved the secondary endpoint of walking alone (as assessed by BSID GM item #43; $p<0.0001$) and also achieved walking alone as per the WHO definition at any visit up to 24 months of age. The fifteenth patient was observed walking alone by a clinical evaluator during the 24-month assessment conducted via video call, but video was not recorded and, per study protocol, in the absence of

independent video review this patient was not recorded as having achieved the motor milestone

- None of the patients in the *SMN2* three-copy cohort required nutrition through mechanical support. Ten (66.7%) patients maintained weight at or above the third percentile without the need for non-oral or mechanical feeding support at all visits up to 24 months of age

- Onasemnogene abeparvovec had a manageable safety profile and no serious adverse events were considered related to treatment

- The long-term follow-up study of patients who received onasemnogene abeparvovec (LT-002) will follow patients for up to 15 years

[redacted]

- [redacted]

B.2.1 *Identification and selection of relevant studies*

B.2.1.1 *Search strategy*

A systematic literature review (SLR) was conducted to identify clinical evidence regarding the efficacy and safety of onasemnogene abeparvovec and other relevant comparators for the treatment of infants from a screened population with a confirmed genetic diagnosis of 5q SMA with a bi-allelic mutation in the *SMN1* gene and up to three copies of the *SMN2* gene.

The methodology used for the SLR, including the search strategy, databases searched, and selection criteria, is presented in Appendix D. Selection criteria used for the review of published clinical efficacy, safety, and natural history studies are presented in Table 4 and Table 5. To capture all relevant data for the pre-symptomatic population, all SMA types were searched for, and relevant data for the pre-symptomatic population were included from studies evaluating mixed SMA populations.

B.2.1.2 *Study selection*

A summary of the inclusion and exclusion criteria for the clinical SLR is shown in Table 4.

Table 4: Selection criteria used for review of clinical efficacy and safety studies

Inclusion criteria	
Population	Type 1, type 2, and type 3; pre-symptomatic and symptomatic SMA
Interventions	Any of the following interventions used in the treatment of SMA: • Onasemnogene abeparvovec • Nusinersen • Risdiplam • Branaplam • CK-2127107 • 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 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.

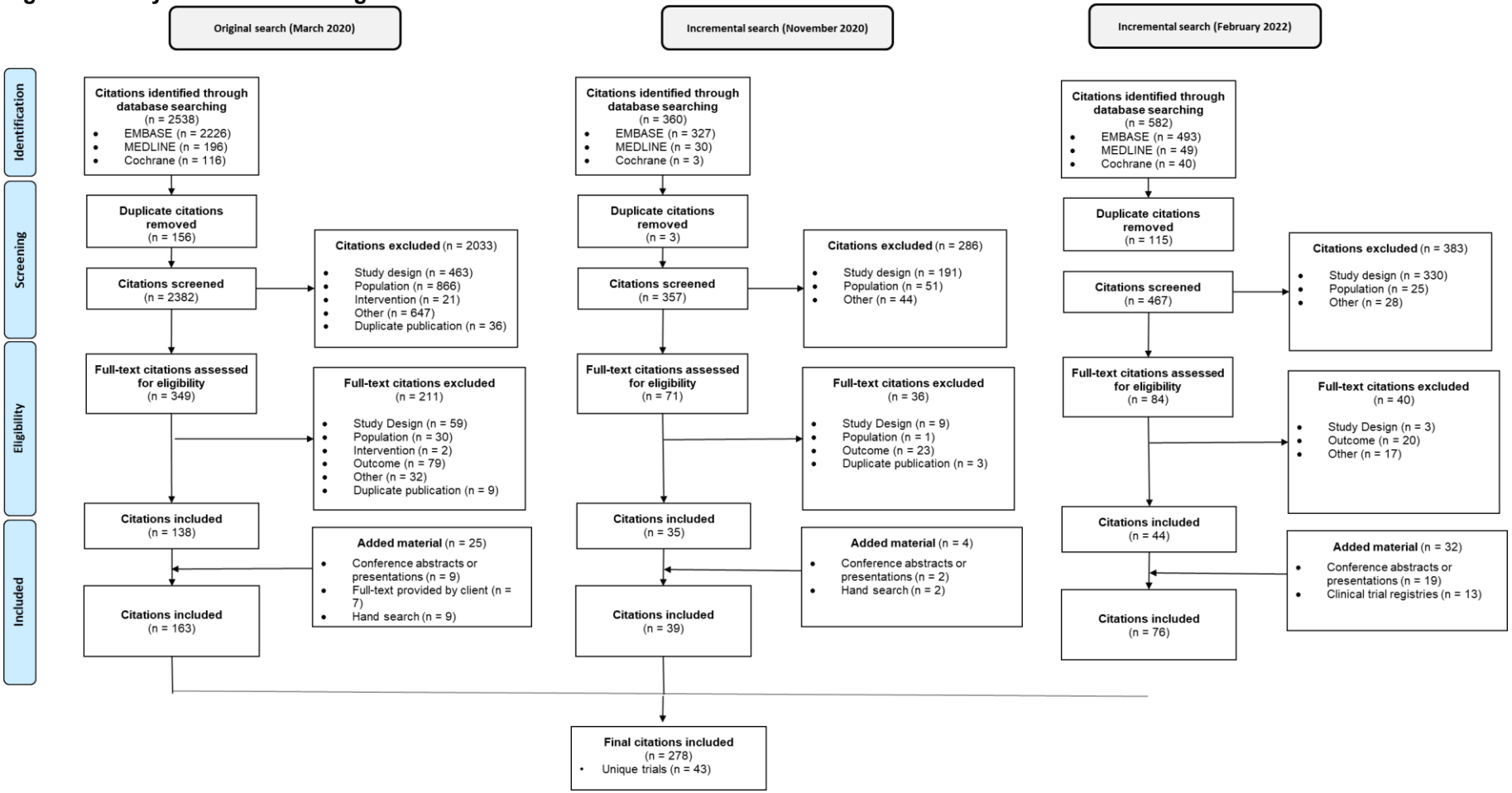
Table 5: Selection criteria used for review of natural history studies

Inclusion criteria	
Population	Type 1, type 2, and type 3; pre-symptomatic and symptomatic SMA
Interventions	No intervention or BSC (natural history)
Comparators	No intervention or BSC (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: BSC, best supportive care; CHOP-INTEND, The Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders; SMA, spinal muscular atrophy.
†The searches for the natural history review did not contain terms for randomised controlled trials, but did contain terms for observational study designs. Randomised controlled trials that were identified from the searches for the separate clinical efficacy and safety SLR were included in the natural history review as "additional materials", if they had a no-intervention or BSC arm.

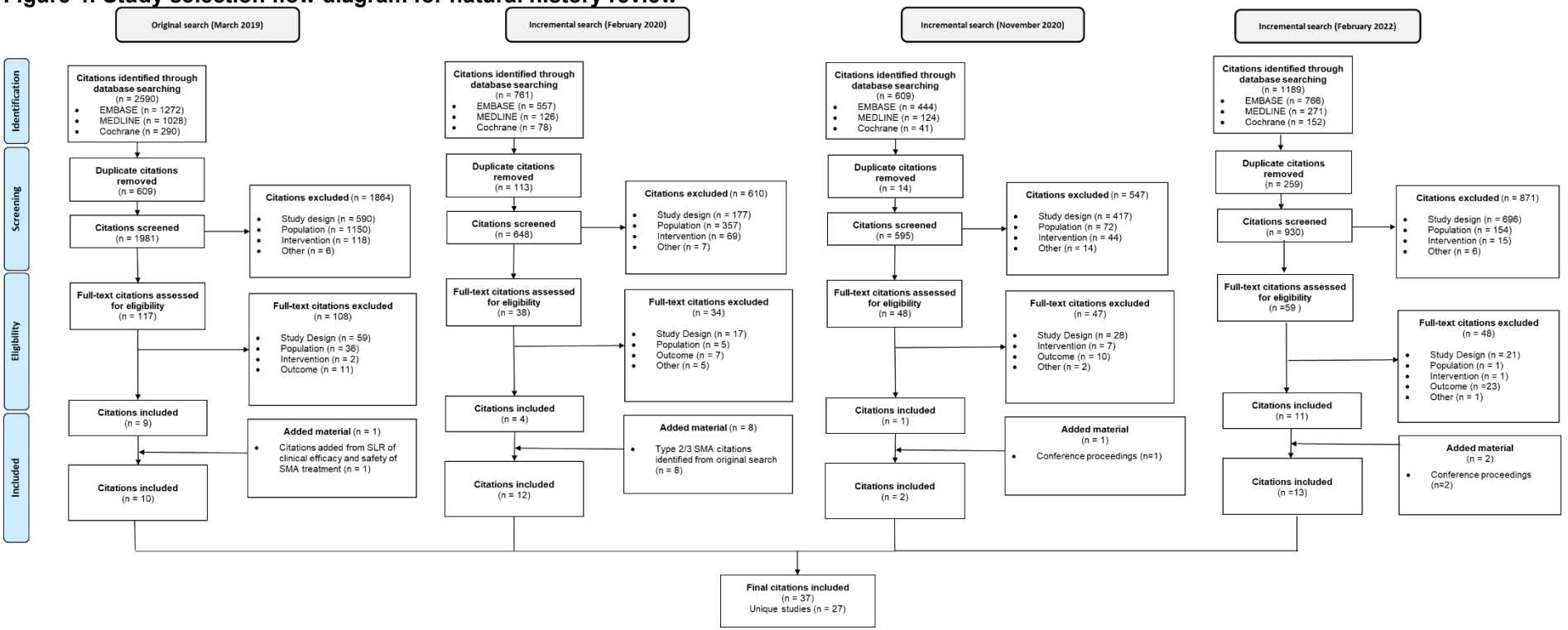
For the clinical review, a search was originally conducted on 3rd March 2020, and two incremental searches have since been conducted on 13th November 2020, and 2nd February 2022. Figure 3 presents the PRISMA flow diagram, which outlines the study selection process for the search to identify studies of interest in the SLR of clinical studies. In total, 278 publications from 43 unique studies have been identified. A reference list of the included studies is provided in Appendix D. However, it should be noted that the clinical review was a broad review, including symptomatic SMA and multiple treatments not considered relevant comparators in the pre-symptomatic population. Therefore, in the following sections, only the identified evidence of relevance to this appraisal, per the decision problem (Section B.1), is included.

Figure 3: Study selection flow diagram for clinical review



For the natural history review, a search was originally conducted on 13th March 2019, and three incremental searches have since been conducted on 26th February 2020, 13th November 2020, and 2nd February 2022. Figure 4 presents the PRISMA flow diagram, which outlines the study selection process for the search to identify studies of interest in the SLR of natural history studies. In total, 37 publications from 27 unique studies have been identified. Of the 27 natural history studies identified, five studies (EMBRACE, ENDEAR, SUNFISH, SMA-001, CY 5021) were RCTs and the remaining studies were either prospective or longitudinal cohort studies. A reference list of the included studies is provided in Appendix D.

Figure 4: Study selection flow diagram for natural history review



B.2.2 *List of relevant clinical effectiveness evidence*

Studies identified in the SLR of clinical evidence of onasemnogene abeparvovec for pre-symptomatic SMA are presented in Table 6. As discussed in Section B.2.1, the clinical review had a broader scope than the decision problem for this appraisal. Therefore, only studies of relevance to this appraisal are included in Table 6. This includes only studies in the pre-symptomatic population and only studies in onasemnogene abeparvovec, as BSC is the only relevant comparator for the current decision problem (with studies in BSC included in the natural history review).

The primary publications for the SPR1NT trial (in patients with two or three copies of *SMN2* (70, 71)) were published after the date of searching and were not identified in the clinical review, but are included in this submission. In addition, the protocol (74), statistical analysis plan (75), and most recent data (76-78) from the ongoing LT-002 study were not identified in the clinical review as they are not currently in the public domain. However, they have been included in this submission.

Table 6: List of relevant clinical evidence

Trial no. (acronym)	Population	Intervention	Comparator	Primary study reference(s)	Additional references	Is study excluded from further discussion ? If yes state rationale
Completed studies						
NCT03505099 (SPRINT)	Pre-symptomatic patients with SMA, ≤6 weeks (≤42 days) of age at the time of gene replacement therapy with bi-allelic deletions of *SMN1* gene and 2 (n=14) or 3 (n= 15) copies of the *SMN2* gene	Onasemnogene abeparvovec (IV)	No comparator	SPR1NT CSR (68) Strauss et al, 2022 (70) Strauss et al, 2022 (71)	Not applicable	No
Ongoing studies						
Data from long-term follow-up study NCT04042025 (LT-002)	Infants who received onasemnogene abeparvovec (IV or IT) within parent studies, including but not limited to STR1VE-US, STR1VE-EU, STR1VE-AP and SPR1NT. (25 patients from SPR1NT parent study were enrolled as of 23 November 2021 data-cut)	No onasemnogene abeparvovec is administered to patients in this study as patients received one-time treatment with onasemnogene abeparvovec in parent studies.	No comparator	Protocol (74) Statistical analysis plan (75) Summary of data from long-term follow-up studies, 23 November 2021 data cut-off (efficacy data only) (76) Summary of Clinical Safety in Spinal Muscular Atrophy. 23 May 2021 data cut-off (77) Addendum to long-term follow-up report, 23 May 2022 data cut-off (78)	Mendell et al, 2022 (79)	No

Abbreviations: IT, intrathecal; IV, intravenous; SMA, spinal muscular atrophy.

Table 7: Clinical effectiveness evidence from SPR1NT

Study	SPR1NT (NCT03505099)	
Study design	Phase 3, open-label, single-arm study of a one-time infusion of onasemnogene abeparvovec in infants with genetically diagnosed and pre-symptomatic SMA	
Population	Pre-symptomatic infants with SMA genetically defined by bi-allelic deletion of *SMN1* with two or three copies of *SMN2* and ≤6 weeks of age at the time of gene replacement therapy who meet enrolment criteria	
Intervention(s)	One-time infusion of onasemnogene abeparvovec	
Comparator(s)	Natural history cohorts[†]	
Indicate if trial supports application for marketing authorisation	Yes	✓
	No	
Indicate if trial used in the economic model	Yes	✓
	No	
Rationale if trial not used in model	NA	
Reported outcomes specified in the decision problem*	Efficacy outcomes (presented in Section B.2.6.1) Primary efficacy: • *SMN2* two-copy cohort: **Proportion of infants achieving the ability of functional independent sitting for at least 30 seconds up to 18 months of age as defined by BSID GM item #26[§]** • *SMN2* three-copy cohort: Proportion of infants achieving the ability to stand without support for at least 3 seconds up to 24 months of age as defined by the BSID GM subtest item #40 Secondary efficacy: • *SMN2* two-copy cohort: o **Proportion of infants 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** o Proportion of infants 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 • *SMN2* three-copy cohort: o **Proportion of infants 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 as defined by BSID GM subtest item #43[§]** Exploratory efficacy endpoints	

Study	SPR1NT (NCT03505099)
	• *SMN2* two-copy cohort: ○ **Achievement of motor milestones as assessed by WHO-MGRS criteria at any visit up to 18 months of age (sitting without support, hands and knees crawling, standing with assistance, walking with assistance, standing alone, 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 infants alive and without tracheostomy at 18 months of age** ○ Proportion of infants achieving an improvement over baseline of ≥15 points on BSID GM and FM subsets (raw score) at any visit up to 18 months of age ○ Ability to achieve a scaled score on BSID GM and FM 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 • *SMN2* three-copy cohort: ○ **Achievement of motor milestones as assessed by WHO MGRS criteria at any visit up to 24 months of age (sitting without support, hands and knees crawling, standing with assistance, walking with assistance, standing alone, walking alone)** ○ Time to respiratory intervention ○ Proportion of infants 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 BSID GM and FM subsets (raw score) at any visit up to 24 months of age ○ Achievement of a scaled score on BSID GM and FM 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

Study	SPR1NT (NCT03505099)
	Safety outcomes (presented in Section B.2.10): • Incidence of AEs and/or serious AEs
All other reported outcomes	See Table 9

*Outcomes marked in bold are incorporated into the economic model
†Well characterised external datasets from SMA natural history studies (PNCR and NeuroNext) are used to provide an external control comparator.
‡As seen on growth charts, meaning that 3% of children are a lower weight than the child, and 97% of children are the same weight or a greater weight than the child.
§Incorporated into the economic model as part of a scenario analysis.
Abbreviations: AE, adverse events; BSID FM, Bayley Scales of Infant and Toddler Development (Version 3) Fine Motor subtest; BSID GM, Bayley Scales of Infant and Toddler Development (Version 3) Gross Motor subtest; CHOP-INTEND, The Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders; NA, not applicable; SMA, spinal muscular atrophy; SMN, survival motor neuron; WHO-MGRS, World Health Organization Multicentre Growth Reference Study.
Source: SPR1NT CSR (68)

B.2.3 *Summary of methodology of the relevant clinical effectiveness evidence*

B.2.3.1 *Description of clinical assessments*

B.2.3.1.1 Developmental milestones and motor function tests

Developmental milestones were assessed using relevant definitions from BSID Gross Motor (GM) subtest (80) and World Health Organization Multicentre Growth Reference Study (WHO-MGRS) (42). These are standard methodologies used for the assessment of motor development for both children in normal development and in disease settings. Achievement of each developmental milestone was determined by the qualified site clinical evaluator and confirmed by the independent central reviewer based on an assessment of the submitted videos. Repeat assessments were performed during follow-up visits.

Timing of follow-up visits after dosing was based of day of dosing until Day 72, and from 3 months of age onward took place every 3 months, based on patient age. The end of study visits for the *SMN2* two-copy and three-copy cohorts were 18 and 24 months of age, respectively.

Differences between the achievement of seemingly similar milestones when assessed by BSID or WHO-MGRS definitions can arise because developmental milestone criteria differ. The motor milestones assessed in SPR1NT are summarised in Table 8.

Table 8: Motor milestone assessments in SPR1NT

Motor milestone	BSID definition (80)	WHO-MGRS definition (42)
Head control	Child holds head erect for ≥3 seconds without support (BSID GM item #4)	–
Rolls over	Child turns from back to both right and left sides (BSID GM item #20)	–
Sits without support	Sits without support for ≥30 seconds (BSID GM item #26)	Sitting up with back straight and head erect for ≥10 seconds; child does not use arms or hands to balance body or support position
Crawls	Crawls ≥5 feet (BSID GM item #34)	Crawls ≥3 movements (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 three in a row)
Pulls to stand	Child raises self to standing position using chair or other convenient object for support (BSID GM item #35)	–
Stands with assistance	Child supports own weight for ≥2 seconds (BSID GM subtest item #33)	Child stands in upright position on both feet, holding onto a stable object [e.g. furniture] with both

Motor milestone	BSID definition (80)	WHO-MGRS definition (42)
		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	Child stands alone for ≥3 seconds after you release his or her hands (BSID GM subtest item #40)	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	Coordinated alternated stepping movements (BSID GM item #37)	Child is in upright position with the back straight. Child makes sideways or forward steps by holding onto a stable object with one or both hands. One leg moves forward while the other supports part of the body weight. Child takes 5 steps in this manner
Walks alone	Child takes at ≥5 steps independently, displaying coordination and balance	Child takes ≥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: BSID, Bayley Scales of Infant and Toddler Development version 3; GM, Gross Motor; WHO-MGRS, World Health Organization Multicentre Growth Reference Study.

B.2.3.1.2 Survival without permanent ventilation

The survival of SMA infants 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) in the absence of acute illness or perioperatively at 18 or 24 months of age (two- and three-copy *SMN2* cohorts, respectively).

B.2.3.1.3 CHOP INTEND

The Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders (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 (non-sitters), and is administered by a qualified clinical evaluator (81, 82). 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.

The CHOP INTEND was performed for patients with two copies of *SMN2* only. Each CHOP INTEND examination was video recorded. Patients who achieved three

consecutive CHOP INTEND scores ≥58 did not undergo any additional CHOP INTEND examinations. Natural history studies have shown that non-sitters do not achieve and maintain CHOP INTEND scores >40 points beyond 6 months of age (27, 50, 83), experience on average a 10.7-point drop in CHOP INTEND scores between 6 and 12 months of age (83), and never have improvements in CHOP INTEND score following symptom onset (50).

B.2.3.1.4 Hammersmith Functional Motor Scale Expanded

The Hammersmith Functional Motor Scale Expanded (HFMSE) is a validated tool that allows functional assessment of patients with SMA types 2 and 3 (sitters and walkers). It contains 33 items rated on a scale of 0–2, with a total achievable score of 66 (84). The HFMSE was used in the Pediatric Neuromuscular Clinical Research (PNCR) natural history study (Section B.2.3.2). For comparison with patients in SPR1NT, patients from the PNCR database were considered to have achieved the endpoint of ability to stand alone for at least 3 seconds if they had a score of 2 on item #19 of the HFSME. The walks alone milestone was determined by a score of 2 on item #20 of the HFMSE.

The HFMSE is also included in the ongoing long-term extension of the SPR1NT study (Section B.2.11.1).

B.2.3.2 *Natural history study population used for comparisons with the SPR1NT population*

Data from two prospective observational studies (PNCR and NeuroNext/Kolb 2017) were used for comparisons with the study populations (27, 83).

Distinct control populations drawn from the PNCR study were used as a comparison for the primary endpoint of ‘sits without support’ (as defined by BSID GM item #26) and the secondary endpoints of survival and 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 for the *SMN2* two-copy cohort and for the primary and secondary endpoints (‘stands alone’; BSID GM Subtest Item #40 and ‘walk alone’; BSID GM item #43, respectively) for the *SMN2* three-copy cohort. Exploratory endpoints utilised data from PNCR or NeuroNext/Kolb 2017 for comparisons as appropriate.

The control population for the two-copy cohort consisted of 23 patients from the PNCR dataset who were non-sitters with two copies of *SMN2* (2, 27). The control population for the three-copy cohort was a cohort of 81 patients in the PNCR Natural History dataset (2), with any type of SMA and with three copies of *SMN2.*

B.2.3.3 *Summary of trial methodology*

As patients with different *SMN2* copy numbers were expected to have different natural histories and disease severities, the SPR1NT trial was designed with two cohorts of patients with two or three copies of *SMN2* that represent the population in the managed access agreement (MAA) (1). The *SMN2* two-copy and *SMN2* three-copy cohorts have different efficacy outcomes and length of time followed in the trial, and therefore clinical evidence is available for these cohorts separately. However, it should be noted that, although patients with different *SMN2* copy numbers are genetically distinct, 5q SMA is

one disease, with a single underlying cause and a broad spectrum of clinical severity. There is no way to definitively distinguish the clinical severity of SMA in pre-symptomatic patients. For example, although in general fewer copies of *SMN2* may result in a more severe disease phenotype, some patients with three copies of *SMN2* will develop a severe form of SMA (4).

The methodology of the Phase III SPR1NT trial is summarised in Table 9.

Table 9: Summary of methodology for SPR1NT

SPR1NT (NCT03505099)	
Location	Global study conducted in multiple countries including Australia, Belgium, Canada, Japan, the US, and the UK
Trial design	Phase III, open-label, single-arm study of a one-time infusion of onasemnogene abeparvovec in pre-symptomatic infants with SMA genetically defined by bi-allelic deletion of *SMN1* with two or three copies of *SMN2* who meet enrolment criteria
Eligibility criteria for participants (extended information on eligibility criteria is presented in Appendix D)	**All infants** • 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 prenatal screening test method • Up-to-date on childhood vaccinations that include palivizumab prophylaxis (Synagis) to prevent respiratory syncytial virus (RSV) infections are also recommended in accordance with the guidance of local health authorities ***SMN2* two-copy cohort** • Infants with pre-symptomatic SMA and two copies of *SMN2* ***SMN2* three-copy cohort** • Infants with pre-symptomatic SMA and three copies of *SMN2*
Settings and locations where the data were collected	Routine assessments were carried out at the investigational site. Remote monitoring was implemented due to COVID-19
Trial drugs (the interventions for each group with sufficient details to allow replication, including how and when they were administered) **Intervention(s) (n=[x]) and comparator(s) (n=[x])** **Permitted and disallowed concomitant medication**	Onasemnogene abeparvovec at 1.1 X 10^{14} vg/kg administered as a one-time, single-dose IV infusion over approximately 60 minutes (planned n=30, enrolled n=29) Comparator: natural history cohort[†] Disallowed concomitant medication: 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,

SPR1NT (NCT03505099)	
	tacrolimus, methotrexate, cyclophosphamide, IV immunoglobulin, rituximab)
Primary outcomes (including scoring methods and timings of assessments)	**Primary efficacy:** • Two copies of *SMN2*: Proportion of infants achieving the ability of functional independent sitting for at least 30 seconds up to 18 months of age as defined by BSID GM subtest item #26 • Three copies of *SMN2*: Proportion of infants achieving the ability to stand without support for at least 3 seconds up to 24 months of age as defined by the BSID GM subtest item #40 **Safety:** • Incidence of AEs and/or serious AEs • Change from baseline in clinical laboratory parameters
Other outcomes used in the economic model/specified in the scope	**Secondary efficacy:** • Two copies of *SMN2*: o Proportion of infants 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 o Proportion of infants 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 • Three copies of *SMN2*: Proportion of infants 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 as defined by BSID GM subtest item #43 **Exploratory efficacy endpoints** • Two copies of *SMN2*: o Achievement of motor milestones as assessed by WHO MGRS (85) criteria at any visit up to 18 months of age: ▪ Sitting without support ▪ Hands and knees crawling ▪ Standing with assistance ▪ Walking with assistance ▪ Standing alone ▪ Walking alone o Time to respiratory intervention o Requirement for respiratory intervention at 18 months of age

SPR1NT (NCT03505099)	
	○ 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 infants alive and without tracheostomy at 18 months of age ○ Proportion of infants achieving an improvement over baseline of ≥15 points on BSID GM and FM subtests (raw score) at any visit up to 18 months of age ○ Ability to achieve a scaled score on BSID GM and FM 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 • Three copies of *SMN2*: ○ Achievement of motor milestones as assessed by WHO MGRS (85) criteria at any visit up to 24 months of age: ▪ Standing with assistance ▪ Walking with assistance ○ Time to respiratory intervention ○ Proportion of infants 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 BSID GM and FM subsets (raw score) at any visit up to 24 months of age ○ Achievement of a scaled score on BSID GM and FM 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
Pre-planned subgroups	No pre-planned subgroups

† Well characterised external datasets from SMA natural history studies (PNCR and NeuroNext (2)) are used to provide an external control comparator.

Abbreviations: AE, adverse event; BSID FM, Bayley Scales of Infant and Toddler Development (Version 3) Fine Motor subtest; BSID GM, Bayley Scales of Infant and Toddler Development (Version 3) Gross Motor subtest; CHOP-INTEND, Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders; CMAP, compound muscle action potential; IV, intravenous; SMA, spinal muscular atrophy; SMN, survival motor neuron WHO-MGRS, World Health Organization Multicentre Growth Reference Study.
Source: SPR1NT CSR (68).

B.2.3.4 *Patient disposition*

Fourteen patients were enrolled in the *SMN2* two-copy cohort of SPR1NT, and 15 in the *SMN2* three-copy cohort. None of the patients had the *SMN2* gene modifier mutation c.859G>C based on genetic reconfirmation. All patients completed the study. Patient disposition and flow are illustrated in Appendix D.

Fourteen of 44 pre-symptomatic infants with bi-allelic deletion of *SMN1* with two or three copies of *SMN2* were excluded at screening (Table 10).

Table 10: Screening failures in SPR1NT

Exclusion rationale	Number of patients
CMAP value <2 mV at screening	3
Symptomatic at screening/clinical signs strongly suggestive of SMA	3
Anti-AAV9 antibody titre >1:50	2
Withdrew consent	1
Weight-for-age below the third percentile (86)	1
Serious non-respiratory tract illness requiring systemic treatment and/or hospitalization within 2 weeks prior to screening	1
Clinically significant abnormalities in hematology or clinical chemistry parameters	1
No genetic diagnosis of SMA obtained from acceptable newborn or pre-natal screening test method	1
CMAP value <2 mV and symptomatic at screening	1

Abbreviations: AAV9, adeno-association virus-9; CMAP, compound motor action potential; SMA, spinal muscular atrophy.

One additional patient originally included in SPR1NT was excluded from the ITT efficacy analysis as in the protocol amendment dated 27 September 2018, pre-symptomatic infants with four copies of *SMN2* were removed from inclusion. This patient was initially diagnosed as having three copies of *SMN2*, but a re-confirmation test reported post-dose showed four copies of *SMN2.* This patient remains part of the Safety Population but is no longer part of the ITT population and is therefore not reported in the efficacy results.

B.2.3.5 *Patient demographics and baseline characteristics*

Patient demographics and baseline characteristics for the SPR1NT trial are presented in Table 11.

Table 11: Characteristics of participants in the SPR1NT trial

Baseline characteristics	Two copies of *SMN2* (n=14)	Three copies of *SMN2* (n=15)
Enrolment status at data cut	Completed	
Age† at baseline, days		
Mean (SD)	20.6 (7.87)	28.7 (11.68)
Median (min, max)	21 (8, 34)	31 (9, 43)
0−27 days, n (%)	11 (78.6)	6 (40.0)
28 days−23 months, n (%)	3 (21.4)	9 (60.0)
Sex, n (%)		
Female	10 (71.4)	9 (60.0)
Male	4 (28.6)	6 (40.0)
Race, n (%)		
White	7 (50.0)	10 (66.7)
Other	4 (28.6)	2 (13.3)
Black or African American	1 (7.1)	0
Asian	2 (14.3)	2 (13.3)
American Indian or Alaska Native	0	1 (6.7)
Ethnicity, n (%)		
Not Hispanic or Latino	10 (71.4)	13 (86.7)
Hispanic or Latino	4 (28.6)	2 (13.3)
Weight at baseline, kg		
Mean (SD)	3.6 (0.39)	4.1 (0.52)
Median (min, max)	3.7 (3.0, 4.3)	4.1 (3.1, 5.2)
Gestational age at birth, weeks		
Mean (SD)	38.2 (1.42)	38.8 (1.47)
Median (min, max)	38.0 (36, 41)	39.0 (35, 41)
Mean (SD) score on CHOP-INTEND scale‡	46.1 (8.77)	NR
Familial history of SMA including affected siblings or parent carriers, n (%)	8 (57.1)	10 (66.7)
Modality of SMA diagnosis		
Prenatal testing, n (%)	5 (35.7)	1 (6.7)
Newborn screening, n (%)	9 (64.3)	13 (86.7)
Other	0	1 (6.7)
Age at SMA diagnosis (days)		
n	14	9
Mean (SD)	7.2 (4.79)	9.9 (7.69)
Median (min, max)	8.0 (1, 14)	8.0 (2, 26)

Table adapted from Pharmaceutical Benefits Advisory Committee (2008) Guidelines for preparing submissions to the Pharmaceutical Benefits Advisory Committee (Version 4.3). Canberra: Pharmaceutical Benefits Advisory Committee.
Abbreviations: CHOP-INTEND, Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders; NR, not reported; SD, standard deviation; SMA, spinal muscular atrophy.
† Age at dosing = (dose date - date of birth + 1)
‡ Scores on CHOP-INTEND scale of motor function range from 0 to 64, with higher scores indicating better function.
§ Age at SMA diagnosis = SMA diagnosis date − date of birth + 1. Only calculated for patients who were diagnosed after birth.
Source: SPR1NT CSR (68)

B.2.4 *Statistical analysis and definition of study groups in the relevant clinical effectiveness evidence*

A clinical evaluator on site determined developmental motor milestone achievement using assessments conducted at clinic visits, or home videos that demonstrated developmental milestone achievement. An independent central reviewer determined final confirmation as to developmental milestone achievement.

All enrolled, safety, intent-to-treat (ITT) and efficacy completers (EC) populations are equivalent for both cohorts. Therefore, all efficacy analyses were based on the ITT population and no separate efficacy analyses were conducted using the EC population. The ITT population comprised 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 received onasemnogene abeparvovec.

Of note, in the statistical analysis plan (SAP), additional sensitivity analyses to assess the impact of the COVID-19 pandemic on efficacy endpoints were planned. However, there was no impact on the assessment of the primary and secondary outcomes, and no patients were lost to follow-up. Therefore, these sensitivity analyses were not needed and not conducted.

A summary of the statistical methods used in SPR1NT are presented in Table 12.

Table 12: Summary of statistical analyses in SPR1NT

NCT03505099 (SPR1NT)	
Hypothesis objective	To demonstrate the benefit of onasemnogene abeparvovec compared with natural history data in patients with 5q SMA with a bi-allelic mutation in the *SMN1* gene and two or three copies of *SMN2* gene.
Statistical analysis of primary efficacy endpoint	***SMN2* Two-copy cohort** • **Sitting without support** The number and percentage of patients who demonstrated the milestone of sitting without support (BSID GM item #26) at any point up to the 18 months of age visit were summarised. A one-sided exact binomial test was used to test the null hypothesis of p≤0.1% at the significance level of 0.025. The corresponding one-sided 97.5% CI was estimated by the exact method for binomial proportions. Additionally, for patients who demonstrated this milestone, the age at which they first demonstrated the developmental milestone was summarised using descriptive statistics. ***SMN2* Three-copy cohort** • **Standing alone** The number and percentage of patients in the study and in the population-matched control cohort of the PNCR network who demonstrated the milestone of standing alone (BSID GM Subtest item #40) at any visit were summarised. Patients from the PNCR database were considered to have achieved the endpoint of ability to stand alone for at least 3 seconds if they had a score on item #19 of HFMSE. The HFMSE definition of 'stands alone without support for at least 3 seconds' was considered similar to the definition that is used for BSID GM Subtest item #40. The proportions as well as the difference in proportions between the two data sources were summarised and the exact 95% CI provided. The corresponding p-value from a two-sided Fisher's exact test with α=0.05 was computed for the comparison between onasemnogene abeparvovec and PNCR data. The age at which patients first demonstrated the developmental milestone was summarised using descriptive statistics, including the 95% CI for the median age of milestone achieved.

NCT03505099 (SPR1NT)	
Statistical analysis of secondary efficacy endpoints	***SMN2* Two-copy cohort** • **Survival without permanent ventilation** The number and percentage of patients in the study and in the population-matched cohort of the PNCR network surviving event-free to 14 months of age were summarised. Patients who terminated the study prior to reaching 14 months of age for any reason were censored at the point of withdrawal. The proportions as well as the difference in proportions between two data sources were summarised and the exact 95% CI of the difference were provided. The corresponding p-value from a two-sided Fisher's exact test with α=0.05 was computed for the comparison between onasemnogene abeparvovec and PNCR data. A Kaplan-Meier survival curve through 20 months of age was produced. • **Ability to maintain weight at or above the third percentile** The number and percentage of patients who maintained weight at or above the third percentile without the need for non-oral/mechanical feeding support at any visit up to 18 months of age were summarised. A one-sided exact binomial test was used to test the null hypothesis of p≤0.1% at the significance level of 0.025. The corresponding one-sided 97.5% CI was estimated by the exact method. ***SMN2* Three-copy cohort** • **Walking alone** The number and percentage of patients in the study and in the PNCR control who demonstrated the ability to walk alone at any point was summarised. Patients from the PNCR database were considered to have achieved the endpoint of walking alone if they had a score of 2 on item #20 of HFMSE. The proportions as well as the difference of the proportions between the two data sources were summarised and the exact 95% CI provided. The corresponding p-value from a 2-sided Fisher's exact test with α=0.05 was computed for the comparison between onasemnogene abeparvovec and PNCR data. The age at which patients first demonstrated the developmental milestone was summarised using descriptive statistics, including the 95% CI for the median age of milestone achieved. The number and percentage of patients who demonstrated the milestone of walking alone within the 99th percentile for normal development (≤534 days of age), at an age older than the 99th percentile for normal development, and who do not demonstrate the developmental milestone at all was presented.
Statistical analysis of safety endpoints	The analysis of the safety variables was descriptive, and no systematic testing was performed.

NCT03505099 (SPR1NT)	
Sample size, power calculation	***SMN2* Two-copy cohort** At least 14 patients with bi-allelic *SMN1* deletions and two copies of *SMN2* were planned to be enrolled. Based on two widely cited natural history studies of the disease (PNCR and NeuroNext/Kolb 2017), it was expected that no patient meeting the study entrance criteria (two copies of *SMN2* without the gene modifier mutation [c.859G>C]) would attain the ability to sit without support. Based upon data from the completed START study, at least 60% of treated patients with two copies of *SMN2* were expected to achieve the ability to sit without support for at least 30 seconds. With this degree of efficacy, a sample size of 14 patients would provide power of >90% to detect a significant difference compared with a rate of 0.1% (in lieu of zero) with α=0.025 using one-sided Fisher's exact test for binomial proportion. ***SMN2* Three-copy cohort** At least 12 patients with bi-allelic *SMN1* deletions and three copies of *SMN2* were planned to be enrolled. In the PNCR dataset, 19/81 (23.5%) of patients with three copies of *SMN2* achieved the ability to stand alone. Extrapolating from the experience from the onasemnogene abeparvovec Phase I study in infants with SMA type 1, 85% of treated patients with bi-allelic *SMN1* deletions and three copies of *SMN2* were expected to achieve the ability to stand alone. With this degree of efficacy, a sample size of 12 patients would provide power of >90% to detect a significant difference compared with the population-matched control cohort (from PNCR database) with α=0.05 using two sample 2-sided Fisher's exact test.
Data management and patient withdrawals	Electronic case report forms (eCRFs) were used to capture data in this study. Adequate and accurate case records were maintained, and all relevant observations and data related to the study were recorded. No patients were withdrawn.

Abbreviations: BSID GM, Bayley Scales of Infant and Toddler Development (Version 3) Gross Motor subtest;; CI, confidence interval; eCRF, electronic case report form; HFMSE, Hammersmith Functional Motor Scale- Expanded; PNCR, Paediatric Neuromuscular Clinical Research Network for SMA.
Source: SPR1NT CSR (68).

B.2.5 *Quality assessment of the relevant clinical effectiveness evidence*

A quality assessment for SPR1NT is presented in Table 13.

Table 13: Critical appraisal of SPR1NT

Study name	NCT03505099 (SPR1NT)	
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 intervention were fully described.

Was the outcome accurately measured to minimise bias?	Yes	Measurements for primary and secondary outcomes were clearly described (80). Achievement of developmental motor milestones was confirmed by independent central video review.
Have the authors identified all important confounding factors?	Yes	The inclusion criteria were carefully considered by investigators with regard to confounding factors. The protocol specified that all primary and secondary analyses would be performed on the population of patients with bi-allelic *SMN1* deletions with two or three copies of the *SNM2* gene without the c.859G>C genetic modifier in exon 7 of *SMN2* which predicts a milder phenotype of the disease. While they could be enrolled in the study, patients with *SMN1* point mutations or with the c.859G>C mutation would be evaluated separately.
Have the authors taken account of the confounding factors in the design and/or analysis?	Yes	Not applicable, see above.
Was the follow-up of patients complete?	Yes	All patients were alive at the end of the study, and none were lost to follow-up.
How precise (for example, in terms of confidence interval and p values) are the results?	Yes	All statistical analyses were prospectively defined in the protocol and statistical analysis plan, as detailed in Table 12.

Table adapted from Critical Appraisal Skills Programme (CASP): Making sense of evidence 12 questions to help you make sense of a cohort study.

B.2.6 *Clinical effectiveness results of the relevant trials*

B.2.6.1 *SPR1NT*

SMA exists on a broad spectrum, and although patients with different *SMN2* copy numbers are genetically distinct, there is overlap in clinical manifestations and disease severity. Onasemnogene abeparvovec is indicated for patients with 5q SMA with a bi-allelic mutation in the *SMN1* gene and up to three copies of the *SMN2* gene (5). As in the Summary of Product Characteristics (SPC) (5), the targeted screened population genetically diagnosed with SMA with up to three copies of *SMN2* is treated as a single patient population. This is because *SMN2* copy number is only one of several factors that can predict SMA phenotype and, prior to observation of symptoms, there is no definitive way to determine severity of disease. Therefore, clinically, patients in the targeted screened pre-symptomatic population with up to three copies of *SMN2* would be managed in the same way.

The SPR1NT trial was designed with two distinct cohorts of patients with up to three copies of *SMN2* that represent the population in the MAA (1). The *SMN2* two-copy and *SMN2* three-copy cohorts have different efficacy outcomes and length of time followed in the trial, and therefore clinical evidence is available for these cohorts separately. Although, in general, fewer copies of *SMN2* may result in a more severe disease

phenotype, some patients with three copies of *SMN2* will develop a severe form of SMA (4).

Well-characterised external datasets from SMA natural history studies (PNCR and NeuroNext/Kolb 2017 (2, 83)) were used to provide an external control comparator for SPR1NT, as described in Section B.2.3.2.

B.2.6.1.1 Primary efficacy outcomes and other milestones

SMN2 two-copy cohort

Sitting without support for at least 30 seconds at any visit up to 18 months of age

All 14 (100%) patients in the SMN2 two-copy cohort achieved the video-confirmed primary efficacy endpoint of sitting without support for at least 30 secondsb at any visit up to the 18 months of age study visit compared with none of 23 untreated SMA type 1 patients in the PNCR cohort (p<0.0001).

Eleven (78.6%) of the 14 patients who achieved this motor milestone did so within the normal developmental window (99th percentile ≤279 days of age; WHO definition (42)). The mean (SD) age of first achieving this milestone was 8.21 (1.76) months and ranged from 5.7 to 11.8 months.

Other developmental milestones (exploratory efficacy endpoints) achieved by patients in the two-copy cohort are presented in Table 14.

Maintenance of independent sitting

Assessment for the exploratory endpoint of milestone maintenance at 18 months of age was only possible for 12 patients due to patient non-compliance in two cases. All 12 assessed patients (100%) were able to demonstrate maintenance of the achieved milestone of independent sitting at 18 months of age. The remaining two patients could not be assessed.

Other motor milestones

The developmental milestones achieved by patients in the *SMN2* two-copy cohort at any post-dose visit up to and including the 18-month study visit are presented in Table 14 and Figure 5. Prior to dosing, five patients demonstrated the ability to hold head erect without support (BSID GM item #4), and one patient demonstrated the ability to roll from back to sides (BSID GM item #20).

All 14 patients (100%) achieved developmental milestones after one-time infusion with onasemnogene abeparvovec:

The highest milestones achieved up to 18 months of age as assessed by BSID GM were standing with assistance (item #33; two patients, 14.3%), walking with assistance (item #37; one patient, 7.1%), standing alone (item #40; two patients, 14.3%), and walking alone with coordination (item #43; nine patients, 64.3%).

[b] BSID item #26: Child sits alone without support for ≥30 seconds.

The highest motor milestones achieved up to 18 months of age as assessed by WHO-MGRS definition were standing with assistance (two patients, 14.3%), walking with assistance (two patients, 14.3%), and walking alone (10 patients, 71.4%). The highest developmental milestone of walking alone was achieved by nine patients (64.3%) as assessed by BSID GM item #43, and 10 patients (71.4%) as assessed by WHO definition. Differences between the achievement of seemingly similar milestones when assessed by BSID or WHO-MGRS definitions arise because developmental milestone criteria differ and can contribute to differing age of achievement as described in Section B.2.3.1.

Table 14: Proportion of patients demonstrating motor milestones up to 18 months of age in the SPR1NT *SMN2* two-copy cohort (ITT Population [N=14])

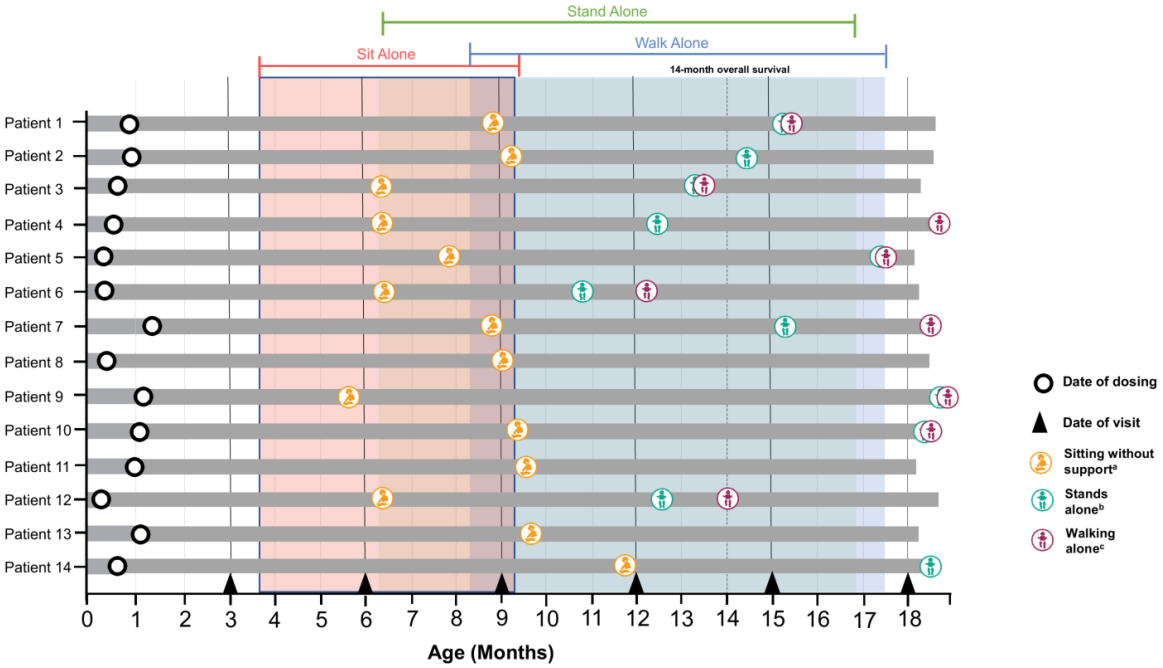
Milestone achieved		Number achieving milestone after dosing/patients without milestone prior to dosing (%)	Age (months) at earliest achievement, median (min, max)	Achieved within 99th percentile of normal development (WHO-MGRS), n (%)
Holds head erect for ≥3 seconds without support†		9/9 (100.0)	1.9 (1.2, 3.4)	NR
Turns from back to both right and left sides‡		13/13 (100.0)	8.9 (3.9,18.4)	NR
Sits alone without support	For ≥30 seconds§	14/14 (100.0)	8.9 (5.7, 11.8)	11 (78.6)
	For ≥10 seconds¶	14/14 (100.0)	9.0 (6.3, 18.5)	10 (71.4)
Crawls	≥5 feet††	9/14 (64.3)	14.4 (8.9, 15.3)	4 (28.6)
	≥3 movements‡‡	10/14 (71.4)	13.4 (10.5, 14.9)	5 (35.7)
Stands with assistance	Supports own weight for ≥2 seconds§§	14/14 (100.0)	13.7 (6.3, 18.8)	6 (42.9)
	Stands holding a stable object¶¶	14/14 (100.0)	13.0 (11.1, 15.3)	5 (35.7)
Pulls to stand†††		11/14 (78.6)	14.9 (8.9, 18.6)	NR
Stands alone	Stands alone ≥3 seconds‡‡‡	11/14 (78.6)	15.3 (10.9, 18.8)	7 (50.0)

Milestone achieved		Number achieving milestone after dosing/patients without milestone prior to dosing (%)	Age (months) at earliest achievement, median (min, max)	Achieved within 99th percentile of normal development (WHO-MGRS), n (%)
	Stands alone ≥10 seconds§§§	10/14 (71.4)	16.4 (14.6, 18.0)	5 (35.7)
Walks with assistance	Walks with assistance¶¶¶	11/14 (78.6)	12.5 (8.9, 18.5)	6 (42.9)
	Walks with assistance ≥5 steps††††	12/14 (85.7)	14.9 (13.3, 16.4)	5 (35.7)
Walks alone	Walks alone ≥5 steps with coordination and balance‡‡‡‡	9/14 (64.3)	17.5 (12.2, 18.8)	5 (35.7)
	Walks alone ≥5 steps§§§§	10/14 (71.4)	16.4 (14.4, 17.9)	6 (42.9)

Abbreviations: BSID, Bayley Scales of Infant and Toddler Development (Version 3) Gross Motor subtest; ITT, intention-to-treat; NR, not reported; *SMN2*, survival motor neuron 2; WHO, World Health Organization; WHO-MGRS, World Health Organization Multicentre Growth Reference Study.
Note: Percentages for each milestone are based on the number of patients who did not demonstrate the milestone prior to dosing.
† BSID GM item #4: Child holds head erect for ≥3 seconds without support.
‡ BSID GM item #20: Child turns from back to both right and left sides
§ BSID GM 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.
†† BSID GM 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.
§§ BSID GM 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.
††† BSID GM item #35: Child raises self to standing position using chair or other convenient object for support.
‡‡‡ BSID GM item #40: Stands alone. 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.
¶¶¶ BSID GM item #37: Walks with assistance. 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 one or both hands. One leg moves forward while the other supports part of the body weight. Child takes ≥5 steps in this manner.
‡‡‡‡ BSID GM item #43: Walks alone. Child takes at ≥5 steps independently, displaying coordination and

balance.
§§§§ WHO MGRS definition: Walking alone Child takes ≥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.
Source: SPR1NT CSR (68)

Figure 5: SPR1NT *SMN2* two-copy cohort achieved video-confirmed developmental motor milestones



Milestones achieved (visit month identified). Months calculated as days/30. Only the first observed instance of a milestone is included in this figure. Sits alone, BSID GM item #26. Stands alone, BSID GM item #40. Walks alone, BSID GM item #43. According to the WHO-MGRS windows for normal development, the 99th percentile (i.e., upper bound of normal development) of sitting and walking without support was 279 days and 534 days, respectively.
Abbreviations: BSID, Bayley Scales of Infant and Toddler Development (Version 3) Gross Motor subtest; ITT, intention-to-treat; WHO, World Health Organization; WHO-MGRS, World Health Organization Multicentre Growth Reference Study

SMN2 three-copy cohort

Standing alone for at least 3 seconds at any visit up to 24 months of age

All 15 (100%) patients in the *SMN2* three-copy cohort had achieved the video-confirmed primary efficacy endpoint of standing alone according to the definition from the BSID GM item #40[c] at any visit up to 24 months of age, compared with 19 of 81 patients (23.5%) in the PNCR population who achieved independent standing (p<0.0001). The mean age of achieving the milestone was 13.5 months and ranged from 9.5 to 18.3 months. Fourteen patients (93.3%) achieved this milestone within the normal developmental window (99th percentile ≤514 days of age; WHO definition (42)).

[c] BSID item #40: Stands alone. Child stands alone for ≥3 seconds after you release his or her hands.

Other developmental milestones (exploratory efficacy endpoints) achieved by the three-copy cohort are presented in Table 15.

Maintenance of standing alone

All 15 patients in the *SMN2* three-copy cohort achieved the milestone of standing alone prior to reaching 24 months of age, and this achievement was maintained at 24 months of age in all patients.

Other motor milestones

The developmental milestones achieved by patients on the *SMN2* three-copy cohort at any post-dose visit up to and including the 24-month study visit are presented in Table 15 and Figure 6.

Prior to dosing with onasemnogene abeparvovec, six patients demonstrated the ability to hold head erect without support (BSID GM item #4). All 15 patients in the three-copy cohort achieved developmental milestones after dosing with onasemnogene abeparvovec:

- The highest milestones achieved up to and including the 24 months of age visit, as assessed by BSID GM, were standing alone (item #40; one patient, 6.7%), and walking alone with coordination (item #43; fourteen patients, 93.3%).
- The highest motor milestones achieved up to 24 months of age as assessed by WHO-MGRS definition were standing alone (one patient, 6.7%), and walking alone (14 patients, 93.3%).

Walking alone at any visit up to 24 months of age is a secondary efficacy endpoint, and is discussed further in Section B.2.6.1.3.

Table 15: Proportion of patients demonstrating video-confirmed developmental milestones up to 24 months of age in the SPR1NT *SMN2* three-copy cohort (ITT Population)

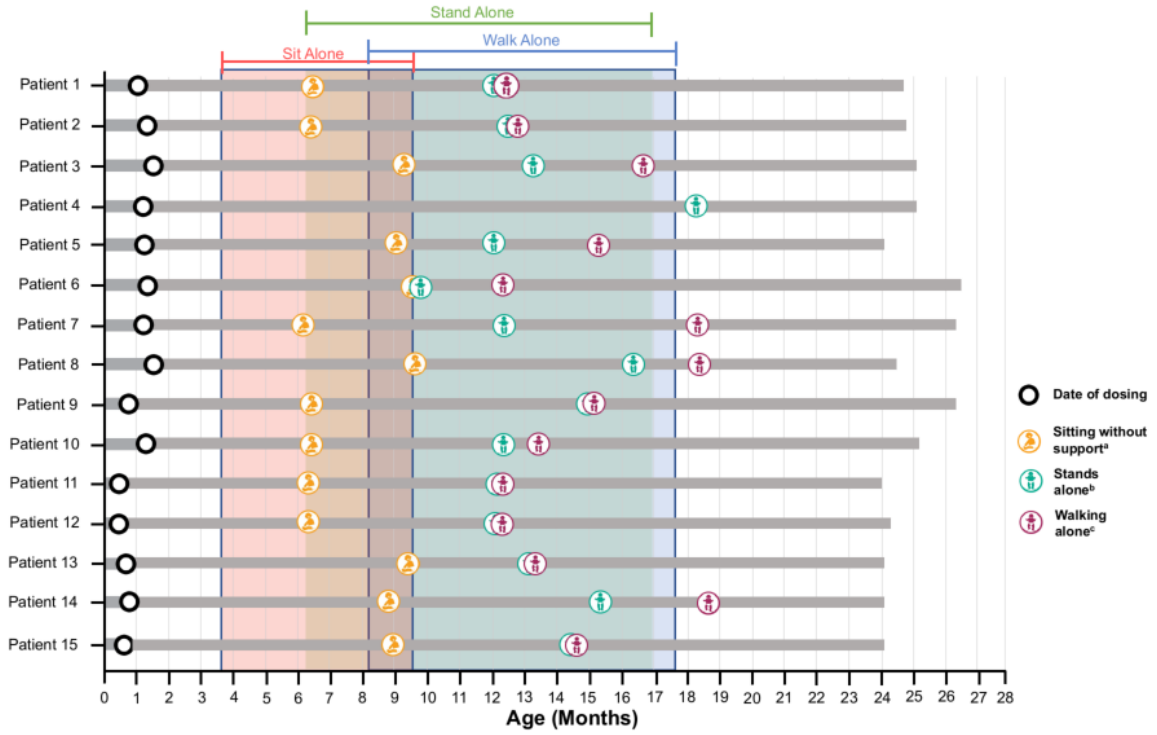
Milestone achieved		Number achieving milestone after dosing/patients without milestone prior to dosing (%)	Age (months) at earliest achievement, median (min, max)	Achieved within 99th percentile of normal development, (WHO-MGRS) n (%)
Holds head erect for ≥3 seconds without support†		9/9 (100.0)	2.2 (1.3,4.3)	NR
Turns from back to both right and left sides‡		15/15 (100.0)	7.8 (5.9, 21.2)	NR
Sits alone without support	For ≥30 seconds§	14/15 (93.3)	7.6 (6.1, 9.6)	11 (73.3)
	For ≥10 seconds¶	14/15 (93.3)	8.8 (6.1, 9.6)	10 (66.7)
Crawls	≥5 feet††	14/15 (93.3)	10.75 (8.9, 13.3)	14 (93.3)
	≥3 movements‡‡	14/15 (93.3)	10.75 (8.9, 16.4)	13 (86.7)
Stands with assistance	Supports own weight for ≥2 seconds§§	14/15 (93.3)	9.25 (6.4, 12.8)	11 (73.3)
	Stands holding a stable object¶¶	14/15 (93.3)	9.3 (8.9, 12.8)	11 (73.3)
Pulls to stand†††		14/15 (93.3)	10.75 (8.9, 16.4)	NR
Stands alone	Stands alone ≥3 seconds‡‡‡	15/15 (100.0)	12.6 (9.5, 18.3)	14 (93.3)
	Stands alone ≥10 seconds§§§	15/15 (100.0)	13.3 (12.0, 18.3)	13 (86.7)
Walks with assistance	Walks with assistance¶¶¶	14/15 (93.3)	12.2 (8.9, 16.4)	13 (86.7)
	Walks with assistance ≥5 steps††††	14/15 (93.3)	12.3 (8.9, 16.4)	12 (80.0)
Walks alone	Walks alone ≥5 steps with coordination and balance‡‡‡‡	14/15 (93.3)¶¶¶¶	14.1 (12.1, 18.8	11 (73.3)
	Walks alone ≥5 steps§§§§	14/15 (93.3)	14.05 (12.1, 18.3)	13 (86.7)

Abbreviations: BSID, Bayley Scales of Infant and Toddler Development (Version 3) Gross Motor subtest; ITT, intention-to-treat; *SMN2*, survival motor neuron 2; WHO, World Health Organization; WHO-MGRS, World Health Organization Multicentre Growth Reference Study..

† BSID GM item #4: Child holds head erect for ≥3 seconds without support.

‡ BSID GM item #20: Child turns from back to both right and left sides
§ BSID GM 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.
†† BSID GM 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.
§§ BSID GM 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.
††† BSID GM item #35: Child raises self to standing position using chair or other convenient object for support.
‡‡‡ BSID GM item #40: Stands alone. Child stands alone for ≥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 ≥10 seconds.
¶¶¶ BSID GM item #37: Walks with assistance. 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 one or both hands. One leg moves forward while the other supports part of the body weight. Child takes ≥5 steps in this manner.
‡‡‡‡ BSID GM item #43: Walks alone. Child takes at ≥5 steps independently, displaying coordination and balance.
§§§§ WHO MGRS definition: Walking alone Child takes ≥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.
¶¶¶¶ A fifteenth patient was observed walking alone by a clinical evaluator during the 24-month assessment conducted via video call, but video was not recorded and hence per study protocol, in the absence of independent video review, this patient was not recorded as having achieved the motor milestone.
Source: SPR1NT CSR (68)

Figure 6: SPR1NT *SMN2* three-copy cohort achieved video-confirmed developmental motor milestones



Note: One patient who did not have video-confirmed assessment was observed standing and walking alone by a clinical evaluator during the 24-month assessment conducted via video call.
Months calculated as days/30. Only the first observed instance of a milestone is included in this figure. Shaded areas indicate the WHO-MGRS windows for normal development; the 99th percentile (i.e., upper bound of normal development) of sits without support is 279 days, stands alone is 514 days, and walks alone is 534 days. BSID GM item #26: child sits alone without support for at least 30 seconds. BSID GM item #40: child stands alone. Child stands alone for at least 3 seconds after you release his or her hands. BBSID GM item #43: child walks alone. Child takes at least five steps independently, displaying coordination and balance.
Abbreviations: BSID, Bayley Scales of Infant and Toddler Development (Version 3) Gross Motor subtest; ITT, intention-to-treat; WHO, World Health Organization; WHO-MGRS, World Health Organization Multicentre Growth Reference Study.

B.2.6.1.2 Secondary analysis of primary outcome

There was no secondary analysis of primary outcome for *SMN2* two- or three-copy cohorts.

B.2.6.1.3 Secondary efficacy outcomes

SMN2 two-copy cohort

Survival and permanent ventilation

The secondary efficacy endpoint of event-free survival was defined as avoidance of both death and permanent ventilation through the 14 months of age visit. All 14 (100%) patients survived event free to ≥14 months of age without permanent ventilation compared with 6 (26.1%) patients in the PNCR control population ($p<0.0001$). No patient in the two-copy cohort used ventilatory support (invasive or non-invasive, including cough assist) at any point during the study. All patients remained independent of ventilatory support at 18 months of age ($p<0.0001$).

Ability to maintain weight without feeding support

The ability to maintain weight without feeding support at any visit up to 18 months of age was a co-secondary endpoint for the *SMN2* two-copy cohort. None of the 14 treated patients received any feeding support at any time during the study. Thirteen (92.9%; 95% CI 66.1, 99.8) achieved the secondary endpoint of maintaining weight at or above the third percentile[d] without the need for non-oral or mechanical feeding support at all visits up to 18 months of age (p<0.0001).

SMN2 three-copy cohort

Walking alone at any visit up to 24 months of age

Fourteen (93.3%) of the infants achieved the video-confirmed secondary efficacy endpoint of walking alone according to the BSID definition,[e] compared with 17 of 81 patients (21.0%) in the PNCR population (p<0.0001). The fifteenth patient was observed walking alone by a clinical evaluator during the 24-month assessment conducted via video call, but video was not recorded and hence per study protocol in the absence of independent video review this patient was not recorded as having achieved the motor milestone.

The mean age of first walking alone was 14.6 months and ranged from 12.1 to 18.8 months of age. Eleven patients (73.3%) achieved this milestone within the normal developmental window (99th percentile ≤534 days [approximately 17.6 months] of age (42)).

B.2.6.1.4 Exploratory efficacy outcomes

The exploratory endpoints of achievement and maintenance of motor milestones are presented in Section B.2.6.1.1. Other exploratory endpoints are presented here.

SMN2 two-copy cohort

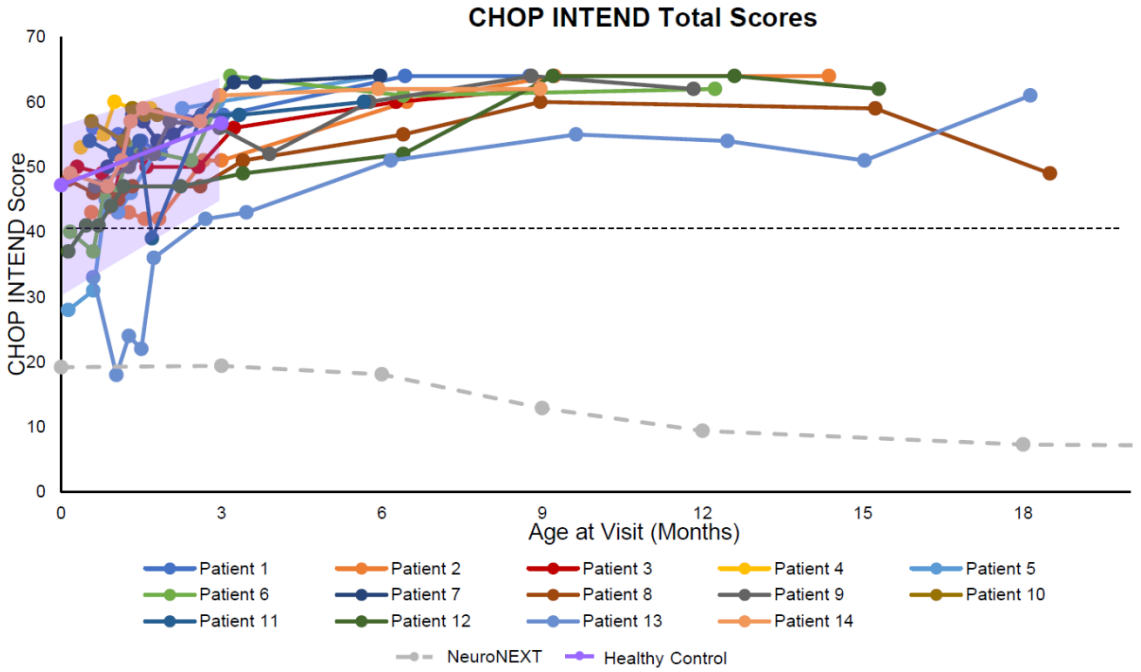
CHOP-INTEND response

The CHOP-INTEND score is a motor function scale developed and validated for use specifically to monitor motor function status and decline in infants with SMA (81, 82). CHOP-INTEND scores for infants enrolled in the two-copy cohort of SPR1NT are presented in Figure 7. The mean (SD) baseline CHOP-INTEND score was 46.1 (8.77). All 14 patients (100%) achieved a CHOP INTEND score greater than 40, a threshold never achieved by patients with untreated SMA type 1 older than six months of age (p<0.0001) (83). All 14 patients ultimately achieved scores ≥58 at any visit up to and including 18 months of age visit (p<0.0001). This data is presented by patient in Figure 7, with natural history data from the NeuroNext/Kolb 2017 study (2, 83) also presented.

[d] As seen on growth charts, meaning that 3% of children are a lower weight than the child, and 97% of children are the same weight or a greater weight than the child.

[e] BSID item #43: Walks alone. Child takes at ≥5 steps independently, displaying coordination and balance.

Figure 7:CHOP-INTEND score over time in the SPR1NT two-copy cohort ITT Population with comparator (natural history) data



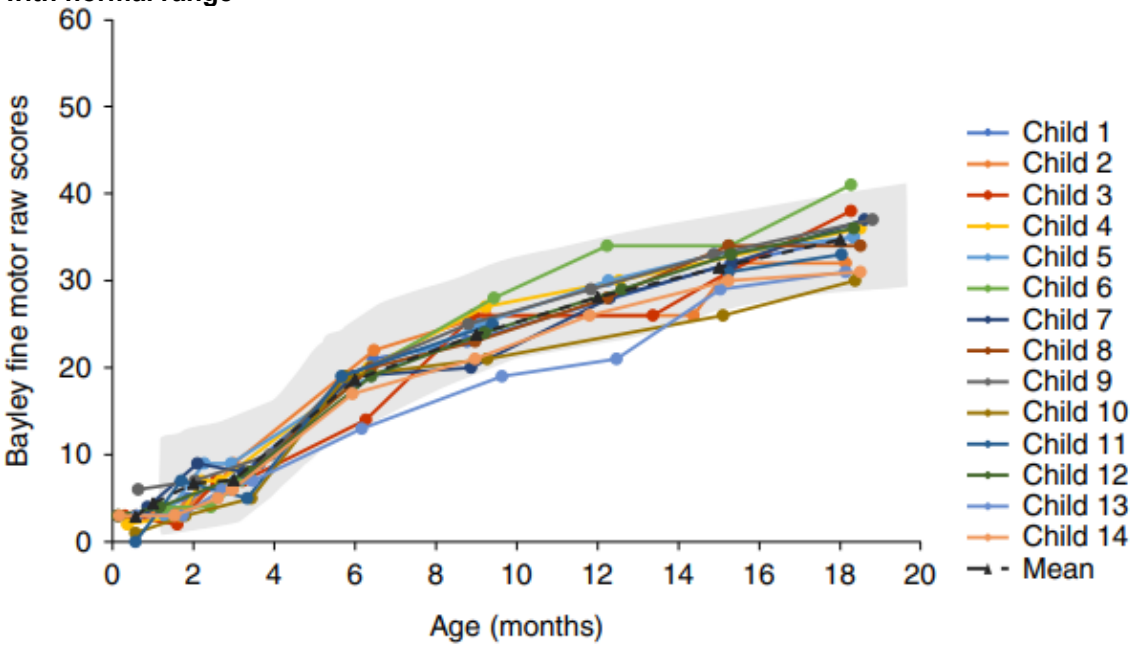
Note: The dashed straight line represents a CHOP-INTEND score of 40, which is a score that untreated non-sitters rarely achieve in the natural history of the disease. Shading represents CHOP-INTEND values obtained from normal healthy control infants in the NeuroNext/Kolb 2017 study with mean values presented as a solid purple line. The dashed grey line represents the mean change in CHOP-INTEND score observed in the NeuroNext/Kolb 2017 study of non-sitters who did not receive disease-modifying treatments.
Abbreviations: CHOP-INTEND, Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders; ITT, intention-to-treat; *SMN2*, survival motor neuron 2.
Comparator data from NeuroNext/Kolb 2017 study (2, 83).

BSID

BSID (80) is a standardized, norm-referenced infant assessment of developmental functioning across five domains of cognitive, language, motor, social-emotional, and adaptive behaviour. The motor scale of BSID is divided into Fine Motor (FM) and Gross Motor (GM) subtests. Results of the FM and GM raw scores for the infants enrolled in the two-copy cohort of SPR1NT are illustrated by patient in Figure 8 and Figure 9, respectively. All 14 patients (100%) achieved an improvement over baseline of ≥15 points on BSID FM and GM subtests (raw score) on at least one visit up to 18 months of age.

The mean scaled score is 10 for other normally developing children, with a SD of ±3. Therefore, approximately 87% of children fall within 1.5 SD of the mean (scores 5.5–14.5). All 14 patients (100%) achieved a scaled score on BSID FM and GM subtests ≥5.5 at any post-baseline visit. Eight of the 14 patients (57.1%) achieved a scaled score ≥5.5 on BSID FM and GM subtests at the 18 months of age visit.

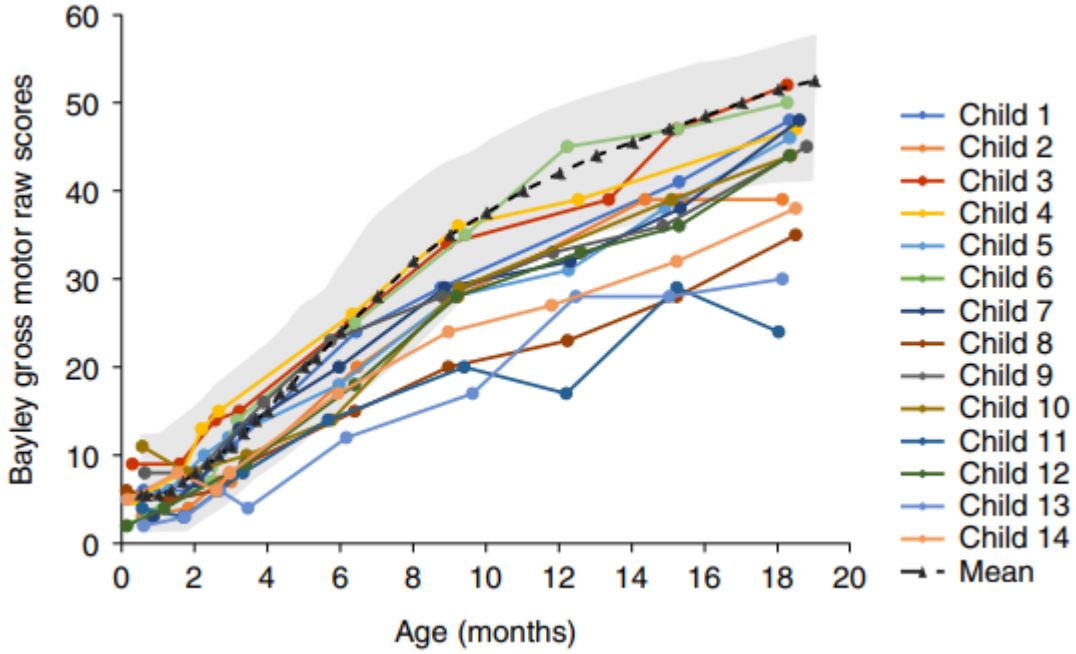
Figure 8: BSID FM subtest raw score over time in SPR1NT two-copy cohort ITT Population with normal range



Source: Strauss et al, 2022 (70)
Abbreviations: BSID FM, Bayley Scales of Infant and Toddler Development (Version 3) Fine Motor subtest; ITT, intention-to-treat; *SMN2*, survival motor neuron 2.
BSID FM normal range (±2 SD) shown in grey highlight.

[redacted]

Figure 9: BSID GM subtest raw score over time in SPR1NT two-copy cohort ITT Population with normal range



Source: Strauss et al, 2022 (70)
Abbreviations: BSID GM, Bayley Scales of Infant and Toddler Development (Version 3) Gross Motor subtest;

ITT, intention-to-treat; *SMN2*, survival motor neuron 2.
BSID GM normal range (±2 SD) shown in grey highlight.

Ability to thrive at 18 months of age

Twelve of the 14 patients met all three criteria of ability to thrive at 18 months of age (defined as the ability to tolerate thin liquids, not requiring nutrition through mechanical support, and maintaining weight consistent with age, p<0.0001). Thirteen of the 14 patients were assessed with formal swallowing tests at month 18 and all 13 were found to tolerate thin liquids. One patient was not assessed for thin or very thin liquids at the 18 month of age visit, but did have a normal swallow for solid consistency recorded at 18 months of age visit.

SMN2 three-copy cohort

Survival and Permanent Ventilation

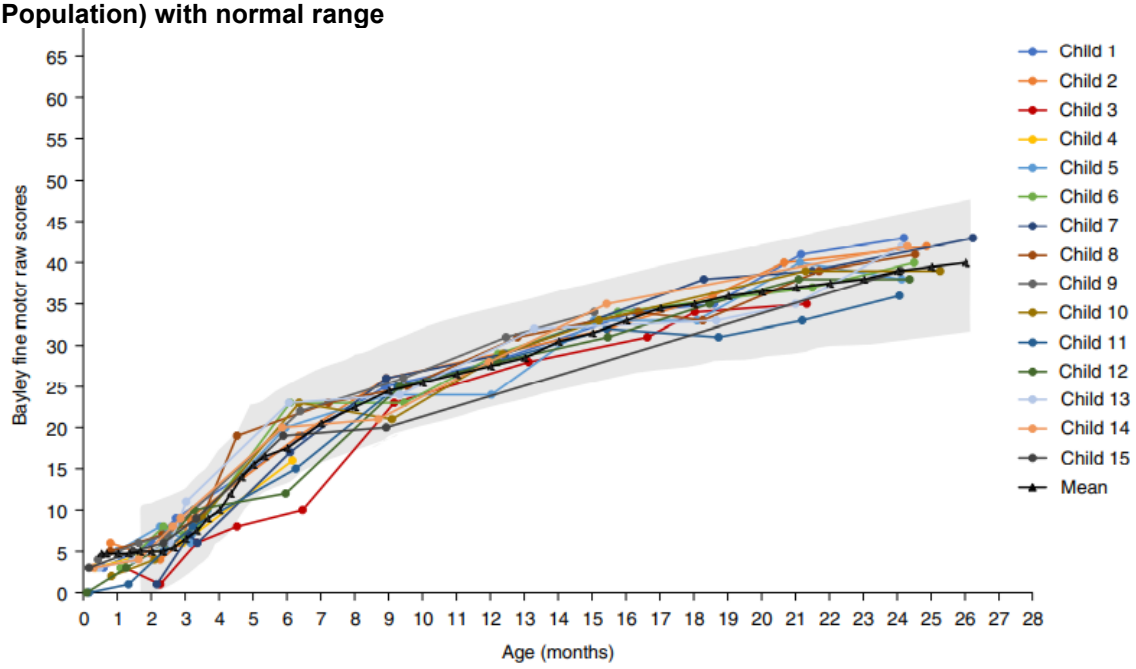
All 15 infants enrolled in the three-copy of SPR1NT survived without permanent ventilation. No patient in the *SMN2* three-copy cohort used ventilatory support (invasive or non-invasive, including cough assist) at any point during the study. All patients remained independent of ventilatory support at 24 months of age (p<0.0001). All (100%) patients survived without tracheostomy up to 24 months of age compared with 96.3% surviving without tracheostomy for the PNCR population.

BSID

Improvements were observed in all patients in both GM and FM subtests of BSID. One patient was excluded from the analysis of change from baseline as they had a missing score at baseline. However, data for this patient are included in listings and figures. Results of the FM and GM subtests for the infants in the three-copy cohort of SPR1NT are presented by patient in Figure 10 and Figure 11, respectively.

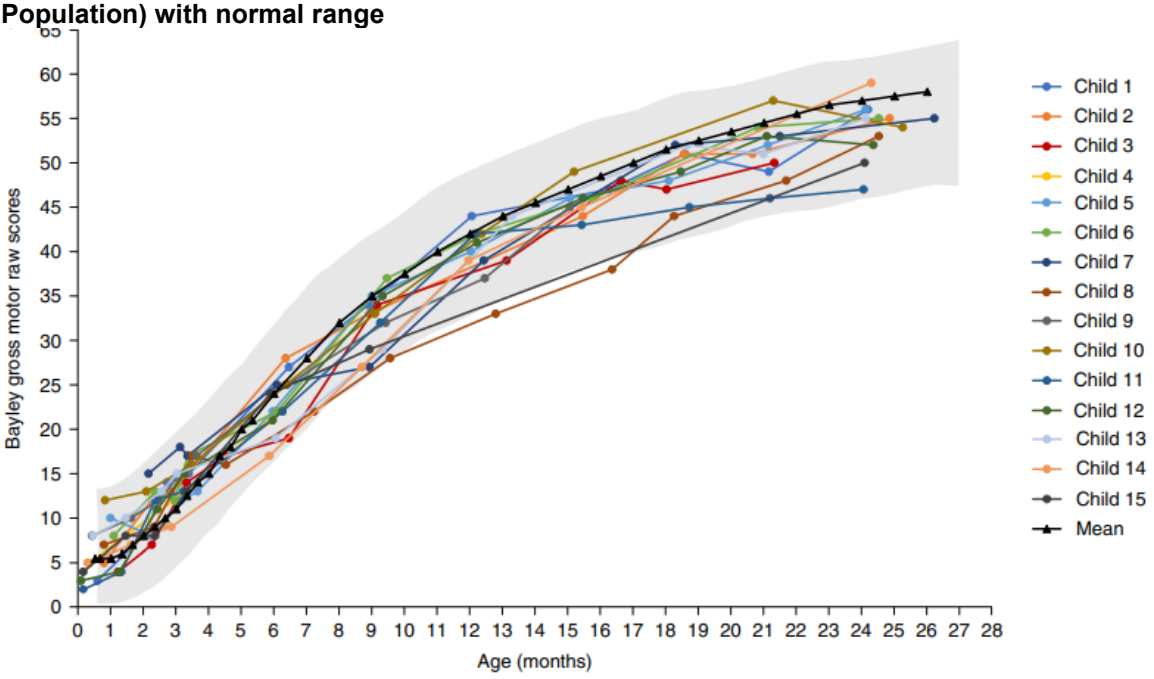
The mean scaled score is 10 for other normally developing children, with a SD of ±3. Therefore, approximately 87% of children fall within 1.5 SD of the mean (scores 5.5–14.5), and approximately 97% fall within 2 SD of the mean (scores 4–16). All patients in the three-copy cohort achieved a scaled score on BSID FM and GM subsets ≥5.5 on at least one post-baseline visit. Nine of the 10 assessed patients (90%) achieved a scaled score ≥5.5 on BSID FM and GM subsets at the Age 24 months visit. All patients in the three-copy cohort achieved a scaled score on BSID FM and GM subtests ≥4 on at least one post-baseline visit. Ten of the 10 assessed patients (100%) achieved a scaled score ≥4 at the Age 24 months visit.

Figure 10: BSID FM (raw score) score over time in SPR1NT three-copy cohort (ITT Population) with normal range



Source: Strauss et al, 2022 (71)
Abbreviations: BSID FM, Bayley Scales of Infant and Toddler Development (Version 3) Fine Motor subtest; ITT, intention-to-treat; *SMN2*, survival motor neuron 2.
BSID FM normal range (±2 SD) shown in grey highlight

Figure 11: BSID GM (raw score) score over time in SPR1NT three-copy cohort (ITT Population) with normal range



Source: Strauss et al, 2022 (71)
Abbreviations: BSID GM, Bayley Scales of Infant and Toddler Development (Version 3) Gross Motor subtest; ITT, intention-to-treat; *SMN2*, survival motor neuron 2.
BSID GM normal range (±2 SD) shown in grey highlight.

Ability to maintain weight without feeding support

None of the patients in the *SMN2* three-copy cohort required nutrition through mechanical support. Ten patients (66.7%) achieved the ability to maintaining weight at or above the 3rd percentile without the need for non-oral or mechanical feeding support at all visits up to 24 months of age. Due to COVID-19, it was not possible for weight to be assessed at every visit per protocol.

B.2.6.1.5 Conclusion

In the Phase III SPR1NT trial, patients with two or three copies of *SMN2* who received a one-time infusion of onasemnogene abeparvovec achieved age-appropriate milestones that would never be achieved in patients receiving BSC alone and may not have been achieved if treatment had been delayed until symptoms developed. All (100%) patients in the *SMN2* two- or three-copy cohorts of SPR1NT were alive and free of permanent ventilation at their last study visit. No patients required mechanical or non-oral support with feeding, or ventilatory support of any kind (including cough assist) during the SPR1NT trial.

[redacted] patients from the SPR1NT parent study went on to enrol in the ongoing long-term follow-up study, LT-002, and the details of this study are described in Section B.2.11.1.

B.2.7 *Subgroup analysis*

No subgroup analysis was carried out for the included studies. As discussed in Section B.1, onasemnogene abeparvovec is indicated for patients with 5q SMA with a bi allelic mutation in the *SMN1* gene and up to three copies of the *SMN2* gene (5). The SPR1NT trial was designed with two cohorts of patients with up to three copies of *SMN2* that represent the population in the MAA (1) The *SMN2* two-copy and *SMN2* three-copy cohorts have different efficacy outcomes and length of time followed in the trial. SMA exists on a broad spectrum, and although patients with different *SMN2* copy numbers are genetically distinct, there is overlap in clinical symptoms and disease severity. For example, although in general, fewer copies of *SMN2* may result in a more severe disease phenotype, some patients with three copies of *SMN2* will develop a severe form of SMA (4). Considering subgroups of patients with differing numbers of *SMN2* separately may exclude some patients with severe disease from early treatment.

B.2.8 *Meta-analysis*

Only one relevant single-arm study evaluating onasemnogene abeparvovec in infants from the screened population with a confirmed genetic diagnosis of 5q SMA with a bi-allelic mutation in the *SMN1* gene and up to three copies of the *SMN2* gene was identified, and therefore no meta-analysis was performed.

B.2.9 *Indirect and mixed treatment comparisons*

As noted in, Section B.2.1, best supportive care (BSC) is the only comparator for onasemnogene abeparvovec in infants from the screened population with a confirmed genetic diagnosis of 5q SMA with a bi-allelic mutation in the *SMN1* gene and up to three copies of the *SMN2* gene. No disease-modifying therapies are routinely commissioned and therefore an indirect treatment comparison/matching-adjusted indirect comparison (ITC/MAIC) have not been conducted.

B.2.10 *Adverse reactions*

B.2.10.1 *Studies reported in Section 2.2*

B.2.10.1.1 Adverse events in SPR1NT

Twenty-nine infants received an IV infusion of onasemnogene abeparvovec in the two-copy and three-copy cohorts of SPR1NT (68). No deaths occurred in SPR1NT and no patient in SPR1NT had a treatment-emergent adverse event (TEAE) resulting in death or discontinuation from the study. All infants (100%) experienced ≥1 treatment-emergent adverse event (TEAE) during the study, with a total 325 TEAEs reported. However, most were mild to moderate in severity. Nine serious TEAEs were reported in eight patients in SPR1NT, but none of these serious AEs were considered by the investigator to be related to onasemnogene abeparvovec.

The most frequently reported TEAEs were pyrexia, upper respiratory tract infection and constipation. Eighteen patients (62.1%) had at least one TEAE that was considered by the investigator to be related to onasemnogene abeparvovec, with increased aspartate aminotransferase, vomiting and rash being most frequently reported.

Adverse reactions reported in the studies identified in Section 2.2 are summarised in Table 16.

Table 16: Proportion of patients in SPR1NT with TEAEs and SAEs

Adverse events	**Two, copies of *SMN2* (N=14) n (%)**	**Three copies of *SMN2* (N=15) n (%)**
Patients with at least 1 TEAE	14 (100.0)	15 (100.0)
TEAEs related to study treatment	10 (71.4)	8 (53.3)
SAEs	5 (35.7)	3 (20.0)
SAEs related to study treatment	0	0
TEAEs causing study discontinuation	0	0
TEAEs resulting in death	0	0
TEAEs reported in ≥2 infants		
Gastrointestinal disorders		
Constipation	4 (28.6)	–
Diarrhoea	3 (21.4)	4 (26.7)
Vomiting	3 (21.4)	2 (13.3)
Gastroesophageal reflux disease	3 (21.4)	3 (20.0)
Teething	2 (14.3)	5 (33.3)
General disorders and administration site conditions		
Pyrexia	7 (50.0)	11 (73.3)
Infections and infestations		
Upper respiratory tract infection	5 (35.7)	9 (60.0)
Viral upper respiratory tract infection	3 (21.4)	–
Nasopharyngitis	2 (14.3)	3 (20.0)
Gastroenteritis	–	2 (13.3)
Otitis media	–	3 (20.0)
Ear infection	2 (14.3)	–
Urinary tract infection	–	2 (13.3)
Influenza	2 (14.3)	–
Hand-foot-and-mouth disease	–	2 (13.3)
Rhinovirus infection	2 (14.3)	–
Investigations		
Aspartate aminotransferase increased	3 (21.4)	4 (26.7)
Alanine aminotransferase increased[†]	–	3 (20.0)
Blood calcium increased	–	2 (13.3)
Blood creatinine phosphokinase MB increased	–	2 (13.3)
Troponin increased	–	2 (13.3)

Adverse events	Two, copies of *SMN2* (N=14) n (%)	Three copies of *SMN2* (N=15) n (%)
Microcytic anemia	–	2 (13.3)
Nervous system disorders		
Tremor	3 (21.4)	–
Muscle contractions involuntary	3 (21.4)	–
Hypotonia	3 (21.4)	2 (13.3)
Areflexia	2 (14.3)	–
Respiratory, thoracic, and mediastinal disorders		
Cough	–	4 (26.7)
Nasal congestion	3 (21.4)	2 (13.3)
Skin and subcutaneous tissue disorders		
Rash	3 (21.4)	2 (13.3)
Dermatitis diaper	–	3 (20.0)
Eczema	2 (14.3)	–

†One patient in the two-copy cohort experienced an increase in alanine aminotransferase, but this is not recorded in this table as this table shows only TEAEs reported in ≥2 infants.
Abbreviations: SAE, severe adverse event; SOC, system organ class; TEAE, treatment-emergent adverse event.
Note: TEAEs are classified by SOC and preferred term using the Medical Dictionary for Regulatory Activities (MedDRA; Version 20.1).Source: SPR1NT CSR (68).

B.2.10.1.2 Adverse events of special interest

Five specific categories of adverse events of special interest (AESI) were assessed in SPR1NT; hepatotoxicity, thrombocytopenia, cardiac adverse events, sensory abnormalities suggestive of ganglionitis, and thrombotic microangiopathy. Fifteen patients had at least one AESI as shown in Table 17.

Table 17: Adverse events of special interest in SPR1NT

Event	Two-copy cohort (N=14) n (%)	Three-copy cohort (N=15) n (%)
Hepatotoxicity		
Any TEAE	3 (21.4)	4 (26.7)
Aspartate aminotransferase increased	3 (21.4)	4 (26.7)
Alanine aminotransferase increased	1 (7.1)	3 (20.0)
Gamma-glutamyl transferase increased	1 (7.1)	1 (6.7)
Blood alkaline phosphatase increased	0	1 (6.7)
Thrombocytopenia		
Any TEAE	3 (21.4)	2 (13.3)
Contusion	0	1 (6.7)

Event	Two-copy cohort (N=14) n (%)	Three-copy cohort (N=15) n (%)
Thrombocytopenia	1 (7.1)	0
Haematochezia	0	1 (6.7)
Hematemesis	0	1 (6.7)
Platelet count decreased	1 (7.1)	0
Vessel puncture site bruise	1 (7.1)	0
Cardiac events		
Any TEAE	2 (14.3)	3 (20.0)
Blood creatine phosphokinase MB increased	1 (7.1)	2 (13.3)
Troponin increased	1 (7.1)	2 (13.3)
Blood creatine phosphokinase increased	1 (7.1)	0
Sensory abnormalities suggestive of ganglionopathy		
Any TEAE	3 (21.4)	1 (6.7)
Areflexia	2 (14.3)	1 (6.7)
Hyporeflexia	1 (7.1)	0
TMA†		
Any TEAE	2 (14.3)	0
Thrombocytopenia	1 (7.1)	0
Platelet count decreased	1 (7.1)	0

† No TEAE representing TMA was identified. Thrombocytopenia and platelet decreased are TEAEs that also fall under the thrombotic microangiopathy AESI category.
Abbreviations: AESI, adverse event of special interest; NR, not reported; MB, myocardial band; TEAE, treatment-emergent adverse event; TMA, thrombotic microangiopathy.
Source: SPR1NT CSR (68).

B.2.10.2 *Safety overview*

Overall, the available data show that treatment with onasemnogene abeparvovec was associated with a favourable safety profile. No patient in SPR1NT had a TEAE resulting in death or discontinuation from the study. No serious TEAEs were considered by the investigator to be related to onasemnogene abeparvovec.

B.2.11 *Ongoing studies*

[LT-002 is an ongoing study that will provide long-term efficacy and safety data for onasemnogene abeparvovec. It is a long-term follow-up study of patients treated with onasemnogene abeparvovec in clinical trials, including patients treated pre-symptomatically in SPR1NT (Section B.2.6.1). In addition, an observational disease registry is being conducted to follow patients with SMA in clinical practice in the US, across Europe, and other countries (RESTORE; Section B.2.11.2).

B.2.11.1 *LT-002*

LT-002 is an ongoing long-term safety follow-up study of patients treated with onasemnogene abeparvovec (IV or IT) in clinical trials (including, but not limited to SPR1NT, STR1VE-EU, STR1VE-AP and STR1VE-US) with the aims of collecting long-term efficacy and safety data from patients with SMA treated with onasemnogene abeparvovec, and to determine whether the milestones achieved in the parent studies are maintained, and whether new milestones are gained over time. SPR1NT followed patients up to 18 and 24 months of age for the SMN2 two- three-copy cohorts, respectively. As 18 months of age is only just past the upper limit of the WHO-defined window for walking independently in normal childhood development (17.6 months is the 99th percentile for walking independently) (42), it is likely that the infants enrolled in SPR1NT will achieve further motor milestones during LT-002.

As onasemnogene abeparvovec is a one-time gene therapy and was administered to all patients prior to enrolment in LT-002 in the parent studies, and data on any concomitant SMA medication use will be captured in LT-002. Data will be collected in LT-002 for up to 15 years, with regular interim data releases. The most recent interim results (as of 23 May 2022 data-cut (72)) are presented in this section, along with an addendum providing details additional motor milestone achievements in LT-002 as of 23 May 2022 data cut, for which full data are not yet available (73). The full results of the 23 May 2022 data cut will be available for sharing with NICE in Q4 2022.

Table 18: Clinical effectiveness evidence from LT-002

Study	LT-002 (NCT04042025)	
Study design	Phase 4, long-term follow-up safety and efficacy study	
Population	Participants who were treated with onasemnogene abeparvovec in Phase 3 clinical trials for SMA (including SPR1NT) are given the option of enrolling in this long-term study	
Intervention(s)	N/A	
Comparator(s)	Natural history cohorts†	
Indicate if trial supports application for marketing authorisation	Yes	
	No	✓
Indicate if trial used in the economic model	Yes	✓
	No	
Rationale if trial not used in model	N/A	
Reported outcomes specified in the decision problem	Safety assessments: • Incidence of SAEs and AESIs Efficacy assessments: • Assessment of developmental milestones with Developmental Milestone Checklist with video	
All other reported outcomes	Event-free survival (alive and free of permanent ventilation)	

†Well characterised external datasets from SMA natural history studies (PNCR and NeuroNext) are used to provide an external control comparator.
Abbreviations: AESI, adverse events of special interest; N/A, not applicable; SAE, serious adverse event; SMA, spinal muscular atrophy.

B.2.11.1.1 Methodology

The methodology of LT-002 is summarised in Table 19. As LT-002 is a long-term follow-up study with safety as the primary outcome measure, sample size was not determined through statistical justification.

Table 19: Summary of methodology for LT-002

LT-002 (NCT04042025)	
Location	Patients may be enrolled in any location worldwide
Trial design	Observational, long-term safety follow-up
Eligibility criteria for participants	• Patients who received onasemnogene abeparvovec (IV or IT) in a Novartis-sponsored clinical study (including, but not limited to STR1VE-US, STR1VE-EU, STR1VE-AP and SPR1NT clinical trials) • Patients/parents/legal guardians willing and able to complete the informed consent process and comply with the study procedures and visit schedule
Settings and locations where the data were collected	Bi-annual follow-up study assessments at the investigational site for 2 years, annual in-person visits for

LT-002 (NCT04042025)	
	Years 3 to 5, and phone contact annually for an additional 10 years
Trial drugs (the interventions for each group with sufficient details to allow replication, including how and when they were administered) **Intervention(s) (n=[x]) and comparator(s) (n=[x])** **Permitted and disallowed concomitant medication**	As onasemnogene abeparvovec is a one-time gene therapy and was administered to all patients prior to enrolment in LT-002 (as infants were dosed in STR1VE-US, STR1VE-EU, STR1VE-AP and SPR1NT), it is not administered to patients in this study. Concomitant therapy with other treatments for SMA is permitted in the study and will be recorded as well as any treatment with mutagenic agents.
Primary outcomes (including scoring methods and timings of assessments)	**Safety assessments:** • 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 **Efficacy assessments:** • 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
Other outcomes used in the economic model/specified in the scope	Event-free survival (alive and free of permanent ventilation)
Pre-planned subgroups	None

Abbreviations: AE, adverse event; AESI, adverse events of special interest; HFMSE, Hammersmith Functional Motor Scale-Expanded; SAE severe adverse event, SMA, spinal muscular atrophy.

B.2.11.1.2 Patient disposition and baseline characteristics

[redacted] patients who were treated with onasemnogene abeparvovec in SPR1NT went on to enrol in LT-002. Current age and follow-up period (months) since dosing at the 23 May 2022 data cut-off are presented in [redacted]

[redacted]

[redacted]						
			[redacted]		[redacted]	
			[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

[redacted]

B.2.11.1.3 Clinical efficacy

[redacted]

Event-free survival

[redacted]

Developmental milestones

[redacted]

B.2.11.1.4 Adverse events reported in LT-002

The safety analysis set for LT-002 included all enrolled patients who received treatment in the parent studies. As per the study protocol, only SAEs and AESIs are being collected in LT-002, and safety data are reported in aggregate across the parent studies (i.e. no SPR1NT-specific safety data are available from LT-002).

[redacted]

[redacted]

[redacted]

[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]

[redacted]

B.2.11.1.5 Conclusion

[redacted]

B.2.11.2 *RESTORE*

To provide further long-term data, Novartis are also conducting a patient SMA registry (RESTORE), which will follow at least 500 patients with SMA in clinical practice in the US, across Europe, and other countries, including patients treated with existing or upcoming approved treatments. The demographics, genetic status, family and medical history of patients, and details of treatments received are being collated. 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, motor milestones and motor function, overall survival and permanent ventilation-free survival, hospitalisations, AEs, and caregiver burden and QoL. In RESTORE, data are collated every 6 months until the 24 month visit and then annually for up to 15 years or until death, whichever is sooner.

As of the 23 November 2021 data cut, data were available for 247 patients with two or three copies of *SMN2* enrolled in RESTORE who had received onasemnogene abeparvovec, of whom 43 were pre-symptomatic (87). However, efficacy and safety data specifically in the pre-symptomatic population are not yet available.

B.2.12 *Interpretation of clinical effectiveness and safety evidence*

B.2.12.1 *Principal (interim) findings from the clinical evidence highlighting the clinical benefits and harms of the technology*

SMA causes irreversible loss of motor neurons resulting in muscle atrophy (10, 11). The earlier patients are diagnosed and treated, the lower the burden of symptoms and the better the clinical outcomes (14-19). Onasemnogene abeparvovec is a one-time gene therapy that provides a functional copy of the *SMN* gene, halting the progression of SMA through continuous and sustained protein expression.

The SPR1NT trial indicates that onasemnogene abeparvovec modifies the clinical course of the disease compared with BSC, in patients with 5qSMA with a bi-allelic mutation in the *SMN1* gene and up to three copies of the *SMN2* gene who are treated before symptoms of SMA are observed. All patients enrolled in SPR1NT survived without mechanical or non-oral feeding support, or ventilatory support of any kind, and achieved motor milestones that would never be achieved in patients receiving BSC only. The majority of patients in both cohorts (78.6% and 93.3% of patients with two and three copies of *SMN2*, respectively) achieved the motor milestones used as primary outcomes in SPR1NT (independent sitting and standing for patients with two and three copies of *SMN2*, respectively) within normal developmental windows (42).

The majority (79%) of infants with two copies of *SMN2* will be non-sitters if receiving BCS only (4) with symptom onset before 6 months of age. They will never achieve independent sitting when managed with BSC only, and would not be expected to survive beyond two years of age (27). All (100%) infants with two copies of *SMN2* in SPR1NT were able to sit without support by 18 months of age, with 11 (78.6%) achieving this motor milestone within the normal developmental window (42). Ten (71.4%) patients with two copies of *SMN2* achieved the milestone of walking alone by 18 months of age.

Patients with three copies of *SMN2* who do achieve sitting will either never walk unaided or eventually become wheelchair bound (4, 39-41). All 15 (100%) infants with three copies of *SMN2* in SPR1NT were able to stand alone by 24 months of age, with 14 (93.3%) achieving this motor milestone within the normal developmental window (42). Furthermore, 14 (93.3%) achieved the endpoint of walking alone by 24 months of age.[f]

The benefit of onasemnogene abeparvovec in patients from SPR1NT has been shown to be maintained in the LT-002 long-term follow-up study. [redacted]

[f] A fifteenth patient was observed walking alone by a clinical evaluator during the 24-month assessment conducted via video call, but video was not recorded and hence per study protocol, in the absence of independent video review, this patient was not recorded as having achieved the motor milestone.

[redacted]

Onasemnogene abeparvovec treatment-related adverse events were transient and manageable. No patient in SPR1NT had a TEAE resulting in death or discontinuation from the study.

B.2.12.2 *Strengths and limitations of the clinical evidence base for the technology*

The SPR1NT Phase III trial addresses the decision problem:

- The population included in the SPR1NT matches that of the final scope, i.e. pre-symptomatic patients with 5q SMA with a bi-allelic mutation in the SMN1 gene and up to three copies of the *SMN2* gene
- The key outcomes as outlined in the NICE scope have been evaluated in SPR1NT, i.e. motor function (including, where applicable, age-appropriate motor milestones), need for non-invasive or invasive ventilation, mortality and adverse effects of treatment. Developmental motor milestones were video-confirmed. The outcomes measures included in SPR1NT are recognised methods in SMA, and align with those used to assess the effectiveness of onasemnogene abeparvovec in the symptomatic patient population in HST15 (59)
- The trial was well-conducted (see Section B.2.5), with clearly pre-defined recruitment processes, eligibility criteria, assessments and outcomes, and analyses. While SPR1NT was a single-arm trial, this was due to ethical considerations. Based on a Phase 1 study in patients with symptomatic SMA (88, 89), which demonstrated unprecedented survival, motor milestone achievement, and motor function in patients treated with onasemnogene abeparvovec compared with matched natural history datasets, it was considered unethical by trial investigators to randomise patients to receive a placebo. As no alternative disease-modifying therapies had received marketing authorisation at the time of clinical trial design, it was not possible to conduct a randomised controlled trial. However, the availability of well-characterised natural history datasets allowed comparison with historical controls (Section B.2.3.2)

Limitations of the SPR1NT trial include:

- As may be expected given the very rare nature of SMA, the patient population enrolled in SPR1NT was relatively small (14 patients in the *SMN2* two-copy cohort and 15 patients in the three-copy cohort). Despite this, the SPR1NT trial has demonstrated clear benefit of treatment of the screened population with onasemnogene abeparvovec before symptoms are observed, and data collection, including real-world data collection, which will confirm whether outcomes achieved in clinical trials are also achieved in clinical practice, (Section B.2.11.2) is ongoing
- SPR1NT is a single-arm study. Given the extremely poor prognosis of infants who did not receive treatment in natural history studies and the unprecedented efficacy and

the favourable safety profile observed in the START trial (88, 89) suggesting a positive benefit/risk profile in symptomatic SMA (non-sitters), it was considered unethical to include placebo in further trials of onasemnogene abeparvovec. Well-characterised external datasets from SMA natural history studies (PNCR and NeuroNext/Kolb 2017) were used to provide an external control comparator for SPR1NT. 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

- SPR1NT was not designed to capture the earliest point of motor milestone development, with motor milestones captured every 3 months as part of scheduled clinical assessments. As such, some patients may have achieved milestones between assessments, but only recorded as having achieved the milestone at the later assessment point
- Duration of follow up in the SPR1NT trial is limited. Patients in the SMN2 two-copy cohort were followed for 18 months, and the three-copy cohort for 24 months. However, with patients and/or their parents'/guardians' consent, patients will be followed for up to 15 years in the long-term extension study, LT-002, and currently available interim data indicate that achieved milestones are being maintained in LT-002, and additional milestones are being achieved (Section B.2.11.1)
- Inclusion criteria must be set up for clinical trials, and for SPR1NT the age at time of dose was set at ≤6 weeks (≤42 days), although this timeframe is not evidence based or clinically meaningful. For this reason, SPR1NT findings would need to be extrapolated to reflect clinical practice, so that patients are not disadvantaged due to later diagnosis as a result of healthcare system variability. However, it should be noted that older patients are generally more likely to experience symptomatic SMA and, therefore, fall outside the decision problem for this appraisal for pre-symptomatic patients with SMA

B.3. Cost effectiveness

- A *de novo* model structure was developed to address the decision problem (Section B.1) to assess the cost-effectiveness of onasemnogene abeparvovec compared with BSC in patients with pre-symptomatic SMA. In the absence of routinely commissioned disease-modifying therapy for pre-symptomatic SMA, BSC is the only relevant comparator for onasemnogene abeparvovec in this patient population
- The key sources of clinical effectiveness data used to inform the model were:
  - The Phase III SPR1NT trial in pre-symptomatic patients and long-term follow-up study including patients treated in SPR1NT, LT-002 (Section B.2) for onasemnogene abeparvovec
  - Well-characterised natural history data sets for the BSC arm, which were identified through SLR (Section B.2.1)
- The modelling approach, assumptions, and inputs used have been validated with UK clinical experts (Section B.3.3.4) and, where applicable, assumptions and inputs have been based on those previously adopted for HST15 (59)
- The base case ICER for onasemnogene abeparvovec versus BSC is £70,610 per QALY gained using list price for onasemnogene abeparvovec and [redacted] using the price with the PAS discount, indicating that onasemnogene abeparvovec is cost-effective relative to BSC in pre-symptomatic patients (Section B.3.9)
- Cost-effectiveness of onasemnogene abeparvovec persists under a wide range of scenario and sensitivity analysis (Section B.3.10)

B.3.1 *Published cost-effectiveness studies*

B.3.1.1 *Identification and selection of relevant studies*

B.3.1.1.1 Search strategy

A SLR was conducted to identify evidence regarding the costs of SMA and onasemnogene abeparvovec and other relevant comparators for the treatment of infants from a pre-symptomatic population with a confirmed genetic diagnosis of 5q SMA with a bi-allelic mutation in the *SMN1* gene and up to three copies of the *SMN2* gene. The full search strategies are presented in Appendix G.

B.3.1.1.2 Study selection

A summary of the inclusion and exclusion criteria for the economic SLR is shown in Table 22.

Table 22: Selection criteria used for review of economic studies

Population	Type 1, type 2, and type 3; pre-symptomatic and symptomatic SMA
Interventions	Any of the following interventions used in the treatment of SMA: • Onasemnogene abeparvovec (ZOLGENSMA; AVXS-101) • Nusinersen • Risdiplam • Branaplam • CK-2127107 • 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	• 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	• Primary research studies, including: 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

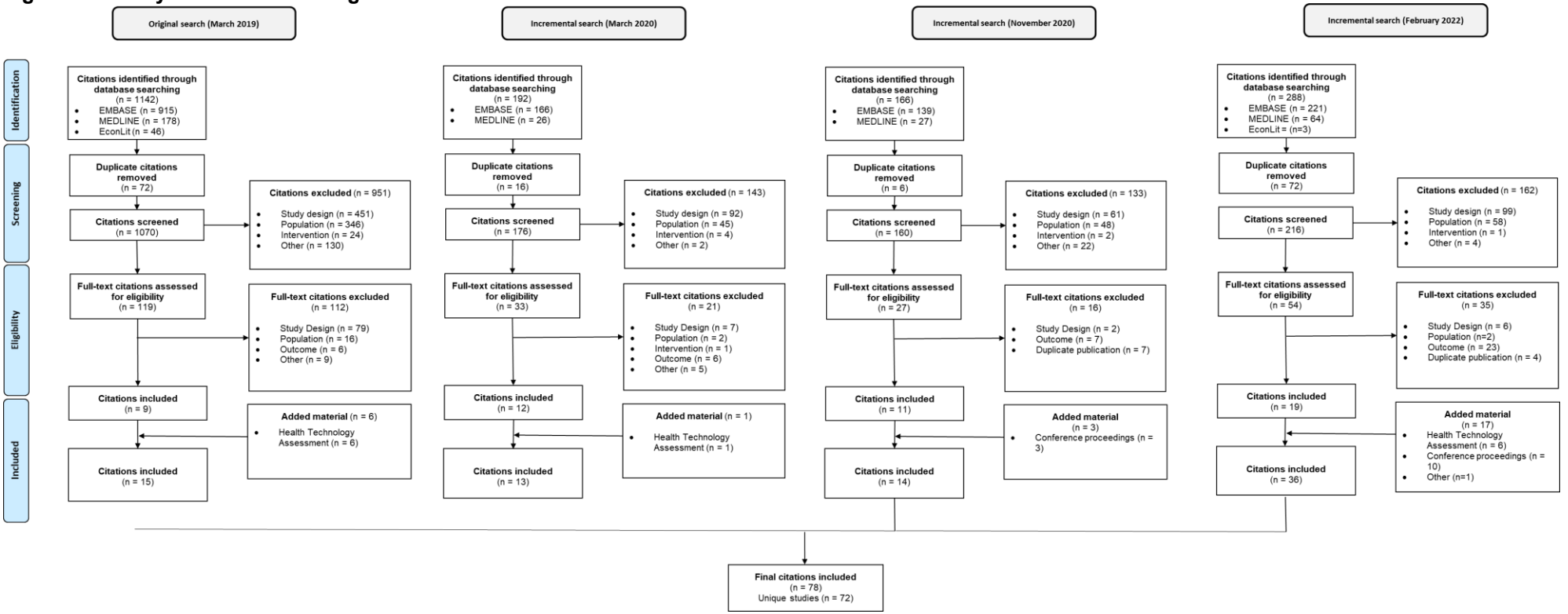
	trials ○ Single arm studies ○ Full economic evaluations (e.g. cost-effectiveness, cost-utility, and cost-benefit analyses) ○ Partial economic evaluations/cost analyses (e.g. cost-of-illness, cost-minimisation, cost-consequence, and budget impact analyses) • Pooled analyses presenting cost or resource use estimates • Health technology assessment documents • Literature reviews summarising results of primary research studies and/or economic evaluations*
Language restrictions	Unrestricted
Search dates	Unrestricted

*Literature reviews that involve some kind of methodology for study identification and study selection were of interest. This included systematic literature reviews, structured literature reviews, scoping reviews, and landscape reviews. Narrative reviews that did not involve study identification via databases and primarily summarize an author's viewpoints were not of interest.
Abbreviations: SMA, spinal muscular atrophy.

A search was originally conducted on 11th March 2019, and three incremental searches have since been conducted on 26th February 2020, 13th November 2020, and 2nd February 2022.

Figure 12 presents the PRISMA flow diagram, which outlines the study selection process for the search to identify studies of interest in the SLR of economic studies. In total, 78 publications from 72 unique studies have been identified. Among these studies, 31 were full economic evaluations that modelled the cost-effectiveness or cost-utility of treatments for SMA. Of these 31 economic evaluations, 13 were reported in documentation that supported either submissions to or recommendations from HTA agencies in the UK (n=7; separately for England & Wales, Ireland, and Scotland), Canada (n=3), Croatia (n=1), Sweden (n=1), and US (n=1). Finally, among the remaining 15 studies, one was a clinical trial study that reported healthcare resource utilisation (HRU) outcomes, five reported resource utilization associated with SMA, while the others were a systematic literature review of economic burden and economic evaluations in SMA. A list of all included studies in the economic SLR is provided in Appendix G.

Figure 12: Study selection flow diagram for economic review



B.3.2 *Economic analysis*

B.3.2.1 *Patient population*

The patient group included in the cost-effectiveness analysis is a population of newborn infants with genetically confirmed, pre-symptomatic SMA with two or three copies of the *SMN2* gene who were age ≤6 weeks (≤42 days) at time of treatment.

All patients with bi-allelic loss of function mutation, most commonly deletion, of the *SMN1* gene will develop SMA, and, prior to observation of symptoms, there is no definitive way to determine the severity of disease or to predict survival. One factor that may help to predict the prognosis of patients with SMA is the number of copies of the *SMN2* gene. In general, fewer copies of *SMN2* result in a more severe disease phenotype (4, 20, 21). As such, clinical efficacy data from the SPR1NT clinical trial are available separately for the two cohorts of included patients (those with two and three copies of *SMN2*). However, for decision-making purposes, the patient population should be treated as a single population as it is not possible to predict the prognosis of SMA in individual patients identified pre-symptomatically.

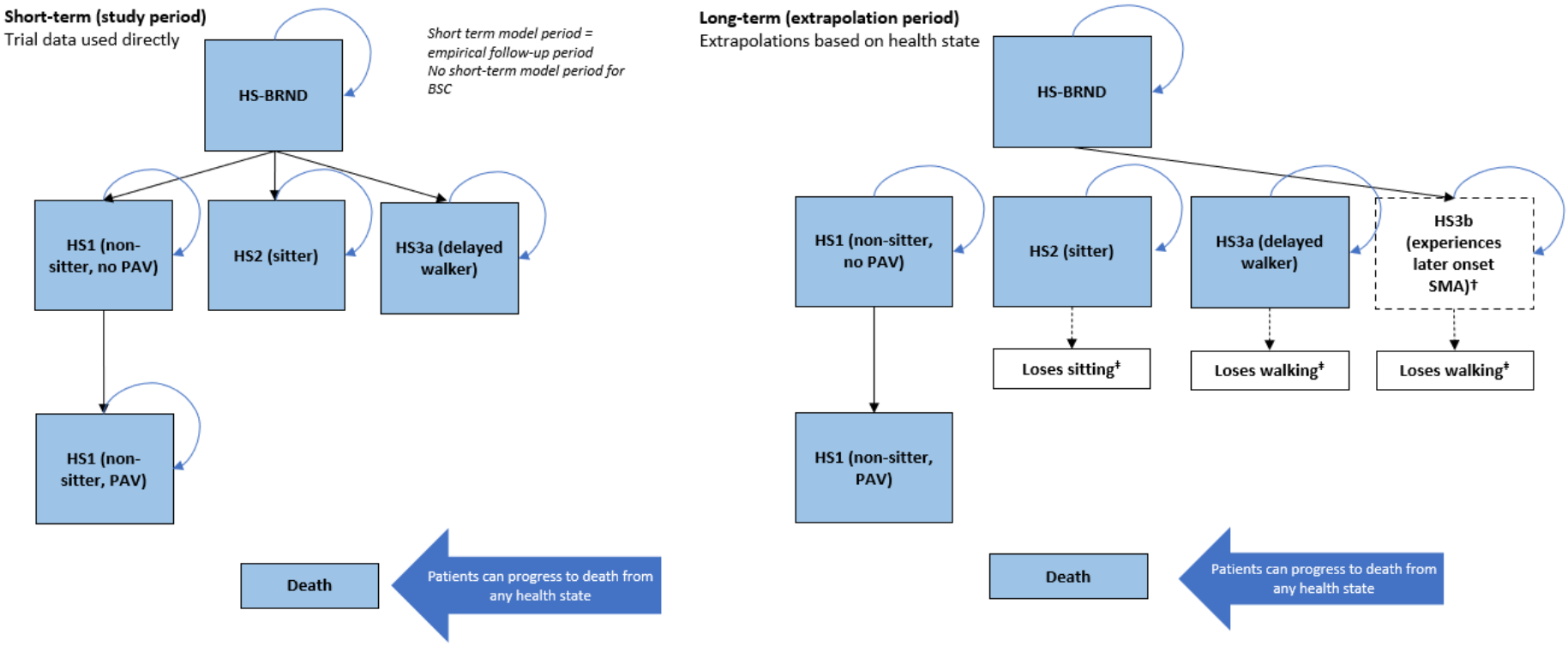
The base case incremental cost-effectiveness ratio (ICER) is weighted according to the likely ratio of *SMN2* two-copy to *SMN2* three-copy infants identified through screening in England to provide a cost-effectiveness estimate in the population of the decision problem (i.e., infants with pre-symptomatic SMA with up to three copies of *SMN2*). This is referred to as the 'combined cohort' in this submission. The weighting is derived from seven NBS screening studies from other countries (Germany, Australia, the US, Taiwan, and Belgium) (90-96), with pooled data from these studies indicating that 65.1% of patients identified through screening have two copies of *SMN2*, and 34.8% have three copies.

For completeness, each of the *SMN2* copy number cohorts (two-copy and three-copy) are also analysed separately.

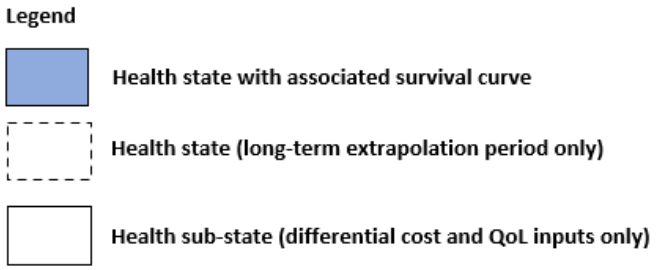
B.3.2.2 *Model structure*

The cost-effectiveness model is a cohort Markov state-transition model. The structure of the model is shown in Figure 13. Key features of the analysis are presented in Table 23, along with previous NICE technology evaluations in SMA.

Figure 13: Model schematic



Health state	Criteria
HS-BRND	Individual sits and walks independently within normal motor development† + no gastrostomy + no PAV
HS1 (non-sitter, no PAV)	Individual does not sit independently and does not require permanent assisted ventilation
HS1 (non-sitter, PAV)	Individual does not sit independently and requires permanent assisted ventilation
HS2 (sitter)	Individual sits independently but does not walk independently
HS3a (delayed walker)	Individual sits and walks independently but outside normal motor development† i.e. delayed milestones indicative of late onset SMA
HS3b (experiences later onset SMA)‡	Proportion of "Broad Range of Normal Development" projected to experience late onset SMA; only applicable to the BSC arm in the base case analysis



† Normal motor development: ages defined by user. Default milestone threshold inputs: 286 days for sitting, 547 days for walking. These are the WHO 99th percentiles, upper 95% confidence limit (42). An allowance for intermittent visits of 21 days is added to account for first observed milestones at ages slightly above the threshold. This is to account for the fact that individuals will have first presented with the milestone before the clinically confirmed date. The allowance for intermittent visits applies to all treatment arms.

‡ Only applicable to the BSC arm in the base case analysis.

Abbreviations: BRND, broad range of normal development; BSC, best supportive care; PAV, Permanent Assisted Ventilation; SMA, Spinal Muscular Atrophy; WHO, World Health Organization.

Table 23: Features of the economic analysis

	Previous appraisal	Current appraisal	
Parameter	**HST15 (97): Onasemnogene abeparvovec for treating SMA**	**Chosen values**	**Justification**
Time horizon	Lifetime (100 years)	Lifetime (100 years)	NICE guidance states that model time horizons should be long enough to capture all benefits of the treatment (98). As SMA is a progressive, lifelong, life-limiting disease and treatment with onasemnogene abeparvovec can increase the life span of patients vs no treatment, a lifetime time horizon is required to capture all benefits of treatment.
Source of utilities	For the within HS-BRND and walking health states (HS3a [delayed walker] and HS3b [experiences later onset SMA]), utility values from the general population were applied from Ara and Brazier 2010 (99). For the sitting unassisted health state, values from Tappenden et al. 2018 (100) were applied; for the not sitting health state, values from Thompson et al. 2017 (101) were applied; for HS1 (non-sitter, PAV) values were sourced from the interim ERG report, Edwards et al. 2020 (102)	HS3a (delayed walker), HS3b (experiences later onset SMA), and HS-BRND: Ara and Brazier 2010 (99)	Approach taken by US ICER, adapted to UK general population Walking unassisted by 2 years of age is reflective of normal development, as per the WHO reported windows of motor milestone achievement. Therefore, general population utility values are applied for HS3a (delayed walker), HS3b (experiences later onset SMA), and HS-BRND (calculation as reported in Ara and Brazier 2010 (99))

	Previous appraisal	Current appraisal	
		'Loses walking' sub-health states: Thompson et al. 2017 (101)	• Provided utility values in a population that matches the health state definition: an SMA population that loses the ability to walk
		HS2 (sitter): Tappenden et al. 2018 (100)	• Approach taken by US ICER • Informed by UK expert clinical advice, sourced by an independent research group (NICE ERG)
		HS1 (non-sitter, no PAV) and 'lose sitting' sub-health state: Thompson et al. 2017 (101)	• Approach taken by US ICER • Uses parent-proxy via EQ-5D-3L for UK-specific SMA type 1 population
		HS1 (non-sitter, PAV): HST15. Edwards et al. 2020 (102)	Input amended to match 'ERG-preferred base case' assumption per HST15 Informed by UK expert clinical advice, sourced by the ERG for HST15
Source of costs	Cost were sourced from a UK HCRU study (103) and the NHS Schedule of Reference Costs 2017–18 (104)	Cost were sourced from a UK HCRU study (103), the NHS Schedule of Reference Costs 2019–2020 (105), Prescription Cost Analysis 2021/22 (106) and from literature searches (inflated to 2021/22 values where necessary)	NICE guide to the methods of technology appraisal 2022 (107)

Abbreviations: BRND, broad range of normal development; ERG, evidence review group; EQ-5D, EuroQol-Five Dimension; HCRU, healthcare resource utilisation; HSUV, health-state utility value; NHS, National Health Service; SMA, spinal muscular atrophy; UK, United Kingdom; US ICER, United States Institute for Clinical and Economic Review; WHO, World Health Organization.

B.3.2.3 *Health states*

The model health states differ based on the highest motor function milestones achieved by the patient, the need for permanent assisted ventilation (PAV) and time to death:

- Non-sitter, PAV health state (HS1 [non-sitter, PAV])
- Non-sitter, no PAV health state (HS1 [non-sitter, no PAV])
- Sitter health state (HS2 [sitter])
- Delayed walker health state (HS3a [delayed walker])
- Experiences late onset SMA health state (HS3b [experiences later onset SMA])
- Within a broad range of normal development (BRND) health state (HS-BRND)

Whilst the health states are broadly defined by the highest motor function milestone achieved, each health state also captures the likely associated symptoms and complications of SMA, which are described in Table 24.

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 onasemnogene abeparvovec 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

Infant milestone achievement is used as a proxy for SMA severity (type) and prognosis, which was validated at a UK clinical advisory board by clinical experts (8). Costs and health outcomes of patients with SMA type 1, 2 and 3 are used as proxies for each health state:

- HS1 (non-sitter, PAV): SMA type 1 used as a proxy
- HS1 (non-sitter, no PAV): SMA type 1 used as a proxy
- HS2 (sitter): SMA type 2 used as a proxy
- HS3a (delayed walker): SMA type 3 used as a proxy
- HS3b (experiences later onset SMA): SMA type 3 used as a proxy

Table 24: Functional status across health states

Health state	Description of model health state	Additional features
HS1 (non-sitter, PAV)	Individual does not sit independently and requires permanent assisted ventilation.	• Require ≥16 hours 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
HS1 (non-sitter, no PAV)	Individual does not sit independently and does not require permanent assisted ventilation.	• Experiences breathing problems and requires regular NIV for <16 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
HS2 (sitter)	Individual sits independently but does not walk independently.	• 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

Health state	Description of model health state	Additional features
		• Temporary placement of a gastric tube may be required • Requires help moving • Can talk, but ability to speak will deteriorate over time
HS3a (delayed walker)	Individual sits and walks independently but outside normal motor development (i.e. delayed milestones [outside WHO 99th percentiles for sitting and walking independently]* indicative of late onset SMA).	• 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
HS3b (experiences later onset SMA)	Individual sits and walks independently within normal motor development (within WHO 99th percentiles) but experiences late onset SMA. This health state is modeled for patients in the BSC arm.	Patients treated with BSC only initially follow the normal range of development with no delays to achieving developmental milestones. Later in life, when they develop late onset SMA, they may experience regression of motor skills and impairment of motor function.
HS-BRND	Individual sits and walks independently within normal motor development (within WHO 99th percentiles*) • no gastrostomy • no PAV	Follow the normal range of development with no delays to achieving developmental milestones.

*For the onasemnogene abeparvovec arm, on top of the WHO 99th percentile, an additional 21 days of allowance was included to account for intermittent visits (more details are added to Section B.3.3.1).
Abbreviations: NIV, non-invasive ventilation; PAV, permanent assisted ventilation; SMA, spinal muscular atrophy; WHO, World Health Organization.

B.3.2.4 *Transitions*

Observed clinical outcomes are captured in the model by moving patients into lower functioning health states if they do not meet developmental milestones; lower functioning health states are associated with poorer survival, lower QoL, and higher healthcare resource use (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). Patients can progress to death from any health state.

Onasemnogene abeparvovec arm

For the onasemnogene abeparvovec arm, the model consists of two parts: 1) a short-term model, and 2) a long-term extrapolation model. The data used to inform the model are observed and extrapolated data from SPR1NT and LT-002 (observed data up to 23 May 2022 data cut).

All patients in the onasemnogene abeparvovec arm enter the short-term model in the BRND health state. Based on their probability of achieving sitting and walking from the observed clinical data (SPR1NT and LT-002), patients then either remain in HS-BRND or move into one of the five SMA onset health states. The transition to those health states are based on highest milestone attainment and age of symptom onset (Table 31). Transition to the HS1 (non-sitter, PAV) is only possible for patients in HS1 (non-sitter, no PAV). For patients in the HS1 (non-sitter, PAV), overall survival and PAV-free survival were modelled. However, no patients in the model who received onasemnogene abeparvovec in SPR1NT required PAV or died. Patients who achieved motor function milestones (sitting or walking) were not considered to be at risk of transitioning to HS1 (non-sitter, PAV). This feature of the model structure (i.e. no risk of entering HS1 [non-sitter, PAV] for those who can sit or walk) was validated by clinical experts during model conceptualisation and aligns with the Committee's preferred assumption for HST15.

After the short-term phase reflecting the empirical period, patients enter the long-term extrapolation phase occupying the same health state assigned in the short-term model (based on motor function milestones achieved at the end of follow-up in SPR1NT and latest available interim data from LT-002), where they remain until death. To date, there has been no loss of previously attained milestones for pre-symptomatic patients who received the therapeutic dose of onasemnogene abeparvovec as part of the long-term follow up of SPR1NT (LT-002). Furthermore, there is no evidence of the loss of milestones in interim analysis from LT-001, a long-term ongoing trial for onasemnogene abeparvovec in non-sitters. Therefore, patients in the onasemnogene abeparvovec arm do not transition from higher to lower functioning health sub-states in the long-term model. This aligns with the Committee's preferred assumption for HST15. Milestone achievement following treatment with onasemnogene abeparvovec in the model is based only on observed data from SPR1NT and LT-002 only, with no extrapolation of motor milestones assumed.

Best supportive care arm

For patients in the BSC arm, a long-term extrapolation model is used to model the entire lifetime time horizon as SPR1NT was a single-arm trial and clinical trial data were not available from SPR1NT for the BSC arm.

Based on natural history data (age of symptom onset, ratio of *SMN2* two- and three-copy patients, and proportions of *SMN2* two- and three-copy patients who are non-sitters, sitters, and delayed walkers [all of which are informed by published epidemiology and natural history studies]), infants in the BSC arm enter the long-term model in any of the SMA onset health states (HS1 [non-sitter, no PAV], HS2 [sitter], HS3a [delayed walker] or HS3b [experiences later onset SMA]) according to their highest achieved motor milestone. Although patients in the BSC arm enter the model in one of the SMA onset health states, they only begin accruing costs and utilities associated with that health state according to the average of age at symptom onset (13); prior to this age, general population utility and costs (i.e. zero) are applied.

As SMA patients receiving BSC alone lose function over time (reflecting natural history disease progression), patients in HS1 (non-sitter, no PAV) can transition to HS1 (non-sitter, PAV). Patients in HS2 (sitter), HS3a (delayed walker), and HS3b (experiences later onset SMA) can also lose motor milestones, transitioning to sub-health states (HS2 [sitter, loses sitting]; HS3a, [delayed walker, loses walking]; and HS3b [experiences later onset SMA, loses walking]).

The proportion of patients in HS1 (non-sitter, no PAV) requiring PAV is expected to differ by *SMN2* copy number (Table 25). For the two-copy cohort, it is assumed that 12.5% of patients in HS1 (non-sitter, no PAV) would require PAV by 18.4 months of age and for the three-copy cohort, it is assumed that 21.9% (7 [i.e. 7 out of 17 assumed to reach mechanical ventilation ≥16 hours per day] out of 32 patients) of patients in HS1 (non-sitter, no PAV) would require PAV by 4.8 years of age (median age at composite survival endpoint). To match the sources used for the survival estimates for the HS1 (non-sitter, no PAV) state, these data and assumptions were derived from the NeuroNext/Kolb 2017 two-copy non-sitter cohort data (2, 83) (for the two-copy cohort) and from the Wijngaarde et al, 2020 (3) study's SMA type 1c cohort (used as a proxy for three-copy patients in the HS1 (non-sitter, no PAV) health state; n=35 patients (n=27 [84.4%] are three-copy)) for three-copy patients.

Table 25: Proportion of untreated non-sitter patients requiring PAV

***SMN2* copy number**	**% of non-sitters receiving PAV**	**Age by when % of non-sitters receive PAV**
Two-copy	12.5%	18.4 months
Three-copy	21.9%	4.8 years

Sources: Two-copy cohort: Novartis, data on file (2); Three-copy cohort: Wijngaarde et al, 2020 (3).
Abbreviations: PAV, permanent assisted ventilation; SMN, survival motor neuron.

B.3.2.5 *Rationale of the chosen structure*

The model framework was initially conceptualised with clinical experts (29), drawing on frameworks developed for other SMA pharmacotherapies and models for similar rare genetic neuromuscular disorders, such as Duchenne's muscular dystrophy. The model structure is based on a similar model which was used in a previously accepted submission for onasemnogene abeparvovec in SMA type 1 (HST15). In addition, using a five functioning SMA health state model framework (from PAV [HS1 (non-sitter, PAV)] to within BRND [HS-

BRND]) 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 published an assessment of SMA therapies (108).

Prior to the development of disease-modifying therapies for SMA, patients with SMA type 1 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, and patients with SMA type 2 and 3 would experience delays in achieving motor milestones as well as motor impairments. With the development of innovative therapies, children with SMA now have the potential to attain motor milestones not previously achievable without treatment, which correlate with improved functionality, HRQoL and survival.

Furthermore, clinical trials of infants with genetically confirmed, pre-symptomatic SMA have demonstrated the benefits of newborn screening and the value of early treatment as opposed to treatment at symptom onset. Many children treated pre-symptomatically can be expected to achieve motor milestones within the windows established by WHO for healthy children. The economic model consequently includes a health state to capture the infants who go on to develop motor milestones within windows of normal development.

The model structure captures the main drivers of costs, mortality and HRQoL associated with SMA to ensure that the natural history of SMA is modelled accurately. In addition, the model uses data from SMA type 2 and SMA type 3 populations managed with BSC only as proxies for pharmacotherapy-treated patients' resource utilisation, survival and outcomes in higher functioning health states (HS2 [sitter] and HS3a [delayed walker]).

A de novo UK HCRU study with n=16 UK clinical experts (see Appendix I), was conducted by Novartis Gene Therapies to determine the HCRU costs associated with BSC, to ensure the model accurately captured the current UK clinical pathway of care for SMA patients (103). Aligned to the expert advice provided and literature searched, the model structure accounts for the following costs (using the latest available cost data) associated with BSC:

- Consultations with the multidisciplinary team (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)

B.3.2.6 *Perspective*

NHS and Personal Social Services (PSS) in England, as per NICE guidance (98).

B.3.2.7 *Time horizon*

SMA 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 (98), therefore a lifetime time horizon is applied to the model.

B.3.2.8 *Cycle length*

One month (with half cycle correction applied).

B.3.2.9 *Discounting*

The model assumes an annual discount rate of 3.5% for the UK setting in the base case. In addition, a 1.5% discounting rate has been explored in this submission via a scenario analysis. In HST15, the Committee concluded that the non-reference-case discount rate of 1.5% was applicable for the base case because onasemnogene abeparvovec has a high one-off cost with benefits that accrue over a lifetime, is transformative for people who would die without treatment, and offers the potential for substantial long-term gains that may enable a high quality of life for those with SMA type 1 and those with pre-symptomatic SMA with up to three copies of the *SMN2* gene. The company considers all criteria to adopt the non-reference case discounting rate of 1.5% are also met for this appraisal.

B.3.2.10 *Intervention technology and comparators*

Intervention

- Onasemnogene abeparvovec: one-time, single-dose by IV infusion over approximately 60 minutes at a dose of $1.1x10^{14}$ vg/kg.

Comparator

In line with the final scope and the absence of other available routinely commissioned treatments for newborn infants with genetically confirmed, pre-symptomatic SMA with 2 or 3 copies of the *SMN2* gene who were age ≤6 weeks (≤42 days), BSC is used as a comparator in the cost-effectiveness analysis:

- BSC: standard respiratory, gastrointestinal, and nutritional care for patients with SMA, delivered via an MDT

B.3.3 *Clinical parameters and variables*

B.3.3.1 *Describe how the data from the clinical evidence were used in the cost-effectiveness analysis*

B.3.3.1.1 Motor function milestone achievement

Onasemnogene abeparvovec

In the short-term empirical model, motor function milestone achievement data are from SPR1NT and currently available data as of 23 May 2022 from the long-term follow up study, LT-002. As SPR1NT and LT-002 do not include a BSC arm, there is no BSC arm in the short-term model.

Motor milestone attainment data inputs for onasemnogene abeparvovec from SPR1NT and LT-002 are used directly in the model to capture the proportion of the patients in the different health states, reflecting patients' highest milestones attained in SPR1NT and LT-002 as of 23 May 2022 (Section B.2). As a conservative assumption, one patient who achieved the walking milestone in LT002 after receiving subsequent therapy with another disease-modifying treatment (risdiplam) has not been included in the base case analysis of the economic model.

A summary of patients from SPR1NT achieving sitting and walking (by Bayley Scales of Infant and Toddler Development [BSID] and WHO definitions) included in the model is presented in Table 26 and Table 27 for patients with two and three copies of *SMN2,* respectively.

[redacted]

†Bayley Scales Gross Motor subset item #26: Child sits alone without support for ≥30 seconds.
‡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 subset item #43: Child takes at least 5 steps independently, displaying coordination and balance.
¶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.
††For age that milestones were achieved, please see the economic model excel file (.xlsm) provided with this submission.
Abbreviations: WHO, World Health Organization.

Table 27: Patients from SPR1NT with three copies of *SMN2* achieving sitting and walking

	Sitting without support		Walking without support	
	Bayley Scale†	WHO‡	Bayley Scale§	WHO¶
Patients achieving milestone††, n=15 (%)	100	100	100‡‡	100

†Bayley Scales Gross Motor subset item #26: Child sits alone without support for ≥30 seconds.
‡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 subset item #43: Child takes at least 5 steps independently, displaying coordination and balance.
¶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.
††For age that milestones were achieved, please see the economic model excel file provided with this submission.
‡‡One patient was observed by the clinical evaluator standing and walking alone by video call (due to COVID restrictions on travel and face to face meetings) at 24 months of age, therefore this patient is considered to have met the milestones of sitting and walking in the economic model as they were observed standing and walking without assistance.
Abbreviations: WHO, World Health Organization.

The WHO definitions of achieving sitting and walking milestones are applied in the model base case to the clinical data and informed the health state distributions presented in Table 28 and Table 29 for patients with two and three copies of *SMN2,* respectively. The WHO definitions were chosen as clinical outcome data using these thresholds were available from both SPR1NT and LT-002, whereas clinical outcome data using the BSID were only available for SPR1NT. Therefore, applying the WHO definitions allows use of consistent definitions for motor milestone achievement between SPR1NT and LT-002 data, and this approach was accepted by expert clinicians at the UK clinical advisory board in March 2022, who considered the two measures similar (8). The BSID is included in the model to allow for scenario analysis.

Health distributions at the end of the clinical trial period (short term model) for patients with two and three copies of *SNM2* are presented in Table 28 and Table 29, respectively.

Table 28: Health state distributions by the end of the short-term model for patients with two copies of *SMN2*

Health state	n	%
HS-BRND	10	71
HS1 (PAV)	0	0
HS1 (no PAV)	0	0
HS2	1	7
HS3a	3	22
Dead	0	0

Abbreviations: BRND, broad range of normal development; HS, health state; PAV, permanent assisted ventilation.

Table 29: Health state distributions by the end of the short-term model for patients with three copies of *SMN2*

Health state	n	%
HS-BRND	14	93
HS1 (PAV)	0	0
HS1 (no PAV)	0	0
HS2	0	0
HS3a	1	7
Dead	0	0

Abbreviations: BRND, broad range of normal development; HS, health state; PAV, permanent assisted ventilation.

Rationale for expanding on the WHO developmental windows for meeting motor milestones

The WHO developmental windows for age at meeting motor milestones were applied to the clinical data used in the model for health state transitions. The WHO developmental windows are based on data collected from a cohort of healthy children, where development up to the 99th percentile is interpreted as normal variation in healthy children (42). The WHO developmental window data were collected monthly up to age 12 months and bimonthly thereafter. One of the widest windows is for walking (9.4 months variation), demonstrating the range of ages this milestone can be achieved in healthy children. As acknowledged by the authors of the WHO MGRS study, the process of determining windows of developmental achievement is complex and studies have used various methods to determine these

windows (42). The authors acknowledge that, if two children are assessed during a particular study visit and have not reached a particular milestone, they appear identical regarding the milestone of interest, even if one patient achieves the milestone the following day and the other achieves the milestone the day before the next visit (42). The authors also acknowledge the potential bias of caregivers to reporting earlier dates of milestone achievement, although this was mitigated in the study by combining caregiver-reported data with data reported by trained fieldworkers, with caregiver-reported milestone achievement dates used as the lower bound for developmental windows (42).

In the model, the windows used for sitting and walking are based on the age in days at the upper end of the 95% confidence interval for the estimated 99th percentiles, to allow for natural variation demonstrated in healthy children. This approach has been validated with UK clinical experts (8).

Based on data from SPR1NT, a small number of patients (see Section B.2.6.1.1) achieved motor milestones marginally (1 day to 3 weeks) outside of the WHO motor milestone window. A difference of a few days from the normal development window is not thought to represent a clinically meaningful delay. It should also be noted that motor milestones achievement was assessed only at study visits in SPR1NT, meaning that there would be a delay in recording of milestone achievement for patients achieving milestones between visits. Based on this and the inherent difficulty in determining windows of development (42), it was considered appropriate to include an additional allowance of an additional 21 days above the WHO thresholds for sitting and walking (Table 30).

Table 30: Age thresholds applied in the model base case for normal development of motor functions

Motor function	Age thresholds applied in the model base case
Sitting	WHO threshold for sitting (upper 95% CI of the 99th percentile) (42): 286 days + 21-day increase† (307 days in total)
Walking	WHO threshold for walking (upper 95% CI of the 99th percentile) (42): 547 days + 21-day increase† (568 days in total)

Abbreviations: CI, confidence interval; SMA, spinal muscular atrophy; WHO, World Health Organization.
†A 21-day increase was added to the WHO age thresholds for milestone achievement to capture patients who met motor milestones outside the WHO threshold but whose motor milestone development was not considered to be significantly delayed.

All patients in the onasemnogene abeparvovec arm start in HS-BRND. In order to remain in this state, they need to have achieved sitting and walking within the WHO-defined developmental age windows (+21 days). Patients who do not achieve these milestones within this timeframe are allocated to lower functioning health states based on their highest motor milestone achieved at the end of the study period:

- Patients who achieve walking outside the applied developmental window would transition to HS3a (delayed walker)
- Patients whose highest milestone achievement is sitting are assigned to HS2 (sitter) irrespective of when sitting was achieved
- Patients not achieving milestones reside in HS1 (non-sitter, PAV) or HS1 (non-sitter, no PAV), but no patients from the trial met the criteria for these health states

The model structure allows HS-BRND patients to experience late SMA onset and transition to the corresponding late onset SMA health state. As development of symptoms later in life has not been observed in SPR1NT or LT-002, it is assumed that no treated patients enter the late onset SMA health state.

Patients start accruing costs and QALYs associated with the lower functioning health states when they enter those health states. The time at which patients are transitioned to lower functioning health states is informed by the average age at symptom onset associated with the SMA severity type proxied by their highest milestone achievement (see Section B.3.2.4.). Ages at symptom onset for SMA severity types 1 to 3 applied for each health state are provided in Table 31. For instance, patients whose highest milestone achievement is sitting will be categorised as SMA Type 2 for which symptoms are expected to onset around the age of 10 months. These patients will therefore transition from HS-BRND to HS2 (sitter) at 10 months.

In line with the existing body of clinical evidence and clinical opinion, onasemnogene abeparvovec-treated patients are assumed to maintain the milestone they achieve. Whilst clinical data from long-term follow-up studies (LT-001 and LT-002) suggest that patients can achieve even further motor development in the longer term, the level of motor achievement achieved at the end of the short-term study determines health state occupancy throughout the rest of patients' lives in the model. In other words, no transition to improved motor function heath states (e.g. from HS2 [sitter] to HS3a [delayed walker]) is allowed in the long-term model.

Table 31: Age of SMA symptom onset in the short- and long-term model periods

Age of SMA symptom onset in the short-term model	**Age (months)**
HS1 (non-sitter, no PAV)	6
HS2 (sitter)	10
HS3a (delayed walker)	18
Age of SMA symptom onset in the long-term model	**Age (years)**
HS3b (experiences later onset SMA) (min–max age)	3–24

Source: WHO (42)
Abbreviations: SMA, spinal muscular atrophy.

Health distributions by month for patients with two and three copies that were used in the short-term model are presented in Table 32 and Table 33, respectively.

Table 32: Health distributions by month used in the short-term model (patients with two copies of *SMN2*)

Month	**HS-BRND (%)**	**HS1 (non-sitter, PAV) (%)**	**HS1 (non-sitter, no PAV) (%)**	**HS2 (sitter) (%)**	**HS3a (delayed walker) (%)**	**Death (%)**
0–9	100	0	0	0	0	0
10–17	93	0	0	7	0	0
18–26	71	0	0	7	21	0

Abbreviations: BRND, broad range of normal development; PAV, permanent assisted ventilation.

Table 33: Health distributions by month used in the short-term model (patients with three copies of *SNM2*)

Month	HS-BRND (%)	HS1 (non-sitter, PAV) (%)	HS1 (non-sitter, no PAV) (%)	HS2 (sitter) (%)	HS3a (delayed walker) (%)	Death (%)
0–17	100	0	0	0	0	0
18–24	93	0	0	0	7	0

Abbreviations: BRND, broad range of normal development; PAV, permanent assisted ventilation.

Best supportive care

As there was no BSC arm in SPR1NT or LT-002, the distribution of BSC patients to the model health states (Table 34 and Table 35) was informed by the distribution of patients across SMA severity type reported by a large epidemiology study (n=3,459), based on the proxy relationship between SMA severity type and motor milestone achievement outlined in Section B.3.2.4. This approach was validated by clinical experts (109). Patients were allocated to their health states from the first model cycle.

Table 34: Health state distribution of patients in the BSC arm with two copies of *SMN2*

Health state	Proxy	%	Source
HS1 (non-sitter, no PAV)	SMA type 1	79	Calucho et al. 2018 (4)
HS2 (sitter)	SMA type 2	16	
HS3a (delayed walker)	SMA type 3a	5	
HS3b (experiences later onset SMA)	SMA type 3b	0	

Abbreviations: PAV, permanent assisted ventilation; SMA, spinal muscular atrophy.

Table 35: Health state distribution of patients in the BSC arm with three copies of *SMN2*

Health state	Proxy	%	Source
HS1 (non-sitter, no PAV)	SMA type 1	15	Calucho et al. 2018 (4)
HS2 (sitter)	SMA type 2	54	
HS3a (delayed walker)	SMA type 3a	16	
HS3b (experiences later onset SMA)	SMA type 3b	15	

Abbreviations: PAV, permanent assisted ventilation; SMA, spinal muscular atrophy.

B.3.3.2 *Motor function milestone loss*

Onasemnogene abeparvovec

To date, there has been no loss of previously attained motor milestones for patients who received the therapeutic dose of onasemnogene abeparvovec in START as part of LT-001 (long-term follow-up of START), ongoing Phase III trials or the extension study LT-002.

In line with these clinical data and clinical expert opinion, onasemnogene abeparvovec-treated patients are assumed to maintain their achieved milestones. Such an approach is also aligned with committee preferred assumption in HST15.

Best supportive care

Based on the various studies of natural history of the disease, a non-negligible proportion of SMA patients who do not receive disease-modifying therapy is expected to lose milestones previously achieved. Therefore, transitions associated with loss of milestones (HS2 [sitter] to HS2 [sitter, loses sitting], HS3a [delayed walker] to HS3a [delayed walker, loses walking], and HS3b [experiences later onset SMA] to HS3b [experiences later onset SMA, loses walking]) apply to patients in the BSC arm according to the natural progression of SMA in those who have received no disease-modifying treatment. As there is a lack of data available by copy number, the same milestone loss data were applied for the two-copy and three-copy cohorts. Motor milestone loss in patients receiving BSC is summarised in Table 36 and Table 37 for patients with two and three copies of *SMN2*, respectively. It is assumed that milestone losses happen between the ages at which they were reported in the natural history study (46) using a linear increase from minimum to the maximum age (i.e. reaching the proportion losing a milestone by the maximum age).

Loss of milestones in patients on BSC (e,g. losing walking for those patients in HS3a [delayed walker] or HS3b [experiences later onset SMA]) is conservatively assumed not to reduce patients' survival. However, it does have an impact on their HCRU and health-related quality of life

Table 36: Milestone loss in patients receiving BSC with two copies of *SMN2*

Transition	%	Source
Infants from HS2 (sitter) who lose sitting	25	Wadman et al, 2018 (weighted average of patients with SMA type 2a and 2b)
Infants from HS3a (delayed walker) who lose independent walking	68	Wadman et al, 2018
Infants from HS3b (experiences later onset SMA) who lose independent walking†	47	Wadman et al, 2018

†Not applicable as there are no two-copy patients receiving BSC in this health state.
Abbreviations: PAV, permanent assisted ventilation; SMA, spinal muscular atrophy.

Table 37: Milestone loss in patients receiving BSC with three copies of *SMN2*

Transition	%	Source
Infants from HS2 (sitter) who lose sitting	25	Wadman et al, 2018 (weighted average of patients with SMA type 2a and 2b)
Infants from HS3a (delayed walker) who lose independent walking	68	Wadman et al, 2018
Infants from HS3b (experiences later onset SMA) who lose independent walking	47	Wadman et al, 2018

Abbreviations: PAV, permanent assisted ventilation; SMA, spinal muscular atrophy.

B.3.3.3 *Survival*

Sources of survival data used in the base case are summarised in Table 38.

In the short-term phase of the model, survival data from SPR1NT (follow-up: 18 and 24 months of age for the *SMN2* two-copy and three-copy cohorts, respectively) and the long-term follow up study LT-002 [redacted] are used for the onasemnogene abeparvovec arm. As per clinical trial data, no patients who received onasemnogene abeparvovec died or received PAV in the short-term phase. No patients received BSC in SPR1NT. This was due to the extremely poor prognosis of non-sitters treated with BSC only in natural history studies and the unprecedented outcomes with onasemnogene abeparvovec observed in the START trial, making it unethical to include placebo in further trials. Therefore, there is no BSC arm in the short-term phase of the model.

As explained in Section B.3.2.3., patients on BSC are distributed to the model health states, based on the proxy relationship between SMA severity type and motor milestone achievement, from the first model cycle. Changes in heath state residency in subsequent cycles are only driven by milestone loss and death risk.

For both the BSC and onasemnogene arms, long-term survival in each health state is based on extrapolated survival curves from natural history studies using the methods described in Diaby et al. 2014 (110), as used in HST15. To model long-term survival for pre-symptomatic patients with genetically diagnosed SMA treated with onasemnogene abeparvovec, the proxy relationship between milestone achievement and SMA severity type was used.

Table 38: Sources of survival data – base case

Health state	Onasemnogene abeparvovec‡	BSC
HS1 (non-sitter, PAV)	**Short-term, observed data** N/A – See Table 31 and Table 32 **Long-term, extrapolated data** N/A – See Table 31 and Table 32	**Long-term, extrapolated data** *SMN2* two- and three-copy cohorts: Parametric survival curve fitted to longitudinal overall survival Kaplan Meier curves for non-invasive ventilation from the Italian natural history study (111)
HS1 (non-sitter, no PAV)	**Short-term, observed data** N/A – See Table 31 and Table 32 **Long-term, extrapolated data** N/A – See Table 31 and Table 32	**Long-term, extrapolated data** *SMN2* two-copy cohort: Projected permanent ventilation-free survival using fitted parametric curve to observed data from the NeuroNext/Kolb 2017 natural history study (2, 83) *SMN2* three-copy cohort: Projected permanent ventilation-free survival using fitted parametric curve to observed data from Wijngaarde et al 2020 (3)
HS2 (sitter)	**Short-term, observed data** *SMN2* two- and three-copy cohorts: Reflecting survival data from SPR1NT and LT-002 (23 May 2022 data cut) **Long-term, extrapolated data** *SMN2* two- and three-copy cohorts: General population survival (from 2018–2020 UK National Life tables (112)) data adjusted by hazard ratio obtained from the best fitting parametric survival curve to the longitudinal overall survival Kaplan Meier curve from Wijngaarde et al 2020 (3)	**Long-term, extrapolated data** *SMN2* two- and three-copy cohorts: General population survival (from 2018–2020 UK National Life tables (112)) data adjusted by hazard ratio obtained from the best fitting parametric survival curve to the longitudinal overall survival Kaplan Meier curve from Wijngaarde et al 2020 (3)
HS3a (delayed walker)	*SMN2* two- and three-copy cohorts: General population survival (from 2018–2020 UK National Life tables (112)) data.	

Health state	Onasemnogene abeparvovec‡	BSC
HS3b (experiences later onset SMA)	N/A – Given the assumption of no treated patients enter this health state (as development of symptoms later in life has not been observed in SPR1NT or LT-002)	*SMN2* two- and three-copy cohorts: General population survival (from 2018–2020 UK National Life tables (112)) data.
HS-BRND	SMN2 two- and three-copy cohorts: General population survival (from 2018–2020 UK National Life tables (112)) data.	N/A – patients on BSC never reside in the within BRND health state

Abbreviations: BRND, broad range of normal development; BSC, best supportive care; ERG, evidence report group; N/A, not applicable; PAV, permanent assisted ventilation; SMA, spinal muscular atrophy; UK, United Kingdom.
† NeuroNext/Kolb 2017 cohort as reported in Novartis Gene Therapies external control database (2, 83).
‡ Survival assumptions used for onasemnogene abeparvovec are the same as for BSC. However, these assumptions are not applicable for all health states because patients treated with onasemnogene abeparvovec do not reside in those health states.

Table 39: Natural history studies used to inform the base case and scenario analyses

Characteristic	Gregoretti et al, 2013 (111)	NeuroNext/Kolb 2017† (2, 83) Novartis Gene Therapies external control database	Wijngaarde et al, 2020 (3)	PNCR‡ (2) Novartis Gene Therapies external control database	Zerres et al, 1997 (39)
Size, n	194 (n=42 in the TV group and n=31 in the NRA group)	Two-copies: n=16 Three-copies: n=5	307	Two-copies: 23 Three-copies: 12	569
Definition of PAV	Tracheostomy and invasive mechanical ventilation ('TV' group in publication) and continuous non-invasive respiratory muscle aid, including non-invasive ventilation; and mechanically assisted cough ('NRA' group in publication)	Intubation only	Mechanical ventilation	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	NR

Characteristic	Gregoretti et al, 2013 (111)	NeuroNext/Kolb 2017† (2, 83) Novartis Gene Therapies external control database	Wijngaarde et al, 2020 (3)	PNCR‡ (2) Novartis Gene Therapies external control database	Zerres et al, 1997 (39)
Genetic profile	NR	Homozygous deletion of exon 7 in the *SMN1* gene Exclusion of the *SMN2* gene modifier mutation c.859G>C	Homozygous deletion of the *SMN1* gene 1–5 copies of the *SMN2* gene	Homozygous deletion of exon 7 in the *SMN1* gene	NR (patients with type 2 or 3 SMA)
Region(s)	Italy	US	The Netherlands	US	Germany, Poland
Enrolment years	1992 to 2010	2012 to 2014	Ongoing	2005 to 2009	Started in 1985 (Germany) and 1960 (Poland)
Length of follow-up	6 years	24 months	Median individual follow-up: 18.3 years (range, 0.01–81.9)	36 months§	30 years
Dead, n (%)	7 (16.7%) and 14 (45.2%) patients died in the tracheostomy and invasive mechanical ventilation, and non-invasive respiratory aid groups, respectively	Two-copies: 8 (50.0) Three-copies: 1 (20.0)	NR¶	Two-copies: 11 (47.8) Three-copies: 4 (33.3)	NR

Abbreviations: NIV, non-invasive ventilation; NR, not reported; PAV, permanent assisted ventilation; SD, standard deviation; SMN, survival motor neuron; US, United States.
† NeuroNext cohort as reported in Novartis Gene Therapies external control database (n=16 patients with two *SMN2* copies, n=5 patients with three *SMN2* copies).
‡ PNCR cohort as reported in Novartis Gene Therapies external control database (n=23 patients with two *SMN2* copies, n=12 patients with three *SMN2* copies).
§ 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 bi-level positive airway pressure (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.
¶ Death is not reported by copy number but only by SMA type.

Extrapolation of survival data

For all survival data, parametric survival curves were fitted to the empirical data to extrapolate survival (where applicable) and calculate transition probabilities using published methods (110). 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 (113, 114). For all survival data, parametric survival curves were fitted to the empirical data to extrapolate survival (where applicable) and calculate transition probabilities using published methods (110). 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 (113, 114).

Selection of models for survival modelling was informed by methods described in the NICE decision support unit (DSU) report 14 (115). Goodness-of-fit was assessed by the following methods:

- Statistically via Akaike information criterion (AIC) and Bayesian information criterion (BIC)
- Visual inspection
- Non-convergence of parametric curves

Parametric curves fitted to the survival data included exponential, log-normal, log-logistic, Weibull, generalized gamma, gamma, and Gompertz curves. All curves were accelerated failure time curves. 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 from HST15. The specific parametric models used in the base case model are shown in Table 40. AIC and BIC statistics can be found in the executable economic model file provided with this submission.

Table 40. Summary of survival curves and limits used in the base case

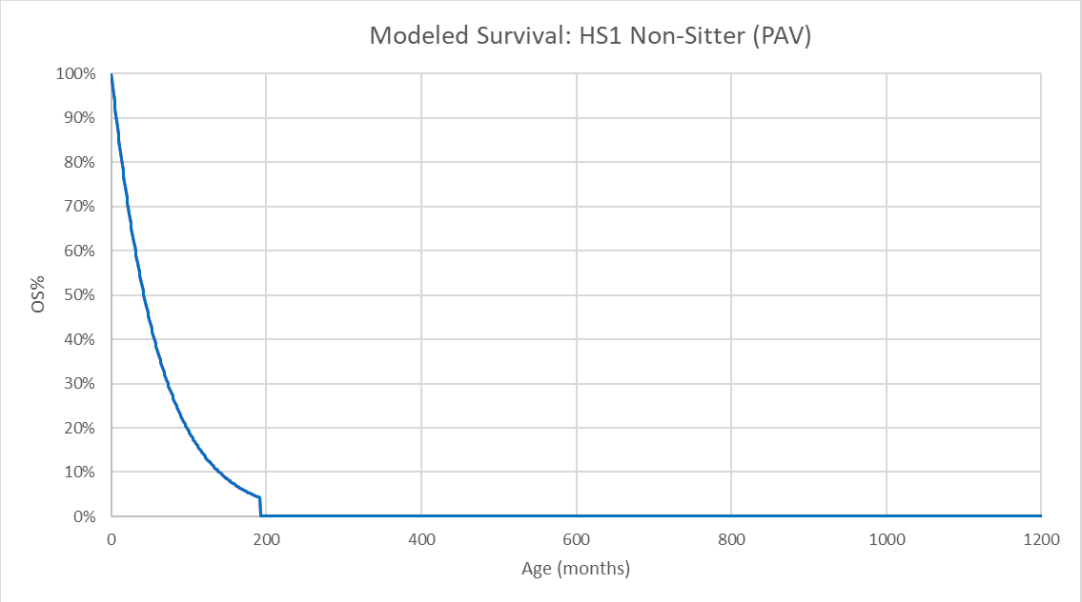
Survival curve	Parametric curve	Survival limit
HS1 (non-sitter, PAV)	Exponential (‘NRA’ group)†	16 years
HS1 (non-sitter, no PAV)	Weibull – 2-copy cohort‡ Gamma – 3-copy cohort	4 years – 2-copy cohort 100 years (lifetime time horizon) – 3-copy cohort
HS2 (sitter)	Exponential	100 years (lifetime time horizon)
HS3a (delayed walker), HS3b (experiences later onset SMA), and HS-BRND	National Life Tables (112)	100 years (lifetime time horizon)

Abbreviations: BRND, broad range of normal development; BSC, best supportive care; EFS, event-free survival; OS, overall survival.
‡In HST15 (SMA type 1) economic model submitted to NICE in the UK, the ERG-preferred base case used the Weibull distribution for the non-sitter health state. This preference is reflected in the base case of this model when using the NeuroNext data source.
†Defined as continuous non-invasive respiratory muscle aid, including non-invasive ventilation; and mechanically assisted cough ('NRA' group in publication) (111)

HS1 (non-sitter, PAV)

Individual parametric curves were fitted to the tracheostomy ('TV' group) and non-invasive permanent ventilation data ('NRA' group) from Gregoretti et al 2013 (111) and incorporated into the economic model. Feedback from clinical experts and the ERG in HST15 indicated that tracheostomy is rarely used in clinical practice for the treatment of patients with SMA in the UK, with non-invasive ventilation preferred. Therefore, in the base case, survival in HS1 (non-sitter, PAV) is based the non-invasive permanent ventilation data only ('NRA' group) from Gregoretti et al 2013 (111), with a survival limit of 16 years applied (Figure 14). These parameter choices match the ERG-preferred assumptions in HST15 for this health state.

Figure 14: Survival estimates for HS1 (non-sitter, PAV)



HS1 (non-sitter, no PAV)

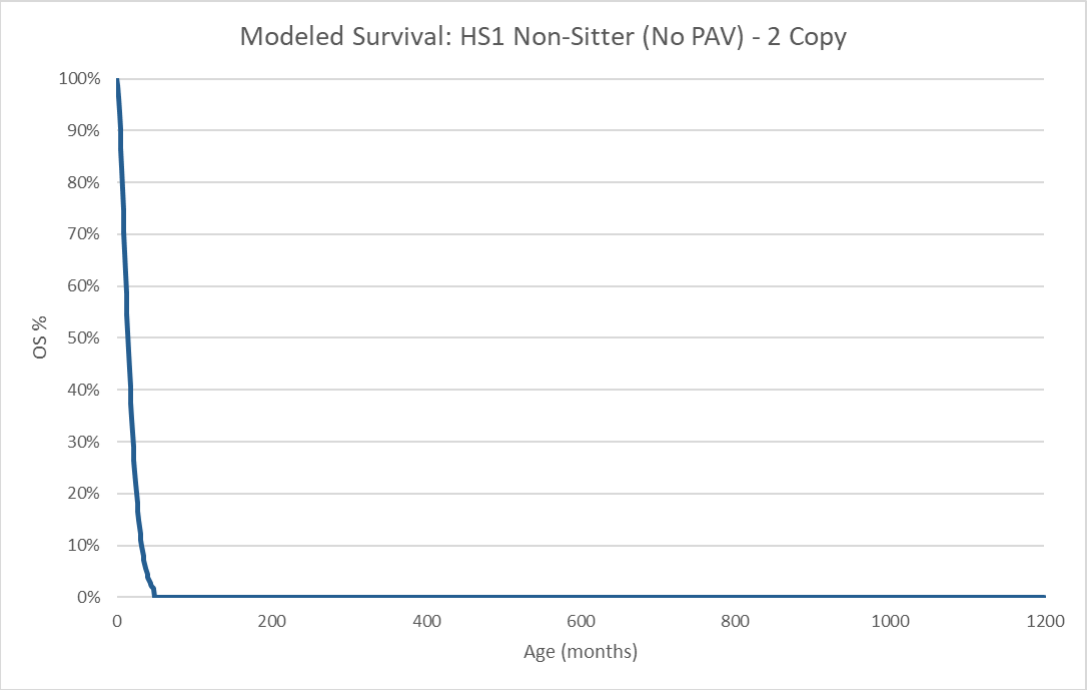
Based on survival data from natural history studies for non-sitter patients requiring no PAV, it is estimated that survival differs for patients with two and three *SMN2* copies.

For patients with two *SMN2* copies in HS1 (non-sitter, no PAV) (Figure 15), survival is based on the NeuroNext/Kolb 2017 natural history trial, using 24-month follow-up data for 16 patients with two copies of the *SMN2* gene. Parametric survival curves were fitted to the generated KM curve of the empirical data (adjusted for patients who are not on permanent assisted ventilation). As per the ERG's preference in HST15, a Weibull curve was selected to extrapolate survival for this cohort. To avoid implausibly long survival predicted by long parametric curve tails, a limit of 4 years (where the Weibull curve

flattens and gets closer 0% OS estimates) is used for the survival threshold, which was also accepted as a reasonable clinical assumption in HST15.

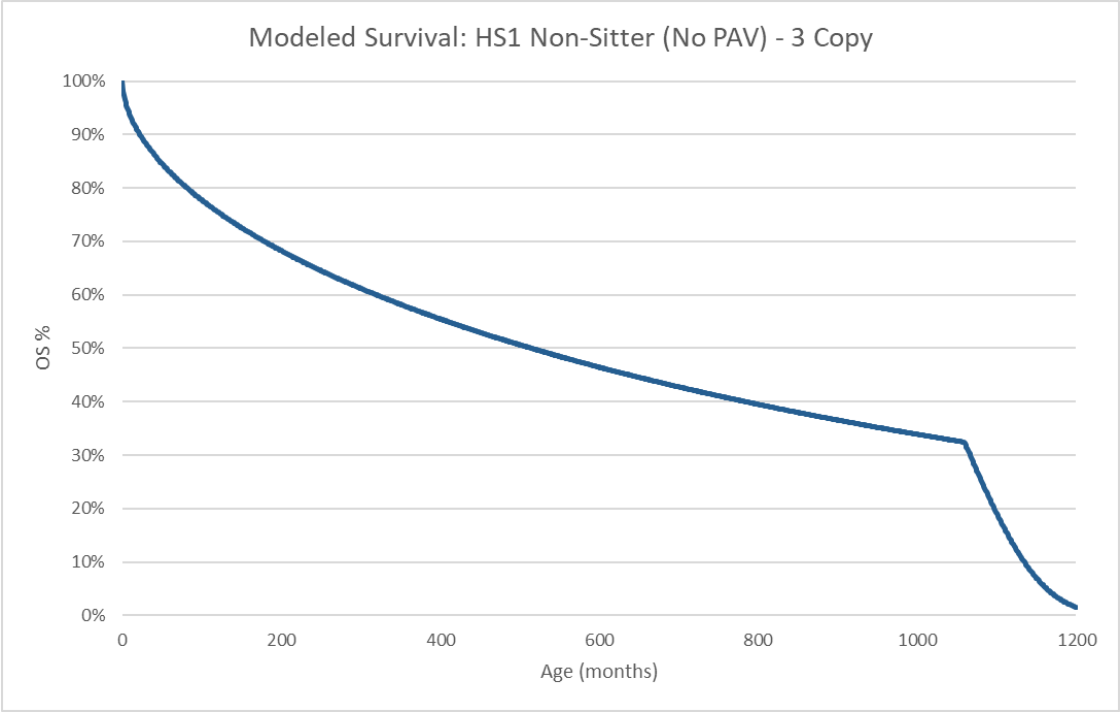
For patients with three *SMN2* copies in HS1 (non-sitter, no PAV) (Figure 16), survival is based on Type 1c cohort's (n=32) OS data reported in a Dutch natural history study (Wijngaarde et al, 2020 (3)). This dataset was used as a proxy for the survival in this health state and patient cohort as it was representative of treatment-naive non-sitter patients with three *SMN2* copies (27 out of 32 patients receiving BSC as per recent clinical practice) and provide the largest dataset available for this patient cohort. Parametric curves were fitted to the KM data extracted from the publication and, based on the best statistical fit (lowest AIC/BIC) and visual inspection, the gamma curve was selected. A survival limit is not applied to this curve as, according to the study, patients can survive up to approximately 60+ years of age.

Figure 15: Survival estimates for HS1 (non-sitter, no PAV) – two-copy



Abbreviations: OS, overall survival.

Figure 16: Survival estimates for HS1 (non-sitter, PAV) – three-copy

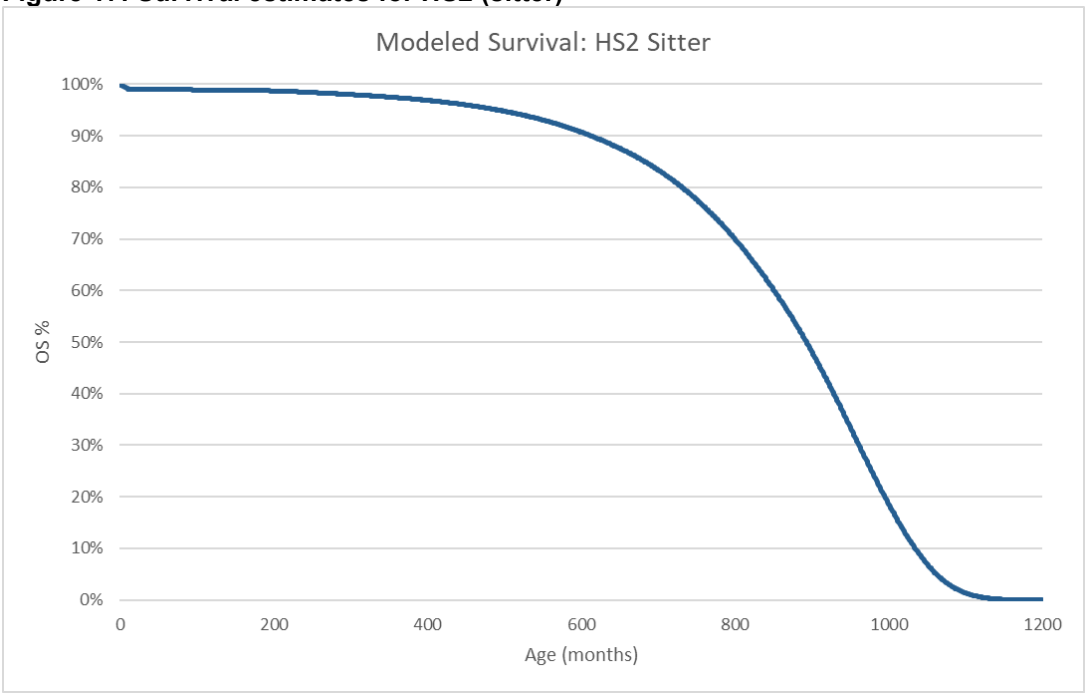


Abbreviations: OS, overall survival.

HS2 (sitter)

For survival in this health state, data for patient cohorts (with SMA types 2a and 2b) are pooled from a recent natural history study based on a Dutch cohort (in which more recent clinical practice is reflected (3)). Due to few deaths in the type 2a population and zero events in the type 2b population, parametric curves fitted to the extracted data resulted in unrealistic flat curves and thus are not used directly in this model. Instead, parametric curves were fitted to the pooled data and then compared with the general population curve for the Netherlands. A constant hazard ratio was calculated relative to general population and applied to the UK general population life tables. Parametric curves and their fit to the original dataset were used to determine which distribution's hazard ratio should be applied. Based on best statistical fit (lowest AIC/BIC) and visual inspection, exponential curve and thus the hazard ratio calculated based on this curve is used in the model to estimate survival for this health state (Figure 17).

Figure 17: Survival estimates for HS2 (sitter)

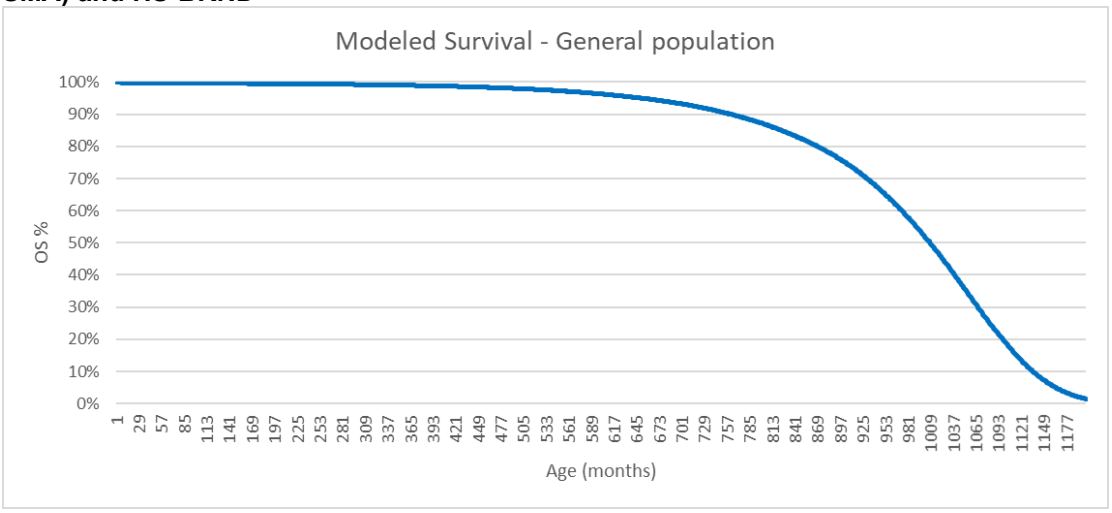


Abbreviations: OS, overall survival.

HS3a (delayed walker), HS3b (experiences later onset SMA), HS-BRND

For these health states, it is assumed that survival would be very similar to general population survival, which has been validated by clinical experts (109). The age-adjusted general population survival estimates for these health states were derived from the UK National Life Tables (112) and are presented in Figure 18.

Figure 18: Survival estimates for HS3a (delayed walker), HS3b (experiences later onset SMA) and HS-BRND



Abbreviations: OS, overall survival.

B.3.3.4 *Clinical expert assessment of applicability of clinical parameters*

Two UK clinical advisory boards have been conducted by Novartis Gene Therapies in order to inform and validate the clinical assumptions and inputs to be included in the

economic model. These advisory boards were conducted in December 2021 (109) and March 2022 (8).

Criteria for selecting experts

For inclusion in the UK clinical advisory boards, 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 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, five clinical experts attended the UK clinical advisory boards.

Experts

The healthcare professionals known to Novartis Gene Therapies to have specialist clinical experience of SMA in the UK were contacted and were asked for their availability to participate in advisory boards. Five clinical experts were able to take part in the advisory boards:

Remuneration and conflict of interest

Each participant received a honorarium at Fair Market Value funded by Novartis Gene Therapies 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 boards, pre-reading materials were circulated to each participant, which included clinical trial data for onasemnogene abeparvovec and key clinical trial publications on BSC.

During the advisory boards, context slides were presented and questions discussed by the group. Discussion points and group consensuses were recorded in report format.

Questions

Full details of all questions asked are provided in the UK advisory board reports (8, 72).

B.3.4 *Measurement and valuation of health effects*

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 (116, 117). Infants 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 (27, 118). Such intensive supportive care, while necessary to keep patients alive, may be traumatic as although cognition is preserved in infants with SMA type 1 (119, 120), very young children cannot understand what is happening to them. Patients with SMA type 2 and 3 experience delays in achieving motor milestones and as well as motor impairments, which may impact QoL.

The QoL of parents, caregivers and families of patients with SMA may be severely impacted. Infants 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 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.

B.3.4.1 *Health-related quality-of-life data from clinical trials*

Not applicable.

B.3.4.2 *Mapping*

Not applicable.

B.3.4.3 *Health-related quality-of-life studies*

B.3.4.3.1 Identification and selection of relevant studies

Search strategy

A SLR was conducted to identify evidence regarding the HRQoL associated with SMA and onasemnogene abeparvovec and other relevant comparators for the treatment of infants from a screened population with a confirmed genetic diagnosis of 5q SMA with a bi-allelic mutation in the *SMN1* gene and up to three copies of the *SMN2* gene. The full search strategies are presented in Appendix H.

Study selection

A summary of the inclusion and exclusion criteria for the HRQoL SLR is shown in Table 22.

Table 41: Selection criteria used for review of HRQoL studies

Population	Type 1, type 2, and type 3; pre-symptomatic and symptomatic SMA
Interventions	Any of the following interventions used in the treatment of SMA: • Onasemnogene abeparvovec (ZOLGENSMA; AVXS-101) • Nusinersen • Risdiplam • Branaplam

	• CK-2127107 • 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	HRQoL measures: • EuroQoL 5 Dimension (EQ-5D) • Pediatric Quality of Life Inventory (PedsQL) • For types 2-3 SMA, other relevant QoL scales are also included • Caregiver QoL scales are also included Health state utility values: • Health Utility Index (HUI)-2 • HUI-3S • Short-Form Six-Dimension (SF-6D) • Short-form survey with 36 items (SF-36)
Study design	• RCTs or single-arm or non-randomized 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

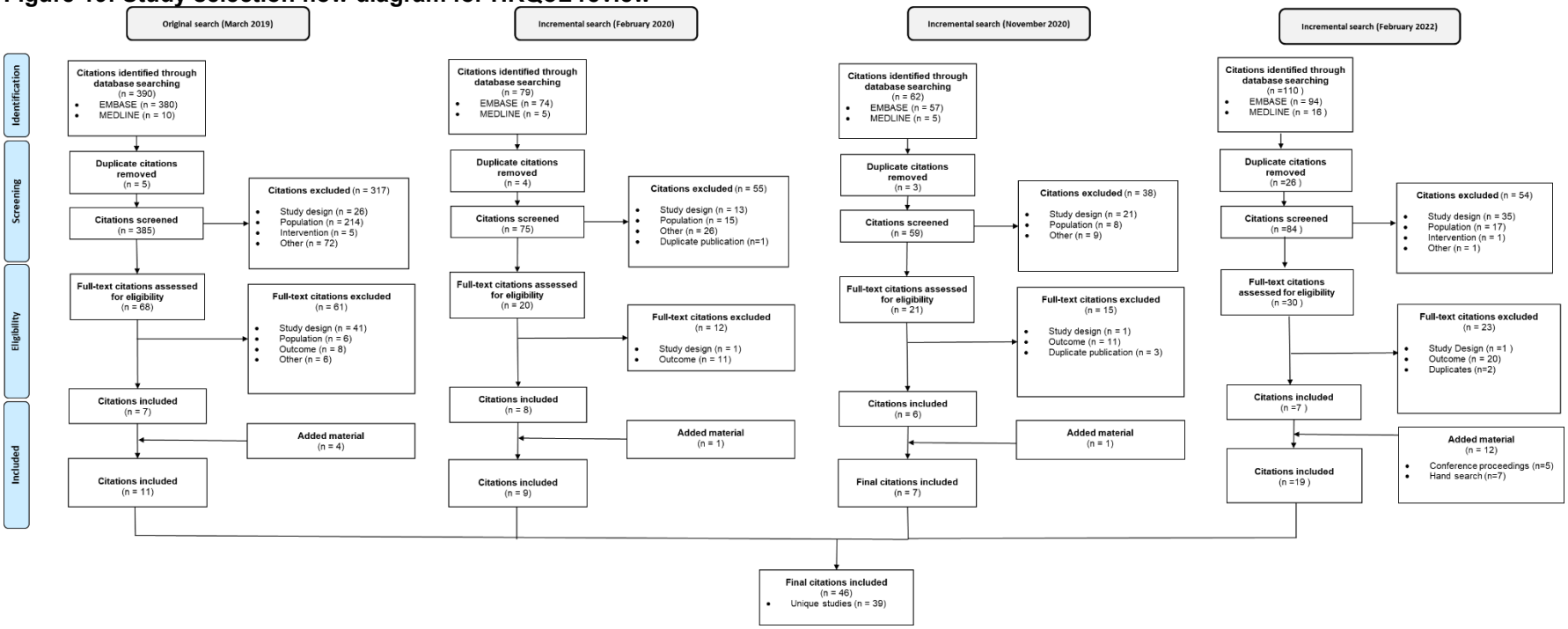
Search dates	Unrestricted

*Literature reviews that involve some kind of methodology for study identification and study selection were of interest. This included systematic literature reviews, structured literature reviews, scoping reviews, and landscape reviews. Narrative reviews that did not involve study identification via databases and primarily summarize an author's viewpoints were not of interest.
Abbreviations: SMA, spinal muscular atrophy.

A search was originally conducted on 13th March 2019, and three incremental searches have since been conducted on 9th March 2020, 13th November 2020, and 2nd February 2022.

Figure 19 presents the PRISMA flow diagram, which outlines the study selection process for the search to identify studies of interest in the SLR of HRQoL studies. In total, 46 publications from 39 unique studies have been identified. A list of all included studies in the HRQoL SLR is provided in Appendix H.

Figure 19: Study selection flow diagram for HRQoL review



B.3.4.4 *Health-related quality-of-life data used in cost-effectiveness analysis*

B.3.4.4.1 Base case – health state utility values

The base case patient health state utility values used in the cost-effectiveness model are drawn from the US ICER assessment of SMA therapies and UK expert clinical advice independently sourced by the NICE ERG. Utility values are the same as the ones used in the previous submission for patients with SMA type 1 (HST15), with the addition of HS2 (sitter, loses sitting), HS3a (delayed walker, loses walking), and HS3b (experiences later onset SMA, loses walking). These values are presented below and in Table 42 and were derived from multiple sources:

- **HS1 (non-sitter, PAV) [0.00]:** The utility value of 0.00 for HS1 (non-sitter, PAV) is sourced from the 'ERG-preferred base case' assumptions in the previous submission for patients with SMA type 1 (HST15) (59). Clinical expert advice sourced independently by the ERG, indicated that HS1 (non-sitter, PAV) should have a lower utility value than HS1 (no PAV)
- **HS1 (non-sitter, no PAV), HS2 (sitter, lose sitting) [0.19]:** The utility value of 0.190 for HS1 (non-sitter, no PAV) is adopted in the US ICER assessment. It is sourced from Thompson et al. 2017 (101), 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). For HS2 (sitter, lose sitting), the utility value is assumed to be the same as for non-sitter patients (i.e. HS1 [non-sitter, no PAV]).
- **HS2 (sitter) [0.60]:** The utility value of 0.600 for HS2 (sitter) is adopted in the US ICER assessment. It is sourced from the ERG report evaluating the nusinersen submission for NICE TA588. Tappenden et al. 2018 (100) 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
- **HS3a (delayed walker), HS3b (experiences later onset SMA), and HS-BRND [general population]:** The utility for the HS3a (delayed walker), HS3b (experiences later onset SMA), and HS-BRND are sourced from general population utilities presented in Table 43, and calculated annually as per the well-established methodology of Ara and Brazier (99) using the equation below. The sex coefficient used is male= 49.4% as per the demographics of patients enrolled in SPR1NT
- **HS3a (delayed walker, loses walking) and HS3b (experiences later onset SMA, loses walking) [0.774]:** The utility for HS3a (delayed walker, loses walking) and HS3b (experiences later onset SMA, loses walking) was taken from Thompson et al, 2017 (101), which reported utilities an SMA population that loses the ability to walk

$$Utility\ (EQ\text{-}5D) = 0.9508566 + (0.0212126 \times male) - (0.0002587 \times age) - (0.0000332 \times age^2)$$

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

- They were considered most appropriate by the US ICER independent assessment group and/or the clinical experts advising the ERG for the previous appraisal for patients with SMA type 1

- HS1 (non-sitter, no PAV), HS3a (delayed walker), HS3b (experiences later onset SMA) and HS-BRND 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 (March 2022) (8)
- Measuring robust utility values in infants 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 patients with SMA) in preference to healthcare professionals; in the base case parent-proxy EQ-5D values were sourced for HS1 (non-sitter, no PAV)

As baseline utility values are extrapolated over a lifetime time horizon, age and gender adjustment were applied to each health state utility to reflect decreases in HRQoL seen in the general population and to make sure that they do not exceed general population values at a given age or for each gender. For this adjustment, a standard approach published in Ara and Brazier (100) was used.

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.

As a conservative assumption, additional utility benefits (‘on-treatment utilities’) in the onasemnogene abeparvovec treatment arm were not applied in the base case although they were implemented by US ICER and the ERG-preferred base case in HST15. Clinicians during the advisory board (8) for this submission agreed that there would be a difference in QoL in treated and untreated patients and it would be reasonable to assume additional QoL benefit for treated patients. Therefore, in a scenario analysis, this is explored by applying an increment of 0.05 for HS2 as per the assumption used for sitter patients in the US ICER assessment and in the ERG-preferred base case in HST15. For lower or higher motor functioning health states no utility increment is applied as no treated patient reside in lower motor functioning health states and general population utility estimates are used in higher motor functioning health states (i.e. no further improvement in quality of life would be reasonable).

Table 42: Summary of patient utility values used in the base case cost-effectiveness analysis

Health state	Description	Utility value	Reference	Justification
HS1 (non-sitter, PAV)	Individual does not sit independently and requires permanent ventilation.	0	Interim ERG report. Edwards et al. 2020 (102) Thompson et al. 2017 (101)	• 'ERG-preferred base case' assumption • Informed by UK expert clinical advice, sourced by the ERG for the previous appraisal for patients with SMA type 1 • Approach taken by US ICER • Uses parent-proxy via EQ-5D-3L for UK-specific SMA type 1 population
HS1 (non-sitter, no PAV) and HS2 (sitter, loses sitting)	Individual does not sit independently and does not require permanent assisted ventilation.	0.190		
HS2 (sitter)	Individual sits independently (is outside WHO 99th percentiles for normal motor development).	0.600	Tappenden et al. 2018 (100)	• Approach taken by US ICER • Informed by UK expert clinical advice, sourced by an independent group (NICE ERG)
HS3a (delayed walker)	Individual sits and walks independently but outside normal motor development (i.e. delayed milestones indicative of late onset SMA).	General population	Ara and Brazier 2010 (99)	• Approach taken by US ICER, adapted to UK general population
HS3b (experiences later onset SMA)	Individual sits and walks independently within normal motor development (within WHO 99th percentiles) but experiences late onset SMA. This health state is modeled for patients in the BSC arm only.			
HS3a (delayed walker, loses	Individual sits independently and loses walking that was	0.774	Thompson et al. 2017 (101)	• Provided utility values in a population that matches the health state definition: an SMA population that loses the ability to walk

Health state	Description	Utility value	Reference	Justification
walking) and HS3b (experiences later onset SMA, loses walking)	previously achieved outside (HS3a) or within (HS3b) normal motor development (WHO 99th percentile)			
HS-BRND	Individual sits and walks independently within normal motor development (within WHO 99th percentiles) + no gastrostomy + no PAV	General population	Ara and Brazier 2010 (99)	• Approach taken by US ICER, adapted to UK general population

Abbreviations: BRND, broad range of normal development; 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 43: General population utilities used for within BRND and delayed walker and experiences late onset SMA health states

Description	Reference	Justification
Annual age-related utility using the following equation: EQ-5D = 0.9508566 + (0.0212126 x 0.417) – (0.0002587 x age) – (0.0000332 x age^2)	Calculation as reported in Ara and Brazier 2010 (99)	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 delayed walker, experiences late onset SMA, and BRND health states, as patients in these health states would all be expected to meet the milestone of walking unassisted by 2 years of age.

Abbreviations: BRND, broad range of normal development; SMA, spinal muscular atrophy; WHO, World Health Organization.

B.3.5 *Cost and healthcare resource use identification, measurement and validation*

Relevant cost and healthcare resource data were identified as part of the economic SLR presented in Section B.3.1 and Appendix D. The SLR identified 26 published cost analyses, 13 of which were conducted in the US, two in Canada, two in Spain, two in Italy, one in Australia, one in Germany, one in Turkey, one in the UK, one in France, one in Portugal, and one in Europe (United Kingdom, France and Germany), respectively. Six published healthcare resource utilisation analyses were identified, two from the US, one from Qatar, and two from multiple countries (US, France, Germany, Italy, Spain, UK). A list of included studies from the economic SLR is provided in Appendix D.

B.3.5.1 *Intervention and comparators' costs and resource use*

Costs and resource use associated with onasemnogene abeparvovec in the cost-effectiveness analysis is summarised in Table 44.

Table 44: Unit costs associated with onasemnogene abeparvovec in the economic model

Items	Intervention (£)	Source
Onasemnogene abeparvovec cost	List price: 1,795,000 [redacted]	Department of Health and Social Care List price/price with PAS discount
Administration cost	3,139	NHS Schedule of Reference Costs 2019–2020 (105) (inflated to 2021 using PSSRU's NHSCII (121)) 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	With list price: 1,798,139 [redacted]	Calculation [redacted]

Abbreviations: NHS, National Health Service; NHSSCII, National Health Service cost inflation index; NHS, National Health Service, PSSRU, Personal Social Services Research Unit.
[†]All economic analyses are run using the confidential PAS price, unless otherwise stated

B.3.5.2 *Health-state costs and resource use*

A list of health states and associated costs applied in the economic model is summarised in Table 45.

Table 45. List of health states and associated annual costs in the economic model

Health states	SMA proxy applied	Items	Value (£)[†]
HS1 (non-sitter, PAV)	SMA type 1	Drugs	619
		Medical tests	880
		Medical visits	3,669
		Hospitalisations	218,987
		GP and emergency	375
		Health material	3,590
		Social services	55,590
		Total	**283,710**
HS1 (non-sitter, no PAV)	SMA type 1	Drugs	810
		Medical tests	1,152
		Medical visits	4,801
		Hospitalisations	70,829
		GP and emergency	490
		Health material	4,400
		Social services	30,019
		Total	**112,500**
HS2 (sitter)	SMA type 2	Drugs	781
		Medical tests	917
		Medical visits	2,805
		Hospitalisations	40,577
		GP and emergency	201
		Health material[†]	2,274
		Social services	20,013
		Total	**67,567**
HS2 (sitter, loses sitting)	SMA type 1	Drugs	810
		Medical tests	1,152
		Medical visits	4,801
		Hospitalisations	70,829
		GP and emergency	490
		Health material	4,400
		Social services	30,019
		Total	**112,500**

Health states	SMA proxy applied	Items	Value (£)[†]
HS3a (delayed walker)	SMA type 3	Drugs	1,012
		Medical tests	675
		Medical visits	2,461
		Hospitalisations	276
		GP and emergency	80
		Health material	652
		Social services	3,177
		Total	**8,333**
HS3a (delayed walker, loses walking)	SMA type 2	Drugs	781
		Medical tests	917
		Medical visits	2,805
		Hospitalisations	40,577
		GP and emergency	201
		Health material	2,274
		Social services	20,013
		Total	**67,567**
HS3b (experiences later onset SMA)	SMA type 3	Drugs	1,012
		Medical tests	675
		Medical visits	2,461
		Hospitalisations	276
		GP and emergency	80
		Health material	652
		Social services	3,177
		Total	**8,333**
HS3b (experiences later onset SMA, loses walking)	SMA type 2	Drugs	781
		Medical tests	917
		Medical visits	2,805
		Hospitalisations	40,577
		GP and emergency	201
		Health material[†]	2,274
		Social services	20,013
		Total	**67,567**

Health states	SMA proxy applied	Items	Value (£)†
HS-BRND	SMA type 3	Drugs	1,012
		Medical tests	675
		Medical visits	2,461
		Hospitalisations	276
		GP and emergency	80
		Health material	652
		Social services	3,177
		Total	**8,333**

Abbreviations: BRND, broad range of normal development; GP, general practitioner; NHSSCII, National Health Service cost inflation index; PSSRU, Personal Social Services Research Unit; SMA, spinal muscular atrophy.
†Costs were sourced from NHS Schedule of Reference Costs 2019–2020 (105), PCA 2021/22 (106) and publications (where applicable inflated to 2021 using PSSRU's NHSCII (121))

B.3.5.3 *Adverse reaction unit costs and resource use*

Given the nature of SMA, it can be 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, in line with the modelling for HST15 (59).

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 times the upper limit of normal, but who appeared to respond to prednisolone. However, since the cost of prednisolone is low, it was not included in the cost-effectiveness model.

B.3.5.4 *Miscellaneous unit costs and resource use*

In the opinion of Novartis Gene Therapies, the model captures all of the major costs and cost savings that arise with the introduction of onasemnogene abeparvovec in England.

Patients with SMA are identified via targeted screening (e.g. via sibling identification) and genetic testing, which would be done regardless of onasemnogene abeparvovec becoming available for patients with pre-symptomatic SMA, therefore the cost of genetic testing prior to treatment is not captured in the model.

B.3.6 *Uncertainty*

As discussed in Section B.2.12.2, as may be expected given the very rare nature of SMA, the patient population enrolled in SPR1NT was relatively small (14 patients in the *SMN2* two-copy cohort and 15 patients in the three-copy cohort). In addition, it was considered unethical to include a BSC treatment arm in the SPR1NT trial given the poor prognosis for SMA and the unprecedented clinical outcomes observed in previous clinical trials for onasemnogene abeparvovec. As such, it was necessary to use natural history data to compare onasemnogene abeparvovec with BSC, potentially resulting in uncertainty in the clinical outcomes included in the model. However, population-matched

cohorts were included from natural history studies, and the impact of using different sources of natural history data was assessed in scenario analyses.

Another potential source of uncertainty in the model is the limited follow-up data available to inform the treatment effect over patients' lifetime, resulting in a need for extrapolation of clinical data. However, in the onasemnogene abeparvovec arm, motor milestone attainment is based on milestone achievement observed in SPR1NT and currently available data from LT-002 only. This is a conservative assumption as patients are continuing to achieve milestones in the ongoing LT-002 study.

Noting that there is uncertainty in the model outputs, the company has conducted sensitivity analyses using well-characterised and researched methods to explore the impact of uncertainty on economic outcomes (Section B.3.10). These include a deterministic sensitivity analysis (DSA), probabilistic sensitivity analysis (PSA), and scenario analyses testing key model assumptions and inputs (discounting rates, milestone data, survival data, utility values, and costs of SMA-related care.

B.3.7 *Managed access proposal*

Not applicable. The population under review in this appraisal is already captured in an MAA.

B.3.8 *Summary of base-case analysis inputs and assumptions*

B.3.8.1 *Summary of base-case analysis inputs*

Base cases analysis inputs are summarised in Table 46.

Table 46: Summary of base case inputs

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 2022	B.3.2.9
Discount rate (outcomes)	3.5%	N/A for PSA 0% – 5% used in additional scenario analyses		
Costs				
Monthly SMA care costs				
HS1 (PAV)	£23,643	SE: £4,728.50 (Gamma)	NHS Reference costs 2019/20 (inflated to 2021 value) PCA 2021/22 PSSRU 2021 Other various publications	B.3.5.1
HS1 (no PAV)	£9,375	SE: £1,875.01 (Gamma)		
HS2 lost sitting	£9,375	SE: £1,875.01 (Gamma)		
HS2 sitting	£5,631	SE: £1,126.11 (Gamma)		
HS3a walking	£694	SE: £138.88 (Gamma)		
HS3a lost walking	£5,631	SE: £1,126.11 (Gamma)		
HS3b walking	£694	SE: £138.88 (Gamma)		
HS3b lost walking	£5,631	SE: £1,126.11 (Gamma)		
HS-BRND	£694	SE: £138.88 (Gamma)		
Onasemnogene abeparvovec costs				
Onasemnogene abeparvovec drug acquisition cost	[redacted]	Fixed in PSA [redacted] variation in DSA	UK price with PAS discount	B.3.5.1

Variable	Base case value	Range, SE or 95% CI (distribution)	Source	Section(s)
Onasemnogene abeparvovec administration cost	£3,139	SE: £627.71 (Gamma)	NHS reference costs 2019/20 (105) (inflated to 2021 value) 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)	B.3.5.1
Quality of life				
HS1 (non-sitter, PAV)	0.000	SE: 0.0379 (Gamma) in PSA	Interim ERG report. Edwards et al. 2020 (102) Thompson et al. 2017 (101)	B.3.4
HS1 (non-sitter, no PAV)	0.190	SE: 0.0379 (Gamma) in PSA		
HS2 (sitter)	0.600	SE: 0.0135 (Gamma) in PSA		
HS2 (sitter, loses sitting)	0.190	SE: 0.0379 (Gamma) in PSA		
HS3a (delayed walker)	General population		Ara and Brazier 2010 (99)	
HS3a (delayed walker, loses walking)	0.774	SE: 0.0135 (Gamma) in PSA	Thompson et al. 2017 (101)	
HS3b (experiences later onset SMA)	General population		Ara and Brazier 2010	
HS3b (experiences later onset SMA, loses walking)	0.774	SE: 0.0135 (Gamma) in PSA	Thompson et al. 2017 (101)	
HS-BRND	General population		Ara and Brazier 2010 (99)	
HS3a (delayed walker, loses walking) and HS3b (experiences later onset SMA, loses walking): % male in equation	0.494	N/A for PSA	Ara and Brazier 2010 (99)	
HS3a (delayed walker, loses walking) and HS3b (experiences later onset SMA, loses walking): equation intercept	0.9508566	SE: 0.0475 (Beta) in PSA		

Variable	Base case value	Range, SE or 95% CI (distribution)	Source	Section(s)
HS3a (delayed walker, loses walking) and HS3b (experiences later onset SMA, loses walking): equation sex coefficient	0.0212126	SE: 0.0011 (Beta) in PSA		
HS3a (delayed walker, loses walking) and HS3b (experiences later onset SMA, loses walking): equation age coefficient	0.0002587	SE: 0.000013 (Beta) in PSA		
HS3a (delayed walker, loses walking) and HS3b (experiences later onset SMA, loses walking): equation age^2 coefficient	0.0000332	SE: 0.000002 (Beta) in PSA		
Survival and other clinical inputs				
Survival limits				
Survival limit (years) for HS1 (non-sitter, PAV)	16 years	SE: 3.20 (Gamma)	Assumption	B.3.3.3
Survival limit (years) for HS1 (non-sitter, no PAV) – 2 copy	4 years	SE: 0.80 (Gamma)	Interim ERG report. Edwards et al. 2020 (102)	
Survival limit (years) for HS1 (non-sitter, no PAV) – 3 copy	100 years (life time)	SE: 20.00 (Gamma)	Assumption	
Survival curve parameters				
HS1 (non-sitter, PAV): Exponential distribution: lambda	0.017	Cholesky decomposition	Gregoretti et al. 2013 (111)	B.3.3.3
HS1 (non-sitter, no PAV) two-copy: Weibull distribution: lambda	18.199	Cholesky decomposition	NeuroNext/Kolb 2017 (2, 83)	
HS1 (non-sitter, no PAV) two-copy: Weibull distribution: gamma	1.494	Cholesky decomposition	NeuroNext/Kolb 2017 (2, 83)	
HS1 (non-sitter, no PAV) three-copy: Gamma distribution: shape	0.537	Cholesky decomposition	Wijngaarde et al. 2020 (3)	

Variable	Base case value	Range, SE or 95% CI (distribution)	Source	Section(s)
HS1 (non-sitter, no PAV) three-copy: Gamma distribution: rate	0.001	Cholesky decomposition	Wijngaarde et al. 2020 (3)	
HS2 (sitter): Exponential distribution: HR	2.580	SE: 0.177 (Lognormal)	Wijngaarde et al. 2020 (3)	
HS3a (delayed walker)	See model sheet: NatLifeTable	N/A	UK National Life Tables 2018-2020 (112)	
HS3b (experiences later onset SMA)				
HS-BRND				
Natural history and clinical inputs				
Percent of patients with 2 *SMN2* copy	0.6515	0.13 (Beta)	Pooled data from studies on NBS screening (90-96)	B.3.3
BSC percent of two-copy patients become a non-sitter	0.790	Dirichlet - gamma	Calucho, 2018 (4)	
BSC percent of two-copy patients become a sitter	0.163			
BSC percent of two-copy patients become a delayed walker	0.046			
BSC percent of two-copy patients become a patient with late onset SMA	0.000			
BSC percent of three-copy patients become a non-sitter	0.150			
BSC percent of three-copy patients become a sitter	0.540			
BSC percent of three-copy patients become a delayed walker	0.160			

Variable	Base case value	Range, SE or 95% CI (distribution)	Source	Section(s)
BSC percent of three-copy patients become a patient with late onset SMA	0.150			
BRND sitting threshold	286.0	Fixed	WHO 2006 (42)	
BRND walking threshold	547.0			
Age onset of SMA1 (HS1 [non-sitter])	6.0	Fixed	Wadman et al. 2018 (46)	
Age onset of SMA2 (HS2 [sitter])	10.0			
Age onset of SMA3a (HS3a [delayed walker])	18.0			
Age onset of SMA3b (HS3b [experiences later onset SMA]) - min	3.0			
Age onset of SMA3b (HS3b [experiences later onset SMA]) - max	24.0			
BSC HS1 (non-sitter) - percent of two-copy patients on PAV	12.5%	SE: 0.03 (Beta)	NeuroNext/Kolb 2017 (2, 83)	
BSC HS1 (non-sitter) – two-copy patients on PAV - max age	18.4	Fixed		
BSC HS1 (non-sitter) - percent of three-copy patients on PAV	21.9%	SE: 0.04 (Beta)	Wijngaarde et al. 2020 (3)	
BSC HS1 (non-sitter) – three-copy patients on PAV - max age	57.6	Fixed		
BSC HS2 (sitter) - percent lose sitting	25.0%	SE: 0.05 (Beta)	Wadman et al. 2018 (46)	
BSC HS2 (sitter, loses sitting) - min age	0.7	SE: 0.14 (Gamma)		
BSC HS2 (sitter, loses sitting) - max age	29.1	SE: 5.82 (Gamma)		

Variable	Base case value	Range, SE or 95% CI (distribution)	Source	Section(s)
BSC HS3a (delayed walker) - percent lose walking	68.0%	SE: 0.14 (Beta)		
BSC HS3a (delayed walker, loses walking) - min age	2.5	SE: 0.50 (Gamma)		
BSC HS3a (delayed walker, loses walking) - max age	34.5	SE: 6.90 (Gamma)		
BSC HS3b (experiences later onset SMA) - percent lose walking	47.0%	SE: 0.09 (Beta)		
BSC HS3b (experiences later onset SMA, loses walking) - min age	6.5	SE: 1.30 (Gamma)		
BSC HS3b (experiences later onset SMA, loses walking) - max age	65.7	SE: 13.14 (Gamma)		

Abbreviations: BRND, broad range of normal development; BSC, best supportive care; DSA, deterministic sensitivity analysis; HR, hazard ratio; HS, health state; PAV, permanent assisted ventilation; PSA, probabilistic sensitivity analysis; SE, standard error.

B.3.8.2 *Assumptions*

Onasemnogene abeparvovec is expected to have a lifelong duration of effect as it addresses the underlying genetic cause of disease by providing a functional copy of the *SMN1* gene.

The assumption that onasemnogene abeparvovec will have a lifelong duration of effect is supported by the results of two long-term studies, LT-001 and LT-002. LT-001 and LT-002 are the long-term extension studies of START and the Phase III onasemnogene abeparvovec trials, respectively. Both will follow patients up to 15 years of age. All 10 patients who received the therapeutic dose of onasemnogene abeparvovec in START had either maintained previously attained motor milestones or gained new milestone of "standing with assistance" in the ongoing long-term extension trial LT-001 (with a maximum duration of follow up of 6.6 years for patients who received the therapeutic dose of onasemnogene abeparvovec). Data from the Phase III long-term extension trial, LT-002, show that [redacted] Clinical evidence to date indicates that a one-time administration of onasemnogene abeparvovec at the therapeutic dose provides prolonged efficacy, and there is no evidence to indicate that SMN protein expression would stop or wane over time.

Furthermore, onasemnogene abeparvovec addresses the genetic root cause of SMA by delivering a fully functional human *SMN* gene which activates transcription of the *SMN* transgene and restores continuous and sustained SMN protein expression. The cells targeted and transduced by onasemnogene abeparvovec are post-mitotic, non-dividing cells, thereby reducing the risk for dilution of the episome. The components of onasemnogene abeparvovec (CMV enhancer and chicken-β-actin promotor) lead to continuous and sustained transcription and SMN protein expression, suggesting that the effects of onasemnogene abeparvovec are durable. Several AAV gene therapy studies have demonstrated transgene persistence; in Parkinson's disease transgene persistence for 15 years after gene transfer has been shown in a primate model, with studies in haemophilia showing transgene persistence for up to 10 years of follow-up in humans (89, 122-129).

These assumptions were previously accepted in HST15 (59) and were considered acceptable by key opinion leader (KOL) expert advisors consulted during model conceptualisations at two UK advisory boards (8, 130). In addition, these underpinning assumptions were accepted for use by the independent US ICER in their assessment of SMA pharmacotherapies (108).

A full list of additional assumptions, justification and sources used in the model is provided in Table 47.

Table 47. Base-case model assumptions

Intervention(s)	Assumption and rationale	Source(s)/ justification(s)
Treatment benefit		
Onasemnogene abeparvovec and BSC	All base case pairwise analyses use unanchored and unmatched comparisons. There are no head-to-head trials comparing onasemnogene abeparvovec to BSC, 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	Multiple alternative natural history sources for BSC are presented in the model as scenario analyses. Given the small sample size of available studies, the ERG for HST15 considered 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, hence an unadjusted analysis is used to populate the model
BSC	Without disease modifying treatment, a non-negligible proportion of patients with SMA type 2 and 3 who achieve motor milestones lose them over time	Wadman et al 2018 (46)
Onasemnogene abeparvovec	With disease modifying treatment, patients develop a less severe form of SMA than they would have without treatment, and may even avoid progression to symptomatic SMA	UK clinical advisory board (8)

Intervention(s)	Assumption and rationale	Source(s)/ justification(s)
Survival		
Onasemnogene abeparvovec and BSC	Life expectancy applied in the model can be estimated using proxies: • Patients in the HS1 (non-sitter, PAV and no PAV) are assumed to have a life expectancy of SMA type 1 patients (this only affects patients in the BSC arm as no patients treated with onasemnogene abeparvovec reside in this health state). • Patients in the HS2 (sitter) are assumed to have a life expectancy like that of SMA type 2 • Patients in the HS3a (delayed walker) and HS3b (experiences later onset SMA) are assumed to have the life expectancy of SMA type 3 patients, which is equivalent to the general population • Infants in HS-BRND are assumed to have a life expectancy of the general population	KOL opinion – model conceptualisation UK clinical advisory board (8) US ICER (108)
BSC	Patients in HS1 (non-sitter, PAV) and HS1 (non-sitter, no PAV) are assumed to follow natural history survival curves. This only affects patients in the BSC arm as no patients treated with onasemnogene abeparvovec reside in these health states. 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 from HST15. Base case survival limits: HS1 (non-sitter, PAV): 16 years (non-invasive curve) HS1 (non-sitter, no PAV) (*SMN2* two-copy): 4 years HS1 (non-sitter, no PAV) (*SMN2* three-copy): 100 years (i.e. no limit)	ERG-preferred base case assumption (102) in the previous NICE technology appraisal for patients with SMA type 1 (HST 15) (97)
Costs and utilities		

<table>
<tr><th>Intervention(s)</th><th>Assumption and rationale</th><th>Source(s)/ justification(s)</th></tr>
<tr><td>Onasemnogene abeparvovec and BSC</td><td>Costs and utilities associated with the different motor function milestones are populated using the healthcare costs and utilities of SMA type 1–3 as proxies:
Patients in HS1 (non-sitter, PAV) and HS1 (non-sitter, no PAV) are assumed to have costs of HCRU and utilities of SMA type 1 patients
Patients in HS2 (sitter) are assumed to have HCRU costs and utilities of SMA type 2 patients
Patients in HS3a (delayed walker), HS3b (experiences later onset SMA), and HS-BRND are assumed to have costs of HCRU of SMA type 3 patients and utilities of the general population</td><td>KOL model conceptualisation
UK clinical advisory board (8)
US ICER (108)</td></tr>
<tr><td>Onasemnogene abeparvovec</td><td>It is assumed the HCRU required for the one-time IV administration of onasemnogene abeparvovec (including pre-infusion baseline tests, AAV9 antibody testing [to be funded by Novartis Gene Therapies], 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 (8)</td></tr>
<tr><td>Onasemnogene abeparvovec and BSC</td><td>For the purposes of estimating health state 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></table></td><td>UK clinical advisory board (29)</td></tr>
</table>

Intervention(s)	Assumption and rationale				Source(s)/ justification(s)
	Patients on NIV >16 hours per day	15%	15%	70%	
Onasemnogene abeparvovec and BSC	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. For the same reason, costs of adverse events were not included in the model.				US ICER (108)

Abbreviations: AAV, adeno-associated virus; BRND, broad range of normal development; 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.

B.3.9 *Base-case results*

In the base-case for the combined cohort of patients with two and three copies of *SMN2*, the ICER for onasemnogene abeparvovec versus BSC is £70,610 per QALY gained using list price for onasemnogene abeparvovec (Table 48) and [redacted] using the price with the PAS discount (Table 49). Further results for the base case are presented below for the combined cohort of patients with two and three copies of *SMN2* using list and the PAS discounted price of onasemnogene abeparvovec in Table 48 and Table 49, respectively. To obtain the combined cohort results, a weighted average of the two- and three-*SMN2* copy cohort results was calculated using the likely ratio of *SMN2* two-copy to *SMN2* three-copy infants identified through screening in England (see Section B.3.2.1): 65.15% to 34.85%, respectively.

Base case results by *SMN2* copy number are shown in Appendix J.

Table 48: Base case results for the combined cohort of patients with two and three copies of *SMN2* – list price

Technologies	Total†			Incremental (vs BSC)†			ICER† (£/QALY)
	Costs (£)	LYs	QALYs	Costs (£)	LYs	QALYs	(vs BSC)
BSC	882,564	[redacted]	[redacted]	-	-	-	-
Onasemnogene abeparvovec	2,096,927	[redacted]	[redacted]	1,214,363	[redacted]	[redacted]	70,610

Abbreviations: BSC, best supportive care; ICER, incremental cost-effectiveness ratio; LYs, life years ; N/A, not applicable; QALYs, quality-adjusted life years.
†Values presented are based on discounting of 3.5%.

Table 49: Base case results for the combined cohort of patients with two and three copies of *SMN2* – PAS discounted price

Technologies	Total†			Incremental (vs BSC)†			ICER† (£/QALY)
	Costs (£)	LYs	QALYs	Costs (£)	LYs	QALYs	(vs BSC)
BSC	882,564	[redacted]	[redacted]	-	-	-	-
Onasemnogene abeparvovec	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: BSC, best supportive care; ICER, incremental cost-effectiveness ratio; LYs, life years ; N/A, not applicable; QALYs, quality-adjusted life years.
†Values presented are based on discounting of 3.5%.

Incremental net health benefit and incremental net monetary benefit for the combined cohort of patients with two and three copies of *SMN2*, are calculated based on a willingness to pay (WTP) threshold of [redacted] per QALY are shown in Table 50. The WTP threshold of [redacted] per QALY is estimated using the QALY weighting ([redacted] based on the incremental QALY of [redacted]) applicable to this submission according to the NICE guidelines (98). Results below are based on onasemnogene abeparvovec's PAS discounted price.

Table 50: Incremental net health benefit and incremental net monetary benefit based on a weighted willingness to pay threshold of [redacted] per QALY

	Combined cohort
Incremental net health benefit (QALY)	[redacted]
Incremental net monetary benefit (£)	[redacted]

Abbreviations: QALY, quality-adjusted life year.

B.3.10 *Exploring uncertainty*

To test uncertainty around the parameter values, data sources and assumptions, deterministic, probabilistic, and scenario-based sensitivity analyses were undertaken. In the deterministic sensitivity analysis (DSA), values are varied by +/- 20%. In the probabilistic sensitivity analysis (PSA), distributions were assigned to relevant parameters according to standard practice (see Table 46), which was followed by the run of 1,000 iterations to produce the cost-effectiveness estimate for each iteration and demonstrate the PSA cloud of iterations in a cost-effectiveness plane. In addition, a cost-effectiveness acceptability curve was generated to show the probability of onasemnogene abeparvovec being cost-effective at different WTP thresholds. A description of the scenarios conducted is presented in Section B.3.10.3.

B.3.10.1 *Deterministic sensitivity analysis*

[redacted] shows the impact on the ICER from the DSA for onasemnogene abeparvovec versus BSC using the PAS discounted price for onasemnogene abeparvovec.

The model parameters that have the largest impact on the results are: the drug acquisition cost of onasemnogene abeparvovec, the percentage of two-copy patients in the assessed population, the percentage of BSC two-copy patients who reside in HS1 (non-sitter) and the SMA-care costs for HS2 (sitter) patients.

[redacted]

B.3.10.2 *Probabilistic sensitivity analysis*

[redacted] shows the results from 1,000 simulations on incremental costs and effects of onasemnogene abeparvovec over BSC using the PAS discounted price for onasemnogene abeparvovec.

[redacted]

[redacted] shows the cost-effectiveness acceptability curve from 1,000 simulations comparing onasemnogene abeparvovec with BSC using the PAS discounted price for onasemnogene abeparvovec.

[redacted]

Table 51 shows the maximum and minimum results for costs, life years and QALYs using the PAS discounted price for onasemnogene abeparvovec.

Finally, Table 52 shows the ICER results (onasemnogene abeparvovec versus BSC) from the simulations using the PAS discounted price for onasemnogene abeparvovec.

Table 51: Results from 1,000 simulations of onasemnogene abeparvovec and BSC for combined cohort of patients (using PAS discounted price)

	Min costs (£)	Max costs (£)	Min LYs	Max LYs	Min QALYs	Max QALYs
BSC	442,806	1,455,106	[redacted]	[redacted]	[redacted]	[redacted]
Onasemnogene abeparvovec*	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

*Variation between the minimum and maximum life years for onasemnogene abeparvovec is very minimal as the majority of patients in the onasemnogene abeparvovec arm are in HS3a (delayed walker) and HS-BRND health states, in which patients are assumed to follow the survival of the general population. For the general population survival estimates, no uncertainty is applied in the model.
Abbreviations: BSC, best supportive care; LY, life-ears; QALY, quality-adjusted life-years.

Table 52: ICER (£/QALY) results from 1,000 simulations of onasemnogene abeparvovec and BSC for combined cohort of patients (using PAS discounted price)

ICER ranges	Min ICER	Max ICER	Mean costs/ mean QALYs	Median	95% plausible interval - low	95% plausible interval - high
Onasemnogene abeparvovec versus BSC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: BSC, best supportive care; ICER, incremental cost effectiveness ratio; QALY, quality-adjusted life-years.

B.3.10.3 *Scenario analyses*

In addition to the sensitivity analyses described in Sections B.3.10.1 and B.3.10.2, several scenario analyses were conducted to explore the impact of variation in key base-case assumptions and inputs on the cost-effectiveness of onasemnogene abeparvovec vs BSC. These scenario analyses are summarised in Table 53 and their results presented in Table 54.

Table 53. Scenarios explored

Parameter	Base-case assumption	Scenarios	Rationale
Discount rate	3.5%, aligned with the NICE reference case (Section B.3.2.9)	1.5% 0% 5%	The impact of a discount rate of 1.5% was explored because, in HST15, the Committee concluded that the non-reference-case discount rate of 1.5% was applicable for the base case because onasemnogene abeparvovec has a high one-off cost with benefits that accrue over a lifetime, is transformative for patients who would die without treatment, and offers the potential for substantial long-term gains that may enable a high quality of life for those with SMA type 1 and those with pre-symptomatic SMA with up to three copies of the *SMN2* gene. The company considers all criteria to adopt the non-reference case discount rate of 1.5% are also met for this appraisal. Discount rates of 0% and 5% were also included in scenarios analyses to explore the impact of variation in discounting rates on the ICER for onasemnogene abeparvovec vs BSC.
Milestone data for onasemnogene abeparvovec	Based on milestone data measured using WHO definitions for milestone achievement (Section B.3.3.1.1)	Based on milestone data measured using BSID definitions and where data not available, data measured using WHO definitions are included	BSID (also used for the definition of milestones in the base case economic analysis of HST15) and WHO definitions were used in the SPR1NT trial but during LT002, 'walking' milestone data were collected based only on WHO definitions and some patients achieved their 'walking' milestones after SPR1NT. To assess the difference in the available milestone dataset, a scenario analysis was conducted. However, it should be noted that there are some differences in the definitions, clinicians consider them comparable (especially for the 'walking without support' milestone).
Milestone data for onasemnogene abeparvovec	Based on milestone data measured using WHO definitions for milestone achievement (Section B.3.3.1.1)	• Based on milestone data measured using WHO definitions for milestone achievement	As a conservative assumption, the base case analysis does not include a patient who achieved walking without support during LT002 after receiving a subsequent therapy. The additional treatment benefit after the subsequent therapy could not be confirmed. However, it is expected that initial treatment

Parameter	Base-case assumption	Scenarios	Rationale
		• Including one additional walker who achieved walking without support after receiving subsequent therapy	with onasemnogene abeparvovec strongly contributed to the milestone achievement. Therefore, in a scenario the effect of including this patient as a delayed walker is tested.
Survival in BSC and onasemnogene abeparvovec arm – HS2 (sitter)	Based on Wijngaarde et al, 2020 (3) (Section B.3.3.3)	Based on Zerres et al, 1997 (39)	Zerres et al, 1997 is an alternative source for survival estimates for type 2 patients (used as a proxy for sitters) with older dataset (which might not reflect recent changes in the clinical practice). This publication was used for the survival in the sitter health state in HST15, however, as new data become available for type 2 patients in Wijngaarde et al, 2020, it was deemed more appropriate to apply that for the base case. To test the impact on the results, a scenario with Zerres et al, 1997 was also run.
Survival in BSC arm – HS1 (non-sitter, no PAV)	Three-copy cohort: based on NeuroNext/Kolb 2017 (2, 83) Novartis Gene Therapies external control database Two-copy cohort: Wijngaarde et al, 2020 (3) (Section B.3.3.3)	Both two- and three-copy cohort: based on Type 1c cohort's survival data in Wijngaarde et al, 2020 (3)	Survival data for both two- and three-copy non-sitter cohorts were obtained from Wijngaarde et al, 2020 using the following assumptions: • Two-copy: SMA type 1b (n=35). However, only endpoint-free survival data could be extracted for this cohort (due to unavailability of IPD data) and thus estimates include ventilation events (3 out of 35). • Three-copy: SMA type 1c (n=32) – OS data To match the source of the datasets used for the same health state, a scenario was conducted to use only data from WIjngaarde et al, 2020 for both 2- and 3-copy cohorts in HS1 (no PAV). Note survival limits remain as per base case.
Survival in BSC arm – HS1 (non-sitter, no PAV)	Three-copy cohort: based on NeuroNext/Kolb 2017 (2, 83) Novartis Gene Therapies external control database	Both two- and three-copy cohort: based on NeuroNext/Kolb 2017 (2, 83) Novartis Gene Therapies external control database	Survival data for both two- and three-copy non-sitter cohorts were obtained from NeuroNext/Kolb 2017 (2, 83) using the following assumptions: • Two-copy: SMA type 1 two-copy cohort (n=16) – disaggregated OS data

Parameter	Base-case assumption	Scenarios	Rationale
	Two-copy cohort: Wijngaarde et al, 2020 (3) (Section B.3.3.3)		• Three-copy: SMA type 1 three-copy cohort (n=5) – disaggregated OS data To match the source of the datasets used for the same health state, a scenario was conducted to use only data from NeuroNext/Kolb 2017 (2, 83) for both two- and three-copy cohorts in HS1 (no PAV). Note survival limits remain as per base case.
Survival in BSC arm – HS1 (non-sitter, no PAV)	Three-copy cohort: based on NeuroNext/Kolb 2017 (2, 83) Novartis Gene Therapies external control database Two-copy cohort: Wijngaarde et al, 2020 (3) (Section B.3.3.3)	Both two- and three-copy cohort: based on PNCR (2)	Survival data for both two- and three-copy non-sitter cohorts were obtained from PNCR using the following assumptions: • Two-copy: SMA type 1 two-copy cohort (n=23) – disaggregated OS data • Three-copy: SMA type 1 three-copy cohort (n=12) – disaggregated OS data To match the source of the datasets used for the same health state, a scenario was conducted to use only data from NeuroNext/Kolb 2017 (2, 83) for both two- and three-copy cohorts in HS1 (non-sitter, no PAV). Note survival limits remain as per base case.
Utility values	No utility increment due to treatment effect	Utility increment (0.05) applied in HS2 (sitter) to account for additional treatment benefit	Based on clinical advice and previous economic evaluations (US ICER assessment and in the ERG-preferred base case in HST15), it is expected that there would be some difference in quality of life in treated and untreated patients and it would be reasonable to assume additional quality of life benefit for treated patients. Therefore, in a scenario analysis this is explored by applying an increment of 0.05 for HS2 as per the assumption used for sitter patients in the evaluations mentioned above.
Utility values	Values as per HST15 (59) and from	Based on Belter et al. (131) for health states where alternative value is available (i.e. for	Some alternative health state utility values were identified in Belter et al. and are tested in a scenario as described.

Parameter	Base-case assumption	Scenarios	Rationale
	Thompson et al. 2017 (101) (Section B.3.4)	other health states, utility values remain as per base case) Utilities that are amended to: • HS1 (non-sitter, PAV): -0.05 • HS1 (non-sitter, no PAV): 0.06 • HS2 (sitter): 0.26 • HS2 (sitter, loses sitting): 0.12 • HS3a (delayed walker), HS3b (experiences later onset SMA): 0.64 • HS3a (delayed walker, loses walking), HS3b (experiences later onset SMA, loses walking): 0.23	However, it should be noted that clinicians considered most of these values unrealistic (8).
Utility values	Values as per HST15 (59) and from Thompson et al. 2017 (101) (Section B.3.4)	Based on CHERISH for health states where alternative value is available (i.e. for other health states, utility values remain as per base case) Utilities that are amended to: • HS2 (sitter): 0.756 • HS2 (sitter, loses sitting): 0.730 • HS3a (delayed walker), HS3b (experiences later onset SMA): 0.878 • HS3a (delayed walker, loses walking), HS3b (experiences later onset SMA, loses walking): 0.774	Some alternative health state utility values were identified in CHERISH (132)and are tested in a scenario as described.
Utility values	Values as per HST15 (59) and from Thompson et al. 2017 (101) (Section B.3.4)	Based on Dangouloff et al. 2022 (94) for health states where alternative value is available (i.e. for other health states, utility values remain as per base case)	Some alternative health state utility values were identified in a recent publication by Dangouloff et al. 2022 and are tested in a scenario as described.

Parameter	Base-case assumption	Scenarios	Rationale
		Utilities that are amended to: • HS1 (non-sitter, no PAV), HS2 (sitter, loses sitting): 0.34 (weighted average of treated and untreated patients with two *SMN2* copies using two-copy patient utility as a proxy for SMA type 1) • HS2 (sitter), HS3a (delayed walker, loses walking), HS3b (experiences later onset SMA, loses walking): 0.443 (weighted average of treated and untreated patients with three *SMN2* copies using three-copy patient utility as a proxy for SMA type 2) • HS3a (delayed walker), HS3b (experiences later onset SMA): 0.569 (weighted average of treated and untreated patients with four *SMN2* copies using four-copy patient's utility as a proxy for SMA type 3)	
Utility values	Values as per HST15 (59) and from Thompson et al. 2017 (101) (Section B.3.4)	Based on input from clinical advisors of the nusinersen NICE appraisal (TA588) (28) and also applied in the risdiplam NICE appraisal (TA755) (133) for health states where alternative value is available (i.e. for other health states, utility values remain as per base case) Utilities that are amended to: • HS1 (non-sitter, PAV): 0.200 • HS1 (non-sitter, no PAV), HS2 (sitter, loses sitting): 0.250 • HS2 (sitter): 0.475	Some alternative health state utility values were identified in the NICE TA588 (and NICE TA755) and are tested in a scenario as described.

Parameter	Base-case assumption	Scenarios	Rationale
		• HS3a (delayed walker, loses walking), HS3b (experiences later onset SMA, loses walking): 0.750 • HS3a (delayed walker), HS3b (experiences later onset SMA): 0.800	
SMA-care cost values for HS-BRND	Based in UK HCRU data, assuming SMA type 3 costs for the HS-BRND (Section B.3.5)	Assuming no costs for HS-BRND	As a conservative assumption in the base case, it is assumed that SMA-care costs for HS-BRND are as high as for a patient with SMA type 3. However, in practice, children with pre-symptomatic SMA with 2 or 3 copies of the *SMN2* gene who follow normal development would require less healthcare resources and thus incur less costs (even very small or no SMA-care related costs). Therefore, a scenario was run to assess when no SMA-care costs are applied to HS-BRND.
SMA-care cost values for all health states	Based on UK HCRU data (Section B.3.5)	Based on real-world evidence (RWE) study presented in the Risdiplam NICE TA755 (133) (and originally presented in the nusinersen NICE TA588) (28) Annual SMA-care costs applied by health states: • HS1 (non-sitter, PAV): £259,375 • HS1 (non-sitter, no PAV), HS2 (sitter, loses sitting): £148,214 • HS2 (sitter), HS3a (delayed walker, loses walking), HS3b (experiences later onset SMA, loses walking): £68,322 • HS3a (delayed walker), HS3b (experiences later onset SMA), HS-BRND: £21,765	RWE data for SMA-care costs were collected and applied in the nusinersen TA588 and also used in the risdiplam NICE TA755. To test the impact of using these alternative UK-specific costs, a scenario was conducted by applying the same proxy assumptions as in this appraisal's base case analysis (e.g. type 2 costs applied to HS2 [sitter]) and assumption applied in TA755 (i.e. SMA-care costs for HS1 (non-sitter, PAV) is calculated to be 175% of the SMA-care costs for type 1 patients).

Abbreviations: BRND, broad range of normal development; BSC, best supportive care; HCRU, healthcare resource utilisation; ICER, incremental cost-effectiveness ratio; PAS, patient access scheme; SMA, spinal muscular atrophy; SMN, survival motor neuron; UK, United Kingdom; WHO, World Health Organization.

Table 54: Scenario analysis results

	Arm	Total cost (£)/ patient (discounted)*	QALYs (discounted)*	Incremental cost (£)/ patient(discounted)*	Incremental QALYs (discounted)	ICER (£/QALY)	INMB† (£)
Base case results (PAS)	BSC	882,564	[redacted]	-	-	-	-
	Onasemnogene abeparvovec	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
DISCOUNT RATES							
Costs and effects at 1.5%	BSC	1,428,660	[redacted]	-	-	-	-
	Onasemnogene abeparvovec	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Costs and effects at 0%	BSC	2,341,482	[redacted]	-	-	-	-
	Onasemnogene abeparvovec	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Costs and effects at 5%	BSC	678,696	[redacted]	-	-	-	-
	Onasemnogene abeparvovec	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
MILESTONE ACHIEVEMENT							
Using BSID with WHO data when BSID not available	BSC	882,564	[redacted]	-	-	-	-
	Onasemnogene abeparvovec	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Inclusion of one additional Walker	BSC	882,564	[redacted]	-	-	-	-
	Onasemnogene abeparvovec	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

	Arm	Total cost (£)/ patient (discounted)*	QALYs (discounted)*	Incremental cost (£)/ patient(discounted)*	Incremental QALYs (discounted)	ICER (£/QALY)	INMB† (£)
SURVIVAL							
HS2 (sitter) – Zerres	BSC	715,162	[redacted]	-	-	-	-
	Onasemnogene abeparvovec	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
HS1 (non-sitter, no PAV) - Wijngaarde – All copies	BSC	828,858	[redacted]	-	-	-	-
	Onasemnogene abeparvovec	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
HS1 (non-sitter, no PAV) - NeuroNext/Kolb - All copies	BSC	824,795	[redacted]	-	-	-	-
	Onasemnogene abeparvovec	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
HS1 (non-sitter, no PAV) - PNCR - All copies	BSC	929,893	[redacted]	-	-	-	-
	Onasemnogene abeparvovec	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
UTILITIES							
HRQoL benefit (0.05) applied to HS2 (sitter)- OA arm	BSC	882,564	[redacted]	-	-	-	-
	Onasemnogene abeparvovec	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Belter et al data source	BSC	882,564	[redacted]	-	-	-	-
	Onasemnogene abeparvovec	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

	Arm	Total cost (£)/ patient (discounted)*	QALYs (discounted)*	Incremental cost (£)/ patient(discounted)*	Incremental QALYs (discounted)	ICER (£/QALY)	INMB† (£)
CHERISH data source	BSC	882,564	[redacted]	-	-	-	-
	Onasemnogene abeparvovec	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Dangouloff et al 2022 data source	BSC	882,564	[redacted]	-	-	-	-
	Onasemnogene abeparvovec	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Nusinersen NICE TA588 ERG clinical advisors data source	BSC	882,564	[redacted]	-	-	-	-
	Onasemnogene abeparvovec	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
COSTS							
No cost in HS-BRND state	BSC	872,941	[redacted]	-	-	-	-
	Onasemnogene abeparvovec	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Nusinersen TA588 - RWE values	BSC	1,012,284	[redacted]	-	-	-	-
	Onasemnogene abeparvovec	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

*discounting is not applied in the scenario where the discount rate = 0%.

†INMB is calculated as; (incremental QALYs x willingness to pay threshold) – incremental cost. Positive incremental INMB indicates that onasemnogene abeparvovec is cost-effective compared with BSC at a willingness-to-pay threshold of [redacted]. The higher the INMB value is, the more value for money onasemnogene abeparvovec provides compared with BSC.

Abbreviations: BRND, broad range of normal development; BSC, best supportive care; ERG, evidence review group; HS, health state; ICER, incremental cost-effectiveness ratio; INMB, incremental net monetary benefit; NICE, National Institute for Health and Care Excellence; PAV, permanent assisted ventilation; QALY, quality-adjust life year.

B.3.11 *Subgroup analysis*

As discussed in Section B.3.2.1, the base case ICER is weighted according to the likely ratio of *SMN2* two-copy to *SMN2* three-copy infants identified through screening in England to provide a cost-effectiveness estimate in the population of the decision problem (i.e., infants with pre-symptomatic SMA with up to three copies of *SMN2*). The company believes that this is the most appropriate base case as *SMN2* copy numbers do not provide a definitive way of predicting the course of disease.

However, the company acknowledges both the final scope and NICE's request for subgroup data where possible. Therefore, deterministic, DSA, and PSA results for each of the *SMN2* copy number cohorts (two-copy and three-copy) are also provided separately in Appendix J.

B.3.12 *Benefits not captured in the QALY calculation*

As discussed in Section B.1.2.4, screening for SMA was not recommended by the UK NSC in the review completed in October 2018 (69). This was partially due to a lack of evidence for effective treatments for patients with SMA without observed symptoms. In order to support adoption of a national SMA screening programme, availability and effectiveness of a routinely commissioned disease-modifying therapy is essential. Adoption of a national screening programme will be beneficial to patients, who will be diagnosed earlier, resulting in markedly better outcomes and in line with expert recommendations and consensus statements (14-19).

Screening programmes are not expected to increase the total number of patients eligible for SMA treatment(s), but will allow for earlier identification of infants with SMA, allowing earlier treatment and improved prognosis.

B.3.13 *Validation*

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 B.3.3.4. The validity of the model 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 inputs to extreme values, and turning off specific costs and utility components as well as mortality.

B.3.14 *Interpretation and conclusions of economic evidence*

A *de novo* model structure was developed to address the decision problem (Section B.1) to assess the cost-effectiveness of onasemnogene abeparvovec compared with BSC in patients with pre-symptomatic SMA. In the absence of routinely commissioned disease-modifying therapy for pre-symptomatic SMA, BSC is the only relevant comparator for onasemnogene abeparvovec in this patient population.

The number of copies of the *SMN2* gene is one factor that may help to predict the prognosis of patients with SMA. In the base-case cost-effectiveness analysis, results are

presented for a combined cohort of patients with two and three copies of *SMN2*, with the proportions of patients based on studies of population-based NBS screening from several countries (Section B.3.2.1), therefore representing real-world proportions of pre-symptomatic patients with two and three copies of *SMN2*. In general, fewer copies of *SMN2* result in a more severe disease phenotype (4, 20, 21). As such, clinical efficacy data from the SPR1NT clinical trial are available separately for the two cohorts of included patients (those with two and three copies of *SMN2*). However, for decision-making purposes, the patient population should be treated as a single population as it is not possible to predict the prognosis of SMA in individual patients identified pre-symptomatically. In this combined cohort, the base case ICER for onasemnogene abeparvovec versus BSC is £70,610 per QALY gained using list price for onasemnogene abeparvovec and [redacted] using the price with the PAS discount. This indicates that onasemnogene abeparvovec is cost-effective relative to BSC in pre-symptomatic patients. For completeness, separate cost-effectiveness results have been presented for each of the two patient cohorts in Appendix J, with cost-effectiveness demonstrated.

As discussed in Section B.3.6, clinical data availability is the key area of uncertainty in the economic evaluation. This is due to the very rare nature of SMA resulting in a relatively small patient population enrolled in the key clinical trial informing the model, SPR1NT (14 patients in the *SMN2* two-copy cohort and 15 patients in the three-copy cohort). In addition, it was considered unethical to include a BSC treatment arm in the SPR1NT trial given the poor prognosis for SMA and the unprecedented clinical outcomes observed in previous clinical trials for onasemnogene abeparvovec. As such, it was necessary to use natural history data to compare onasemnogene abeparvovec with BSC, potentially resulting in uncertainty in the clinical outcomes included in the model. However, population-matched cohorts were included from natural history studies, and the impact of using different sources of natural history data was assessed in scenario analyses. Limited follow-up data available to inform the treatment effect over patients' lifetime, resulting in a need for extrapolation of clinical data was another potential source of uncertainty. However, in the onasemnogene abeparvovec arm, motor milestone attainment is based on milestone achievement observed in SPR1NT and currently available data from LT-002 only. This is a conservative assumption as patients are continuing to achieve milestones in the ongoing LT-002 study.

While there are some uncertainties in the cost-effectiveness analysis, the modelling approach, assumptions, and inputs have been validated with UK clinical experts (Section B.3.3.4) and, where applicable, assumptions and inputs previously accepted by the committee for HST15 (59) have been used in this analysis. Furthermore, in addition to the DSA and PSA, key model inputs and assumptions have been tested in scenario analyses, with ICERs ranging from [redacted] to [redacted] per QALY gained using the PAS discount price for onasemnogene abeparvovec. Therefore, despite limitation, the analysis provides robust evidence for the cost-effectiveness of onasemnogene abeparvovec relative to BSC in a population of patients with pre-symptomatic SMA.

B.3.15 Cost to the NHS and Personal Social Services

Full details of budget impact assumptions and inputs are provided in the company budget impact analysis submission. Budget impact results presented for Years 1–5 in the

below tables are for approximately 1.4 to 2.1 eligible incident patients with two or three copies of *SMN2*. The budget impact model contains clinical effectiveness data for incident pre-symptomatic SMA patients from the cost-effectiveness model.

Five-year budget impact results with the list price of onasemnogene abeparvovec (£1,795,000) are provided in Table 55. The total 5-year budget impact using the list price (sum of years 1 to 5 in 'net budget impact, total' row in Table 55) is £12,716,608.

Five-year budget impact results based on the PAS price of onasemnogene abeparvovec [redacted] is presented in Table 56. The total 5-year budget impact using the PAS price (sum of years 1 to 5 in 'net budget impact, total' row in Table 56) is [redacted].

Table 55: Expected budget impact - list price of onasemnogene abeparvovec

	Year 1	Year 2	Year 3	Year 4	Year 5
Eligible incident population	2.2	2.2	1.8	1.4	1.4
Population expected to receive onasemnogene abeparvovec	1.8	1.8	1.5	1.2	1.2
Cost (saving) of treatment pathway without onasemnogene abeparvovec (total, £)	146,731	232,659	267,499	280,682	305,876
Pharmacy costs (£)	0	0	0	0	0
SMA-care related costs (£)	146,731	232,659	267,499	280,682	305,876
Cost (saving) of treatment pathway with onasemnogene abeparvovec (total, £)	3,280,214	3,310,828	2,796,087	2,273,812	2,289,114
Pharmacy costs (£)	3,240,452	3,237,093	2,699,340	2,160,907	2,158,792
SMA-care related costs (£)	39,761	73,735	96,747	112,906	130,321
Net budget impact (total, £)	**3,133,483**	**3,078,169**	**2,528,588**	**1,993,131**	**1,983,238**
Pharmacy budget impact (£)	3,240,452	3,237,093	2,699,340	2,160,907	2,158,792

	Year 1	Year 2	Year 3	Year 4	Year 5
SMA-care budget impact (£)	-106,969	-158,923	-170,752	-167,776	-175,554
Cumulative total from Year 1 (£)	**3,133,483**	**6,211,652**	**8,740,240**	**10,733,371**	**12,716,608**

Abbreviations: SMA, spinal muscular atrophy.

Table 56: Expected budget impact – PAS price of onasemnogene abeparvovec

	Year 1	Year 2	Year 3	Year 4	Year 5
Eligible incident population	2.2	2.2	1.8	1.4	1.4
Population expected to receive onasemnogene abeparvovec	1.8	1.8	1.5	1.2	1.2
Cost (saving) of treatment pathway without onasemnogene abeparvovec (total, £)	146,731	232,659	267,499	280,682	305,876
Pharmacy costs (£)	0	0	0	0	0
SMA-care related costs (£)	146,731	232,659	267,499	280,682	305,876
Cost (saving) of treatment pathway with onasemnogene abeparvovec (total, £)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Pharmacy costs (£)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
SMA-care related costs (£)	39,761	73,735	96,747	112,906	130,321
Net budget impact (total, £)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Pharmacy budget impact (£)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
SMA-care budget impact (£)	-106,969	-158,923	-170,752	-167,776	-175,554
Cumulative total from Year 1 (£)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: PAS, patient access scheme; SMA, spinal muscular atrophy.

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NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

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Onasemnogene abeparvovec for treating pre-symptomatic spinal muscular atrophy (MAA partial review of HST 15) [ID4051]

Summary of Information for Patients (SIP)

August 2022

File name	Version	Contains confidential information	Date
NICE_ID4051_onasemnogene abeparvovec_11Aug22_SiP	1.0	No	11th August 2022

Summary of Information for Patients (SIP):

The pharmaceutical company perspective

What is the SIP?

The Summary of Information for Patients (SIP) is written by the company who is seeking approval from NICE for their treatment to be sold to the NHS for use in England. It is a plain English summary of their submission written for patients participating in the evaluation. It is not independently checked, although members of the public involvement team at NICE will have read it to double-check for marketing and promotional content before it is sent to you.

The **Summary of Information for Patients** template has been adapted for use at NICE from the Health Technology Assessment International – Patient & Citizens Involvement Group (HTAi PCIG). Information about the development is available in an open-access IJTAHC journal article

SECTION 1: Submission summary

Note to those filling out the template: Please complete the template using plain language, taking time to explain all scientific terminology. Do not delete the grey text included in each section of this template as you move through drafting because it might be a useful reference for patient reviewers. Additional prompts for the company have been in red text to further advise on the type of information which may be most relevant and the level of detail needed. You may delete the red text.

1a) Name of the medicine (generic and brand name):

Generic name: Onasemnogene abeparvovec Brand name: Zolgensma® ▼ ▼ This medicine is subject to additional monitoring. This will allow quick identification of new safety information. You can help by reporting any side effects you may get. See https://yellowcard.mhra.gov.uk for how to report side effects.

1b) Population this treatment will be used by. Please outline the main patient population that is being appraised by NICE:

The population being appraised for this treatment by the NICE appraisal includes infants whose genetic profile means they will develop symptoms of SMA, but that so far these have not been observed (pre-symptomatic). The genetic profile includes infants with pre-symptomatic 5q spinal muscular atrophy (SMA) and up to three copies of the *SMN2* gene. NICE assessed onasemnogene abeparvovec in 2021 and approved its use within NHS England for infants who have symptomatic SMA type 1[†] who the meet eligibility criteria. However, as the key clinical trial for infants with pre-symptomatic SMA had not been completed at the time of the appraisal, NICE set up a managed access agreement (MAA) for one year, for infants with pre-symptomatic SMA and up to and including three copies of *SMN2*. This was so that NICE would be able to review these clinical trial results and evaluate the cost-effectiveness of onasemnogene abeparvovec infants with pre-symptomatic SMA and up to and including three copies of *SMN2.* The current appraisal is therefore a partial review of the previous assessment conducted by NICE, focusing only on the pre-symptomatic infant population.

It should be noted that some infants show symptoms of SMA before or immediately after birth (sometimes referred to as having SMA type 0†). The majority sadly do not survive past 1 month of age (1). As they have shown symptoms from birth, they will not have been identified pre-symptomatically and so are not part of the population being considered by this appraisal.

†Before disease-modifying therapy became available, SMA was classified as five discrete clinical types (0 through 4) based on the age at symptom onset and motor milestone achievement (1). Although this classification is widely used, particularly in studies on the natural history of SMA, it has now been unequivocally shown that 5q SMA is one disease, with a single underlying cause and a broad spectrum of clinical severity (2, 3). Clinicians are moving away from describing SMA as specific 'types'. However, the previous NICE assessment refers to SMA type 1, which is a severe form of SMA characterised by onset before 6 months of age and failure to ever achieve a sitting position if not treated.

1c) Authorisation: Please provide marketing authorisation information, date of approval and link to the regulatory agency approval. If the marketing authorisation is pending, please state this, and reference the section of the company submission with the anticipated dates for approval.

Onasemnogene abeparvovec was recommended by the European Medicine Agency (EMA) for conditional marketing authorisation in the European Union (EU) on 18th May 2020. Conditional marketing authorisation means that patients have access to a treatment that addresses their unmet medical needs with less comprehensive data than are normally required by the EMA, with a company commitment to provide further clinical data in the future. As further data for onasemnogene abeparvovec have since been provided to the EMA, a positive opinion from the Committee for Medicinal Products for Human Use (CHMP) was received on 11th July 2022 for full marketing authorisation.

Onasemnogene abeparvovec (EMEA/H/C/004750) is indicated for the treatment of (4):

- 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

The European Public Assessment Report (EPAR), which includes the summary of product characteristics (SmPC) and patient information leaflet (PIL) can be accessed at: Zolgensma | European Medicines Agency (europa.eu).

The original EMA marketing authorisation was valid in the UK. As a consequence of exiting the EU (Brexit), the marketing authorisation transferred to the UK medicines regulator (the Medicines and Healthcare products Regulatory Agency [MHRA]). Currently, the marketing authorisation is being renewed, which is a normal procedure.

1d) Disclosures. Please be transparent about any existing collaborations (or broader conflicts of interest) between the pharmaceutical company and patient groups relevant to the medicine. Please outline the reason and purpose for the engagement/activity and any financial support provided:

Novartis Gene Therapies would like to disclose the following collaborations with patient groups:

- **SMA UK:** In 2021, SMA UK was contracted to provide support to Novartis Gene Therapies with the development of the 'Flexterity' physiotherapy app. In 2021 and 2022, SMA UK is also contracted to provide feedback on onasemnogene abeparvovec Patient Support Programme activities. Contracting is currently in progress for Novartis Gene Therapies to provide a grant to support general activities of SMA UK in 2020, 2022 and 2023
- **UK Newborn Screening Alliance grant:** In 2021 and 2022, Novartis Gene Therapies has provided a grant to MDUK and SMA UK to support the work of patient organisations and clinicians, including their work on the UK national NBS screening programme for SMA. Novartis Gene Therapies has also sponsored meetings organised by MDUK.

Transparency is important to Novartis and details of funding of patient groups across Novartis is disclosed on the Novartis UK website (https://www.novartis.co.uk/partnerships/patient-group-partnerships).

SECTION 2: Current landscape

Note to authors: This SIP is intended to be drafted at a global level and typically contain global data. However, the submitting local organisation should include country-level information where needed to provide local country-level context.

Please focus this submission on the **main indication (condition and the population who would use the treatment)** being assessed by NICE rather than sub-groups, as this could distract from the focus of the SIP and the NICE review overall. However, if relevant to the submission please outline why certain sub-groups have been chosen.

2a) The condition – clinical presentation and impact

Please provide a few sentences to describe the condition that is being assessed by NICE and the number of people who are currently living with this condition in England.

Please outline in general terms how the condition affects the quality of life of patients and their families/caregivers. Please highlight any mortality/morbidity data relating to the condition if available. If the company is making a case for the impact of the treatment on carers this should be clearly stated and explained.

What is SMA?

SMA is a very rare, devastating, genetically inherited neuromuscular condition, which causes progressive muscle wasting (atrophy) and weakness, leading to a loss of movement. This can affect an infant's ability to crawl, walk, move their head and neck, swallow, and breathe (1, 5).

Approximately 1 in 10,000 babies are born with SMA (6), and there is a wide spectrum of how severely these infants are affected. The majority of infants born with SMA (approximately 60%) develop symptoms before 6 months of age and, without treatment, never achieve age-appropriate developmental milestones (e.g. crawling and sitting) and, without intervention for breathing difficulties, die before 2 years of age (7). Other children with less severe forms of SMA develop symptoms between 6 months and 7 years of age and achieve some milestones (e.g. sitting or walking), but often experience significant complications, including feeding and breathing difficulties (8, 9), and lose their ability to stand or walk as they get older (10-12). Although many children survive into adulthood, there is often substantial impact on quality of life.

What causes SMA?

SMA is caused by a missing or abnormal gene (survival motor neuron gene 1 [*SMN1*]), which results in a lack of survival motor neuron (SMN) protein production (1, 5). This causes the nerve cells that control muscles (motor neurons) to die, resulting in progressive muscle weakness and loss of movement (1, 5).

SMA is passed from parents to their children through faulty *SMN1* genes. People who inherit two faulty copies of the *SMN1* gene (one from each parent) will have SMA. Those who inherit one faulty copy from one parent and one healthy copy from the other parent will not have SMA, but will be carriers of SMA, potentially passing the faulty gene to the next generation. Parents may be unaware that they are carriers of the faulty *SMN1* gene but, if two carriers have a child together, there is a 25% chance for each pregnancy, that the child will inherit both faulty genes and will have SMA (6).

A second gene, *SMN2*, sometimes referred to as the SMA 'back-up' gene, also has a role in SMN protein production. However, most of the SMN protein produced by the *SMN2* gene is 'non-

functional' because it lacks a key building block that is usually produced by the *SMN1* gene. Therefore, while *SMN2* can make some functional SMN protein (approximately 10% of SMN protein produced is functional per copy of the *SMN2* gene), it cannot produce enough to fully make up for the faulty or missing *SMN1* gene in people with SMA. Unlike most genes, the number of copies of the *SMN2* gene can vary from person to person, and can be between 0 and 8 (6). At a population level, the severity of SMA is linked to how much SMN protein is made, meaning that there is a general relationship between the number of *SMN2* copies that a person has and the severity of their symptoms (i.e. having more copies of *SMN2* is generally associated with less severe disease) (13-15). However, at an individual level, several factors other than *SMN2* copy number have an impact on the severity of SMA, and it is impossible to predict precisely the severity of SMA before symptoms develop.

What is the impact of SMA on patients and caregivers?

Infants with SMA commonly experience severe health complications, including feeding and breathing difficulties, that can be fatal and can dramatically impact their lives. Without treatment, those with the most severe form of SMA often have short lives, with many hours spent in hospital (16). Those with less severe disease can also develop severe complications, including feeding and breathing complications, which can be fatal (10). Even those who are able to walk may never be able to run, jump, or climb stairs independently, and may also face losing the ability to walk into adolescence or adulthood (10, 17).

SMA has substantial effects on families and carers, including the impact of caring for the child, the need for specialist equipment and ongoing emotional, financial and social impacts. More than half of caregivers of infants with SMA report feeling that their lives are "hard," and that they often feel "tied down" (18). In a UK study, voluntary caregivers of infants who never achieve sitting report a substantial burden on their time due to the need for feeding support, physical therapy, and cough assist (19). Many caregivers of children with SMA are forced to change their work hours or stop work entirely, and they also report monthly expenses for home adaptations and home health care. The burden of caregiving can also extend to multiple family members and affect those without direct caring responsibilities, with grandparents, siblings and family friends often severely affected (20-22). In addition to the time spent caregiving and having to bear high costs associated with their child's condition, parents of children and adolescents with SMA are likely to have to face difficult decisions around their child's treatment and care. Following SMA diagnosis of their child, parents my experience physical and mental health problems, with some parents experiencing post-traumatic symptoms (23).

2b) Diagnosis of the condition (in relation to the medicine being evaluated)

Please briefly explain how the condition is currently diagnosed and how this impacts patients. Are there any additional diagnostic tests required with the new treatment?

SMA can be diagnosed quicker through screening, before the development of symptoms.

In England, screening for SMA is currently conducted only in infants who have siblings with SMA or those with parents known to be carrying the faulty gene for SMA (as discussed in Section 2a, parents may be carriers for SMA without having SMA themselves).

With new treatments for SMA becoming available (and being routinely commissioned by NHS England), including onasemnogene abeparvovec, there is potential for implementing a national programme in which all infants are screened for SMA at birth in the UK so that they can be treated as early as possible. This is being considered by the UK National Screening Committee. A UK population-based pilot study is also currently being conducted in the Thames Valley region of

England to evaluate the feasibility of conducting national population-based screening for SMA, using a blood sample already routinely collected from newborn babies (24).

2c) Current treatment options:

The purpose of this section is to set the scene on how the condition is currently managed:

- What is the treatment pathway for this condition and where in this pathway the medicine is likely to be used? Please use diagrams to accompany text where possible. Please give emphasis to the specific setting and condition being considered by NICE in this review. For example, by referencing current treatment guidelines. It may be relevant to show the treatments people may have before and after the treatment under consideration in this SIP.
- Please also consider:
    - if there are multiple treatment options, and data suggest that some are more commonly used than others in the setting and condition being considered in this SIP, please report these data.
    - are there any drug–drug interactions and/or contraindications that commonly cause challenges for patient populations? If so, please explain what these are.

Over the past few years, the NHS has revolutionised care for people with SMA with three disease-modifying treatments and all three disease-modifying treatments are available in England through MAAs for pre-symptomatic infants. These treatments significantly improve survival and motor function compared with what would be the natural course of SMA described above. It should be noted that none of the disease-modifying treatments are routinely commissioned by NHS England for pre-symptomatic infants. This means that the data presented to NICE by the companies was not sufficient for NICE to make a recommendation at that time. However, the good news is that eligible infants can still access the treatments, through MAAs while the requested data is collected and/or the trial completes and during the NICE re-evaluation period. Once the company submits the data, NICE can decide whether the treatment is cost-effective. If NICE gives a positive recommendation, then NHS England will commission (continue to pay for) the treatment (and it becomes routinely commissioned). Therefore, for the purpose of this appraisal, NICE methods and process mean that other disease-modifying treatments are not considered as viable options, as they are not routinely commissioned for pre-symptomatic infants with SMA. BSC is therefore considered the only other option available for purposes of the assessment.

Treating early maximises outcomes and gives children with SMA the best chance of a healthy life. It is critical to help reduce the rapid and progressive degeneration seen in SMA and to support age-appropriate motor milestone attainment (25). A greater therapeutic benefit is seen in those who are treated pre-symptomatically. However, because SMA is rare and difficult for parents and healthcare professionals to spot, and because there is currently no national screening programme in the UK, most infants will experience irreversible loss of nerve cells before they are diagnosed and treated. Early diagnosis and treatment can prevent this loss of nerve cells before the irreversible damage is done.

Without routinely available disease-modifying treatments for pre-symptomatic SMA, infants receive best supportive care (BSC) to manage the symptoms of SMA once they develop. In general, the goal of BSC is to reduce the burden of illness on the child and family (26, 27). BSC focuses on several areas, such as respiratory care, gastrointestinal (GI) and nutritional support, orthopaedic care and rehabilitation, and palliative care (26-28). It does not halt or delay disease progression or prevent the premature death of infants. Furthermore, it does not improve motor function, and infants receiving BSC continue to have poor quality of life.

2d) Patient-based evidence (PBE) about living with the condition

Context:

- **Patient-based evidence (PBE)** is when patients input into scientific research, specifically to provide experiences of their symptoms, needs, perceptions, quality of life issues or experiences of the medicine they are currently taking. PBE might also include carer burden and outputs from patient preference studies, when conducted in order to show what matters most to patients and carers and where their greatest needs are. Such research can inform the selection of patient-relevant endpoints in clinical trials.

In this section, please provide a summary of any PBE that has been collected or published to demonstrate what is understood about **patient needs and disease experiences**. Please include the methods used for collecting this evidence. Any such evidence included in the SIP should be formally referenced wherever possible and references included.

It is not possible to obtain self-reported information about living with SMA from babies due to their young age. However, surveys of caregivers of children with SMA in the UK demonstrate the impact of SMA on patient and caregiver lives.

Based on a survey of caregivers of children with a severe form of SMA, who never achieve the ability to sit, conducted in the UK in 2021 (29):

- On average, caregivers spent 102 hours per week caring for their child with SMA. The activities requiring the most time from caregivers included feeding their child, driving their child to healthcare visits for physical therapy, and maintaining hygiene and any specialist equipment that the child requires
- Over three quarters (76%) of children had one or more overnight hospitalisation within the 6 months before the survey
- Almost half (48%) of caregivers had to stop work to provide care, with another 20% having to reduce their working hours and 12% changing jobs. As a result, caregivers reported an average reduction in their monthly income of £1,012
- Caregivers had substantial expenses with home adaptations and home health care required by their child with SMA, as well as facing additional costs of travel to medical appointments and finding accommodation close to hospital

A caregiver survey was also conducted in 2018 in the UK (30, 31), which included people with less severe forms of SMA (those who achieve sitting or walking independently) as well as those who never achieve the ability to sit. While those who achieved walking independently required the least support from unpaid caregivers, they still required an average of 2.2 unpaid carers to provide support. Those with who did not achieve sitting or achieved sitting as their highest milestone required an average of 2.8 caregivers for their support. Caregivers included parents and close relatives, as well as friends and neighbours. The survey demonstrates the devastating emotional impact of the progressive deterioration of muscle strength that is characteristic of SMA, highlighting that children with SMA "struggle to understand why they are no longer able to do the few things which they were able to do a few months before".

A systematic literature review has also been conducted to identify studies assessing the burden of SMA on caregivers (23). This review found that, in addition to the time spent caregiving and having to bear high costs associated with their child's condition, parents of children and adolescents with SMA, particularly the more severe forms of SMA, are likely to have to face difficult decisions around their child's treatment and care. Following SMA diagnosis of their child, parents my experience physical and mental health problems, with some parents experiencing post-traumatic symptoms (23).

SECTION 3: The treatment

Note to authors: Please complete each section with a concise overview of the key details and data, including plain language explanations of any scientific methods or terminology. Please provide all references at the end of the template. Graphs or images may be used to accompany text if they will help to convey information more clearly.

3a) How does the new treatment work?

What are the important features of this treatment?

Please outline as clearly as possible important details that you consider relevant to patients relating to the mechanism of action and how the medicine interacts with the body

Where possible, please describe how you feel the medicine is innovative or novel, and how this might be important to patients and their communities.

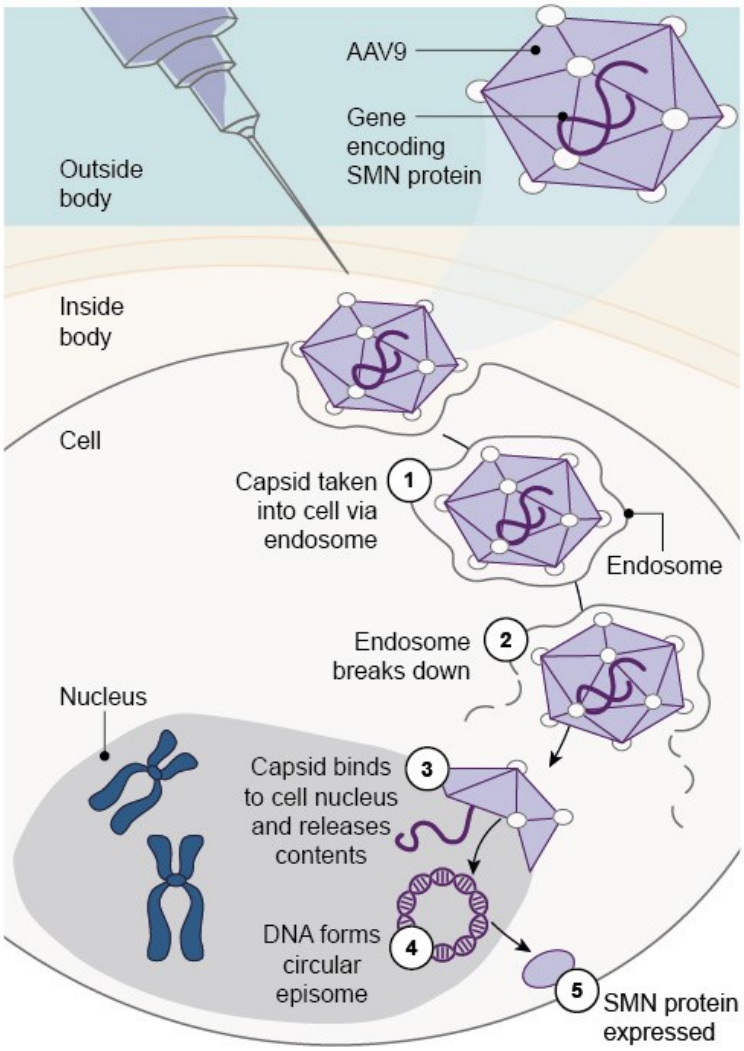
If there are relevant documents which have been produced to support your regulatory submission such as a summary of product characteristics or patient information leaflet, please provide a link to these.

Onasemnogene abeparvovec is a gene therapy. Gene therapies represent a major leap forward in medicine, delivering transformative benefits for patients. In contrast to many conventional treatments that must be taken continually (for weeks, months, or even for life), gene therapies are generally one-time treatments that work by replacing the missing or faulty gene responsible for causing the disease.

Onasemnogene abeparvovec is a gene therapy delivered as a one-time treatment by intravenous (IV) infusion by a healthcare professional at one of four specialist centres in the UK. It addresses the underlying genetic cause of SMA by replacing the missing or faulty *SMN1* gene, resulting in patient's cells producing the functional SMN protein needed for nerve cell function.

The gene is delivered into patient's cells through the bloodstream using a modified virus (adeno-associated virus 9 [AAV9]), known as a vector, that does not cause disease in humans. The gene is enclosed in the protein shell of the vector (known as the capsid), allowing it to enter the patient cells. Once inside the patient's cells, the vector releases the functional *SMN1* gene replacement, and this leads to production of SMN protein (Figure 1). In the long term, the gene replacement remains in the patient cell as an episome, which means that it exists independently of the cell's deoxyribonucleic acid (DNA). This allows sustained production of functional SMN protein, which is why only a single dose of onasemnogene abeparvovec is required.

Figure 1: Onasemnogene abeparvovec mechanism of action



Onasemnogene abeparvovec is the only treatment for SMA provided as a single dose and is the only gene therapy available for SMA.

The European Public Assessment Report (EPAR), which includes the summary of product characteristics (SmPC) and patient information leaflet (PIL) can be accessed at: Zolgensma | European Medicines Agency (europa.eu).

3b) Combinations with other medicines

Is the medicine intended to be used in combination with any other medicines?

- Yes / No

If yes, please explain why and how the medicines work together. Please outline the mechanism of action of those other medicines so it is clear to patients why they are used together.

If yes, please also provide information on the availability of the other medicine(s) as well as the main side effects.

If this submission is for a combination treatment, please ensure the sections on efficacy (3e), quality of life (3f) and safety/side effects (3g) focus on data that relate to the combination, rather than the individual treatments.

As part of treatment with onasemnogene abeparvovec, patients are given a corticosteroid medicine (e.g. prednisolone) for approximately 2 months or longer. This is to help to manage any increase in liver enzymes that patients may experience after receiving onasemnogene abeparvovec. As corticosteroids can affect the immune system, the infants' vaccination schedule may need to be modified while they are receiving corticosteroids.

3c) Administration and dosing

How and where is the treatment given or taken? Please include the dose, how often the treatment should be given/taken, and how long the treatment should be given/taken for.

How will this administration method or dosing potentially affect patients and caregivers? How does this differ to existing treatments?

Gene therapies need to be administered in a specialist clinical setting under the supervision of an experienced clinician. Careful monitoring and ongoing contact are also needed to identify any potential side effects.

Patients will receive a one-time treatment of onasemnogene abeparvovec, administered via a syringe pump as a single-dose IV infusion over approximately 60 minutes. Patients will receive onasemnogene abeparvovec at a dose of 1.1×10^{14} vg/kg, with the total volume being determined by patient body weight. An immunomodulation regimen with corticosteroids, as described above, is recommended.

Four infusion sites have already been established for the administration of onasemnogene abeparvovec for children with SMA in the UK.

3d) Current clinical trials

Please provide a list of completed or ongoing clinical trials for the treatment. Please provide a brief top-level summary for each trial, such as title/name, location, population, patient group size, comparators, key inclusion and exclusion criteria and completion dates etc. Please provide references to further information about the trials or publications from the trials.

The clinical effectiveness of onasemnogene abeparvovec in infants with pre-symptomatic SMA has been evaluated in a completed Phase III clinical trial (SPR1NT) (32, 33), with ongoing long-term data collection in the long-term follow up study, LT-002.

SPR1NT (NCT03505099)

The SPR1NT trial evaluated the safety and efficacy of a one-time infusion of onasemnogene abeparvovec in pre-symptomatic infants with genetically diagnosed 5q SMA with a faulty or missing *SMN1* gene and two or three copies of the *SMN2* gene.

In general, fewer copies of *SMN2* may result in a more severe disease phenotype. The SPR1NT trial was designed with two distinct cohorts of infants based on the number of copies (two or three copies) of the *SMN2* gene. The *SMN2* two-copy and *SMN2* three-copy cohorts have different efficacy outcomes and length of time followed in the trial, and therefore clinical evidence is available for these cohorts separately. However, it should be noted that, prior to observation of symptoms, there is no definitive way to determine the severity of disease or to predict survival, and some infants with three copies of *SMN2* will develop a severe form of SMA (14).

As may be expected given that SMA is a very rare disease, the patient population included in SPR1NT was relatively small (14 infants in the *SMN2* two-copy cohort and 15 infants in the three-copy cohort). Despite this, clear benefit of onasemnogene abeparvovec was demonstrated. In addition, SPR1NT was a single-arm study (i.e. it did not directly compare infants treated with

onasemnogene abeparvovec with infants treated with best supportive care [BSC] alone). This was because it was would have been unethical to conduct such a study given:

- The extremely poor outcomes experienced by infants with SMA treated with BSC alone
- The unprecedented clinical benefits of onasemnogene abeparvovec shown in infants with symptomatic SMA in a previous clinical trial (34, 35)

However, previously conducted studies assessing the natural course of SMA without treatment were used to provide control data to allow comparison between onasemnogene abeparvovec and BSC.

LT-002 (NCT04042025)

Novartis Gene Therapies has an ongoing commitment to the SMA community, which includes collecting and sharing long-term data on the efficacy and safety of onasemnogene abeparvovec. LT-002 is an ongoing long-term safety follow-up study of patients treated with onasemnogene abeparvovec in clinical trials (including SPR1NT and other trials in symptomatic patients with SMA) with the aims of collecting long-term efficacy and safety data from patients with SMA treated with onasemnogene abeparvovec, and to determine whether the motor milestones achieved are maintained, and whether new motor milestones are gained over time.

3e) Efficacy

Efficacy is the measure of how well a treatment works in treating a specific condition.

In this section, please summarise all data that demonstrate how effective the treatment is compared with current treatments at treating the condition outlined in section 2a. Are any of the outcomes more important to patients than others and why? Are there any limitations to the data which may affect how to interpret the results? Please do not include academic or commercial in confidence information but where necessary reference the section of the company submission where this can be found.

In the Phase III SPR1NT trial (32, 33), infants with two or three copies of *SMN2* who received a one-time infusion of onasemnogene abeparvovec achieved age-appropriate motor milestones that would never be achieved in untreated infants and may not have been achieved if treatment had been delayed until symptoms developed:

- All 29 (100%) infants in the *SMN2* two- or three-copy cohorts of SPR1NT were alive and free of permanent ventilation at their last study visit
- No child required mechanical or non-oral support with feeding (e.g. tube feeding), or ventilatory support during the SPR1NT trial
- In the two-copy cohort:
    - All 14 (100%) children achieved independent sitting (the primary efficacy outcome) at any visit up to 18 months of age, and 11 (78.6%) children achieved this within the age-appropriate developmental window
    - In contrast, none of the 23 children in the matched natural history population achieved this endpoint up to 18 months of age ($p<0.0001$)
- In the three-copy cohort:
    - All 15 (100%) children achieved standing alone (the primary efficacy endpoint) at any visit up to 24 months of age, compared with 19 of 81 children (23.5%) in the matched natural history population ($p<0.0001$)
    - Fourteen children (93.3%) achieved this milestone within the age-appropriate developmental window, and 14 children (93.3%) also achieved walking alone at any visit up to 24 months of age

Children treated with onasemnogene abeparvovec in SPR1NT are continuing to achieve additional milestones in the long-term follow up study, LT-002.

3f) Quality of life impact of the medicine and patient preference information

What is the clinical evidence for a potential impact of this medicine on the quality of life of patients and their families/caregivers? What quality of life instrument was used? If the EuroQol-5D (EQ-5D) was used does it sufficiently capture quality of life for this condition? Are there other disease specific quality of life measures that should also be considered as supplementary information?

Please outline in plain language any quality of life related data such as **patient reported outcomes (PROs).**

Please include any **patient preference information (PPI)** relating to the drug profile, for instance research to understand willingness to accept the risk of side effects given the added benefit of treatment. Please include all references as required.

It is not possible to obtain self-reported health-related quality of life (HRQoL) information from babies due to their young age and, therefore, these data could not be collected in the SPR1NT clinical trial.

However, as highlighted in Sections 2a and 2d, SMA has substantial effects on families and carers, including the impact of caring for the child, the need for specialist equipment and ongoing emotional, financial and social impacts. This may be alleviated by early treatment with onasemnogene abeparvovec that prevents disease progression and enables children to achieve milestones that would never be achieved in children treated with BSC alone.

3g) Safety of the medicine and side effects

When NICE appraises a treatment, it will pay close attention to the balance of the benefits of the treatment in relation to its potential risks and any side effects. Therefore, please outline the main side effects (as opposed to a complete list) of this treatment and include details of a benefit/risk assessment where possible. This will support patient reviewers to consider the potential overall benefits and side effects that the medicine can offer.

Based on available data, please outline the most common side effects, how frequently they happen compared with standard treatment, how they could potentially be managed and how many people had treatment adjustments or stopped treatment. Where it will add value or context for patient readers, please include references to the Summary of Product Characteristics from regulatory agencies etc.

Safety of onasemnogene abeparvovec in clinical trials

Overall, the available data show that treatment with onasemnogene abeparvovec was associated with a favourable safety profile in pre-symptomatic infants with SMA (32, 33).

Twenty-nine infants received an IV infusion of onasemnogene abeparvovec in the two-copy and three-copy cohorts of SPR1NT. No infant in SPR1NT had any unexpected medical problem that was not present before treatment or any unexpected medical problem already present that worsened in either intensity or frequency following treatment - a 'treatment-emergent adverse event' (TEAE) - resulting in death or discontinuation from the study. All infants (100%) experienced one or more TEAE during the study, with a total 325 TEAEs reported. However, most were mild to moderate in severity. None of the nine serious AEs reported in SPR1NT were considered by the investigator to be related to onasemnogene abeparvovec.

The most frequently reported TEAEs were raised body temperature or fever (pyrexia), upper respiratory tract infection and constipation. Eighteen children (62.1%) had at least one TEAE that was considered by the investigator to be related to onasemnogene abeparvovec, with increased aspartate aminotransferase (an enzyme found in the liver, heart, and other tissues - a high level of aspartate transaminase released into the blood may be a sign of liver or heart damage), vomiting and rash being most frequently reported.

As of the 23 May 2022 (the latest available data cut), no child in LT-002 had a TEAE resulting in death or discontinuation from the study.

Safety considerations in clinical practice

To ensure that children with SMA are monitored appropriately after receiving onasemnogene abeparvovec, the treatment is only administered at four commissioned infusion sites in England. Side effects and measures taken to monitor and mitigate side effects are described in Section 3i.

3h) Summary of key benefits of treatment for patients

Issues to consider in your response:

- Please outline what you feel are the key benefits of the treatment for patients, caregivers and their communities when compared with current treatments.
- Please include benefits related to the mode of action, effectiveness, safety and mode of administration
-

The key benefits of onasemnogene abeparvovec for patients with SMA include (4, 32, 33):

- Onasemnogene abeparvovec is a gene therapy and the only therapy that works by correcting the underlying genetic cause of SMA (i.e. it provides a functional copy of the missing or abnormal *SMN1* gene)
- Patients receiving onasemnogene abeparvovec require only a one-time, single dose of IV therapy and, after receiving the dose, there is no need for routine hospital admissions, procedures, or continued dosing
- The data from the SPR1NT clinical trial clearly demonstrates the efficacy of treating pre-symptomatic infants with SMA, in terms of motor function, motor milestones achieved, and respiratory function. Some children have achieved age-appropriate development in line with that expected for children without SMA
- Safety data from SPR1NT and LT-002 demonstrate favourable benefit-risk profile of onasemnogene abeparvovec in pre-symptomatic infants

Expert recommendations and consensus statements recognise that the early initiation of disease-modifying treatment for SMA, ideally before symptoms become apparent, can halt this irreversible motor neuron loss, improve neuromuscular function, and prevent disease progression (25, 36-40).

3i) Summary of key disadvantages of treatment for patients

Issues to consider in your response:

- Please outline what you feel are the key disadvantages of the treatment for patients, caregivers and their communities when compared with current treatments. Which disadvantages are most important to patients and carers?
- Please include disadvantages related to the mode of action, effectiveness, side effects and mode of administration
- What is the impact of any disadvantages highlighted compared with current treatments

The key disadvantages of onasemnogene abeparvovec for patients with SMA include (4):

- Onasemnogene abeparvovec triggers the immune system, which can cause a rise in liver enzymes or even, rarely, hepatitis and liver failure. Risk is mitigated by giving a corticosteroid (see Section 3b) alongside onasemnogene abeparvovec, which may mean that some vaccinations need to be delayed. In addition, corticosteroids can increase the risk of infections, particularly respiratory infections, while being taken. As a result, vaccination schedules may need to be altered while patients are taking corticosteroids. In premature infants, administration of onasemnogene abeparvovec should be carefully considered

because concomitant treatment with corticosteroids may adversely affect neurological development. Clinicians also need to be aware of a potential risk of adrenal insufficiency (a condition that causes low blood pressure, low blood sugar levels, and other symptoms, which may be life-threatening) if the corticosteroid dose is increased or if treatment is prolonged

- Onasemnogene abeparvovec temporarily reduces levels of blood platelets, which are involved in blood clotting. This may result in some bruising and, extremely rarely, can result in thrombotic microangiopathy (TMA), which can severely affect the kidneys and can even be fatal if not recognised and treated
- Patients treated with onasemnogene abeparvovec may 'shed' treatment temporarily after dosing, primarily through bodily waste. This means that caregivers must take care with hand hygiene when dealing with bodily waste and disposal of nappies for 1 month after dosing

Regular blood tests for the first 3 months after onasemnogene abeparvovec dosing are used to monitor the potential risks associated with treatment.

It should also be noted that AAV9 (the vector for onasemnogene abeparvovec) exists naturally in the environment, meaning that some people are exposed to it and produce antibodies against AAV9. Therefore, infants must be tested for the presence of AAV9 antibodies prior to treatment with onasemnogene abeparvovec as 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 (4). Therefore, some infants may not be able to receive onasemnogene abeparvovec due to a high anti-AAV9 antibody titre. Re-testing may be performed if AAV9 antibody titres (a laboratory test that measures the level of antibodies in a blood sample) are reported as above 1:50.

3i) Value and economic considerations

Introduction for patients:

Health services want to get the most value from their budget and therefore need to decide whether a new treatment provides good value compared with other treatments. To do this they consider the costs of treating patients and how patients' health will improve, from feeling better and/or living longer, compared with the treatments already in use. The drug manufacturer provides this information, often presented using a health economic model.

In completing your input to the NICE appraisal process for the medicine, you may wish to reflect on:

- The extent to which you agree/disagree with the value arguments presented below (e.g., whether you feel these are the relevant health outcomes, addressing the unmet needs and issues faced by patients; were any improvements that would be important to you missed out, not tested or not proven?)
- If you feel the benefits or side effects of the medicine, including how and when it is given or taken, would have positive or negative financial implications for patients or their families (e.g., travel costs, time-off work)?
- How the condition, taking the new treatment compared with current treatments affects your quality of life.

As discussed in Section 2c, there are currently no disease-modifying therapies routinely available for infants with pre-symptomatic SMA in NHS England, making BSC the only option available for the management of these children. However, early initiation of disease-modifying treatment for SMA, ideally before symptoms become apparent, can halt irreversible nerve cell loss, improve neuromuscular function, and prevent disease progression (25, 36-40). As a one-time treatment that addresses the underlying genetic cause of SMA by providing a functional copy of the *SMN1*

gene (4), onasemnogene abeparvovec can fulfil the need for a routinely available disease-modifying therapy that can halt the progression of disease in those with pre-symptomatic SMA.

The results of the clinical trial for onasemnogene abeparvovec in the pre-symptomatic population (SPR1NT) show that motor milestones that would never be achieved in infants receiving BSC only, can be achieved by infants with genetically confirmed SMA who are treated before symptoms are observed. Furthermore, the majority of these milestones are achieved within windows of age-appropriate development (32, 33, 41).

Based on the evidence available and the company's economic analysis, onasemnogene abeparvovec would be considered as offering a good use of NHS resources as a treatment for infants with pre-symptomatic SMA.

3j) Innovation

NICE considers how innovative a new treatment is when making its recommendations.

If the company considers the new treatment to be innovative please explain how it represents a 'step change' in treatment and/ or effectiveness compared with current treatments. Are there any QALY benefits that have not been captured in the economic model that also need to be considered (see section 3f)

Onasemnogene abeparvovec offers a significant advance in treatment and has the potential to significantly improve patient quality of life. Earlier treatment may help to maximise its benefits (42).

Onasemnogene abeparvovec is a gene therapy and the only treatment that works by correcting the underlying genetic cause of SMA (i.e. it provides a functional copy of the missing or faulty *SMN1* gene). Patients receiving onasemnogene abeparvovec require only a one-time, single dose of IV therapy.

Onasemnogene abeparvovec is already available for the treatment of children who have symptomatic SMA type 1.[†] However, early initiation of disease-modifying treatment for SMA, ideally before symptoms become apparent, can halt the irreversible nerve cell loss associated with SMA, improve neuromuscular function, and prevent disease progression (25, 36-40). The availability of onasemnogene abeparvovec for the pre-symptomatic infant population represents a step change in the treatment of SMA, allowing for early treatment before symptoms develop and giving infants the best chance of achieving the best possible clinical outcomes.

As discussed in Section 2b, there is currently no national screening programme for SMA in the UK, but the possibility of introducing one is being assessed by the UK National Screening Committee, with a whole newborn population pilot study currently underway in the Thames Valley area (24). While newborn screening is currently limited only to those with a family history of SMA, whole population screening would allow identification of all infants born with pre-symptomatic SMA, giving them the opportunity for early treatment, resulting in better outcomes. The availability of a routinely available treatment for pre-symptomatic SMA is one of the key criteria being considered by the National Screening Committee in decision making around the introduction of a national screening programme for SMA. Novartis Gene Therapies supports the implementation of a national screening programme for SMA. However, it should be noted that the decision to implement this is not within the scope of the appraisal currently being conducted by NICE.

†Before disease-modifying therapy became available, SMA was classified as five discrete clinical types (0 through 4) based on the age at symptom onset and motor milestone achievement (1). Although this classification is widely used, particularly in studies on the natural history of SMA, it has now been unequivocally shown that 5q SMA is one disease, with a single underlying cause and a broad spectrum of clinical severity (2, 3). Clinicians are moving away from describing SMA as specific 'types'. However, the previous NICE assessment refers to SMA type 1, which is a severe form of SMA characterised by onset before 6 months of age and failure to ever achieve a sitting position if not treated.

3k) Equalities

Are there any potential equality issues that should be taken into account when considering this condition and this treatment? Please explain if you think any groups of people with this condition are particularly disadvantaged. Equality legislation includes people of a particular age, disability, gender reassignment, marriage and civil partnership, pregnancy and maternity, race, religion or belief, sex, and sexual orientation or people with any other shared characteristics More information on how NICE deals with equalities issues can be found in the NICE equality scheme Find more general information about the Equality Act and equalities issues here
There are no special equality considerations in the treatment of the pre-symptomatic population with a genetic diagnosis of SMA with onasemnogene abeparvovec.

SECTION 4: Further information, glossary and references

4a) Further information

Feedback suggests that patients would appreciate links to other information sources and tools that can help them easily locate relevant background information and facilitate their effective contribution to the NICE assessment process. Therefore, please provide links to any relevant online information that would be useful, for example, published clinical trial data, factual web content, educational materials etc. Where possible, please provide open access materials or provide copies that patients can access.
Further information on NICE and the role of patients**:** • Public Involvement at NICE Public involvement | NICE and the public | NICE Communities | About | NICE • NICE's guides and templates for patient involvement in HTAs Guides to developing our guidance | Help us develop guidance | Support for voluntary and community sector (VCS) organisations | Public involvement | NICE and the public | NICE Communities | About | NICE • EUPATI guidance on patient involvement in NICE: https://www.eupati.eu/guidance-patient-involvement/ • EFPIA – Working together with patient groups: https://www.efpia.eu/media/288492/working-together-with-patient-groups-23102017.pdf • National Health Council Value Initiative. https://nationalhealthcouncil.org/issue/value/ • INAHTA: http://www.inahta.org/ • European Observatory on Health Systems and Policies. Health technology assessment - an introduction to objectives, role of evidence, and structure in Europe: http://www.inahta.org/wp-content/themes/inahta/img/AboutHTA_Policy_brief_on_HTA_Introduction_to_Objectives_Role_of_Evidence_Structure_in_Europe.pdf Previous NICE appraisals in SMA • HST15 (onasemnogene abeparvovec): Overview | Onasemnogene abeparvovec for treating spinal muscular atrophy | Guidance | NICE • TA588 (nusinersen): Overview | Nusinersen for treating spinal muscular atrophy | Guidance | NICE

- TA755 (risdiplam): Overview | Risdiplam for treating spinal muscular atrophy | Guidance | NICE

Patient groups and charities:

- Muscular Dystrophy UK: Muscular Dystrophy UK | Muscular Dystrophy UK
- SMA UK: Spinal Muscular Atrophy UK - SMA Charity (smauk.org.uk)

4b) Glossary of terms

Adeno-associated virus 9: A small virus often used to deliver gene therapies into the human body.

Antibody: Protective proteins produced by the immune system.

Best supportive care: A term used when a cure is not achievable with existing treatments and the care provided is for management of the symptoms of a disease only (e.g. managing pain, nutritional support, respiratory support).

Capsid: The protein shell of a virus.

Corticosteroid: Anti-inflammatory medicines used to treat a range of conditions.

Gene therapy: Treatments that repair of reconstruct defective genetic material.

Health-related quality of life: An individual's or group's perceived physical and mental health over time.

Intravenous infusion: A method of administering fluids or medications directly into a person's vein.

National Screening Committee: Committee that advises ministers and the NHS in the four UK countries about all aspect of screening and supports implementation of screening programmes.

Orthopaedic: Branch of medicine concerned with conditions involving the musculoskeletal system.

Pulmonary: Relating to the respiratory tract.

Palliative care: Care aimed at optimising quality of life and mitigating suffering at the end of life.

Pilot study: A small-scale preliminary study.

Treatment-emergent adverse events: Events that emerge during treatment, having been absent before treatment, or that worsen during treatment relative to pre-treatment.

Vector: An agent (in this case, a virus) used as a vehicle to artificially carry foreign genetic material into cells.

4c) References

Please provide a list of all references in the Vancouver style, numbered and ordered strictly in accordance with their numbering in the text:

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NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Highly Specialised Technology

Onasemnogene abeparvovec for treating pre-symptomatic spinal muscular atrophy (MAA partial review of HST 15) [ID4051]

Clarification questions

August 2022

File name	Version	Contains confidential information	Date
ID4051 onasemnogene abeparvovec responses to EAG clarification questions [REDACTED]_MASTER_FINAL_200922	1	Yes	20th September 2022

Notes for company

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Issue of concern: comparator treatment

Priority question

The focus of this appraisal is on patients with pre-symptomatic spinal muscular atrophy who have up to three copies of the *SMN2* gene. The intervention is onasemnogene abeparvovec. Following discussions with NICE about Appraisal Committee expectations, please provide *clinical and cost effectiveness* evidence to support the following comparator treatment pathways versus onasemnogene abeparvovec for treating pre-symptomatic SMA:

- no specific treatment followed by treatment with onasemnogene abeparvovec upon a clinical diagnosis of type 1 spinal muscular atrophy and
- tailored best supportive care upon a clinical diagnosis of type 2, type 3 or type 4 spinal muscular atrophy.

Please ensure that:

- evidence is stratified by number of *SMN2* copies, where possible
- the submitted evidence addresses the questions raised in Sections A, B and C of this clarification letter
- where it is necessary to update or conduct new reviews, the complete study selection process is described (as has been requested for the existing reviews in Questions C5 to C7).

Response:

Part 1: Issues with the request

As per the final scope of the appraisal, the decision problem under review relates to the use of onasemnogene abeparvovec compared with best supportive care (BSC) for people with pre-symptomatic 5q SMA and up to three copies of the *SMN2* gene. For the decision problem under consideration, Novartis Gene Therapies does not believe that the analysis requested will be informative for the reasons outlined below.

The analysis represents a hypothetical scenario

SMA is a genetic disease that causes rapid and progressive motor neuron loss, which can begin prenatally in SMA type 1. By the time that symptoms are overtly present, significant, irreversible motor neuron loss has already occurred (1, 2). Expert recommendations and consensus statements support immediate treatment following genetic diagnosis, recognising that early initiation of disease-modifying treatment for SMA, ideally before symptoms become apparent, can halt this irreversible motor neuron loss, improve neuromuscular function, and prevent disease progression (3-8). As there is currently no nationwide programme of newborn blood spot (NBS) screening for SMA in England, almost all people with SMA in England will be identified only when symptoms become apparent. Therefore, in these cases, it is appropriate to treat patients at symptom onset. If NBS is introduced, a very small proportion (estimated to be <5%) would still present symptomatically – e.g. due to presence of an unusual genotype (point mutation) that is not identifiable through the routine genetic screening. These people would continue to present symptomatically and would need to receive treatment at symptom onset.

However, the requested analysis implies that, if a patient were diagnosed with SMA pre-symptomatically on the basis of genetic testing, a decision may be taken to withhold treatment until symptoms develop. Given the irreversible nature of the motor neuron loss that occurs with SMA and the severe consequences that ensue, considering such a decision option appears highly unethical (9). In fact, even in a clinical trial setting, it is not considered ethical to use a placebo comparator if there are harms from delaying or foregoing treatment (10). As such, following the completion of the START clinical trial for onasemnogene abeparvovec, it was considered unethical to include a placebo arm in subsequent clinical trials given the universally dismal prognosis for those who do not receive active treatment. It is also unrealistic to assume that, in clinical practice, a clinician would wait for symptom onset to treat an infant with genetically diagnosed SMA. Not only would this lead to serious anxiety for parents, but would increase the burden of follow-up for clinicians (9).

Therefore, any comparative analysis of the cost-effectiveness of pre-symptomatic treatment vs treatment after symptom onset in a population of pre-symptomatic

patients, i.e. patients who are known to be affected by the disease, is purely hypothetical and models a clinical scenario that would never occur.

The analysis is part of a broader analysis, which falls outside the decision problem

As discussed above, there is currently no nationwide programme of NBS screening for SMA in England. Pre-symptomatic identification of SMA only occurs via family screening (for infants with a sibling history of SMA or whose parents who are known carriers) or through a pilot study for NBS screening currently being conducted in the Thames Valley area. While Novartis Gene Therapies and numerous professional and patient organisations support the introduction of nationwide NBS screening for SMA (11, 12), the cost-effectiveness and other implications of setting up a nationwide NBS screening programme to identify pre-symptomatic patients with SMA are not within the scope of the current decision problem. This wider decision problem will be assessed by the National Screening Committee (NSC).

Without availability of appropriate interventions, screening programmes are not necessarily helpful, and may actually be harmful (13). Therefore, for the NSC, some of the key criteria for appraising the viability, effectiveness, and appropriateness of a population screening programme are that there should be an effective intervention for patients identified through screening, and that there should be agreed, evidence-based policies covering which individuals should be offered interventions (14). In the context of pre-symptomatic SMA, it is therefore essential that a treatment has been assessed by NICE and is recommended for routine commissioning for pre-symptomatic patients within the NHS prior to the NSC review.

While the NSC review will be completely independent, Novartis Gene Therapies has also conducted a cost-utility analysis to estimate the lifetime health effects and costs of NBS screening for SMA compared with no NBS screening, from the perspective of the National Health Service (NHS) in England. Base case results of this analysis indicate that NBS screening is dominant (less costly and more effective) compared with no NBS. This analysis will be presented at the meeting of the International Society for Pharmacoeconomics and Outcomes Research (ISPOR) in November 2022.

Part 2: Requested analysis

Acknowledging the issues highlighted in Part 1 of this response, Novartis Gene Therapies has conducted the requested analysis.

Treatment strategies compared

For patients with two and three copies of *SMN2*, respectively, we compared the following two strategies (S1 & S2):

- (S1) providing onasemnogene abeparvovec pre-symptomatically to the pre-symptomatic patient
- (S2) providing onasemnogene abeparvovec to the patient with a pre-symptomatic diagnosis only at symptom onset if the patient develops SMA type 1 and BSC if they develop SMA type 2 or 3

Outcomes under S1, stratified by *SMN2* copy number, were provided as part of the submitted dossier (Appendix J). The approach to derive outcomes under S2 is described in the following sections.

Quantifying outcomes under strategy S2

Key inputs: SMN2 copy-stratified probabilities of developing a given SMA type and proxy relationship between SMA type and motor milestone achievement

A core component of the analysis consists of the *SMN2* copy-stratified probabilities that a patient untreated pre-symptomatically will develop SMA type 1, 2, or 3. These probabilities were derived from a large epidemiological study of SMA patients (n=3,459) (15). They are reproduced in Table 1 (columns 1-3) below for convenience.

As there is no BSC arm in the SPR1NT clinical trial, in the pre-symptomatic cost-effectiveness model that is structured around motor milestone-related health states, the health state allocation of patients receiving BSC is informed by the probabilities that a pre-symptomatic patient will present with each SMA type and a proxy relationship between SMA type and motor milestone achievement. This approach was validated by clinical experts at a UK clinical advisory board. The proxy links

between each SMA type and motor milestone achievement are provided in column 4 of Table 1 for convenience.

Table 1: Probabilities of developing SMA type 1, 2 or 3 according to *SMN2* copy-number and proxy links between motor milestone achievement and SMA type used to inform the allocation of BSC patients to the model's heath states

	Probability of developing SMA type		Highest motor milestone achievement
	Patient with two *SMN2* copies	Patient with three *SMN2* copies	
SMA type 1	79%	15%	Non-sitter
SMA type 2	16%	54%	Sitter
SMA type 3	5%	31%	Delayed walker / Experience late SMA onset*

* Calucho (2018) (15) data suggests that two-copy patients with SMA type 3 will all be delayed walkers but that three-copy patients with SMA type 3 will have an equal chance of being a delayed walker or to experience late SMA onset.

Abbreviations: SMA, spinal muscular atrophy.

A second core component of the analysis consists in quantifying the health and healthcare costs impacts associated with the SMA type that patients will develop if they are untreated pre-symptomatically. Such analysis needs to capture SMA-type stratified probabilities of survival and, for those on BSC, of motor milestone loss and the treatment to be received at symptom onset (onasemnogene abeparvovec or BSC).

Outcomes for patients who are treated only once they develop SMA type 1 symptoms

Outcomes for patients diagnosed pre-symptomatically but who receive onasemnogene abeparvovec only once they develop SMA type 1 symptoms are computed in the newly added sheet 'SO_Ona' - whereby SO stands for symptom onset. The modelling structure follows a short-term and a long-term extrapolation phase as was done to evaluate outcomes in patients who are treated pre-symptomatically.

The short-term model follows patients until they reach 60 months of age. It is informed by the pooled clinical trial data for patients with SMA type 1 with two *SMN2* copies from START, STR1VE-US, and STR1VE-EU clinical trials. The monthly transitions between motor milestone-related health states, including death, that were derived from the pooled clinical data are provided in the newly added sheet 'SO_IPD'. These empirical transitions feed into the Markov trace and economic outcomes computations of the 'SO_Ona' sheet. It is worth noting that, unlike for patients treated pre-symptomatically who all enter the short-term model in the broad range of normal development (BRND) state, pre-symptomatic patients who are treated only once they develop SMA type 1 symptoms all enter the model in the "non-sitter" state.

Please note that, in the absence of efficacy data on onasemnogene abeparvovec for patients with SMA type 1 with three *SMN2* copies in the pivotal studies (START/STR1VE), to undertake the requested analysis for three-copy patients, we assumed that the efficacy of onasemnogene abeparvovec for patients with SMA type 1 with three copies of *SMN2* was the same as the reported efficacy for patients with SMA type 1 with two copies of *SMN2* copies, as was agreed during the EAG clarification meeting.

From the age of 61 months onwards, patients enter the long-term model where, until death, they are assumed to stay within the same health state that they reached at the end of the short-term model based on the motor milestone they achieved at the end of the empirical trial period. Similar to the approach used for patients treated pre-symptomatically, long-term survival in pre-symptomatic patients who are treated with onasemnogene abeparvovec only once they develop SMA type 1 symptoms is based on extrapolated survival curves from natural history studies for each SMA severity type.

Outcomes for patients not treated pre-symptomatically who develop SMA type 2 and SMA type 3 and remain on BSC

As discussed above, patients on BSC are distributed to the model health states, from the first cycle, based on the proxy relationship between SMA type and motor

milestone achievement that was validated by clinical experts and is summarised in Table 1.

Based on this proxy relationship, outcomes for patients who develop SMA type 2 are modelled by assuming that all patients in the BSC comparator arm are sitters. The calculation of outcomes for these patients are therefore implemented in the model by setting the proportion of sitters in the 'BSC-Inputs' sheet to 100%.

Under the same approach, outcomes for patients who develop SMA type 3 are modelled by assuming that patients in the BSC comparator arm are either delayed walkers or experience late SMA onset. Since the epidemiological evidence available (15) suggests that two-copy patients with SMA type 3 will at best be delayed walkers (i.e. it is very unlikely any will have late SMA onset), outcomes for two-copy patients with SMA type 2 were modelled by setting the proportion of delayed walkers in the 'BSC-Inputs' sheet to 100%.

In contrast, since the epidemiological evidence available (15) suggests that about half of three-copy patients with SMA type 3 will be delayed walkers and half will have late SMA onset, outcomes for three-copy patients with SMA type 3 were modelled by setting the proportions of delayed walkers and the proportion of patients with late SMA onset in the 'BSC-Inputs' sheet to 50% each.

As detailed in document B of the submitted dossier, transitions between health states for patients under BSC are informed, from the first model cycle, by expectations of milestone loss and natural history studies. Survival in sitters is informed by survival data for the general UK population (2018–2020 UK National Life tables) adjusted upwards by a hazard ratio obtained by comparing survival statistics in the general population with survival in the sub-population of SMA patients who are sitters reported in Wijngaarde et al, 2020 (16). In contrast, survival in delayed walkers and in patients who experience later SMA onset is assumed to be the same as in the general UK population.

Comparative analysis results

The comparative analysis of patient outcomes under treatment strategies S1 and S2 stratified by *SMN2* copy-number is provided in the newly added sheet 'SO_Results'. Findings are summarised in Table 2 **and**

Table 3 below. Comparative results are also provided, in Table 4, for the combined 1-patient cohort using the ratio of *SMN2* two-copy to *SMN2* three-copy infants expected to be identified through screening in England, that is 65.15% to 34.85% (12, 17-22).

Results show that providing onasemnogene abeparvovec pre-symptomatically to patients with two and three copies of *SMN2* (strategy S1) dominates the alternative strategy of providing onasemnogene abeparvovec at symptom onset in patients only when, and if, they develop SMA type 1 and providing BSC if they develop SMA type 2 or type 3 (strategy S2).

For a pre-symptomatic patient with either two or three copies of *SMN2*, providing onasemnogene abeparvovec pre-symptomatically, instead of waiting for clinical diagnosis at symptom onset and providing treatment with onasemnogene abeparvovec if the patient develops SMA type 1 and BSC otherwise, generates substantial health gains ([redacted] undiscounted QALYs and [redacted] discounted QALYs for a two-copy patient and three-copy patient, respectively) and discounted healthcare cost savings ([redacted] for a two-copy patient and 3-copy patient, respectively).

For the average patient in the population of the decision problem, that is infants with pre-symptomatic SMA with up to three copies of *SMN2*, providing onasemnogene abeparvovec pre-symptomatically is expected to generate [redacted] undiscounted QALYs, [redacted] discounted QALYs and [redacted] of discounted cost-savings over the alternative of waiting for the pre-symptomatic patient to develop symptoms to start his/her active treatment (if SMA type 1).

A core finding of this analysis is that, even when factoring the fact that not all pre-symptomatic patients will go on to develop the most severe type of SMA (SMA type 1) – especially those with three copies of *SMN2*, of whom a substantial proportion are expected to develop SMA type 2 or 3 – treating all patients pre-symptomatically with onasemnogene abeparvovec dominates the strategy of delaying treatment until symptom onset for those who develop SMA type 1.

These findings were produced based on the evidence available at the time of analysis with regards to efficacy data of onasemnogene abeparvovec in patients with

SMA type 1 and the most recent and robust epidemiological evidence of the probabilities of a pre-symptomatic patient to develop SMA type 1, 2 or 3. Findings are consistent with the fact that, since motor neuron loss is irreversible, even if the extent of neuron loss will vary between patients, treating SMA as early as possible will maximise the lifetime outcomes for the patient.

Table 2: Cost-effectiveness outcomes for patients with two SMN2 copies associated with S1: providing onasemnogene abeparvovec pre-symptomatically and S2: providing onasemnogene abeparvovec at symptom onset if the patient develops SMA type 1 and BSC if they develop SMA type 2 or SMA type 3

	Cost (£)†	**QALYs (Undiscounted)**	**LYs†**	**QALYs†**			
(S1) Onasemnogene as pre-symptomatic treatment	[redacted]	[redacted]	[redacted]	[redacted]	-	-	-
(S2) Onasemnogene at symptom-onset if patient is SMA type 1 and BSC otherwise	[redacted]	[redacted]	[redacted]	[redacted]	-	-	-
	Cost (£)†	**QALYs (Undiscounted)**	**LYs†**	**QALYs†**	**INMB at £100,000 /QALY**	**INMB at £300,000 /QALY**	**ICER**
S1 versus S2	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: BSC, best supportive care; ICER, incremental cost-effectiveness ratio; LYs, life years; QALYs, quality-adjusted life years; INMB, Incremental Net Monetary Benefit.

†Values presented are based on a discount rate of 3.5%.

Table 3: Cost-effectiveness outcomes for patients with three copies of *SMN2* associated with S1: providing onasemnogene abeparvovec pre-symptomatically and S2: providing onasemnogene abeparvovec at symptom onset if the patient develops SMA type 1 and BSC if they develop SMA type 2 or SMA type 3

	Cost (£)†	**QALYs (Undiscounted)**	**LYs†**	**QALYs†**			
(S1) Onasemnogene as pre-symptomatic treatment	[redacted]	[redacted]	[redacted]	[redacted]	-	-	-
(S2) Onasemnogene at symptom-onset if patient is SMA type 1 and BSC otherwise	[redacted]	[redacted]	[redacted]	[redacted]	-	-	-
Incremental outcomes (S1 versus S2) †							
	Cost (£)	**QALYs (Undiscounted)**	**LYs**	**QALYs**	**INMB at £100,000 /QALY**	**INMB at £300,000 /QALY**	**ICER**
S1 versus S2	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: BSC, best supportive care; ICER, incremental cost-effectiveness ratio; LYs, life years; QALYs, quality-adjusted life years; INMB, Incremental Net Monetary Benefit.

†Values presented are based on a discount rate of 3.5%.

Table 4: Cost-effectiveness outcomes for the combined cohort of patients with two and three copies of *SMN2* associated with S1: providing onasemnogene abeparvovec pre-symptomatically and S2: providing onasemnogene abeparvovec at symptom-onset if the patient develops SMA type 1 and BSC if they develop SMA type 2 or SMA type 3

	Cost (£)†	**QALYs (Undiscounted)**	**LYs†**	**QALYs†**			
(S1) Onasemnogene as pre-symptomatic treatment	[redacted]	[redacted]	[redacted]	[redacted]	-	-	-
(S2) Onasemnogene at symptom-onset if patient is SMA type 1 and BSC otherwise	[redacted]	[redacted]	[redacted]	[redacted]	-	-	-
Incremental outcomes (S1 versus S2) †							
	Cost (£)	**QALYs (Undiscounted)**	**LYs**	**QALYs**	**INMB at £100,000 /QALY**	**INMB at £300,000 /QALY**	**ICER**
S1 versus S2	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: BSC, best supportive care; ICER, incremental cost-effectiveness ratio; LYs, life years; QALYs, quality-adjusted life years; INMB, Incremental Net Monetary Benefit.

†Values presented are based on a discount rate of 3.5%.

Clarification on INMB values submitted in main dossier

It came to the company's attention that the value used to monetise the incremental QALY gains associated with onasemnogene abeparvovec as pre-symptomatic treatment vs BSC was based on an incorrect weighting factor of [redacted].The latter reflects the difference of [redacted] discounted QALYs between the two comparator arms, whilst it should have been informed by the difference in undiscounted QALYs.

Since onasemnogene abeparvovec as pre-symptomatic treatment provides a gain of [redacted] undiscounted QALYs over BSC then the maximum weighting applies, resulting in a WTP value per QALY of 300,000/QALY.

Table 5-7 therefore aim to complement Tables 48-50 of document B of the submitted dossier by providing undiscounted QALY estimates under each comparator arm alongside discounted life years, QALYs and cost estimates) and net monetary benefit (NMB) and incremental NMB estimates using the WTP values for a QALY of £100,000 and £300,000 respectively, instead of [redacted] /QALY.

Table 5: Base case results for the combined cohort of patients with two and three copies of *SMN2* – list price

	Cost (£)†	**QALYs (Undiscounted)**	**LYs†**	**QALYs †**			
BSC	882,564	[redacted]	[redacted]	[redacted]	-	-	-
Onasemnogene abeparvovec	2,096,927	[redacted]	[redacted]	[redacted]	-	-	-
Incremental outcomes (vs BSC)							
	Cost (£)†	**QALYs (Undisc)**	**LYs†**	**QALYs †**	**INMB at £100,000 /QALY**	**INMB at £300,000 /QALY**	**ICER† (£/QALY)**
Onasemnogene abeparvovec versus BSC	1,214,363	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: BSC, best supportive care; ICER, incremental cost-effectiveness ratio; LYs, life years ; N/A, not applicable; QALYs, quality-adjusted life years.
†Values presented are based on discounting of 3.5%.

Table 6: Base case results for the combined cohort of patients with two and three copies of *SMN2* – PAS discounted price

	Cost (£)†	QALYs (Undiscounted)	LYs†	QALYs †			
BSC	882,564	[redacted]	[redacted]	[redacted]	-	-	-
Onasemnogene abeparvovec	[redacted]	[redacted]	[redacted]	[redacted]	-	-	-
Incremental outcomes (vs BSC)							
	Cost (£)†	**QALYs (Undiscounted)**	**LYs†**	**QALYs †**	**INMB at £100,000 /QALY**	**INMB at £300,000 /QALY**	**ICER† (£/QALY)**
Onasemnogene abeparvovec versus BSC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: BSC, best supportive care; ICER, incremental cost-effectiveness ratio; LYs, life years ; N/A, not applicable; QALYs, quality-adjusted life years.
†Values presented are based on discounting of 3.5%.

Table 7: Incremental net health benefit and incremental net monetary benefit based on unweighted and weighted willingness to pay thresholds of £100,000 and £300,000 per QALY

	Combined cohort
Incremental net health benefit (undiscounted QALY)	[redacted]
Incremental net monetary benefit (£) at £100,000/QALY	[redacted]
Incremental net monetary benefit (£) at £300,000/QALY	[redacted]

Abbreviations: QALY, quality-adjusted life year.

Section A: Clarification on effectiveness data

SPR1NT trial and control population

A1. Priority question. For the *SMN2* three-copy cohort, please provide 18-month study results for all efficacy outcomes listed in Table 7. If results for any outcomes are not available, please explain why not.

Response:

Novartis Gene Therapies would like to clarify that, as the two *SMN2* copy cohorts have different natural histories and disease severities, they also have different primary endpoints and follow-up periods. Per the protocol for SPR1NT (provided as part of the reference pack for this response document), the primary and secondary efficacy endpoints were assessed at any visit up to the 24 months of age visit for the *SMN2* three-copy cohort. Therefore, the results available for this cohort are at any visit up to 24 months of age, whereas the results for the two-copy cohort are provided at any visit up to 18 months of age.

Novartis Gene Therapies has reviewed the list of efficacy outcomes listed in Table 7 for which full results were not provided in the submission and has provided these results in the following sections. Additional details can also be found in the SPR1NT CSR (23) and three-copy cohort publication (24) provided as part of the accompanying reference pack.

Achievement of a scaled score on BSID GM and FM subtests within 1.5 standard deviations of a chronological development reference standard as assessed at any visit up to 24 months of age

A formulated table was used to transform Bayley raw scores into scaled scores (25). This scaled score reflects performance according to age as compared with other, normally developing children of the same age, who have a mean scaled score of 10, with ±3 points. Therefore, approximately 87% of children tested will fall within 1.5 SD of the mean (scores 5.5–14.5) and 97% will fall within 2 SD of the mean (scores 4–16).

All patients in the *SMN2* three-copy cohort achieved a scaled score of ≥5.5 on the Bayley GM and FM Subtests on at least one post-baseline visit. At the 24 months of age visit, 9 out of 10 patients (90%) assessed achieved a scaled score of ≥5.5, and all 10 patients (100%) assessed achieved a scaled score of ≥4.

Time to respiratory intervention

No patient in the *SMN2* three-copy cohort used ventilatory support (invasive or non-invasive, including cough assist) at any point during the study. Therefore, time to respiratory intervention is not reported.

Maintenance of achieved milestones

All 15 patients in the *SMN2* three-copy cohort achieved the milestone 'stands alone' as defined by the BSID GM Subtest Item #40 prior to reaching 24 months of age, and all maintained this achievement at 24 months of age. Fourteen patients achieved the milestone 'walks alone', as defined by the BSID GM Subtest Item #43 prior to reaching 24 months of age. The fifteenth patient was observed walking alone by a clinical evaluator during the 24-month assessment conducted via video call, but video was not recorded and hence per study protocol, in the absence of independent video review, the patient was not recorded as having achieved this motor milestone.

A2. In the company submission (p49) it is stated that "One additional patient originally included in SPR1NT was excluded from the ITT efficacy analysis ... This patient remains part of the Safety Population but is no longer part of the ITT population and is therefore not reported in the efficacy results". However, on p52, it is stated that "All enrolled, safety, intent-to-treat (ITT) and efficacy completers (EC) populations are equivalent for both cohorts" and that the numbers of patients for whom data are reported are the same for both efficacy and safety outcomes (two-copy cohort: n=14; three-copy cohort: n=15). Please explain this inconsistency.

Response:

Novartis Gene Therapies would like to confirm that this is a mistake on page 49 of the submission as this additional patient was not included as part of the Safety Population. We can confirm that the patient completed the study as planned but that

the results for this patient are not presented as part of the results for the *SMN2* two- or three-copy cohorts.

A3. In the SPR1NT trial, infants were permitted to receive concomitant therapy with other treatments for spinal muscular atrophy (company submission, Table 19). Please provide a breakdown of the additional treatment patients received (i.e., the type of treatment received, frequency of treatment and the number of patients receiving each type of treatment).

Response:

[redacted]

The company wishes to clarify that infants were permitted to receive concomitant therapy with other treatments for SMA during LT-002, a long-term follow-up study including patients who had completed the SPR1NT trial. No patients received concomitant therapy with other treatments for SMA during SPR1NT, as this was prohibited during the trial.

Safety data

A4. It is reported in the company submission (Table 21) that one patient in LT-002 experienced a SAE related to study treatment. Please state the nature of this SAE. Was this patient treated pre-symptomatically?

[redacted]

Section B: Clarification on cost-effectiveness data

B1. Priority question. Please provide full details of how the health state costs (company submission, Table 45) used in the cost effectiveness model were calculated. For each health state cost, please include details of resource use, unit costs and cite references.

Response:

Costs were sourced from the NHS Schedule of Reference Costs 2019–2020 (26), PCA 2021/22 (27) and publications (where applicable inflated to 2021 using PSSRU's NHSCII (28)) and the resulting health care resource use and costs estimates were validated by the advisory board members.

The full detail or resource use, unit costs and data sources for all six cost items used to derive final estimates of health care resource use (HCRU) for patients with SMA type 1 to 3 - used to proxy HCRU associated with the model's health states - have now been provided in the 'SMA_alltypes_HCRU_July22' Excel file.

The cost values provided in the 'Summary' sheet of the 'SMA_alltypes_HCRU_July22' Excel file correspond to the hard-coded values provided in the green-coloured cells in column K of the 'MedicalCostCalculator' sheet of the cost-effectiveness model (CEM).

These cost values are complemented within the CEM ('MedicalCostCalculator' sheet) with data regarding: (i) patients' setting of care (ITU vs high-dependency setting vs home) that was informed by an ad-hoc piece of research on HCRU costs

of SMA relying on interviews with healthcare professionals in the UK (now added to the reference pack) (ii) and the costs of care in ITU and high-dependency settings derived from Noyes et al. (2006) (29) study (now added to the reference pack as well). This data on patients' setting of care and its associated costs is incorporated using computations shown in columns O to W of the CEM of the 'MedicalCostCalculator' sheet. The final cost values resulting from these computations are provided in column X of 'MedicalCostsCalculator' sheet and Table 45 of document B.

B2. Priority question. Please provide clinical evidence to justify why the survival estimates used in the 'Sitter (no PAV)' health state vary by number of *SMN2* copies (two copy/three copy), whilst number of *SMN2* copies does not influence estimated life expectancy in any of the other model health states.

Response:

All outcomes in the health states associated with a greater motor achievement than non-sitters are proxied by outcomes in patients with SMA type 2 (for sitters/delayed walkers that lost walking) or with SMA type 3 (for delayed walkers/experiences later onset).

Patients with SMA type 2 and type 3 have typically 3 or more *SMN2* copies (Wijngaarde, 2020 (16), Calucho 2018 (15)) since the greater the number of copies, the least severe the consequences on patients' motor development are.[1] Consequently, stratifying survival outcomes in the health states associated with a greater motor achievement than non-sitters, according to whether patients had 2 vs 3 *SMN2* copies, did not seem justified, nor was it feasible due to the lack of data on patients with SMA type 2 or type 3 with only 2 *SMN2* copies.

Outcomes in non-sitters are proxied by outcomes in patients with SMA type 1. Unlike for patients with SMA type 2 or type 3, who typically have 3 or more *SMN2* copies (Wijngaarde, 2020 (16), Calucho 2018 (15)), a non-negligible proportion of patients with SMA type 1 can have either 2 or 3 *SMN2* copies. In Wijngaarde's 2020 large population-based cohort study (n=307) of SMA patients (16), for instance, out of 62

[1] It should be noted that, prior to observation of symptoms, there is no definitive way to determine the severity of disease or to predict survival.

patients with SMA type 1 for which *SMN2* copy number was known, 50% of patients had 2 copies and 48% had 3 copies (with the remaining 2% having 4 copies).

Wijngaarde's 2020 study also showed that the median survival in SMA type 1 patients differed substantially according to whether patients had 2 or 3 copies. The SMA type 1 subgroup that had mostly 3 *SMN2* copies had a median survival of 17 years vs 6.4 months for the SMA type 1 subgroup with only 2 *SMN2* copies. On this basis, survival in non-sitters (no PAV) was stratified by *SMN2* copy number. The natural history studies used to inform survival in each subgroup (Neuronext/Kolb 2017 for the 2-copy patients and Wijngaarde 2020 for the 3-copy patients) were chosen based on considerations of sample size, follow-up duration and previous feedback from ERG received as part of HST15 submission.

Survival in non-sitters on PAV was not stratified by copy-number since a large majority of these patients are expected to have 2 *SMN2* copies only. Although the company acknowledges that some 3-copy infants will never sit and will require PAV (Kolb, 2017; PNCR internal data), the evidence base available to inform survival in these patients (Gregoretti et al 2013) does not provide survival estimates stratified by copy number so the effect of copy number on survival within this particular population is not known and therefore not modelled. In addition, it is worth underlining that the survival outcomes in the PAV health state are essentially intended to capture the effect of the intervention (PAV), rather than underlying patient characteristics, on survival.

Section C: Textual clarification and additional points

C1. Priority question. Please provide the protocol and statistical analysis plan (SAP) for the SPR1NT trial**.**

Response:

The company has provided the protocol and SAP as part of the reference pack to this response document.

C2. Priority question. Please provide a summary of the Blueteq data collected as part of the Managed Access Agreement.

Response:

As part of the managed access agreement (MAA) (30), it was agreed that the primary source of data collection would be the SPR1NT trial. The secondary source would be routinely collected clinical data through the Blueteq system from all patients in England who receive treatment with onasemnogene abeparvovec during the term of the MAA. It was agreed that the following anonymised outcomes for the population covered by the MAA would be collected:

- Number of applications to start treatment
- Baseline characteristics, including gender, age, date of diagnosis, and *SMN2* copy number

To the company's knowledge, there has been only one patient diagnosed and treated during the MAA period. Due to confidentiality, NHS England remain the custodians of the details of this patient.

C3. Please clarify when data from the RESTORE spinal muscular atrophy registry (company submission, B.2.11.2) will be available.

Response:

Novartis Gene Therapies would like to clarify that data from the RESTORE registry (23 November 2021 data cut-off) have been presented at conferences (31-34), and relevant posters have therefore provided as part of the reference pack accompanying this response document. However, the currently available data do not include efficacy and safety data specifically for the pre-symptomatic population. As analyses are currently being conducted, the timelines for availability of these data are yet to be confirmed. The company is committed to providing relevant data to NICE as soon as they become available and will provide a further update as soon as possible.

C4. It is usually possible for the EAG to directly export references from a company submission (and appendices) to EndNote using links attached to inserted references.

However, the company submission and appendices do not appear to contain such links. Please provide access to versions of the company submission and appendices with these links, or a copy of an EndNote file that includes all the references cited in the company submission and appendices.

Response:

A RIS file has been provided as part of the reference pack for this response document.

Systematic literature reviews

C5. The company has presented the study selection criteria (company submission, Table 4) and study selection process (company submission, Figure 3) used for the clinical effectiveness SLR. The company identified 43 studies that met the selection criteria but reported that only two studies were relevant to the appraisal (company submission, Table 6). Please provide the study selection criteria used to identify the 2/43 relevant studies and a PRISMA flow diagram that summarises the full study selection process.

Response:

The clinical review was a broad review, including symptomatic SMA and multiple treatments not considered relevant comparators in the pre-symptomatic population. The full list of included publications in the SLR is provided in Table 78 of the submission (Appendix D, page 21 of the appendix document), which aligns with the PRISMA flow diagram provided in Figure 3 (page 35) in the main submission document.

However, given the broad nature of the SLR, only the studies relevant to the current decision problem have been written up as clinical evidence in the submission. The company understands why EAG are seeking further clarity on this and can elaborate on what was provided in the submission by providing an additional column to Table 78 of the submission (‘Rationale for exclusion from submission’), which outlines the reasons for exclusion of studies included in the SLR but not included as clinical evidence in the submission.

Table 78: Clinical efficacy and safety: Publications included after full-text review

Author	Year	Title	Journal	Rationale for exclusion from submission
Acsadi et al	2018	Rapid therapeutic response to spinraza in sma3 patients	Annals of Neurology	Comparator not within scope
Alfano et al	2018	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	Neurology. Conference: 70th Annual Meeting of the American Academy of Neurology, AAN	Population not within scope (not pre-symptomatic)
Alvarez Molinero et al	2019	Ep.110clinical and neurophysiological outcome of a patient with predicted type 1 SMA presymptomatically treated with nusinersen	Neuromuscular Disorders	Comparator not within scope
Al-Zaidy et al	2018	Health outcome improvements in spinal muscular atrophy type 1 patients with avxs-101 gene replacement therapy	Value in Health	Population not within scope (not pre-symptomatic)
Al-Zaidy et al	2019	Health outcomes in spinal muscular atrophy type 1 following avxs-101 gene replacement therapy	Pediatric Pulmonology	Population not within scope (not pre-symptomatic)
Al-Zaidy et al	2018	Avxs-101 phase-1 gene replacement therapy clinical trial in SMA type-1: Continued event free survival and achievement of developmental milestones	European Journal of Neurology	Population not within scope (not pre-symptomatic)
Al-Zaidy et al	2017	Avxs-101 phase 1 gene replacement therapy clinical trial in SMA type 1: Ventilation support free survival and achievement of developmental milestones	Annals of Neurology	Population not within scope (not pre-symptomatic)
Al-Zaidy et al	2016	Gene therapy for spinal muscular atrophy type 1 shows potential to improve survival and motor functional outcomes	Journal of Neuromuscular Diseases	Population not within scope (not pre-symptomatic)
AveXis	2019	Day 180_AVXS-101_Efficacy Update_[Data cut 31DEC2019]_FINAL (efficacy); Day 180_AVXS-101_Safety Update__[Data cut 31DEC2019]_FINAL (safety)	--	Superseded by SPR1NT publications and CSR
AveXis	2020	Nusinersen committee papers	--	Comparator not within scope
AveXis	2020	SPRINT 31 December 2019 data cut	--	Superseded by SPR1NT publications and CSR

Author	Year	Title	Journal	Rationale for exclusion from submission
AveXis	2020	STR1VE-US 31 December 2019 data cut	--	Population not within scope (not pre-symptomatic)
AveXis	2020	STRONG (102) 31 December 2019 data cut	--	Intervention not within scope (study in intrathecal rather than intravenous onasemnogene abeparvovec)
AveXis	2020	START 24 month final delivery TFLs; START TFLs	--	Population not within scope (not pre-symptomatic)
AveXis	2018	START CSR	--	Population not within scope (not pre-symptomatic)
Baranello et al	2018	FIREFISH: Risdiplam (RG7916) improves motor function in babies with Type 1 SMA	--	Comparator not within scope
Baranello et al	2019	P.353firefish part 1: 16-month safety and exploratory outcomes of risdiplam (rg7916) treatment in infants with type 1 spinal muscular atrophy	Neuromuscular Disorders	Comparator not within scope
Baranello et al	2019	Firefish part 1: 1-year results on motor function in babies with type 1 SMA	Neurology. Conference: 71st Annual Meeting of the American Academy of Neurology, AAN	Comparator not within scope
Baranello et al	2020	SMA - THERAPY: P.259 FIREFISH Part 1: 24-month safety and exploratory outcomes of risdiplam (RG7916) in infants with Type 1 spinal muscular atrophy (SMA).	--	Comparator not within scope
Baranello et al	2020	FIREFISH Part 1: 16-month safety and exploratory outcomes of risdiplam (RG7916) treatment in infants with Type 1 spinal muscular atrophy (SMA).	--	Comparator not within scope
Barp et al	2019	The c.859g > c variant in smn2 modulates clinical severity in SMA: A case report	Acta Myologica	Case report – not a clinical trial

Author	Year	Title	Journal	Rationale for exclusion from submission
Bazancir et al	2018	Nusinersen and early physiotherapy in patients with spinal muscular atrophy type 1: Case series	Acta Myologica	Comparator not within scope
Bertini	2019	The importance of early treatment: New nurture data	Acta Myologica	Comparator not within scope
Bertini et al	2017	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 Neurology	Comparator not within scope
Birsak et al	2019	P.366nusinersen improves motor function in ambulatory SMA iii patients	Neuromuscular Disorders	Comparator not within scope
Bulut et al	2018	Comparison of the effect of aquatherapy and cycle ergometer training in a child with spinal muscular atrophy type ii: A case report	Acta Myologica	Comparator not within scope
Burghes et al	2018	Gene therapy for SMA	Journal of Neuromuscular Diseases	Not a clinical trial
Butterfield	2019	165. Nusinersen in Infants who Initiate Treatment in a Presymptomatic Stage of Spinal Muscular Atrophy: Interim Results from the Phase 2 NURTURE Study	Child Neurology Society	Comparator not within scope
Butterfield et al	2019	Nusinersen in infants who initiate treatment in a presymptomatic stage of spinal muscular atrophy: Interim results from the phase 2 nurture study.	--	Comparator not within scope
Castro et al	2018	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	--	Comparator not within scope
Castro et al	2018	Longer-term assessment of the safety and efficacy of nusinersen for the treatment of infantile-onset spinal muscular atrophy: An interim analysis of the shine study	Neurology	Comparator not within scope
Castro et al	2020	Nusinersen in infantile-onset spinal muscular atrophy: Results from longer-term treatment from the open-label shine extension study.	--	Comparator not within scope
Castro et al	2020	Motor function change over time among nusinersen-treated participants with infantile-onset spinal muscular atrophy	--	Comparator not within scope

Author	Year	Title	Journal	Rationale for exclusion from submission
		(SMA) in the ENDEAR-SHINE study who met the permanent ventilation (PV) definition.		
Caumo et al	2019	Longitudinal functional changes in a cohort of adult nusinersen-treated spinal muscular atrophy patients at the padova neuromuscular center	Acta Myologica	Comparator not within scope
Chand et al	2020	SMA - THERAPY: P.255 One-time administration of AVXS-101 intrathecal (IT) for spinal muscular atrophy in the phase 1 study (STRONG): safety report.	--	Intervention not within scope (study in intrathecal rather than intravenous onasemnogene abeparvovec)
Chen et al	2019	Pulmonary function test changes in spinal muscular atropy patients receiving nusinersen treatments	American Journal of Respiratory and Critical Care Medicine. Conference	Comparator not within scope
Chen et al	2010	Randomized, double-blind, placebo-controlled trial of hydroxyurea in spinal muscular atrophy	Neurology	Comparator not within scope
Chiriboga	2019	166. Interim Report on the Safety and Efficacy of Longerterm Treatment with Nusinersen in Later-onset Spinal Muscular Atrophy (SMA): Results from the SHINE Study	Child Neurology Society	Comparator not within scope
Chiriboga et al	2018	JEWELFISH: Risdiplam (RG7916) increases SMN protein in non-naïve patients with SMA	--	Comparator not within scope
Chiriboga et al	2018	Nusinersen experience in individuals with spinal muscular atrophy (SMA) type iii: A case series	Annals of Neurology	Comparator not within scope
Chiriboga et al	2013	Results of an open-label, escalating dose study to assess the safety, tolerability, and dose range finding of a single intrathecal dose of isis-smnrx in patients with spinal muscular atrophy	Neurology. Conference: 65th American Academy of Neurology Annual Meeting. San Diego, CA United States. Conference Publication:	Comparator not within scope
Chiriboga et al	2018	Pd and safety data from jewelfish, a study of rg7916 in SMA patients previously enrolled in a smn2-splicing modifier study	Journal of Neuromuscular Diseases	Comparator not within scope

Author	Year	Title	Journal	Rationale for exclusion from submission
Chiriboga et al	2016	Results from a phase 1 study of nusinersen (isis-smn(rx)) in children with spinal muscular atrophy	Neurology	Comparator not within scope
Chiriboga et al	2020	Longer-term treatment with nusinersen: Results in later-onset spinal muscular atrophy from the shine study.	--	Comparator not within scope
Chiriboga et al	2020	Lack of effect on ambulation of dalfampridine-ER (4-AP) treatment in adult SMA patients.	Neuromuscular Disorders	Comparator not within scope
Cobb et al	2020	Abstract no. 727 a new spin on spinal muscular atrophy: Breathing new life into an adult population living with spinal muscular atrophy	Journal of Vascular and Interventional Radiology	Comparator not within scope
Crawford et al	2018	Nusinersen in infants who initiate treatment in a presymptomatic stage of spinal muscular atrophy (SMA): Interim efficacy and safety results from the phase 2 nurture study	Annals of Neurology	Comparator not within scope
Crawford et al	2020	SMA - THERAPY: P.268 Nusinersen effect in infants who initiate treatment in a presymptomatic stage of SMA: NURTURE results.	--	Comparator not within scope
Dabbous	2019	199. The Value of AVXS-101 Gene-Replacement Therapy (GRT) for Spinal Muscular Atrophy Type 1 (SMA1): Improved Survival, Pulmonary and Nutritional Support, and Motor Function with Decreased Hospitalization	Child Neurology Society	Population not within scope (not pre-symptomatic)
Dabbous et al	2018	Rapid improvements in motor function in spinal muscular atrophy type 1 following avxs-101 gene replacement therapy	Value in Health	Population not within scope (not pre-symptomatic)
Dabbous et al	2019	Early diagnosis and speed to effect in spinal muscular atrophy type 1 (SMA-1)	Neuropediatrics. Conference: 47th Annual Meeting of the Societe Europeenne de Neurologie Pediatrique, SENP	Population not within scope (not pre-symptomatic)
Dabbous et al	2019	P.358the value of avxs-101 gene-replacement therapy (grt) for spinal muscular atrophy type 1 (sma1): Improved survival, pulmonary and nutritional support, and motor function with decreased hospitalization	Neuromuscular Disorders	Population not within scope (not pre-symptomatic)

Author	Year	Title	Journal	Rationale for exclusion from submission
Dabbous et al	2019	The value of avxs-101 gene-replacement therapy (grt) for spinal muscular atrophy type 1 (sma1): Improved survival, pulmonary and nutritional support, and motor function with decreased hospitalization	Developmental Medicine and Child Neurology	Population not within scope (not pre-symptomatic)
Dabbous et al	2019	The value of onasemnogene abeparvovec (avxs-101) gene-replacement therapy for spinal muscular atrophy type 1	Journal of the Neurological Sciences	Population not within scope (not pre-symptomatic)
Dabbous et al	2019	The value of avxs-101 gene-replacement therapy for spinal muscular atrophy type 1 (sma1)	Canadian Journal of Neurological Sciences	Population not within scope (not pre-symptomatic)
Dabbous et al	2019	The value of avxs-101 gene replacement therapy for spinal muscular atrophy type 1: Improved survival, pulmonary and nutritional support, and motor function with decreased hospitalization	Neurology. Conference: 71st Annual Meeting of the American Academy of Neurology, AAN	Population not within scope (not pre-symptomatic)
Dabbous et al	2019	The value of avxs-101 gene-replacement therapy (grt) for spinal muscular atrophy type 1 (sma1)	No To Hattatsu	Population not within scope (not pre-symptomatic)
Dabbous et al	2019	Event-free survival and motor milestone achievement following onasemnogene abeparvovec and nusinersen interventions contrasted to natural history for spinal muscular atrophy type 1 (SMA1) patients.	--	Population not within scope (not pre-symptomatic)
Dabbous et al	2019	The value of AVXS-101 gene-replacement therapy (GRT) for spinal muscular atrophy type 1 (SMA1): Improved survival, pulmonary and nutritional support, and motor function with decreased hospitalization.	--	Population not within scope (not pre-symptomatic)
D'Amico et al	2019	P.371nusinersen treatment in spinal muscular atrophy: The experience of bambino gesu children's hospital	Neuromuscular Disorders	Comparator not within scope
D'Amico et al	2019	Nusinersen treatment in spinal muscular atrophy: The experience of bambino gesu hospital	Acta Myologica	Comparator not within scope
Darras et al	2013	Results of a first-in-human phase i study to assess the safety, tolerability, and dose range finding of a single intrathecal dose of isis-smnrx in patients with spinal muscular atrophy	Annals of Neurology	Comparator not within scope

Author	Year	Title	Journal	Rationale for exclusion from submission
Darras et al	2019	Nusinersen in later-onset spinal muscular atrophy: Long-term results from the phase 1/2 studies	Neurology	Comparator not within scope
Darras et al	2019	An integrated safety analysis of infants and children with symptomatic spinal muscular atrophy (SMA) treated with nusinersen in seven clinical trials	CNS Drugs	Comparator not within scope
Darras et al	2020	Safety profile of nusinersen in presymptomatic and infantile-onset spinal muscular atrophy (SMA): Interim results from the nurture and endear-shine studies.	--	Comparator not within scope
Darras et al	2020	SMA - THERAPY: P.254 Nusinersen in adolescents and young adults with SMA: Longitudinal experience from an expanded cohort of CS2/CS12 and SHINE participants.	--	Comparator not within scope
Day	2019	169. Onasemnogene Abeparvovec Gene-Replacement Therapy (GRT) for Spinal Muscular Atrophy Type 1 (SMA1): Pivotal Phase 3 Study (STR1VE) Update	Child Neurology Society	Population not within scope (not pre-symptomatic)
Day et al	2019	P.349onasemnogene abeparvovec gene-replacement therapy (grt) for spinal muscular atrophy type 1 (sma1): Pivotal phase 3 study (str1ve) update	Neuromuscular Disorders	Population not within scope (not pre-symptomatic)
Day et al	2019	Avxs-101 gene replacement for spinal muscular atrophy type 1 (sma1): Pivotal study (str1ve)update	No To Hattatsu	Population not within scope (not pre-symptomatic)
Day et al	2019	Avxs-101 gene-replacement therapy (grt) for spinal muscular atrophy type 1 (sma1): Pivotal phase 3 study (str1ve) update	Canadian Journal of Neurological Sciences	Population not within scope (not pre-symptomatic)
Day et al	2019	Avxs-101 gene-replacement therapy for spinal muscular atrophy type 1: Pivotal phase 3 study (str1ve) update	Acta Myologica	Population not within scope (not pre-symptomatic)
Day et al	2018	Avxs-101 gene replacement therapy for SMA type 1: Pivotal study (str1ve) update	Neurology	Population not within scope (not pre-symptomatic)
Day et al	2018	Experience using spinraza to treat adults with spinal muscular atrophy	Muscle and Nerve	Comparator not within scope

Author	Year	Title	Journal	Rationale for exclusion from submission
Day et al	2020	Longer-term experience with nusinersen in teenagers and young adults with spinal muscular atrophy: Results from the CS2/CS12 and shine studies.	--	Comparator not within scope
Day et al	2019	Onasemnogene abeparvovec gene-replacement therapy (GRT) for spinal muscular atrophy type 1 (SMA1): Pivotal phase 3 study (STR1VE) update.	--	Population not within scope (not pre-symptomatic)
Day et al	2020	Onasemnogene Abeparvovec-xioi Gene-Replacement Therapy for Spinal Muscular Atrophy Type 1 (SMA1): Phase 3 US Study (STR1VE) Update	--	Population not within scope (not pre-symptomatic)
De Vivo et al	2017	One-year outcomes following treatment with nusinersen: Interim results from the nurture study of presymptomatic infants with genetically diagnosed spinal muscular atrophy (SMA)	Annals of Neurology	Comparator not within scope
De Vivo et al	2018	Nusinersen in infants who initiate treatment in a presymptomatic stage of spinal muscular atrophy (SMA): Interim results from the phase 2 nurture study	Canadian Journal of Neurological Sciences	Comparator not within scope
De Vivo et al	2019	Nusinersen initiated in infants during the presymptomatic stage of spinal muscular atrophy: Interim efficacy and safety results from the phase 2 nurture study	Neuromuscular Disorders	Comparator not within scope
De Vivo et al	2017	Interim efficacy and safety results from the phase 2 nurture study evaluating nusinersen in presymptomatic infants with spinal muscular atrophy	Neurology. Conference: 69th American Academy of Neurology Annual Meeting, AAN	Comparator not within scope
De Vivo et al	2019	Nusinersen in infants who initiate treatment in a presymptomatic stage of spinal muscular atrophy (SMA): Interim efficacy and safety results from the phase 2 nurture study	Neurology. Conference: 71st Annual Meeting of the American Academy of Neurology, AAN	Comparator not within scope
Deconinck et al	2018	Branaplam in type 1 spinal muscular atrophy: Respiratory support and feeding	Journal of Neuromuscular Diseases	Comparator not within scope
Deconinck et al	2019	Nusinersen experience in teenagers and young adults with spinal muscular atrophy (SMA): Results from cs2/cs12 and shine	European Journal of Neurology	Comparator not within scope

Author	Year	Title	Journal	Rationale for exclusion from submission
Devivo	2018	Treatment in a Presymptomatic Stage of SMA: Interim Efficacy and Safety Results from the Phase 2 NURTURE Study	Muscular Dystrophy Association	Comparator not within scope
Drory et al	2019	Nusinersen treatment in adults with SMA - the first year experience at a large center	Neurology. Conference: 71st Annual Meeting of the American Academy of Neurology, AAN	Comparator not within scope
Elsheikh et al	2018	Nusinersen treatment for adults with spinal muscular atrophy; a single center experience	Neurology. Conference: 70th Annual Meeting of the American Academy of Neurology, AAN	Comparator not within scope
Finkel	2019	PL1-5. Intrathecal Administration of Onasemnogene Abeparvovec Gene-Replacement Therapy (GRT) for Spinal Muscular Atrophy Type 2 (SMA2): Phase 1/2a Study (STRONG)	Child Neurology Society	Intervention not within scope (study in intrathecal rather than intravenous onasemnogene abeparvovec)
Finkel	2019	174. Interim Report on the Safety and Efficacy of Longerterm Muscular Atrophy (SMA): Updated Results from the SHINE Study	Child Neurology Society	Comparator not within scope
Finkel et al	2016	Interim results of a phase 2 clinical study of nusinersen (isis-smnrx) in patients with infantile-onset spinal muscular atrophy	Annals of Neurology	Comparator not within scope
Finkel et al	2019	O.40intrathecal administration of onasemnogene abeparvovec gene-replacement therapy (grt) for spinal muscular atrophy type 2 (sma2): Phase 1/2a study (strong)	Neuromuscular Disorders	Intervention not within scope (study in intrathecal rather than intravenous onasemnogene abeparvovec)
Finkel et al	2018	Longer-term assessment of nusinersen safety/efficacy in infantile-onset spinal muscular atrophy: Interim analysis of shine	Journal of Neuromuscular Diseases	Comparator not within scope
Finkel et al	2019	Interim report on the safety and efficacy of longer-term treatment with nusinersen in infantile-onset spinal muscular atrophy (SMA): Updated results from the shine study	Neurology. Conference: 71st Annual Meeting of the American Academy of Neurology, AAN	Comparator not within scope

Author	Year	Title	Journal	Rationale for exclusion from submission
Finkel et al	2016	Treatment of infantile-onset spinal muscular atrophy with nusinersen: A phase 2, open-label, dose-escalation study	Lancet	Comparator not within scope
Finkel et al	2019	Intrathecal administration of avxs-101 gene-replacement therapy (grt) for spinal muscular atrophy type 2 (sma2): Phase 1/2a study (strong)	Journal of the Neurological Sciences	Intervention not within scope (study in intrathecal rather than intravenous onasemnogene abeparvovec)
Finkel et al	2017	Nusinersen versus sham control in infantile-onset spinal muscular atrophy	New England journal of medicine	Comparator not within scope
Finkel et al	2020	Nusinersen in infants who initiate treatment in a presymptomatic stage of spinal muscular atrophy (SMA): Interim results from the phase 2 nurture study.	--	Comparator not within scope
Finkel et al	2020	SMA - THERAPY: P.266 Nusinersen in infantile-onset spinal muscular atrophy: results from longer-term treatment from the open-label SHINE extension study.	--	Comparator not within scope
Finkel et al	2020	SMA - THERAPY: P.264 Longer-term effects of nusinersen on motor function outcomes based on age at treatment initiation.	--	Comparator not within scope
Finkel et al	2019	Interim report on the safety and efficacy of longerterm treatment with nusinersen in infantile-onset spinal muscular atrophy (SMA): Updated results from the shine study.	--	Comparator not within scope
Finkel et al	2019	Intrathecal administration of onasemnogene abeparvovec gene-replacement therapy (GRT) for spinal muscular atrophy type 2 (SMA2): Phase 1/2a study (STRONG).	--	Intervention not within scope (study in intrathecal rather than intravenous onasemnogene abeparvovec)
Finkel et al	2020	One-Time Intrathecal (IT) Administration of AVXS-101 IT Gene-Replacement Therapy for Spinal Muscular Atrophy: Phase 1 Study (STRONG)	--	Intervention not within scope (study in intrathecal rather than intravenous onasemnogene abeparvovec)
Frongia	2018	Salbutamol treatment in Type 2 SMA patients: 18 months assessment	--	Comparator not within scope

Author	Year	Title	Journal	Rationale for exclusion from submission
Hashiguchi et al	2019	The effects of nusinersen in SMA patients more than 50 years after onset	Journal of the Neurological Sciences	Comparator not within scope
Hwu et al	2017	Outcomes after 1-year in presymptomatic infants with genetically diagnosed spinal muscular atrophy (SMA) treated with nusinersen: interim results from the NURTURE study.	--	Comparator not within scope
Kaufmann et al	2019	Avxs-101 gene-replacement therapy (grt) for spinal muscular atrophy (SMA): From bench to bedside	Journal of Neuromuscular Diseases	Summary of pre-clinical and clinical data available at time of publication, not clinical trial
Kaufmann et al	2019	Onasemnogene abeparvovec gene-replacement therapy for spinal muscular atrophy: From bench to bedside	Thorax	Summary of pre-clinical and clinical data available at time of publication, not clinical trial
Kern-Smith and Verma	2019	Clinical and electrophysiological outcomes of spinal muscular atrophy type 1 patients treated with nusinersen	Neurology. Conference: 71st Annual Meeting of the American Academy of Neurology, AAN	Comparator not within scope
Kichula et al	2019	Motor outcomes after clinical treatment with nusinersen: A single-center experience	Neurology. Conference: 71st Annual Meeting of the American Academy of Neurology, AAN	Comparator not within scope
Kirschner	2014	Somatropin treatment of spinal muscular atrophy: A placebo-controlled, double-blind crossover pilot study	--	Comparator not within scope
Kirschner et al	2019	P.352interim report on the safety and efficacy of longer-term treatment with nusinersen in later-onset spinal muscular atrophy (SMA): Results from the shine study	Neuromuscular Disorders	Comparator not within scope
Kirschner et al	2019	Interim report on the safety and efficacy of longer-term treatment with nusinersen in later-onset spinal muscular atrophy (SMA): Results from the shine study	Journal of the Neurological Sciences	Comparator not within scope
Kirschner et al	2018	Nusinersen experience in individuals with spinal muscular atrophy type iii: A case series	Journal of Neuromuscular Diseases	Comparator not within scope

Author	Year	Title	Journal	Rationale for exclusion from submission
Kissel et al	2011	Sma carni-val trial part ii: A prospective, single-armed trial of l-carnitine and valproic acid in ambulatory children with spinal muscular atrophy	PLoS ONE	Comparator not within scope
Krosschell et al	2018	Clinical trial of l-carnitine and valproic acid in spinal muscular atrophy type i	Muscle and Nerve	Comparator not within scope
Kuntz et al	2018	Time to motor function response among nusinersen-treated infants from the endear study	Annals of Neurology	Comparator not within scope
Lowes et al	2018	Avxs-101 trial experience: Chop-intend effectively quantifies early, rapid, and sustained improvements that precede subsequent milestone achievement but is not sensitive to continued advances in motor function in infants with SMA type 1	Annals of Neurology	Population not within scope (not pre-symptomatic)
Lowes et al	2018	Avxs-101 trial experience: Chop-intend detects early improvements in infants with SMA type 1 but is not sensitive to continued advances in motor function	Neurology. Conference: 70th Annual Meeting of the American Academy of Neurology, AAN	Population not within scope (not pre-symptomatic)
Lowes et al	2017	Amvxs-101 phase 1 gene therapy clinical trial in SMA type 1: Correlation between chop-intend and motor milestone achievements	Neurology. Conference: 69th American Academy of Neurology Annual Meeting, AAN	Population not within scope (not pre-symptomatic)
Mazurkiewicz-BeLtdzinska et al	2019	Nusinersen for spinal muscular atrophy - results of an expanded access programme	Neurology. Conference: 71st Annual Meeting of the American Academy of Neurology, AAN	Comparator not within scope
Mcgill et al	2019	AVXS-101 Gene-Replacement Therapy in Presymptomatic Spinal Muscular Atrophy (SMA) : Study Update.	--	Superseded by SPR1NT publications and CSR
Mendell	2019	183. Gene-Replacement Therapy (GRT) in Spinal Muscular Atrophy Type 1 (SMA1): Long-Term Follow- Up From the Onasemnogene Abeparvovec Phase 1/2a Clinical Trial	Child Neurology Society	Population not within scope (not pre-symptomatic)
Mendell et al	2018	Avxs-101 phase 1 gene therapy clinical trial in spinal muscular atrophy type 1 (sma1): Event-free survival and achievement of developmental milestones	Annals of Neurology	Population not within scope (not pre-symptomatic)

Author	Year	Title	Journal	Rationale for exclusion from submission
Mendell et al	2017	Avxs-101 phase 1 gene therapy clinical trial in sma type 1: Event free survival and achievement of developmental milestones	Molecular therapy	Population not within scope (not pre-symptomatic)
Mendell et al	2018	Avxs-101 phase 1 gene replacement therapy clinical trial in SMA type 1: Continued event free survival and achievement of developmental milestones	Neurology. Conference: 70th Annual Meeting of the American Academy of Neurology, AAN	Population not within scope (not pre-symptomatic)
Mendell et al	2019	P.351gene-replacement therapy (grt) in spinal muscular atrophy type 1 (sma1): Long-term follow-up from the onasemnogene abeparvovec phase 1/2a clinical trial	Neuromuscular Disorders	Population not within scope (not pre-symptomatic)
Mendell et al	2018	Avxs-101 phase 1 gene therapy clinical trial in SMA type 1: Event-free survival and achievement of developmental milestones	Journal of Neuromuscular Diseases	Population not within scope (not pre-symptomatic)
Mendell et al	2018	Avxs-101 phase-1-gene therapy clinical trial in SMA type 1: Event-free survival and achievement of developmental milestones	Neuropediatrics. Conference: 44th Annual Meeting of the Society for Neuropediatrics. Germany.	Population not within scope (not pre-symptomatic)
Mendell et al	2019	Avxs-101 phase 1 gene-replacement therapy (grt) clinical trial in spinal muscular atrophy type 1 (sma1): 24-month event-free survival and achievement of developmental milestones	Neuropediatrics. Conference: 47th Annual Meeting of the Societe Europeenne de Neurologie Pediatrique, SENP	Population not within scope (not pre-symptomatic)
Mendell et al	2018	Gene transfer and translation in neuromuscular disease	Journal of Gene Medicine. Conference: Joint 10th Australasian Gene and Cell Therapy Society, AGCTS and Australasian Society for Stem Cell Research, ASSCR Annual Scientific Meeting. Australia.	Not a clinical trial
Mendell et al	2017	Single-dose gene-replacement therapy for spinal muscular atrophy	New England Journal of Medicine	Population not within scope (not pre-symptomatic)

Author	Year	Title	Journal	Rationale for exclusion from submission
Mendell et al	2019	Avxs-101 gene-replacement therapy (grt) in spinal muscular atrophy type 1 (sma1): Long-term follow-up from the phase 1 clinical trial	Canadian Journal of Neurological Sciences	Population not within scope (not pre-symptomatic)
Mendell et al	2019	Gene-replacement therapy (grt) in spinal muscular atrophy type 1 (sma1): Long-term follow-up from the onasemnogene abeparvovec phase 1/2a clinical trial	Journal of the Neurological Sciences	Population not within scope (not pre-symptomatic)
Mendell et al	2020	SMA - THERAPY: P.261 Long-term follow-up of onasemnogene abeparvovec gene therapy in spinal muscular atrophy type 1 (SMA1).	--	Population not within scope (not pre-symptomatic)
Mendell et al	2020	Gene Therapy in Spinal Muscular Atrophy Type 1 (SMA1): Long-Term Follow-Up (LTFU) From the Onasemnogene Abeparvovec Phase 1 Clinical Trial.	--	Population not within scope (not pre-symptomatic)
Mercuri et al	2019	Avxs-101 gene replacement therapy (grt) for spinal muscular atrophy type 1 (sma1): Pivotal studies clinical update (str1ve-eu and str1ve)	European Journal of Neurology	Population not within scope (not pre-symptomatic)
Mercuri et al	2019	Onasemnogene abeparvovec gene-replacement therapy (grt) for spinal muscular atrophy type 1 (sma1): Global pivotal phase 3 study program (str1ve-us, str1ve-eu, str1ve-ap)	Journal of the Neurological Sciences	Population not within scope (not pre-symptomatic)
Mercuri et al	2018	Sunfish part 1: Rg7916 treatment results in a sustained increase of smn protein levels and the first clinical efficacy results in patients with type 2 or 3 SMA	Annals of Neurology	Comparator not within scope
Mercuri et al	2019	Update from sunfish part 1: Safety, tolerability and pk/pd from the dose-finding study, including exploratory efficacy data in patients with type 2 or 3 spinal muscular atrophy (SMA) treated with risdiplam (rg7916)	Neurology. Conference: 71st Annual Meeting of the American Academy of Neurology, AAN	Comparator not within scope
Mercuri et al	2018	Nusinersen versus sham control in later-onset spinal muscular atrophy	New England Journal of Medicine	Comparator not within scope
Mercuri et al	2017	Infants and children with spinal muscular atrophy (sma) treated with nusinersen in clinical trials: An integrated safety analysis	Developmental Medicine and Child Neurology	Comparator not within scope

Author	Year	Title	Journal	Rationale for exclusion from submission
Mercuri et al	2020	SMA - THERAPY: P.258 Onasemnogene aveparvovec gene therapy for spinal muscular atrophy type 1 (SMA1): Phase 3 study update (STR1VE-EU).	--	Population not within scope (not pre-symptomatic)
Mercuri et al	2020	SMA - THERAPY: P.257 Longer-term treatment with nusinersen: Results in later-onset spinal muscular atrophy from the SHINE study.	--	Comparator not within scope
Mercuri et al	2017	Efficacy and safety of nusinersen in children with later-onset spinal muscular atrophy (SMA): end of study results from the phase 3 CHERISH study.	--	Comparator not within scope
Mercuri et al	2020	Onasemnogene abeparvovec gene replacement therapy (GRT) for spinal muscular atrophy type 1 (SMA1): Pivotal phase 3 studies clinical update (STR1VE-EU and STR1VE-US).	--	Population not within scope (not pre-symptomatic)
Mercuri, E. et al.	2020	Motor Milestone Achievement and Maintenance in Infants and Children Treated With Nusinersen: Integrated Data From the SHINE Study	--	Comparator not within scope
Montalvo et al	2019	Case series: Spinal muscular atrophy patients' response to nusinersen in a caribbean cohort	Neurology. Conference: 71st Annual Meeting of the American Academy of Neurology, AAN	Comparator not within scope
Montes et al	2019	Nusinersen improves walking distance and reduces fatigue in later-onset spinal muscular atrophy	Muscle & Nerve	Comparator not within scope
Montes et al	2018	Ambulatory function and fatigue in nusinersen-treated children with spinal muscular atrophy	Neurology. Conference: 70th Annual Meeting of the American Academy of Neurology, AAN	Comparator not within scope
Mousa et al	2018	Intrathecal nusinersen injections: Molecular therapy for spinal muscular atrophy	Pediatric Radiology	Comparator not within scope
Mueller-Felber et al	2020	Longer-term nusinersen treatment according to age at first dose: Results from the shine study in later-onset spinal muscular atrophy.	--	Comparator not within scope
Muntoni et al	2018	A long-term, open-label follow-up study of olesoxime in patients with type 2 or non-ambulatory type 3 spinal	Neurology. Conference: 70th annual meeting of the	Comparator not within scope

Author	Year	Title	Journal	Rationale for exclusion from submission
		muscular atrophy who participated in a placebo-controlled phase 2 trial	american academy of neurology, AAN	
Muntoni et al	2017	A long-term, open-label follow-up study of olesoxime in patients with type 2 or non-ambulatory type 3 spinal muscular atrophy from a placebo-controlled phase 2 trial	Developmental Medicine and Child Neurology	Comparator not within scope
Muntoni et al	2018	The oleos trial: A long-term follow-up of olesoximetreated type 2 and nonambulatory type 3 SMA patients	Journal of Neuromuscular Diseases	Comparator not within scope
Muntoni et al	2017	Olesoxime in patients with type 2 or non-ambulatory type 3 Spinal muscular atrophy: a placebo-controlled phase 2 trial including a long-term, open-label follow-up study.	--	Comparator not within scope
Muntoni et al	2020	Longer-term experience with nusinersen in teenagers and young adults with spinal muscular atrophy: Phosphorylated neurofilament heavy chain (pNF-H) and efficacy results from the CS2-12/SHINE studies.	--	Comparator not within scope
Ogawa et al	2019	Respiratory assessment in a spinal muscular atrophy infant treated with nusinersen	Pediatrics International	Comparator not within scope
Pane et al	2019	Nusinersen in type 1 spinal muscular atrophy: Twelve-month real-world data	Annals of Neurology	Comparator not within scope
Patel et al	2014	A novel method for noninvasive ventilation in spinal muscular atrophy with respiratory distress type 1 (smard-1)	Chest. Conference: CHEST	Comparator not within scope
Russman et al	2003	A phase 1 trial of riluzole in spinal muscular atrophy	Archives of neurology	Comparator not within scope
Ryan et al	2019	P.356nusinersen in infants who initiate treatment in a presymptomatic stage of spinal muscular atrophy: Interim results from the phase 2 nurture study	Neuromuscular Disorders	Comparator not within scope
Ryan et al	2019	Nusinersen in infants who initiate treatment in a presymptomatic stage of spinal muscular atrophy (SMA): Interim results from the phase 2 nurture study	Journal of the Neurological Sciences	Comparator not within scope
Schultz	2019	198. Onasemnogene Abeparvovec Gene-Replacement Therapy (GRT) in Pre-symptomatic Spinal Muscular Atrophy (SMA)	Child Neurology Society	Superseded by SPR1NT publications and CSR

Author	Year	Title	Journal	Rationale for exclusion from submission
Schultz et al	2019	Avxs-101 gene-replacement therapy (grt)) in presymptomatic spinal muscular atrophy (SMA): Study update	Canadian Journal of Neurological Sciences	Superseded by SPR1NT publications and CSR
Schultz et al	2019	P.350onasemnogene abeparvovec gene-replacement therapy (grt) in pre-symptomatic spinal muscular atrophy (SMA)	Neuromuscular Disorders	Superseded by SPR1NT publications and CSR
Schultz et al	2019	Avxs-101 gene-replacement therapy in presymptomatic spinal muscular atrophy(SMA): Study update	No To Hattatsu	Superseded by SPR1NT publications and CSR
Schultz et al	2019	Onasemnogene abeparvovec gene-replacement therapy (GRT) in pre-symptomatic spinal muscular atrophy (SMA).	--	Superseded by SPR1NT publications and CSR
Scoto et al	2018	The use of nusinersen in the "real world": The uk and ireland experience with the expanded access program (eap)	Neuromuscular Disorders	Comparator not within scope
Scoto et al	2019	The use of nusinersen for spinal muscular atrophy (SMA) in the real world: The uk and ireland experience with the expanded access program (eap)	Developmental Medicine and Child Neurology	Comparator not within scope
Seabrook et al	2019	Firefish part 1:1-year event-free survival and swallowing ability in infants with type 1 SMA	No To Hattatsu	Comparator not within scope
Seabrook et al	2019	Firefish part 1: 1-year results on motor function in infants with type 1 spinal muscular atrophy (SMA) receiving risdiplam (rg7916)	Canadian Journal of Neurological Sciences	Comparator not within scope
Servais et al	2019	Firefish part 1: Survival, ventilation and swallowing ability in infants with type 1 SMA receiving risdiplam (rg7916)	Neurology. Conference: 71st Annual Meeting of the American Academy of Neurology, AAN	Comparator not within scope
Servais et al	2019	Firefish part 1:1-year motor function results in infants with type 1 spinal muscular atrophy(SMA)	No To Hattatsu	Comparator not within scope
Sheikh et al	2019	Treatment of spinal muscular atrophy with nusinersen produces improvement in pulmonary function in children with SMA ii and SMA iii	American Journal of Respiratory and Critical Care Medicine. Conference	Comparator not within scope
Shell et al	2018	Avxs-101 phase 1 gene therapy clinical trial in spinal muscular atrophy type 1 (sma1): Improvement in	Annals of Neurology	Population not within scope (not pre-symptomatic)

Author	Year	Title	Journal	Rationale for exclusion from submission
		respiratory and bulbar function reduces frequency and duration of hospitalizations compared to natural history		
Shell et al	2018	Avxs-101 phase 1 gene replacement therapy clinical trial in spinal muscular atrophy type 1: Improvement in respiratory and swallowing function stabilizes the need for ventilatory and nutritional support, and reduces frequency and duration of hospitalizations compared with natural history	Journal of Pediatric Gastroenterology and Nutrition	Population not within scope (not pre-symptomatic)
Shell et al	2018	Avxs-101 phase 1 gene replacement therapy clinical trial in SMA type 1: Continued independence from nutritional and ventilatory support in patients dosed early in disease progression	Neurology. Conference: 70th Annual Meeting of the American Academy of Neurology, AAN	Population not within scope (not pre-symptomatic)
Shell et al	2017	Avxs-101 phase 1 gene therapy clinical trial in SMA type 1: Interim data demonstrates improvements in supportive care use	European Journal of Paediatric Neurology	Population not within scope (not pre-symptomatic)
Shell et al	2018	Avxs-101 phase 1 gene therapy clinical trial in SMA type 1: Continued event-free survival, achievement of developmental milestones, and continued respiratory and nutritional support independence	American Journal of Respiratory and Critical Care Medicine. Conference: American Thoracic Society International Conference, ATS	Population not within scope (not pre-symptomatic)
Shell et al	2019	Avxs-101 gene replacement therapy (grt) for spinal muscular atrophy type 1 (sma1): Pivotal phase 3 study (str1ve) update	American Journal of Respiratory and Critical Care Medicine. Conference	Population not within scope (not pre-symptomatic)
Shell et al	2019	Onasemnogene abeparvovec gene-replacement therapy (grt) for spinal muscular atrophy type 1 (sma1): Preliminary pulmonary and ventilatory findings from the phase 3 study (str1ve)	Thorax	Population not within scope (not pre-symptomatic)
Shell et al	2020	Onasemnogene abeparvovec-xioi gene-replacement therapy for spinal muscular atrophy type 1: Pulmonary and ventilatory findings from the pivotal phase 3 us study (STR1VE).	--	Population not within scope (not pre-symptomatic)
Shieh et al	2018	Safety and Efficacy of Nusinersen in Infants/Children With Spinal Muscular Atrophy (SMA): Part 1 of the Phase 2 EMBRACE Study	--	Comparator not within scope

Author	Year	Title	Journal	Rationale for exclusion from submission
Shieh et al	2018	Safety and efficacy of nusinersen in infants/children with spinal muscular atrophy (sma): Part 1 of the phase 2 embrace study	Neurology. Conference: 70th annual meeting of the american academy of neurology, AAN	Comparator not within scope
Sproule et al	2017	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	Annals of Neurology	Population not within scope (not pre-symptomatic)
Strauss et al	2019	Onasemnogene abeparvovec gene-replacement therapy (grt) in presymptomatic spinal muscular atrophy (SMA): Spr1nt study update	Journal of the Neurological Sciences	Superseded by SPR1NT publications and CSR
Strauss et al	2020	SMA - THERAPY: P.260 Onasemnogene abeparvovec gene therapy in presymptomatic spinal muscular atrophy (SMA): SPR1NT study update.	--	Superseded by SPR1NT publications and CSR
Strauss et al	2020	Onasemnogene Abeparvovec-xioi Gene Therapy in Presymptomatic Spinal Muscular Atrophy (SMA): SPR1NT Study Update.	--	Superseded by SPR1NT publications and CSR
Strauss et al	2020	Onasemnogene abeparvovec gene-replacement therapy in presymptomatic spinal muscular atrophy: SPR1NT study update.	--	Superseded by SPR1NT publications and CSR
Swoboda	2018	Nusinersen in infants who initiate treatment in a presymptomatic stage of spinal muscular atrohpy (SMA): Interim efficacy and safety results from the Phase 2 NURTURE study	World Muscle Congress	Comparator not within scope
Swoboda et al	2013	First-in-human phase i study to assess safety, tolerability and dose for intrathecal injection of isis-smnrx in SMA patients	Neuromuscular Disorders	Comparator not within scope
Swoboda et al	2013	A multicenter phase ii open-label trial of l-carnitine and valproic acid in infants with spinal muscular atrophy type i	Neurology. Conference: 65th American Academy of Neurology Annual Meeting. San Diego, CA United States. Conference Publication:	Comparator not within scope

Author	Year	Title	Journal	Rationale for exclusion from submission
Swoboda et al	2012	A multicenter phase ii open-label trial of valproic acid and l-carnitine in infants with SMA type i	Annals of Neurology	Comparator not within scope
Swoboda et al	2010	Sma carni-val trial part i: Double-blind, randomized, placebo-controlled trial of l-carnitine and valproic acid in spinal muscular atrophy	PLoS ONE	Comparator not within scope
Swoboda et al	2009	Phase ii open label study of valproic acid in spinal muscular atrophy	PLoS ONE	Comparator not within scope
Tozawa et al	2019	Intrathecal nusinersen treatment after ventriculo-peritoneal shunt placement: A case report focusing on the neurofilament light chain in cerebrospinal fluid	Brain and Development.	Comparator not within scope
Vlodavets et al	2019	Firefish part 1: Survival, ventilation and swallowing ability in infants with type 1 spinal muscular atrophy (SMA) treated with risdiplam (rg7916)	European Journal of Neurology	Comparator not within scope
Waldrop et al	2019	P.365clinical outcomes in patients with spinal muscular atrophy type 1, 2 or 3 after 1 year of nusinersen therapy	Neuromuscular Disorders	Comparator not within scope
Walter et al	2019	Safety and treatment effects of nusinersen in longstanding adult 5q-SMA type 3 - a prospective observational study	Journal of Neuromuscular Diseases	Comparator not within scope
Weiss et al	2018	Intrathecal administration of nusinersen in patients with sma: Experience and challenges-a single-center report	Neuropediatrics. Conference: 44th Annual Meeting of the Society for Neuropediatrics. Germany.	Comparator not within scope
Yeo et al	2019	Outcome measures for nusinersen efficacy in adults with spinal muscular atrophy	Neurology. Conference: 71st Annual Meeting of the American Academy of Neurology, AAN	Comparator not within scope
--	2020	A Study of CK-2127107 in Patients With Spinal Muscular Atrophy	--	Comparator not within scope
--	2020	Gene Replacement Therapy Clinical Trial for Participants With Spinal Muscular Atrophy Type 1 (STR1VE)	--	Population not within scope (not pre-symptomatic)
Acsadi G	2021	Safety and efficacy of nusinersen in spinal muscular atrophy: the EMBRACE study	Muscle & nerve. 63(5):668-677, 2021.	Comparator not within scope

Author	Year	Title	Journal	Rationale for exclusion from submission
Day J	2020	SMA - THERAPY: P.263 SUNFISH Part 1: 24-month safety and exploratory outcomes of risdiplam (RG7916) treatment in patients with Type 2 or 3 spinal muscular atrophy (SMA)	Neuromuscular disorders. Vol.30, pp.S123-, 2020.	Comparator not within scope
EUCTR2017-004600-22-IT	2021	Clinical study evaluating the effect of Amifampridine Phosphate in Ambulatory Patients with Spinal Muscular Atrophy (SMA) Type 3	https://trialsearch.who.int/Trial2.aspx?TrialID=EUCTR2017-004600-22-IT. 2021.	Comparator not within scope
Finkel R	2021	Part A Results from the Ongoing DEVOTE Study to Explore Higher-Dose Nusinersen in SMA	Annals of neurology. 90(SUPPL 26):S154-, 2021.	Comparator not within scope
Mercuri E	2020	SUNFISH Part 2: efficacy and safety of risdiplam (RG7916) in patients with Type 2 or non-ambulant Type 3 spinal muscular atrophy (SMA)	European journal of neurology. Vol.27, pp.869-, 2020.	Comparator not within scope
Mercuri E	2021	SMA - TREATMENT: EP.271 Part A results from the ongoing DEVOTE study to explore higher-dose nusinersen in SMA	Neuromuscular disorders. Vol.31, pp.S132-, 2021.	Comparator not within scope
Nascimento A,	2021	SUNFISH part 2: 24-month efficacy and safety of risdiplam in type 2/nonambulant type 3 SMA	Journal of neuromuscular diseases. 8(SUPPL 1):S45-, 2021.	Comparator not within scope
Niguidula N,	2021	Predictive factors of nusinersen treatment response in infantile-onset SMA: results from the endear/shine studies	Journal of neuromuscular diseases. 8(SUPPL 1):S128-, 2021.	Comparator not within scope
Rudnicki SA,	2021	Reldesemtiv in Patients with Spinal Muscular Atrophy: a Phase 2 Hypothesis-Generating Study	Neurotherapeutics. 2021.	Comparator not within scope
Sergott RC,	2021	Risdiplam treatment has not led to retinal toxicity in patients with spinal muscular atrophy	Annals of clinical and translational neurology. 8(1):54-65, 2021.	Comparator not within scope
Servais L,	2021	Longer-term effects of Nusinersen on motor function outcomes based on age at treatment initiation	Developmental medicine and child neurology. 63(SUPPL 1):23-, 2021.	Comparator not within scope
Muntoni F.	2021	Long-term follow-up of patients with type 2 and non-ambulant type 3 spinal muscular atrophy (SMA) treated with olesoxime in the OLEOS trial	Neuromuscular disorders. 30(12):959-969, 2020.	Comparator not within scope

Author	Year	Title	Journal	Rationale for exclusion from submission
Baranello G.	2021	FIREFISH Part 1: 24-month safety and exploratory outcomes of risdiplam (RG7916) in infants with Type 1 spinal muscular atrophy (SMA).	Developmental Medicine and Child Neurology. Conference: Annual Meeting of the British Paediatric Neurology Association. Virtual. 63(SUPPL 1) (pp 11), 2021. Date of Publication: January 2021.	Comparator not within scope
Baranello G.	2021	SMA - TREATMENT: EP.280 Pooled safety data from the risdiplam clinical trial development program.	Neuromuscular Disorders. Conference: WMS 2021 Virtual Congress. Virtual, Online. 31(Supplement 1) (pp S135), 2021. Date of Publication: October 2021.	Comparator not within scope
Baranello G.	2020	FIREFISH Part 2: Efficacy and safety of risdiplam (RG7916) in infants with Type 1 spinal muscular atrophy (SMA).	European Respiratory Journal. Conference: European Respiratory Society International Congress, ERS 2020. Virtual. 56(Supplement 64) (no pagination), 2020. Date of Publication: September 2020.	Comparator not within scope
Bertini E.	2021	RAINBOWFISH: A study of risdiplam in infants with presymptomatic SMA.	European Journal of Neurology. Conference: 7th Congress of the European Academy of Neurology. Virtual. 28(SUPPL 1) (pp 396), 2021. Date of Publication: June 2021.	Comparator not within scope
Bruno C.	2021	JEWELFISH: 12-month safety, pharmacodynamic and exploratory efficacy of risdiplam in non-naive patients with SMA.	European Journal of Neurology. Conference: 7th Congress of the European Academy of Neurology.	Comparator not within scope

Author	Year	Title	Journal	Rationale for exclusion from submission
			Virtual. 28(SUPPL 1) (pp 396-397), 2021. Date of Publication: June 2021.	
Chiriboga C	2021	JEWELFISH: Safety and pharmacodynamic data in non-naive patients with spinal muscular atrophy receiving treatment with risdiplam (RG7916).	Developmental Medicine and Child Neurology. Conference: Annual Meeting of the British Paediatric Neurology Association. Virtual. 63(SUPPL 1) (pp 30), 2021. Date of Publication: January 2021.	Comparator not within scope
Darras B.T.	2021	Risdiplam-treated infants with type 1 spinal muscular atrophy versus historical controls.	New England Journal of Medicine. 385(5) (pp 427-435), 2021. Date of Publication: 29 Jul 2021.	Comparator not within scope
Darras B.T.	2021	FIREFISH Part 2: 24-month efficacy and safety of risdiplam in infants with type 1 spinal muscular atrophy (SMA).	Neurology. Conference: 73rd Annual Meeting of the American Academy of Neurology, AAN 2021. Virtual. 96(15 SUPPL 1) (no pagination), 2021. Date of Publication: May 2021.	Comparator not within scope
Day J.	2021	Long-term Follow-up (LTFU) of Onasemnogene Abeparvovec Gene Therapy in Spinal Muscular Atrophy (SMA).	Annals of Neurology. Conference: 50th Annual Meeting of the Child Neurology Society. Boston, MA United States. 90(SUPPL 26) (pp S151-S152), 2021. Date of Publication: September 2021.	Superseded by updated interim results from LT-002
Day J.W.	2021	Onasemnogene abeparvovec gene therapy for symptomatic infantile-onset spinal muscular atrophy in	The Lancet Neurology. 20(4) (pp 284-293), 2021.	Population not within scope (not pre-symptomatic)

Author	Year	Title	Journal	Rationale for exclusion from submission
		patients with two copies of SMN2 (STR1VE): an open-label, single-arm, multicentre, phase 3 trial.	Date of Publication: April 2021.	
Farrar M.	2021	Longer-term safety data in individuals with later-onset sma support the favourable tolerability profile of nusinersen.	European Journal of Neurology. Conference: 7th Congress of the European Academy of Neurology. Virtual. 28(SUPPL 1) (pp 287), 2021. Date of Publication: June 2021.	Comparator not within scope
Finkel R.	2021	Part A Results from the Ongoing DEVOTE Study to Explore Higher-Dose Nusinersen in SMA.	Annals of Neurology. Conference: 50th Annual Meeting of the Child Neurology Society. Boston, MA United States. 90(SUPPL 26) (pp S154), 2021. Date of Publication: September 2021.	Comparator not within scope
Finkel R.	2021	Treatment of infantile-onset spinal muscular atrophy with nusinersen: final report of a phase 2, open-label, multicentre, dose-escalation study.	The Lancet Child and Adolescent Health. 5(7) (pp 491-500), 2021. Date of Publication: July 2021.	Comparator not within scope
Finkel R..	2021	Onasemnogene abeparvovec gene therapy for Spinal muscular atrophy type 1: Phase 3 study (str1ve-us).	Thorax. Conference: British Thoracic Society Winter Meeting 2021. Online. 76(SUPPL 1) (pp A10-A11), 2021. Date of Publication: February 2021.	Population not within scope (not pre-symptomatic)
Jevtic S.	2021	SMA - TREATMENT: EP.281 Branaplam in type 1 spinal muscular atrophy: second and third part of a phase II study.	Neuromuscular Disorders. Conference: WMS 2021 Virtual Congress. Virtual, Online. 31(Supplement 1) (pp S135), 2021. Date of Publication: October 2021.	Comparator not within scope

Author	Year	Title	Journal	Rationale for exclusion from submission
McMillan H.	2021	Onasemnogene Abeparvovec Gene Therapy in Presymptomatic Spinal Muscular Atrophy (SMA): SPR1NT Study Update in Children with 3 Copies of SMN2.	Annals of Neurology. Conference: 50th Annual Meeting of the Child Neurology Society. Boston, MA United States. 90(SUPPL 26) (pp S152), 2021. Date of Publication: September 2021.	Superseded by SPR1NT publications and CSR
Mendell J.R.	2021	Long-term follow-up of the phase 1 start trial of onasemnogene abeparvovec gene therapy in Spinal muscular atrophy type 1.	Thorax. Conference: British Thoracic Society Winter Meeting 2021. Online. 76(SUPPL 1) (pp A10), 2021. Date of Publication: February 2021.	Population not within scope (not pre-symptomatic)
Mercuri E.	2021	Onasemnogene abeparvovec gene therapy for spinal muscular atrophy type 1 (SMA1): Phase III study update (STR1VE-EU).	Developmental Medicine and Child Neurology. Conference: Annual Meeting of the British Paediatric Neurology Association. Virtual. 63(SUPPL 1) (pp 22-23), 2021. Date of Publication: January 2021.	Population not within scope (not pre-symptomatic)
Mercuri E.	2021	Onasemnogene abeparvovec gene therapy for symptomatic infantile-onset spinal muscular atrophy type 1 (STR1VE-EU): an open-label, single-arm, multicentre, phase 3 trial.	The Lancet Neurology. 20(10) (pp 832-841), 2021. Date of Publication: October 2021.	Population not within scope (not pre-symptomatic)
Muntoni F.	2021	Gene replacement therapy for symptomatic spinal muscular atrophy type 1: Final results of the Phase III STR1VE-EU study.	European Journal of Neurology. Conference: 7th Congress of the European Academy of Neurology. Virtual. 28(SUPPL 1) (pp 834), 2021. Date of Publication: June 2021.	Population not within scope (not pre-symptomatic)

Author	Year	Title	Journal	Rationale for exclusion from submission
Niguidula N.	2021	Longer-term treatment with nusinersen: Results in later-onset spinal muscular atrophy from the SHINE study.	Journal of Neuromuscular Diseases. Conference: 16th International Congress on Neuromuscular Diseases, ICNMD 2021. Virtual. 8(SUPPL 1) (pp S67), 2021. Date of Publication: 2021.	Comparator not within scope
Niguidula N.	2021	Predictive factors of nusinersen treatment response in infantile-onset SMA: Results from the endear/shine studies.	Journal of Neuromuscular Diseases. Conference: 16th International Congress on Neuromuscular Diseases, ICNMD 2021. Virtual. 8(SUPPL 1) (pp S128), 2021. Date of Publication: 2021.	Comparator not within scope
Place A.	2021	TOPAZ: Phase 2 study evaluating efficacy and safety of apitegromab in later-onset spinal muscular atrophy.	Journal of Neuromuscular Diseases. Conference: 16th International Congress on Neuromuscular Diseases, ICNMD 2021. Virtual. 8(SUPPL 1) (pp S9), 2021. Date of Publication: 2021.	Comparator not within scope
Sansone V.	2021	Integrated analysis of annualized incidence of serious adverse events in infantile-onset SMA treated with nusinersen.	Journal of Neuromuscular Diseases. Conference: 16th International Congress on Neuromuscular Diseases, ICNMD 2021. Virtual. 8(SUPPL 1) (pp S152-S153), 2021. Date of Publication: 2021.	Comparator not within scope
Servais L.	2021	RAINBOWFISH: A study of risdiplam (RG7916) in infants with presymptomatic spinal muscular atrophy (SMA).	Developmental Medicine and Child Neurology. Conference: Annual Meeting of the British Paediatric Neurology	Comparator not within scope

Author	Year	Title	Journal	Rationale for exclusion from submission
			Association. Virtual. 63(SUPPL 1) (pp 27), 2021. Date of Publication: January 2021.	
Strauss K.	2021	SMA - TREATMENT: EP.274 Onasemnogene Abeparvovec Gene Therapy in Presymptomatic spinal muscular atrophy (SMA): SPR1NT study update in children with 3 Copies of SMN2.	Neuromuscular Disorders. Conference: WMS 2021 Virtual Congress. Virtual, Online. 31(Supplement 1) (pp S133), 2021. Date of Publication: October 2021.	Superseded by SPR1NT publications and CSR
Strauss K.	2021	Onasemnogene abeparvovecgene therapy in presymptomatic spinal muscular atrophy (SMA): Spr1nt study update in children with 2 Copies of SMN2.	Neurology. Conference: 73rd Annual Meeting of the American Academy of Neurology, AAN 2021. Virtual. 96(15 SUPPL 1) (no pagination), 2021. Date of Publication: May 2021.	Superseded by SPR1NT publications and CSR
Tulinius M.	2021	Longer-term improved/maintained motor function in nusinersen-treated children with later-onset SMA in CS2/CS12 and SHINE.	European Journal of Neurology. Conference: 7th Congress of the European Academy of Neurology. Virtual. 28(SUPPL 1) (pp 394), 2021. Date of Publication: June 2021.	Comparator not within scope
Baranello G	2021	Risdiplam in Type 1 Spinal Muscular Atrophy.	N Engl J Med	Comparator not within scope
Day JW	2021	Clinical Trial and Postmarketing Safety of Onasemnogene Abeparvovec Therapy.	Drug Saf	Not a clinical trial, but summary of safety data from onasemnogene abeparvovec clinical trials
Mercuri E	2022	Safety and efficacy of once-daily risdiplam in type 2 and non-ambulant type 3 spinal muscular atrophy (SUNFISH part 2): a phase 3, double-blind, randomised, placebo-controlled trial.	Lancet Neurol	Comparator not within scope

Author	Year	Title	Journal	Rationale for exclusion from submission
Mohseni R	2022	An open-label phase 1 clinical trial of the allogeneic side population adipose-derived mesenchymal stem cells in SMA type 1 patients.	Neurol Sci	Comparator not within scope
L. Servais	2021	RAINBOWFISH: A study of risdiplam in infants with presymptomatic spinal muscular atrophy (SMA)	--	Comparator not within scope
R. Masson	2021	FIREFISH Parts 1 and 2: 24-month safety and efficacy of risdiplam in type 1 spinal muscular atrophy (SMA)	--	Comparator not within scope
C. Chiriboga	2021	JEWELFISH: Safety, pharmacodynamic and exploratory efficacy data in non-naïve patients with spinal muscular atrophy (SMA) receiving risdiplam	--	Comparator not within scope
G. Baranello	2021	Pooled safety data from the risdiplam clinical trial development program	--	Comparator not within scope
V. Sansone	2021	Preserved swallowing function in infants who initiated nusinersen treatment in the presymptomatic stage of SMA: results from the NURTURE study	--	Comparator not within scope
A. Nascimento	2021	SUNFISH Part 2: 24-month efficacy and safety of risdiplam in patients with Type 2 or nonambulant Type 3 spinal muscular atrophy (SMA)	--	Comparator not within scope
T. Crawford	2021	Apitegromab in SMA: an analysis of multiple endpoints and PD relationships to efficacy in the TOPAZ trial	--	Comparator not within scope
Michelle A Farrar	2021	Plasma Phosphorylated Neurofilament Heavy Chain (pNF-H) Level is Associated with Future Motor Function in Nusinersen-treated Individuals with Later-onset Spinal Muscular Atrophy (SMA)	--	Comparator not within scope
Kevin Strauss	2021	Onasemnogene Abeparvovec Gene Therapy in Presymptomatic Spinal Muscular Atrophy (SMA): SPR1NT Study Update in Children with 3 Copies of SMN2	--	Superseded by SPR1NT publications and CSR
Amy Place	2021	A Phase 2 Study to Evaluate the Efficacy and Safety of SRK-015 in Patients with Later-Onset Spinal Muscular Atrophy (TOPAZ): A Study Update	--	Comparator not within scope
Maryam Oskoui	2021	SUNFISH Part 2: 24-month Efficacy and Safety of Risdiplam in Patients with Type 2 or Non-ambulant Type 3 Spinal Muscular Atrophy (SMA)	--	Comparator not within scope

Author	Year	Title	Journal	Rationale for exclusion from submission
Richard S Finkel	2021	RAINBOWFISH: A Study of Risdiplam in Newborns with Presymptomatic Spinal Muscular Atrophy (SMA)	--	Comparator not within scope
John W. Day	2021	Escalating Dose and Randomized, Controlled Study of Nusinersen in Participants With Spinal Muscular Atrophy (SMA); Study Design and Part A Data for the Phase 2/3 DEVOTE (232SM203) Study to Explore High Dose Nusinersen	--	Comparator not within scope
McMillan H	2021	Onasemnogene Abeparvovec Gene Therapy in Presymptomatic Spinal Muscular Atrophy (SMA): SPR1NT Study Update in Children with 3 Copies of SMN2	--	Superseded by SPR1NT publications and CSR
Place A	2021	TOPAZ: Phase 2 Study Evaluating Efficacy and Safety of Apitegromab in Later-Onset Spinal Muscular Atrophy	--	Comparator not within scope
Vlodavets D.	2021	FIREFISH Part 2: 24-month Efficacy and Safety of Risdiplam in Infants with Type 1 SMA	--	Comparator not within scope
Bruno C.	2021	JEWELFISH: Safety and Pharmacodynamic Data in Non-Naïve Patients with SMA Receiving Treatment with Risdiplam	--	Comparator not within scope
Servais L.	2021	RAINBOWFISH: A study of Risdiplam in Infants with Presymptomatic SMA	--	Comparator not within scope
NCT03837184	2022	Single-Dose Gene Replacement Therapy Using for Patients With Spinal Muscular Atrophy Type 1 With One or Two SMN2 Copies	--	Population not within scope (not pre-symptomatic)
NCT02122952	2021	Gene Transfer Clinical Trial for Spinal Muscular Atrophy Type 1	--	Population not within scope (not pre-symptomatic)
NCT03505099	2022	Pre-Symptomatic Study of Intravenous Onasemnogene Abeparvovec-xioi in Spinal Muscular Atrophy (SMA) for Patients With Multiple Copies of SMN2 (SPR1NT)	--	Included (based on publications and CSR)
NCT02292537	2021	A Study to Assess the Efficacy and Safety of Nusinersen (ISIS 396443) in Participants With Later-onset Spinal Muscular Atrophy (SMA)	--	Comparator not within scope
NCT02193074	2021	A Study to Assess the Efficacy and Safety of Nusinersen (ISIS 396443) in Infants With Spinal Muscular Atrophy	--	Comparator not within scope

Author	Year	Title	Journal	Rationale for exclusion from submission
NCT01839656	2021	A Study to Assess the Efficacy, Safety and Pharmacokinetics of Nusinersen (ISIS 396443) in Infants With Spinal Muscular Atrophy (SMA)	--	Comparator not within scope
NCT01703988	2021	An Open-label Safety, Tolerability and Dose-Range Finding Study of Multiple Doses of Nusinersen (ISIS 396443) in Participants With Spinal Muscular Atrophy	--	Comparator not within scope
NCT02462759	2021	A Study to Assess the Safety and Tolerability of Nusinersen (ISIS 396443) in Participants With Spinal Muscular Atrophy (SMA)	--	Comparator not within scope
NCT03306277	2021	Gene Replacement Therapy Clinical Trial for Participants With Spinal Muscular Atrophy Type 1	--	Population not within scope (not pre-symptomatic)
NCT03781479	2021	Controlled Trial to Evaluate Amifampridine Phosphate in Spinal Muscular Atrophy Type 3 Patients	--	Comparator not within scope
NCT02913482	2022	Investigate Safety, Tolerability, PK, PD and Efficacy of Risdiplam (RO7034067) in Infants With Type1 Spinal Muscular Atrophy	--	Comparator not within scope
NCT02908685	2021	A Study to Investigate the Safety, Tolerability, Pharmacokinetics, Pharmacodynamics and Efficacy of Risdiplam (RO7034067) in Type 2 and 3 Spinal Muscular Atrophy (SMA) Participants	--	Comparator not within scope
NCT03461289	2021	Single-Dose Gene Replacement Therapy Clinical Trial for Participants With Spinal Muscular Atrophy Type 1	--	Population not within scope (not pre-symptomatic)
J. Mendell	2021	Long-term follow-up (LTFU) of onasemnogene abeparvovec gene therapy in spinal muscular atrophy (SMA)	--	Superseded by updated interim data from LT-002

C6. The company has presented the study selection criteria (company submission, Table 5) and study selection process (company submission, Figure 4) for the natural history study SLR. The company identified 27 studies that met the selection criteria but data from only two studies (PNCR and NeuroNext/Kolb 2017) were used for comparisons with outcome data from the SPR1NT trial. Please provide details of the rationale/selection criteria used to select these 2/27 studies and an updated PRISMA flow diagram that summarises the full study selection process.

Response:

The PRISMA diagram presented in the submission reflects the studies included in the SLR. Only PNCR and NeuroNext/Kolb 2017 were used for comparisons with outcome data from the SPR1NT trial. The use of the PNCR study was pre-specified in the protocol for the SPR1NT trial and was used for comparison for primary and secondary endpoints, as well as exploratory endpoints as appropriate. Where PNCR data were not available or complete for a specific exploratory endpoint, NeuroNext/Kolb 2017 data were used for post hoc comparison. NeuroNext/Kolb 2017 comparator data were used only in an analysis of CHOP INTEND data over time for the *SMN2* two-copy cohort. This analysis was illustrative only and statistical significance was not tested for differences between patients receiving onasemnogene abeparvovec and those in the natural history cohort. For all other comparisons, PNCR data were used as pre-specified in the protocol. The PNCR and NeuroNext/Kolb 2017 datasets have previously been accepted by the regulatory authorities as appropriate controls for the onasemnogene abeparvovec clinical trial programme.

C7. Information about the company SLR of cost effectiveness studies comparing treatment with onasemnogene abeparvovec versus best supportive care (relevant to the UK) for patients with spinal muscular atrophy is missing from the company submission. The provided information should include selection criteria, selection process, data extraction, quality assessment, a summary of the evidence and interpretation of the findings. In line with the NICE company evidence submission

template, the summary of the evidence should include a comparison of the methods and results of published studies.

Response:

The full SLR report, which includes all of the details outlined above for the cost-effectiveness SLR and the other SLRs conducted, has been provided as part of the reference pack accompanying this response document.

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muscular atrophy: real-world outcomes from the RESTORE registry. Abstract submitted with the target of presenting at Cure SMA, June 15-17, 2022. 2022.
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Onasemnogene abeparvovec for treating pre-symptomatic spinal muscular atrophy (MAA partial review of HST 15) [ID4051]

Thank you for agreeing to give us your organisation's views on this treatment following a period of managed access. You can provide a unique perspective on conditions and their treatment that is not typically available from other sources.

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This form has 8 sections

NICE National Institute for Health and Care Excellence

Section 1. About you

Table 1 Name, job, organisation

1. Your name	[redacted] and [redacted]
2. Name of organisation	Spinal Muscular Atrophy UK (SMA UK) and Muscular Dystrophy UK (MDUK)
3. Job title or position	[redacted] and [redacted]
4a. Provide a brief description of the organisation. How many members does it have?	**Spinal Muscular Atrophy UK (SMA UK)** SMA UK is the charity that is working to ensure everyone affected by SMA has access to the best care, support and drug treatments; research continues to bring breakthroughs that improve people's quality of life. 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. 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. **Muscular Dystrophy UK**

	Muscular Dystrophy UK is the charity bringing individuals, families and professionals together to beat muscle-wasting conditions. Founded in 1959, we have been leading the fight against muscle-wasting conditions ever since. We bring together more than 60 rare and very rare progressive muscle-weakening and wasting conditions, affecting around 110,000 children and adults in the UK, including SMA. We have 450 individuals on our database with a personal interest in SMA. Muscular Dystrophy UK is here from the moment of diagnosis and beyond. We understand what it's like to live with muscular dystrophy and how it affects families and friends too. We're here with 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. Muscular Dystrophy UK also funds pioneering research for better treatments to improve lives today and transform those of future generations. And we're pressing for better recognition of muscular dystrophy so that people get the best care and support and access to potential drugs much sooner.
4b. Has the organisation received any funding from the company/companies of the treatment and/or comparator products in the last 12 months? [Relevant companies are listed in the appraisal stakeholder list which was provided to you when the appraisal started] **If so, please state the name of company, amount, and purpose of funding.**	SMA UK • **Novartis** - £7380 for consultancy inc. £400 expenses. - £66,732.83 to fund New Born Screening Alliance of which SMA UK are the accountable body. • Though not a direct comparator, we made our views on access to Risdiplam known publicly via our submissions and as patient experts to NICE and to the SMC consultations. • We are members of and form the secretariat for the UK SMA NBS Alliance https://smanewbornscreening.org.uk/ MDUK **Funding received from the manufacturers (Novartis/Novartis Gene Therapies EU LtD)** **26-Aug-21: £2,000.00; Sponsorship of MDUK's Muscles Matter Seminar Series 2021** **30-Mar-22: £3,000.00 Support for MDUK's Neuromuscular Physiotherapist Conference 2022**

4c. 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. In addition to a support group of 31 families where 28 are being treated with Zolgensma. SMA UK and MDUK are also the secretariat for the UK SMA NBS Alliance which is advocating for SMA to be incorporated into the UK Newborn screening as soon as possible. Through the alliance we have heard

	anecdotal evidence on the benefits of treating pre-symptomatically and the impact on the child and the family when treatment is delayed until symptoms appear.

Section 2 Living with the condition and current treatment

Table 2 What it's like for patients, carers and families to live with the condition and current NHS treatment

6. What is it like to live with the condition? Consider the experience of living with the condition and the impact on daily life (physical and emotional health, ability to work, adaptations to your home, financial impact, relationships, and social life). For children, consider their ability to go to school, develop emotionally, form friendships and participate in school and social life. Is there any impact on their siblings?	SMA is a complex, rare inherited neuromuscular condition that affects the lower motor-neurons in the spinal cord. It leads to the gradual loss of the ability to walk, crawl, move, breathe and swallow. It is a condition that requires complex medical support and is the leading genetic cause of death in infants. **SMA Type 1 is the most severe form of SMA** with symptoms usually beginning between 0 and 6 months. (It is worth noting that there is an SMA type 0 however the disease develops in-vitro and thus pre-symptomatic treatment wouldn't be possible.) 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 is 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 is not 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 for the child and their family. **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 do not 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 are 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 is common for children to have unstable hips which may affect one hip or both and will need monitoring. They may be prescribed additional orthotics such as Ankle-Foot Orthosis (AFO's) and Knee-Ankle-Foot Orthosis (KAFO's) to reduce the impact of contractures.

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.
- Nebuliser to loosen secretions in the lungs.
- 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 is not 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. Additionally, a range of postural support equipment is needed, including: standing frame, specialist supportive seating, profiling bed, bath chair, toilet chair, wet room/ specialist bath, and hoists **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 is not 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 hours, 7 days a week.
7. What do carers experience when caring for someone with the condition?	**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 are not 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. 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. 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. 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."
8. What do patients and carers think of current treatments and care available on the NHS Please state how they help and what the limitations are.	The November 2017 international Standards of Care for SMA (SoC)2,3,4 outline what assessments and interventions families and adults should expect to find in any neuromuscular centre anywhere. This is the current core standard for treatment of SMA in England. Management interventions include: • Respiratory support, including chest physiotherapy, oral suctioning, medication to reduce secretions, cough assist and invasive and non-invasive ventilation; • Feeding support; • Help with managing constipation; • Physiotherapy and occupational therapy; • Treatment for spinal scoliosis, including a lycra suit, spinal brace or jacket and surgery.

9. Considering all treatments available to patients are there any unmet needs for patients with this condition? If yes please state what these are	There are currently three treatments for SMA available through managed access schemes in the UK – Spinraza, Risdiplam, and Zolgensma. However, Zolgensma is currently the only option for babies diagnosed pre-symptomatically. As such, it is imperative they continue to access this treatment as multiple studies have demonstrated that any damage cannot be reversed through treatments and that pre-symptomatic treatment is the sole way to provide the highest quality of life and reduce burden of care.

Section 3 Experience during the managed access agreement (MAA)

Table 3 Experience, advantages and disadvantages during the MAA

10. What are patients' and carers' experience of accessing and having the treatment? • Please refer to the MAA re-evaluation patient submission guide	There have been unavoidable inequalities to access to treatment across the UK as the treatment has rolled out across different treatment centres under the MAA. We have seen some examples of delays to access to treatment for some families due to poor communication channels. Communication between secondary and tertiary care centres is not always efficient, and at times, parents have felt 'out of the loop' in discussions about their child. There have also been cases where clinicians, including the NMDT, have changed their minds or added extra tests at the last minute without properly communicating their motives with the family which causes considerable distress.
11. What do patients and carers think are the advantages of the treatment? Please refer to the MAA re-evaluation patient submission guide	Feedback from our survey showed, 100% of respondents found the one-off treatment beneficial and felt a strong improvement in their breathing (92.9%), improvement in motor milestones (78.6%) and noticed a positive impact on their quality of life (85.5%)

12. What do patients or carers think are the disadvantages of the treatment? Please refer to the MAA re-evaluation patient submission guide	No disadvantages were raised.
13. What place do you think this treatment has in future NHS treatment and care for the condition? Consider how this treatment has impacted patients and how it fits alongside other treatments and care pathway.	Despite being a rare disease, left untreated, SMA is the leading genetic cause of death in infants and toddlers. SMA involves the loss of nerve cells called motor neurons that control muscles. Once lost, motor neurons cannot be regenerated. 50-60% of children born with SMA can never sit up independently and without treatment, do not live beyond two years of age. There is no cure for SMA therefore being treated as early as possible is a key issue for babies born with SMA and their families. Being treated pre-symptomatically stops SMA in its tracks and this treatment is currently the only available option to do so.

Section 4 Patients views on assessments used during the MAA

Table 4 Measurements, tests and assessments

14. Results from tests and assessments are used to help reduce uncertainty about the effectiveness of treatment. **How well do you think these tests and assessments worked in measuring the effectiveness of the treatment?**	The outcome of any test or assessment on babies and young children will heavily depend on the mood of the child at the time. Many families living with SMA report that as a result of many blood tests and procedures, their children are very wary of medical professionals, this, often coupled with long journeys to specialist hospitals, can mean children regularly do not cooperate or show their best abilities within an assessment session. Tests and assessments are, of course, an integral part of assessing effectiveness of treatment but should always be looked at as a part of a bigger picture. Videos from everyday life, and discussions with parents and carers should be equally weighted as evidence of effectiveness.

15. Were there any tests or assessments that were difficult or unhelpful from a patient's or carer's perspective?	The requirement for a synacthen test in steroid management seems to vary across the country. Some treatment centres require it, and others do a more basic blood cortisol test which does not require cannulation. The difference in approach has caused some anxiety within the tight-knit community. Any method that avoids cannulation would be the preferred approach . We have heard from several families that the AAV9 test was a very traumatic experience. Cannulation in SMA babies is very difficult. Some clinicians try multiple times to find a vein causing the patient and the family much distress. Other clinicians found they could get enough blood from a simple heel prick. There should be a low limit to the number of attempts to cannulate. If a heel prick is not considered appropriate, ultrasound guided cannulation by a vascular team should be used if possible.
16. Do patients and carers consider that their experiences (clinical, physical, emotional and psychological) were captured adequately in the MAA tests and assessments? If not please explain what was missing.	The MAA quantifiable tests and assessments currently only capture clinical data, measuring progress in motor function. Interviews focus on other clinical disciplines such as diet, respiratory and bulbar function. Emotional and psychological impact on the patient and their family are currently not captured. The psychological impact of diagnosis, treatment and care in SMA is enormous and should be captured as part of assessments going forward, with referrals being made if counselling or alternative treatment is considered appropriate.
17. What outcomes do you think have not been assessed or captured in the MAA data? Please tell us why	Progress in cognition and learning is not captured formally. Typically, SMA does not affect cognition, in many cases individuals living with SMA are exceptionally bright. However, with some cases of developmental and speech and language delay now emerging in the growing treated population, it is important that this is monitored with a more structured approach.

Section 5 Patient population

Table 5 Groups who may benefit and those who declined treatment

18. 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.	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.
19. Were there people who met the MAA eligibility criteria who decided not to start treatment? Please state if known the proportion of eligible patients who did not start the treatment and any reasons for this.	Not that we are aware of.

Section 6 Equality

20. Are there any potential equality issues that that should be taken into account when considering this condition and the treatment? See NICE's equality scheme for more details.

Section 7 Other issues

21. Are there any other issues that you would like the committee to consider?

Nothing else to add.

Section 8 Key messages

In up to 5 sentences, please summarise the key messages of your statement:

- Despite being a rare disease, left untreated, SMA is the leading genetic cause of death in infants and toddlers.
- SMA involves the loss of nerve cells called motor neurons that control muscles. Once lost, motor neurons cannot be regenerated. 50-60% of children born with SMA can never sit up independently and without treatment, do not live beyond two years of age.
- 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.
- There is no cure for SMA therefore being treated as early as possible is a key issue for babies born with SMA and their families. Being treated pre-symptomatically stops SMA in its tracks and this treatment is currently the only available option to do so.
- Feedback from our survey showed this treatment helped in improving their breathing, in motor milestones and noticed a positive impact on their quality of life by and reduced the full burden of the disease as outlined above.

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.

Your privacy

The information that you provide on this form will be used to contact you about the topic above.

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NICE National Institute for Health and Care Excellence

Highly Specialised Technology Evaluation

Onasemnogene abeparvovec for treating pre-symptomatic spinal muscular atrophy (MAA partial review of HST 15) [ID4051]

NHS organisation submission

Thank you for agreeing to give us your views on the technology and the way it should be used in the NHS.

The Department of Health and Social Care and the Welsh Government provide a unique perspective on the technology, which is not typically available from the published literature. NICE believes it is important to involve NHS organisations that are responsible for commissioning and delivering care in the NHS in the process of making decisions about how technologies should be used in the NHS.

To help you give your views, we have provided a template. The questions are there as prompts to guide you. You do not have to answer every question. Short, focused answers, giving a Department of Health and Social Care and Welsh Government perspective on the issues you think the committee needs to consider, are what we need.

NICE National Institute for Health and Care Excellence

About you

Your name	[redacted]
Name of your organisation	NHS ENGLAND
Please indicate your position in the organisation	Department of Health and Social Care or Welsh Government in general? • Commissioning services for the Department of Health and Social Care or Welsh Government specific to the condition for which NICE is considering this technology? YES • Responsible for quality of service delivery in the CCG (e.g. medical director, public health director, director of nursing)? NO • A specialist in the treatment of people with the condition for which NICE is considering this technology? NO • A specialist in the clinical evidence base that is to support the technology (e.g. participation in clinical trials for the technology)? NO • Other (please specify):
Do you have any 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

What is the expected place of the technology in current practice?

How is the condition currently treated in the NHS? Is there significant geographical variation in current practice? Are there differences in 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?	
To what extent and in which population(s) is the technology being used in your local health economy? **Is there variation in how it is being used in your local health economy?** **Is it always used within its licensed indications? If not, under what circumstances does this occur?** **What is the impact of the current use of the technology on resources?** **What is the outcome of any evaluations or audits of the use of the technology?** **What is your opinion on the appropriate use of the technology?**	The technology is currently being used for this indication as part of a managed access agreement and therefore there are specific eligibility criteria. The use of the technology is in existing gene therapy centre and is being used appropriately. There are no evaluations or audits known to NHSE.

NICE National Institute for Health and Care Excellence

Potential impact on the NHS if NICE recommends the technology

What impact would the guidance have on the delivery of care for patients with this condition?	If the technology were approved it would provide an opportunity for access to therapy much earlier in the progression of the disease which could have a significant impact on progression.
In what setting should/could the technology be used – for example, primary or secondary care, specialist clinics? Would there be any requirements for additional resources (for example, staff, support services, facilities or equipment)?	This technology would be used in designated gene therapy centres. These centres will have the required infrastructure and governance in place.
Can you estimate the likely budget impact? If this is not possible, please comment on what factors should be considered (for example, costs, and epidemiological and clinical assumptions).	A separate budget impact assessment will be undertaken by NHSE
Would implementing this technology have resource implications for other services (for example, the trade-off between using funds to buy more diabetes nurses versus more insulin	No

pumps, or the loss of funds to other programmes)?	
Would there be any need for education and training of NHS staff?	No

Equality

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 licenced** **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.**	No additional considerations
Please tell us what evidence should be obtained to enable the committee to identify and consider such impacts.	

NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others.

Other issues

Please include here any other issues you would like the evaluation committee to consider when appraising this technology	

Your privacy

The information that you provide on this form will be used to contact you about the topic above.

Please select YES if you would like to receive information about other NICE topics - YES or NO

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NICE National Institute for Health and Care Excellence

Onasemnogene abeparvovec for treating pre-symptomatic spinal muscular atrophy (MAA partial review of HST 15) [ID4051]

Clinical expert questions

Many thanks for providing your clinical expert opinion on this evaluation. The NICE technical team have prepared 2 questions for your input:

1. The pivotal trial (SPR1NT) inclusion criteria is shown below:

Key inclusion criteria:

- Babies with pre-symptomatic SMA and two or three copies of the SMN2 gene
- Age ≤6 weeks (≤42 days) at time of dose
- Ability to tolerate thin liquids as demonstrated through a formal bedside swallowing test
- Compound muscle action potential (CMAP) ≥2mV at Baseline; centralized review of CMAP data will be conducted
- Gestational age of 35 to 42 weeks

Is the SPR1NT trial generalisable to the presymptomatic SMA population seen in the NHS?

Answer: Currently only a very small number infants with pre-symptomatic SMA are identified in NHS services because of the lack of a neonatal screening programme for SMA. Those identified will either have older siblings affected, leading to antenatal / immediate postnatal testing, or be identified through the Thames Valley neonatal screening programme. My answers remain the same if SMA is included in the directory for newborn screening.

- All would have SMN2 copy number analysis allowing identification of those with 2 or 3 copies of SMN 2.

- It is realistic that any detected babies could commence treatment before 6 weeks old as in the trial. However, if there is a temporary contraindication to treatment in the first 6 weeks of life (eg abnormal liver function requiring further evaluation) in an individual baby / or an unexpected delay in confirmatory genetic results it would be important not to exclude from accessing treatment. If symptoms developed the infant would be treated through the symptomatic SMA treatment pathway.

- Ability to tolerate thin liquids is expected in pre-symptomatic infants unless due to co-morbidity unrelated to SMA.

- CMAP > 2 mV. CMAP is not routinely measured in infants with SMA in clinical practice; CMAP measurement can vary according to electrode position, stimulus intensity, external temperature hence should not be relied on for confirmation of pre-symptomatic status– a clinical assessment (including confirmation of normal deep tendon reflexes) would allow confirmation of pre-symptomatic diagnosis. There is some variability in CMAP used in studies as a 'bar' for pre-symptomatic – eg nusinersen nurture – pre-symptomatic infants used > 1 mV. It is possible that some infants detected through early testing would be clinically pre-symptomatic but if EMG were undertaken found to have CMAP < 2mV.

- Gestational age 35 to 42 weeks – babies detected through neonatal testing may be of any gestation and therefore this range of gestational age does not apply. It would be important to consider how to treat any born at less than 35 weeks gestation. Very few will be born beyond 42 weeks gestation.

2. A key assumption in the analysis is the assumption that motor milestones gained during the SPR1NT trial are assumed to be

maintained over a lifetime – how appropriate is this assumption? Should any loss of motor milestones be considered?

Answer: Onasemnogene abeparvovec has shown durability of effect in infants (symptomatic) over 7/ 8 years, and in pre-symptomatic infants over 4.5 years. Although it is not possible to be absolutely certain that there will be no loss of motor milestones over a life-time it is expected that there will be long term durability of effect through continuing SMN gene expression.

NICE National Institute for Health and Care Excellence

Onasemnogene abeparvovec for treating pre-symptomatic spinal muscular atrophy (MAA partial review of HST 15) [ID4051]

Additional Clinical expert question

Many thanks for providing your clinical expert opinion on this evaluation. The NICE technical team have prepared an additional question for your input and would highly value your expert response:

3. A key (SPR1NT) inclusion criterion is shown below:

    - Age ≤6 weeks (≤42 days) at time of dose

Are there people being diagnosed with pre symptomatic SMA later than 6 weeks of age in the NHS in England currently? if so, how many/how likely is this? How late could diagnosis be made currently in the NHS in England?

Answer: If a child is diagnosed with SMA type 2 or 3 , a younger sibling may then be diagnosed pre-symptomatically and be older than 6 weeks. Some of these (with type 2 SMA) may have 3 (or exceptionally 2 copies) copies SMN2 gene – some (particularly in the case of type 3 SMA) will have 4 copies SMN2 gene.

It is highly unlikely that this scenario would arise with type 1 SMA – any detected through Thames Valley screening would be identified < 6 weeks old, any identified due to sibling affected should be identified < 6 weeks because sibling should have been diagnosed already (type 1 SMA is expected to be symptomatic leading to diagnosis < 6 months, occasionally later diagnosis is made – eg 8 / 9 months).

NICE National Institute for Health and Care Excellence

Onasemnogene abeparvovec for treating pre-symptomatic spinal muscular atrophy (MAA partial review of HST 15) [ID4051]

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- Ability to tolerate thin liquids as demonstrated through a formal bedside swallowing test
- Compound muscle action potential (CMAP) ≥2mV at Baseline; centralized review of CMAP data will be conducted
- Gestational age of 35 to 42 weeks

Is the SPR1NT trial generalisable to the presymptomatic SMA population seen in the NHS?

Answer:

Broadly yes, when NBS will be implemented and process in place to optimize timeline in treatment delivery

2. A key assumption in the analysis is the assumption that motor milestones gained during the SPR1NT trial are assumed to be maintained over a lifetime – how appropriate is this assumption? Should any loss of motor milestones be considered?

Answer:

This assumption is correct, as the need of SMN at a later age is very limited if any

NICE National Institute for Health and Care Excellence

Onasemnogene abeparvovec for treating pre-symptomatic spinal muscular atrophy (MAA partial review of HST 15) [ID4051]

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Are there people being diagnosed with pre symptomatic SMA later than 6 weeks of age in the NHS in England currently? if so, how many/how likely is this? How late could diagnosis be made currently in the NHS in England?

Answer:

It can happen today in the context of a sibling of a patient with type 3. Let's imagine a family with an older and a younger brother, let's say 6 and 2 years old. The 6 years old is diagnosed with type 3 (first symptoms at the age of 5),, then the younger is diagnosed at the age of 2 with no symptoms.

This situation will progressively disappear with newborn screening and all pre-symptomatic will be younger. In the current NHS context, I am afraid that delivering at the dose of 42 days will be challenging anyway as the confirmatory test can take up to 2 weeks- which makes UK the slowest country in the world (by far). A reasonable limit of 2 months should be set

up, with an aspirational of 30 days (the 2 weeks acceptance for confirmatory test should disappear asap)

NICE National Institute for Health and Care Excellence

Highly Specialised Technology

Guidance review following a period of managed access

Onasemnogene abeparvovec for treating pre-symptomatic spinal muscular atrophy (MAA partial review of HST 15) [ID4051]

Patient expert statement

Thank you for agreeing to give us your views on this treatment and its possible use in the NHS.

Your comments are really valued. You can provide a unique perspective on conditions and their treatment that is not typically available from other sources

Information on completing this form

In part 1 we are asking you about living with SMA or caring for a patient with SMA. The text boxes will expand as you type.

In part 2 we are asking you to provide 5 summary sentences on the main points contained in this document.

Help with completing this form

If you have any questions or need help with completing this form please email the public involvement (PIP) team at pip@nice.org.uk (please include the ID number of your appraisal in any correspondence to the PIP team).

Please use this questionnaire with our hints and tips for patient experts. You can also refer to the MAA Revaluation Organisation Submission Guide (attached). **Please note that you do not have to answer every question** – they are prompts to guide you.

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. Please type information directly into the form.

We are committed to meeting the requirements of copyright legislation. If you want to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs. For copyright reasons, we will have to return forms that have attachments without reading them. You can resubmit your form without attachments, but it must be sent by the deadline.

Your response should not be longer than 15 pages.

The deadline for your response is **5pm** on **Wednesday 11 January 2023**. Please log in to your NICE Docs account to upload your completed form, as a Word document (not a PDF).

Thank you for your time.

We reserve the right to summarise and edit comments, or not to publish them at all, if we consider the comments are too long, or publication would be unlawful or otherwise inappropriate.

Comments received are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the comments we received, and are not endorsed by NICE, its officers or advisory committees.

Patient expert statement

Onasemnogene abeparvovec for treating pre-symptomatic spinal muscular atrophy (MAA partial review of HST 15) [ID4051]

Part 1: Living with this condition or caring for a patient with SMA

Table 1 About you, SMA, current treatments and equality

1. Your name	Ben Williams
2. Are you (please tick all that apply)	☐ A patient with SMA? ☐ A patient with experience of the treatment being evaluated? ☒ A carer of a patient with SMA? ☐ A patient organisation employee or volunteer? ☒ Other (please specify): carer of a patient with experience of (i) the treatment being evaluated, and (ii) nusinersen
3. Name of your nominating organisation	Spinal Muscular Atrophy UK (SMA UK) and Muscular Dystrophy UK (MDUK)
4. Has your nominating organisation provided a submission? (please tick all options that apply)	☐ No (please review all the questions and provide answers when possible) ☒ Yes, my nominating organisation has provided a submission ☐ I agree with it and **do not wish to** complete a patient expert statement ☒ Yes, I authored / was a contributor to my nominating organisations submission ☐ I agree with it and **do not wish to** complete this statement ☒ I agree with it and **will be** completing
5. How did you gather the information included in your statement? (please tick all that apply)	☒ I am drawing from personal experience ☐ I have other relevant knowledge or experience (for example, I am drawing on others' experiences). Please specify what other experience:

6. What is your experience of living with SMA? **If you are a carer (for someone with SMA) please share your experience of caring for them** Consider the experience of living with the condition and the impact on daily life (physical and emotional health, ability to work, adaptations to your home, financial impact, relationships, and social life). For children, consider their ability to go to school, develop emotionally, form friendships and participate in school and social life. Is there any impact on their siblings?	I am the father to [redacted], a 2-year-old with SMA Type 1 (the most severe form of SMA). Although some symptoms were present at birth, [redacted] wasn't diagnosed until 3 months old. [redacted] was treated with Nusinersen (at 3 months old) and Zolgensma (at 9 months old). [redacted] is now 2 years old, a milestone that would have been unachievable just a few years ago. Despite being treated with two of the world's most expensive drugs, [redacted] cannot sit, roll, or swallow. He requires Bipap ventilation 14+ hours per day, is PEG fed, and will almost certainly never crawl, walk, or talk. He is profoundly disabled. The ripple effects of [redacted]'s condition are far reaching: • Night nurses are required every night to help reposition and ensure respiratory function. • Leaving the house is not easy and requires significant planning and equipment (e.g. wheelchair, ventilator, clearway, nebuliser, feed-pump, etc., etc.) • [redacted]'s typical day involves at least one medical appointment, and as much physical physiotherapy as is tolerated. • Contracting viral infections (e.g. a common cold) is life-threatening, and typically requires 4+ weeks of intensive care. To reduce the risks, we have to be extremely selective in who we socialise with. • [redacted] has spent a considerable percentage of his life in hospital. • My wife has given up work in order to provide the requisite level of care. • We have not been able to spend a night away from home/hospital in 2-years. • We need to move to a more suitable home. If [redacted] was treated pre-symptomatically, his – and our – lives would likely be very different.

7a. What do you think of the current treatments and care available for SMA on the NHS? **7b. How do your views on these current treatments compare to those of other people that you may be aware of?**	7a) Treatments/care can be sorted into the following categories: • **Specific SMA targeted drugs**: [redacted] has been treated with two of the three treatments available on the NHS (i.e. Nusinersen and Zolgensma). Whilst improvements have been observed (most notably in an extended life expectancy, and improved breathing), the best outcome for [redacted] was to halt decline. Whilst that is an undeniably beneficial outcome, Zolgensma's efficacy is substantially higher if administered pre-symptomatically. We hold a strong belief that it is undesirable for the NHS to adopt a system that requires symptoms to appear before commencing treatment (because, as [redacted] demonstrates, symptomatic patients are likely to have suffered irreversible damage). • **Non-specific drugs:** [redacted] has been treated with a number of drugs which target his wider symptoms (e.g. prophylactic antibiotics, laxatives, nutrition supplements, nebulisers, etc., etc.). [redacted]'s access to, and use of, such drugs have overall been positive – but we do worry about the long-term impact. • **Medical devices**: [redacted] has many medical devices to help improve his daily quality of life (e.g. ventilator, cough assist, SATs monitor, nebuliser, spinal jacket, AFOs, assisted seating equipment, assisted standing equipment, assisted bathing equipment, etc., etc.). It is however extremely disappointing that there is no pathway for SMA children under 3 years old to access an NHS wheelchair. It is also disappointing that the Mobility Scheme (to help lease an appropriate wheelchair accessible vehicle) is unavailable to SMA children under 3. This places unnecessary financial pressure on carers.

	7b) Unknown.
8. If there are disadvantages for patients of current NHS treatments for SMA (for example, how they are given or taken, side effects of treatment, and any others) please describe these	The primary disadvantage in the current NHS treatment for SMA (which is otherwise impressive) is the delay until treatment can begin. In the absence of newborn screening, it is all but impossible to treat SMA pre-symptomatically – this can have a drastic impact on the outcomes (see answer 1 above for practical examples).
9a. If there are advantages of onasemnogene abeparvovec over current treatments on the NHS please describe these. For example, the effect on your quality of life, your ability to continue work, education, self-care, and care for others? **9b. If you have stated more than one advantage, which one(s) do you consider to be the most important, and why?** **9c. Does onasemnogene abeparvovec help to overcome or address any of the listed disadvantages of current treatment that you have described in question 8? If so, please describe these**	9a We have found Zolgensma to have the following advantages over Nusinersen: • Single infusion • Improved breathing • Improved motor functionality (e.g. [redacted] lost the ability to grip anything whilst being treated with Nusinersen – this ability was recovered after Zolgensma). 9b Single infusion – it has meant less time in hospital receiving treatment (Nusinersen requires quarterly doses), and the removal of the otherwise constant fear that access to Nusinersen might be removed (e.g. because of failure to meet ongoing access criteria) 9c See answer to Q8 above.
10. If there are disadvantages of onasemnogene abeparvovec over current treatments on the NHS please describe these.	Zolgensma does have side effects, most notably risks of severe liver harm. We found the monitoring and risk mitigation measures adopted by the NHS to be adequate. My understanding however is that adverse reactions are less likely to occur in younger patients (because, being lighter, they require a lower dose).

For example, are there any risks with onasemnogene abeparvovec? If you are concerned about any potential side effects you have heard about, please describe them and explain why.	
11. Are there any groups of patients who might benefit more from onasemnogene abeparvovec or any who may benefit less? If so, please describe them and explain why Consider, for example, if patients also have other health conditions (for example difficulties with mobility, dexterity or cognitive impairments) that affect the suitability of different treatments	Pre-symptomatic patients are likely to benefit the most. In the absence of newborn screening, diagnosis can only be achieved after symptoms start to appear - by which time, irreversible damage to the motor neurons is likely to have occurred (meaning the effectiveness of Zolgensma is limited). [redacted] has been treated with both Nusinersen (between 3 months and 9 months old) and Zolgensma (at 9 months old). Despite receiving treatment, he still requires: • 14+ hours of non-ventilation per day • 24/7 care, including night nurses • 4+ weeks of intensive care in a specialist children's hospital every time he picks up an infection • feed pumped directly into his stomach (because of an unsafe swallow) • a spinal jacket to sit up • at least x2 rounds of respiratory physiotherapy per day
12. If you have experience of this treatment during the period of Managed Access please tell us your views on the results from tests and assessments that have been used to help reduce uncertainty about the effectiveness of treatment. **How well do you think these tests and assessments worked in measuring the effectiveness of the treatment?**	The primary measure of effectiveness of Zolgensma has been the CHOP INTEND test, a motor test measure. For [redacted] this has shown measurable motor improvement. As Zolgensma is a single infusion drug, poor CHOP INTEND scores do not affect future treatment (contrast this with Nusinersen for example, which is withdrawn under the terms of the MAA if a patient receives two consecutively declining CHOP INTEND scores – this was a constant fear of ours).

13. Were there any tests or assessments that were difficult or unhelpful from a patient's or carer's perspective?	No
14. Were patients experiences captured adequately in the MAA tests and assessments? **If not please explain what was missing.**	Yes.
15. What outcomes (if any) do you think have not been assessed or captured during the Managed Access period? Please tell us why	Not applicable
16. Are there any potential equality issues that should be taken into account when considering SMA and onasemnogene abeparvovec? Please explain if you think any groups of people with this condition are particularly disadvantage Equality legislation includes people of a particular age, disability, gender reassignment, marriage and civil partnership, pregnancy and maternity, race, religion or belief, sex, and sexual orientation or people with any other shared characteristics More information on how NICE deals with equalities issues can be found in the NICE equality scheme Find more general information about the Equality Act and equalities issues here.	Not applicable

17. Are there any other issues that you would like the committee to consider?	There is a belief that more timely and efficient diagnosis of SMA could be sufficiently achieved via an awareness campaign (rather than via newborn screening). This belief should be rejected. An awareness campaign for SMA: (i) at best, would be a short-term response (awareness campaigns cannot last forever), and (ii) at worst, would be ineffective (it is human nature for most medical professionals to assume that the symptoms presented are not SMA because they are statistically far more likely to something else).

Part 2: Key messages

In up to 5 sentences, please summarise the key messages of your statement:

- Zolgensma is most effective when administered pre-symptomatically
- It is substandard that the NHS currently operates a system that necessitates symptoms to appear (and likely irreversible damage to have occurred) before treatment can be commenced.
- Despite being treated with Zolgensma, [redacted] is profoundly disabled.
- If [redacted] was treated pre-symptomatically, his – and our – lives likely would be very different.
- Any suggestion at efficient diagnosis of SMA could be sufficiently achieved via an awareness campaign should be rejected.

Thank you for your time.

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Highly Specialised Technology

Guidance review following a period of managed access

Onasemnogene abeparvovec for treating pre-symptomatic spinal muscular atrophy (MAA partial review of HST 15) [ID4051]

Patient expert statement

Thank you for agreeing to give us your views on this treatment and its possible use in the NHS.

Your comments are really valued. You can provide a unique perspective on conditions and their treatment that is not typically available from other sources

Information on completing this form

In part 1 we are asking you about living with SMA or caring for a patient with SMA. The text boxes will expand as you type.

In part 2 we are asking you to provide 5 summary sentences on the main points contained in this document.

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Patient expert statement

Onasemnogene abeparvovec for treating pre-symptomatic spinal muscular atrophy (MAA partial review of HST 15) [ID4051]

Part 1: Living with this condition or caring for a patient with SMA

Table 1 About you, SMA, current treatments and equality

1. Your name	
2. Are you (please tick all that apply)	☐ A patient with SMA? ☐ A patient with experience of the treatment being evaluated? ☒ A carer of a patient with SMA? ☒ A patient organisation employee or volunteer? ☐ Other (please specify):
3. Name of your nominating organisation	Spinal Muscular Atrophy UK
4. Has your nominating organisation provided a submission? (please tick all options that apply)	☐ No (please review all the questions and provide answers when possible) ☒ Yes, my nominating organisation has provided a submission ☐ I agree with it and **do not wish to** complete a patient expert statement ☒ Yes, I authored / was a contributor to my nominating organisations submission ☐ I agree with it and **do not wish to** complete this statement ☒ I agree with it and **will be** completing
5. How did you gather the information included in your statement? (please tick all that apply)	☒ I am drawing from personal experience ☐ I have other relevant knowledge or experience (for example, I am drawing on others' experiences). Please specify what other experience:

6. What is your experience of living with SMA? **If you are a carer (for someone with SMA) please share your experience of caring for them** Consider the experience of living with the condition and the impact on daily life (physical and emotional health, ability to work, adaptations to your home, financial impact, relationships, and social life). For children, consider their ability to go to school, develop emotionally, form friendships and participate in school and social life. Is there any impact on their siblings?	My son, [redacted], now 6 years old, lives with SMA type 1. Before his diagnosis, he was admitted to PICU at just 5 weeks old in respiratory distress due to a common cold. He failed the first extubation, meaning my husband and I spent his first Christmas with him in intensive care whilst our three daughters were cared for by their grandparents. Little did we know that this was the first of 10 similar admissions over his first 3 years of life, almost every time he caught a cold. The disruption this caused to family life was huge and has had a significant impact on my three other children, particularly effecting the long-term mental health of one of my daughters who was 16 at the time and going through some difficult times personally. As he was recovering, a PICU nurse from the Evelina hospital alerted the Doctors about [redacted]'s lack of muscle tone and movement, despite their experience in SMA, this was put down to the fact he had been swaddled for so long (done to stop babies from pulling out the ventilator tube) and we were sent home without further investigations in the New Year. Back at home we noticed a significant reduction in [redacted]'s strength and movement. We aired our concerns to three different health visitors, and his GP, he even passed his very much delayed 9 week check, all of the professionals put his symptoms down to the fact that he had been ill in intensive care for so long. I trusted their medical opinions, but watching his fast decline over three months was incredibly scary. His breathing was unusually abdominal, he had lost all movement in his legs, he couldn't lift his hand to his mouth or even grasp and was choking on his milk. It wasn't until I broke down in tears at a local health visitor clinic that I was immediately sent to our local hospital and then referred to a Neuromuscular Consultant at the Evelina Children's Hospital, London. Diagnosis at this late stage meant his prognosis was uncertain. Even with Spinraza treatment (which had just been made available via the Expanded Access Programme) clinicians couldn't give us any assurance that he would survive the next cold, let alone make any physical improvements. At best, his condition would be stabilised. This meant accepting a life for my son with complex needs and dangerous vulnerabilities. Six years ago there were many unknowns as to how

	treatment would impact his development, going for Spinraza treatment was a difficult decision and a huge emotional burden, we did not know if it was the right ethical decision, would we be burdening [redacted] with a lifetime of disability? The unknowns were very difficult to process emotionally. Our homelife was suddenly and dramatically changed. I had to give up my career as a Primary School Teacher to care for [redacted], with a mortgage relying on two incomes, this had a concerning impact on our immediate financial security and was a major source of stress at an immensely difficult time. As my husband earned a salary which was slightly above average, we were not eligible for many of the most helpful government benefits. We had to train and adapt to a new routine including daily use of a bi-pap ventilator, a cough assist machine, deep suctioning (up to 12cm down the nose) , enteral feeding, specialist seating, bed and bath support, specialist buggies, liaisons with community nurses, occupational therapists, physiotherapists, ordering medical equipment from three different sources. Adjusting to such huge change, and being responsible for delivering life saving procedures on a daily basis was overwhelming. We were constantly alert for any signs of sudden deterioration, he could be playing happily in the morning and then admitted to PICU the same evening. Realising that despite my best efforts, I was unable to provide the 24 hour care he so desperately needed, I reluctantly accepted a nursing care package. This began with four 8 hour nights a week and has now increased to seven 12 hour nights and five 8 hour days whilst he is at school. This is a huge cost, funded entirely by the NHS through continuing care. We are fortunate to have a dedicated team of nurses working in our home who have, after six years, become like part of the family. Sharing our home with nurses was another huge adjustment. My social life was lost entirely, my friends didn't know what to say to me and it was difficult to take everyone feeling sorry for us. There was nobody that had the skills or the confidence to babysit, even my husband was too nervous to be left alone with [redacted], so what I could do was incredibly limited. With the support of respite from our local hospice, even now we are only just beginning to feel comfortable leaving

	him overnight. Holidays are extremely challenging, not the restful experience they should be. By the age of 3 [redacted] was more stable, the critical admissions were further apart and he started learning to drive a powerchair. With good community support, we were able to access a local mainstream nursery which fed into the school. The school have been very open to adapting the building for [redacted], they have installed ramps and a care suite with a ceiling hoist and a changing bed. From my contact with other families, I am very aware that many schools are not nearly as receptive and access to a local mainstream is a huge challenge for many families whose child is growing up with 'late treated' SMA Type 1. Despite the best efforts from the school, it is still not easy for him to be fully included in school life. His powerchair is considered too high a risk in a classroom full of young children moving around, so he is limited to his supportive seating and can not independently navigate school unless he is outside. [redacted] loves to race about the playground, play football and tag with the other boys, but unfortunately the boys are not of an age where they want to adapt their games for him, nor are they prepared to include his 1:1 nurse. The girls love to 'look after' him, making sure he is comfortable and fetching things for him, so [redacted] does have friends, but it is not his preferred dynamic. The other huge social barrier for him is his speech and language difficulties. The weakness in his bulbar function, respiratory, and facial muscles means that his voice is quiet and hard to understand. He can not be heard in a busy classroom and you have to be very familiar with him to understand what he is saying. His SALT team are working to overcome some of these barriers but it will always be difficult for him. [redacted] can not enjoy lunch with his peers, at lunchtime he stays in the classroom with his nurse for his enteral feed which lasts for 40 minutes, when he has a rest on a beanbag with his bi-pap mask on. This means he misses out on the lunchtime play, again limiting his social experience and development.

7a. What do you think of the current treatments and care available for SMA on the NHS?	Spinraza, now available through a MAA in England has proven to be highly effective, especially with early diagnosis. Without Spinraza my son would not be alive, but because of a lack of awareness of the early symptoms of SMA amongst frontline clinicians, he was treated late and now lives with complex needs. Spinraza targets the SMN2 gene and, in most childhood cases, modifies the progressive nature of the condition and for adults in general helps to stabilise the condition. With targeted, specialist physiotherapy and other carefully monitored individualised interventions such as orthotic provision, some minimal additional gains can also be experienced. Unfortunately, the NHS does not have the capacity to meet these therapeutic demands and many families have to pay privately. Risdiplam, also available through a MAA and another SMN2 targeting treatment, is available to those over 2 months old, outcomes are broadly similar to those I have described in Spinraza, with varied outcomes across the population. As a daily dose medication, there are advantages over Spinraza which has to be administered as an intrathecal injection 3 times a year, a very invasive process. Onasemnogene Abeparvovec , the gene replacement therapy, as a one off treatment, is the number one choice of newly diagnosed families. Again, with early diagnosis and treatment it is radically changing the SMA disease landscape, but there are many families whose children have been diagnosed and treated late with Onasemnogene Abeparvovec that are going through similar journeys to ours 6 years ago. It is unethical to not treat SMA pre-symptomatically. There are treatments available, that can not only ensure survival, but can let children grow up following almost typical developmental milestones - children that would otherwise die or live with extremely life-limiting complex needs that are hugely expensive to manage. The UK needs to screen the whole population for SMA to ensure every baby born with the condition experiences the optimum outcomes from treatment.
7b. How do your views on these current treatments compare to those of other people that you may be aware of?	I am an active member of several SMA online networks. The advent of treatments for SMA has had a huge impact on the community. Some adults living with SMA

	have had expectations of improvements in their condition that have not always been met due to the progressed nature of the disease. All the families that I have contact with are in agreement that current treatments are having an incredible impact on the development of their children, and all want to see pre-symptomatic treatment becoming the norm.
8. If there are disadvantages for patients of current NHS treatments for SMA (for example, how they are given or taken, side effects of treatment, and any others) please describe these	Spinraza dosing is an invasive procedure which has to be done 3 times a year for life at a specialist hospital, often far from home, within strict time frames. This has several disadvantages; procedural discomfort and possible short term side effects including headaches, pain and fatigue. Logistically it impacts schooling, work and holiday plans. Risdiplam, though convenient as a self-dosing medication delivered direct to your home, comes with possible side effects including sickness, diarrhoea and fatigue. It is also only available to children over 2 months old on the NHS. Those families who have been fortunate enough to have an early diagnosis, (often when SMA is known within the family) would like Risdiplam to be available as a bridging drug whilst they await gene therapy as it is less invasive than Spinraza, the only bridging drug currently available for very young babies. One disadvantage of Onasemnogene Abeparvovec is the fact that the older and the heavier the child gets, the less safe the administration becomes, with some heavier children experiencing severe adverse effects. As a one off treatment, it is the number one choice for newly diagnosed families, but those whose children were diagnosed later have to consider the pros and cons through careful discussions with their clinicians. Because of the risk of adverse effects, patients have to be very closely monitored after treatment, and a course of steroids is essential to minimise the risks, weekly blood tests and a period of shielding is required to keep the child safe during this time, which does temporarily limit the family. This is a consequence families are willing to accept in order to access a one off gene therapy.
9a. If there are advantages of onasemnogene abeparvovec over current treatments on the NHS	Unlike the other two disease modifying treatments, Onasemnogene Abeparvovec is a one off treatment, once the child is 12 weeks post treatment and showing no signs

please describe these. For example, the effect on your quality of life, your ability to continue work, education, self-care, and care for others? **9b. If you have stated more than one advantage, which one(s) do you consider to be the most important, and why?** **9c. Does onasemnogene abeparvovec help to overcome or address any of the listed disadvantages of current treatment that you have described in question 8? If so, please describe these**	of any reaction, they are free to continue their lives without the disruptions that come along with being on a long-term medication. It overcomes the disadvantages seen with Spinraza as it is a one off treatment and less invasive procedure. There is no responsibility to remember to take the medicine as there is with Risdiplam and once the steroid course is complete there are no ongoing side effects.
10. If there are disadvantages of onasemnogene abeparvovec over current treatments on the NHS please describe these. For example, are there any risks with onasemnogene abeparvovec? If you are concerned about any potential side effects you have heard about, please describe them and explain why.	The younger the baby, the less severe any adverse reaction. There are many concerns about safety in older, heavier children, mainly to do with liver function. Administration of onasemnogene pre-symptomatically has been shown to lead to the best and safest outcomes.
11. Are there any groups of patients who might benefit more from onasemnogene abeparvovec or any who may benefit less? If so, please describe them and explain why	Pre-symptomatic babies or those diagnosed very early, before too many neurons have been effected by the disease progression, would benefit the most from onasemnogene abeparvovec. The severest form of SMA is a very aggressive disease, delaying treatment by just one day can see further long term deterioration in motor function.

Consider, for example, if patients also have other health conditions (for example difficulties with mobility, dexterity or cognitive impairments) that affect the suitability of different treatments	
12. If you have experience of this treatment during the period of Managed Access please tell us your views on the results from tests and assessments that have been used to help reduce uncertainty about the effectiveness of treatment. **How well do you think these tests and assessments worked in measuring the effectiveness of the treatment?**	
13. Were there any tests or assessments that were difficult or unhelpful from a patient's or carer's perspective?	
14. Were patients experiences captured adequately in the MAA tests and assessments? **If not please explain what was missing.**	
15. What outcomes (if any) do you think have not been assessed or captured during the Managed Access period? Please tell us why	

16. Are there any potential equality issues that should be taken into account when considering SMA and onasemnogene abeparvovec? Please explain if you think any groups of people with this condition are particularly disadvantage Equality legislation includes people of a particular age, disability, gender reassignment, marriage and civil partnership, pregnancy and maternity, race, religion or belief, sex, and sexual orientation or people with any other shared characteristics More information on how NICE deals with equalities issues can be found in the NICE equality scheme Find more general information about the Equality Act and equalities issues here.	
17. Are there any other issues that you would like the committee to consider?	

Part 2: Key messages

In up to 5 sentences, please summarise the key messages of your statement:

- Presymptomatic treatment of SMA with onasemnogene gives children the best chance of living a life without disabilities.

Patient expert statement

- Given the severity of the life limiting impacts post symptomatic treatment brings, it is unethical not to treat infants diagnosed with SMA presymptomatically.
- Onasemnogene is a one-off treatment, enabling those treated to live a less medicalised life.
- Safety and efficacy of onasemnogene increases the earlier it is given.
- Presymptomatic treatment would save the NHS, the Department for Health and Social Care and the Department for Education the significant cost of maintaining post-symptomatic children in the community and of treating them in hospital when poorly.

Thank you for your time.

Your privacy

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NICE National Institute for Health and Care Excellence

Highly Specialised Technology

Guidance review following a period of managed access

Clinical expert statement

Onasemnogene abeparvovec for treating pre-symptomatic spinal muscular atrophy (MAA partial review of HST 15) [ID4051]

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.

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- Your response should not be longer than 13 pages.

About you	
1. Your name	**Dr Elizabeth Wraige.**

2. Name of organisation	**Evelina London Children's Hospital, Guy's and St Thomas' NHS foundation Trust.**
3. Job title or position	**Consultant Paediatric Neurologist.**
4. Are you (please tick all that apply):	☐ an employee or representative of a healthcare professional organisation that represents clinicians? **x**☐ 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)	**x**☐ 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. Do you have a conflict of interest that you wish to declare[1]?	Direct /Indirect – please explain. I have previously undertaken paid and unpaid consultancy/ advisory work for a number of pharmaceutical firms who have developed treatments for spinal muscular atrophy, including Novartis Gene Therapies. I am not currently involved in any consultancy work with Novartis Gene Therapies.
7. 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	
8. What is the main aim of treatment?	Spinal muscular atrophy (SMA) arises because of mutation in the SMN1 gene leading to failure of motor neurones to produce SMN protein, and resultant death of motor neurones and muscle weakness. Onasemnogene abeparvovec is a gene replacement therapy. It aims to restore the SMN1 gene to motor neurones enabling SMN protein production and thereby normal function of motor neurones and prevention of muscle weakness that would otherwise ensue in the absence of SMN protein production. It aims to preserve muscle strength in all skeletal muscle, this includes preservation of bulbar and respiratory muscle function.

[1] A direct interest is when there is, or could be perceived to be, an opportunity for a person involved with NICE's work to benefit. Direct interests can be financial – where the person gets direct financial benefit, non-financial – where the person gets a non-financial benefit such as increasing or enhancing their professional reputation An indirect interest is when there is, or could be perceived to be, an opportunity for a third party closely associated with the person in question to benefit.

9. 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.)	Acquisition and retention of motor milestones that would not otherwise be attained: eg including rolling, sitting, standing, walking. Preservation of bulbar function – continuing ability to feed orally. For babies predicted to develop type 1 SMA acquisition of expressive language. Preservation of breathing without need for intervention (with eg non-invasive ventilation). Longer term survival without the need for ventilator / feeding support (life expectancy in un-treated infants predicted to develop SMA type 1 is less than 2 years).
10. What are the benefits that you expect the technology to provide compared with routinely commissioned care?	Health benefits. Please delete as appropriate: Increased survival Y Increased time to progression Y Improved QOL Y Does the new technology provide other substantial health related benefits not included in the QALY calculation? Y please explain: I would expect that the mental health of someone who is diagnosed and treated prior to symptom onset, averting the co-morbidities that accompany symptomatic SMA, will be better than that of someone diagnosed symptomatically and continuing to have multiple co-morbidities post treatment. Non-health benefits. Please delete as appropriate: Societal benefits such as improved QoL for carers, faster return to work/school, greater productivity etc… Y, please explain: If treated after being diagnosed by newborn screening, normal/ near-normal motor / language development is expected. If only treated after diagnosis is made following symptom onset (ie

	current situation) long term muscle weakness with physical disability is expected and is seen – this means eg reliance on powered wheelchair for mobility, care giver assistance with all acts of daily living, supplemental feeding or complete reliance on tube feeding and often requirement for non-invasive ventilation overnight. These morbidities lead to vulnerability and increased likelihood of frequent hospital admissions. All of this impacts the ability of an affected individual to attend school (in later life likely to impact workplace attendance) and impacts caregivers as there as a reliance on others for health and social care support. Improved accessibility to patients Y please explain: currently there is no routinely commissioned treatment for babies identified by screening. Implications for delivery of the NHS service Y please explain: I expect detection by screening to make NHS delivery easier. Infants detected by screening will be anticipated to have fewer comorbidities at diagnosis and therefore the care delivery in NHS services should be easier. Eg those detected symptomatically (as currently) require speech and language assessment and input of feeding safety, respiratory assessment to identify nocturnal hypoventilation at the same time as planning SMA treatment.
11. Are there any recognised side effects of the technology?	If yes, please explain how they may affect the patient's quality of life. Yes – in the first few days after treatment fever, vomiting and lethargy may occur. These resolve after the first few days and can be treated with medication. These side effects have only a temporary impact on quality of life. Following treatment a rise in liver enzymes (transaminases) is often seen. This is usually asymptomatic and is mitigated by treatment with steroid (prednisolone) that is given routinely. This is expected to resolve

	within 3 months in the majority. A minority may have a longer requirement for prednisolone treatment until transaminases have normalised. Low platelet count can occur in the initial weeks after treatment but is expected to resolve spontaneously and does not usually require any specific treatment. Elevated cardiac enzymes can be seen after treatment, this has not so far been associated with any clinically significant cardiac impairment. There have been rare occurrences of more severe side-effects - liver injury/ synthetic failure, thrombotic microangiopathy. These have not been observed in those treated very soon after birth (ie the screened population) and all side effects appear to be more frequent in those who are older/ heavier which means that for the individual child there is a distinct advantage to being diagnosed and treated earlier. The effect of these side effects is transient but there is a requirement for frequent blood monitoring (weekly / fortnightly) in the first 3 months / until it is possible to discontinue prednisolone.
12.Are there any important outcome data that were not collected during the managed access period?	No - There are no outcome data that would alter the framework of considering the routine commissioning of onasemnogene abeparvovec for those detected by screening.

13. In your view, what is the unmet need for patients and healthcare professionals in this condition?	Patients : currently patients are diagnosed symptomatically in the UK. This means that even with treatment (with onasemnogene abeparvovec) they can expect a life with physical difficulties due to muscle weakness and contractures. This translates to requirement for caregiver help with acts of daily living and requirement for specialist equipment. The frequent occurrence of breathing muscle and bulbar muscle weakness mean that there can be frequent hospital admissions (including for intensive care during respiratory tract infections), need for non-invasive ventilation and requirement for supportive (eg tube) feeding. Individuals so affected are less likely to attain their full social/ economic/ employment prospects. None of this should be necessary if diagnosis occurs by screening allowing very early treatment. The lack of such very early diagnosis therefore constitutes an unmet need.
14. 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?	Yes – there is clinical trial and real world evidence (from other countries that already detect SMA through newborn screening, hence allowing very early treatment) that very early treatment (before symptom onset or when signs of the condition are minimal) is associated with normal / near normal motor milestone acquisition, lack of need for feeding or ventilatory assistance. Provision of the treatment to babies identified by screening therefore provides health and developmental benefits to the individual, reduces care giver need and reduces need for hospital care (eg during intercurrent illness).
15. Are there any groups of patients who might benefit more or less from the technology than others?	All infants with a genetically determined diagnosis of 5q SMA and up to 3 SMN2 copy numbers are expected to benefit from this treatment. Those with 3 copies of SMN2 may reach motor milestones at an earlier age than those with 2 copies of SMN2.

What is the expected place of the technology?	
16. How is the condition currently treated in the NHS? • Are any clinical guidelines used in the treatment of the condition, and if so, which?	N, please provide a link: For infants with a genetic diagnosis of SMA, detected before symptom onset, there is no routinely commissioned treatment available through the NHS. Risdiplam, nusinersen and onasemnogene abeparvovec are available through managed access agreement.
17. Are there other clinical pathways used in England other than those recommended in the guideline?	No
18. Would the new technology require a change in the clinical pathway?	No
19. Will the technology introduce new costs to the NHS or patients other than for the technology itself?	I would expect the technology to save costs – because the earlier provision of treatment should avoid co-morbidities that are associated with need for NHS outpatient and inpatient care (eg the following are often needed for those treated after symptomatic diagnosis : orthopaedic surgery to manage contractures, speech and language therapy assessments for feeding difficulties, respiratory care because of hypoventilation). All infants with a genetic diagnosis of SMA (ie identified before symptom onset) will develop SMA – therefore the number requiring treatment should not be greater than currently (they will just be identified earlier).

20. If there are any rules (informal or formal) for starting and stopping treatment with the technology, would these apply if the technology is routinely commissioned? If not, how would starting and stopping criteria be adapted?	This treatment is given as a single intravenous infusion and therefore stopping rules do not apply. For 'starting' treatment an infant would undergo a medical assessment to ensure that there is no contra-indication to the treatment (eg presence of antibodies to AAV9).
What was your experience of the technology during the managed access agreement [MAA]?	
21. What has been your experience of administering the technology during the period of the MAA?	Positive: I have not personally administered this to any infants detected by screening - this is because nationally extremely small numbers have been identified as there is no screening programme in place. I therefore have no positive or negative experience to report. Negative:

22. Did any people decline treatment? What were their reasons why?	See answer to question 21.
23. What has been the experience of on treatment monitoring and managed access assessments during the period of the MAA?	See answer to question 21.
24. Would routine assessments in clinical practice differ from those that comprise the MAA monitoring? How?	I would expect all infants who receive treatment with onasemnogene abeparvovec to have initial monitoring for side-effects (whether through MAA or routinely commissioned). I would expect there to be 6 month follow up as standard with physiotherapy and medical assessment. It is possible that some assessments might be undertaken by video if children are following normal motor development.
25. Are there other points of learning arising from the period of the managed access agreement that you would like considered?	No – see answer to question 21.

Sources of evidence	
26. Are you aware of any new relevant evidence that might not be found by a systematic review of the trial evidence?	Yes for the technology, please give link: I am not aware of evidence additional to that already provided. Yes for the comparator, please give link:
Equality	
31a. Are there any potential equality issues that should be taken into account when considering this treatment?	No

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NICE National Institute for Health and Care Excellence

Highly Specialised Technology

Guidance review following a period of managed access

Clinical expert statement

Onasemnogene abeparvovec for treating pre-symptomatic spinal muscular atrophy (MAA partial review of HST 15) [ID4051]

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	**Laurent Servais**

2. Name of organisation	**University of Oxford**
3. Job title or position	**Professor of Paediatric Neuromuscular Diseases**
4. Are you (please tick all that apply):	**X** an employee or representative of a healthcare professional organisation that represents clinicians? **X** 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)	**X** 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. Do you have a conflict of interest that you wish to declare[1]?	Direct /Indirect – please explain **I have given lecture and consultancy for Novartis** **Novartis has funded research and educative events that I coordinate**
7. 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.)	**X** yes
The aim of treatment for this condition	
8. What is the main aim of treatment?	If delivered after symptoms : Maintaining patient alive and ventilation free and allowing sitting position, If delivered at birth : Obtaining normal or subnormal motor development
9. What do you consider a clinically significant treatment response? (For example, a reduction in tumour size by	If delivered after symptoms : sitting position, If delivered at birth : ambulation

[1] A direct interest is when there is, or could be perceived to be, an opportunity for a person involved with NICE's work to benefit. Direct interests can be financial – where the person gets direct financial benefit, non-financial – where the person gets a non-financial benefit such as increasing or enhancing their professional reputation An indirect interest is when there is, or could be perceived to be, an opportunity for a third party closely associated with the person in question to benefit.

x cm, or a reduction in disease activity by a certain amount.)	
10. What are the benefits that you expect the technology to provide compared with routinely commissioned care?	Health benefits. Please delete as appropriate: Similar effect than Nusinersen or Risdiplam, but one shot therapy. If we considered that the current routinely commissioned care is supportive care, (Nusinersen and Risdiplam are under MAP), the health benefit is massive, especially if delivered at birth Increased survival Y Increased time to progression Y Improved QOL Y Does the new technology provide other substantial health related benefits not included in the QALY calculation? Y/N, please explain: Less infection, more autonomy Non-health benefits. Please delete as appropriate: Massive improvement of parents quality of life, massive cost saving if delivered at birth Societal benefits such as improved QoL for carers, faster return to work/school, greater productivity etc… Y/N, please explain: Depends if administered at birth or after symptoms. If delivered at birth, allows a full productivity of both parents. If not, parents full time employment is not possible Improved accessibility to patients Y

	Implications for delivery of the NHS service Y The delivery at birth after newborn screening would result in a massive reduction of workload for NHS service
11. Are there any recognised side effects of the technology?	Yes : TMA, liver toxicity. Mostly in older and heavier patients
12.Are there any important outcome data that were not collected during the managed access period?	Yes : The drug that is much more efficient when delivered at birth was very rarely delivered at birth as UK is one of the last country in EU with no newborn screening
13. In your view, what is the unmet need for patients and healthcare professionals in this condition?	The fact that there is no newborn screening. Patients treated after the onset of symptoms will for nearly all of them never be ambulant
14. Do you consider the technology to be innovative in its potential to make a significant and substantial	Yes, certainly

impact on health-related benefits and how might it improve the way that current need is met?	
15. Are there any groups of patients who might benefit more or less from the technology than others?	The younger, the better !
What is the expected place of the technology?	
16. How is the condition currently treated in the NHS? • Are any clinical guidelines used in the treatment of the condition, and if so, which?	The drug is delivered only in 4 centers, which is very sub-obtimal. All NMD centers should be able to deliver the drug in order to save time
17. Are there other clinical pathways used in England other than those	Y/N, please explain important differences and why they occur:

recommended in the guideline?	
18. Would the new technology require a change in the clinical pathway?	I would recommend ++++ to couple it with NBS, and to allow all NMD centers to deliver
19. Will the technology introduce new costs to the NHS or patients other than for the technology itself?	Yes, in absence of NBS. Indeed, patients with SMA1 who were previously dying will survive wheelchair bound, with ventilation…. These costs will not exist if newborn screening is introduced immediately
20. If there are any rules (informal or formal) for starting and stopping treatment with the technology, would these apply if the technology is routinely commissioned? If not, how would starting and stopping criteria be adapted?	No, it is one shot therapy

What was your experience of the technology during the managed access agreement [MAA]?	
21. What has been your experience of administering the technology during the period of the MAA?	Positive: Patients with SMA1 could benefit of this treatment Negative: This drug has been administered to a much to broad spectrum of patients
22. Did any people decline treatment? What were their reasons why?	Not that I am aware
23. What has been the experience of on treatment monitoring and managed access assessments during the period of the MAA?	The splitting of the responsibility of follow up between infusion centers and other does not work wellNo
24. Would routine assessments in clinical practice differ from those that	No

comprise the MAA monitoring? How?	
25. Are there other points of learning arising from the period of the managed access agreement that you would like considered?	NBS is really needed
Sources of evidence	
26. Are you aware of any new relevant evidence that might not be found by a systematic review of the trial evidence?	Yes for the technology, please give link: Yes for the comparator, please give link:
Equality	
31a. Are there any potential equality issues that should be	No

taken into account when considering this treatment?	

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EAG HST REPORT

LIVERPOOL REVIEWS AND IMPLEMENTATION GROUP (LRiG)

Onasemnogene abeparvovec for treating pre-symptomatic spinal muscular atrophy (MAA partial review of HST 15) [ID4051]

Confidential until published

This report was commissioned by the NIHR Evidence Synthesis Programme as project number NIHR135653

Completed 20 October 2022

CONTAINS [redacted]
AND [redacted] DATA

UNIVERSITY OF LIVERPOOL | LIVERPOOL REVIEWS AND IMPLEMENTATION GROUP

A MEMBER OF THE RUSSELL GROUP

Title: Onasemnogene abeparvovec for treating pre-symptomatic spinal muscular atrophy (MAA partial review of HST 15) [ID4051]

Produced by: Liverpool Reviews & Implementation Group (LR*i*G)

Authors: Rebecca Bresnahan, Research Fellow (Clinical Effectiveness), LR*i*G, University of Liverpool

Nigel Fleeman, Senior Research Fellow (Clinical Effectiveness), LR*i*G, University of Liverpool

James Mahon, Director, Coldingham Analytical Services, Berwickshire

Rachel Houten, Health Economic Modeller, LR*i*G, University of Liverpool

Marty Chaplin, Research Associate (Medical Statistician), LR*i*G, University of Liverpool

Sophie Beale, Director, HARE Research, North Yorkshire

Angela Boland, Director, LR*i*G, University of Liverpool

Yenal Dundar, Research Fellow (Clinical Effectiveness), LR*i*G, University of Liverpool

Ashley Marsden, Senior Medicines Information Pharmacist, North West Medicines Information Centre, Liverpool

Pinki Munot, Consultant Paediatric Neurologist, Great Ormond Hospital for Children NHS Foundation Trust, London

Correspondence to: Rebecca Bresnahan, Research Fellow, Liverpool Reviews and Implementation Group, University of Liverpool, Whelan Building, The Quadrangle, Brownlow Hill, Liverpool L69 3GB

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Contributions of authors:

Rebecca Bresnahan	Project lead, critical appraisal of the clinical evidence and supervised the final report
Nigel Fleeman	Critical appraisal of the clinical evidence
James Mahon	Critical appraisal of the economic model
Rachel Houten	Critical appraisal of the economic model
Marty Chaplin	Critical appraisal of the clinical and statistical evidence
Sophie Beale	Critical appraisal of the clinical and economic evidence, editorial input
Angela Boland	Critical appraisal of the clinical and economic evidence, editorial input
Yenal Dundar	Critical appraisal of the company's search strategies
Ashley Marsden	Critical appraisal of the company submission
Pinki Munot	Clinical advice and critical appraisal of the clinical evidence

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LIST OF ABBREVIATIONS

AAV9	adeno-associated virus 9
AE	adverse event
AESI	adverse event of special interest
BRND	broad range of normal development
BSC	best supportive care
BSID	Bayley Scales of Toddler and Infant Development version 3
CI	confidence interval
CHOP-INTEND	Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders
CS	company submission
CSR	clinical study report
EAG	External Assessment group
EMA	European Medicines Agency
ERG	Evidence Review Group
FM	fine motor
GM	gross motor
HRQoL	health-related quality of life
HST	highly specialised technology
ICER	incremental cost-effectiveness ratio
ITT	intent-to-treat
LYG	life years gained
MAA	managed access agreement
MHRA	Medicines and Healthcare products Regulatory Agency
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
PAS	patient access scheme
PAV	permanent assisted ventilation
PNCR	Pediatric Neuromuscular Research Network
PSS	Personal Social Services
QALY(s)	quality adjusted life year(s)
QoL	quality of life
SAE	serious adverse event
SLR	systematic literature review
SMA	spinal muscular atrophy
SMN	survival motor neuron
SMN1	survival motor neuron 1
SMN2	survival motor neuron 2
SmPC	summary of product characteristics
TEAE	treatment-emergent adverse event
TMA	thrombotic microangiopathy
TSAP	trial statistical analysis plan
WHO-MGRS	World Health Organization Multicentre Growth Reference Study
WTP	willingness-to-pay

1 EXECUTIVE SUMMARY

1.1 Overview of the EAG's key issues

Table 1 Summary of key issues

ID4051	Summary of issue	Report sections
Issue 1	Long-term clinical effectiveness of onasemnogene abeparvovec administered pre-symptomatically is not known	Section 4.3.3 and Section 4.7
Issue 2	Clinical effectiveness evidence of onasemnogene abeparvovec is only available from trials with small sample sizes	Section 3.2 and Section 4.7
Issue 3	Population should be considered by number of copies of the *SMN2* gene	Section 7.1.2
Issue 4	EAG exploration of areas of uncertainty	Section 7.2

EAG=External Assessment Group; SMA=spinal muscular atrophy; SMN2=survival motor neuron 2

1.2 Overview of key model outcomes

NICE technology appraisals compare how much a new technology improves length (overall survival) and health-related quality of life (HRQoL), measured using QALYs. An ICER is used to measure the extra cost for every QALY gained. Overall, the technology (onasemnogene abeparvovec for treating pre-symptomatic spinal muscular atrophy [SMA]) is modelled to affect:

- QALYs by improving survival and HRQoL whilst alive
- costs by reducing the need (and therefore cost) of BSC.

The drug cost, hospitalisation costs and social care costs associated with treating SMA are all very high and have the greatest effect on size of the ICERs per QALY gained.

1.3 The decision problem: summary of the EAG's key issues

Issues relating to the decision problem, specifically evidence for the EAG's requested comparison, were resolved at the clarification stage of the appraisal process.

1.4 The clinical effectiveness evidence: summary of the EAG's key issues

Issue 1 Long-term effectiveness of onasemnogene abeparvovec given pre-symptomatically is not known

Report section	Section 4.3.3 and Section 4.7
Description of issue and why the EAG has identified it as important	Motor milestone data for patients treated pre-symptomatically with onasemnogene abeparvovec are available from the SPR1NT trial for a maximum follow-up of up to age 24 months, and from the LT-002 study for a maximum follow-up of [redacted] post-dose and age [redacted] It is not known whether patients treated pre-symptomatically with onasemnogene abeparvovec will maintain their achieved motor milestones for life. Clinical advice to the EAG is that there remains some uncertainty about the long-term efficacy of onasemnogene abeparvovec in clinical practice as some deterioration may occur
What alternative approach has the EAG suggested?	None
What is the expected effect on the cost effectiveness estimates?	Any decrease in the clinical effectiveness of onasemnogene abeparvovec over time will decrease the cost effectiveness of providing onasemnogene abeparvovec pre-symptomatically to the pre-symptomatic patient versus BSC or versus providing onasemnogene abeparvovec to the patient with a pre-symptomatic diagnosis only at symptom onset if the patient develops type 1 SMA and BSC if they develop type 2 or 3 SMA
What additional evidence or analyses might help to resolve this key issue?	The ongoing LT-002 trial is expected to complete in December 2035. The study aims to assess long-term safety and efficacy of onasemnogene abeparvovec treatment and will provide evidence for the durability of response

BSC=best supportive care; EAG=External Assessment Group; SMA=spinal muscular atrophy

Issue 2 Clinical effectiveness evidence of onasemnogene abeparvovec is only available from single arm trials with small sample sizes

Report section	Section 3.2 and Section 4.7
Description of issue and why the EAG has identified it as important	Trial evidence to support the use of onasemnogene abeparvovec as a treatment for patients with pre-symptomatic SMA is available from one single arm trial (SPR1NT trial, n=29). Three single arm trials provide data for patients treated symptomatically, namely the START (n=12), STR1VE-US (n=33) and STR1VE-EU (n=22) trials
What alternative approach has the EAG suggested?	None
What is the expected effect on the cost effectiveness estimates?	Not applicable
What additional evidence or analyses might help to resolve this key issue?	None The EAG recognises that SMA is a rare genetic disorder which limits study sample size and that trials with a comparator arm are not run due to ethical concerns

EAG=External Assessment Group; SMA=spinal muscular atrophy

1.5 The cost effectiveness evidence: summary of the EAG's key issues

Issue 3 Population should be considered by number of copies of the *SMN2* gene

Report section	Section 7.1.2
Description of issue and why the EAG has identified it as important	The company has provided results for the combined cohort and also independently for patients with two and three copies of the *SMN2* gene. The EAG considers that cost effectiveness decisions should be made depending on number of copies of the *SMN2* gene because: • outcomes (mortality, HRQoL and costs) differ substantially by number of copies of the *SMN2* gene. Patients with two copies of the *SMN2* gene have a higher likelihood of having type 1 SMA than patients with three copies of the *SMN2* gene. Further, patients with type 1 SMA with three copies of the *SMN2* gene tend to have longer expected survival than those with two copies of the *SMN2* gene • patients with two copies of the *SMN2* gene and those with three copies of the *SMN2* gene are identified at the time of diagnosis of SMA • approximately 85% of patients with three copies of the *SMN2* gene have type 2 SMA (54.3%) or type 3 SMA (30.9%), not type 1 SMA (14.7%), and so are not eligible for treatment with onasemnogene abeparvovec following the development of symptoms based on the recommendations made by NICE in HST15
What alternative approach has the EAG suggested?	The EAG scenario results have been generated independently for patients with two copies of the *SMN2* gene and patients with three copies of the *SMN2* gene
What is the expected effect on the cost effectiveness estimates?	Model results show that patients with two copies of the *SMN2* gene and patients with three copies of the *SMN2* gene have substantially different QALYs and BSC costs
What additional evidence or analyses might help to resolve this key issue?	None

BSC=best supportive care; EAG=External Assessment Group; HRQoL=health-related quality of life; ICER=incremental cost effectiveness ratio; QALY=quality adjusted life year; SMA=spinal muscular atrophy; *SMN2*=survival motor neuron 2

Issue 4 EAG exploration of areas of uncertainty

Report section	Section 7.2
Description of issue and why the EAG has identified it as important	The EAG has explored two areas of uncertainty: 1. Loss of milestones achieved Due to the absence of long-term clinical effectiveness data, it is not known whether the effect of onasemnogene abeparvovec endures for a patient life-time 2. Social care costs Overall, in the model, social care costs account for the second highest proportion of care costs (after hospitalisations). It is not clear how the company calculated social care costs
What alternative approach has the EAG suggested?	The EAG ran two scenarios to explore whether using extreme values affected the conclusions that can be drawn from model cost effectiveness results Scenario 1: Loss of milestones achieved The EAG applied the company's loss of milestone assumptions for the BSC arm of the long-term model to patients in the onasemnogene abeparvovec arm of the long-term model Scenario 2: Social care costs The EAG set social care costs to zero
What is the expected effect on the cost effectiveness estimates?	For the combined cohort, and for patients with two and three copies of the *SMN2* gene considered independently, all the EAG scenario cost effectiveness results generate an ICER for pre-symptomatic treatment with onasemnogene abeparvovec that is less than £100,000 per QALY gained (irrespective of the comparator)
What additional evidence or analyses might help to resolve this key issue?	None

BSC=best supportive care; EAG=External Assessment Group; ICER=incremental cost effectiveness ratio; *SMN2*=spinal motor neuron 2; QALY=quality adjusted life years

1.6 Summary of EAG's preferred assumptions and resulting ICER

The EAG is satisfied that the cost effectiveness results provided by the company, for providing onasemnogene abeparvovec pre-symptomatically versus BSC and for providing onasemnogene abeparvovec pre-symptomatically versus providing onasemnogene abeparvovec only at symptom onset if the patient develops type 1 SMA and BSC for all other SMA types, are robust and suitable for decision making. Although uncertainty remains around long-term efficacy of onasemnogene abeparvovec and the costs associated with social care provision to children with SMA, these uncertainties are unlikely to change the conclusions that could be drawn on the cost effectiveness of onasemnogene abeparvovec given pre-symptomatically.

For the comparison of pre-symptomatic treatment with onasemnogene abeparvovec versus BSC, the ICER per QALY gained is likely to be <£100,000.

For the comparison of pre-symptomatic treatment with onasemnogene abeparvovec versus onasemnogene abeparvovec on development of symptoms of type 1 SMA and BSC for all other types of SMA, pre-symptomatic treatment with onasemnogene abeparvovec is likely to be dominant.

Modelling issues assessed by the EAG are described in Table 42. For further details of the scenario analyses carried out by the EAG, see Section 6.2.

Table A Company base case/EAG preferred cost effectiveness results

Copies of the SMN2 gene	Incremental		
	Cost	QALYs	ICER per QALY gained
Comparator: BSC			
Two	[redacted]	[redacted]	[redacted]
Three	[redacted]	[redacted]	[redacted]
Comparator: onasemnogene abeparvovec on development of symptoms of type 1 SMA, BSC for all others			
Two	[redacted]	[redacted]	[redacted]
Three	[redacted]	[redacted]	[redacted]

BSC=best supportive care; ICER=incremental cost effectiveness ratio; QALY=quality adjusted life year; SMA=spinal muscular atrophy
Source: Company model (EAG report, Table 41 to Table 44)

2 INTRODUCTION AND BACKGROUND

2.1 Introduction

On completion of Highly Specialised Technology (HST) evaluation 15,[1] in July 2021, the National Institute for Health and Care Excellence (NICE) made the following recommendations:

> 1.1 Onasemnogene abeparvovec is recommended as an option for treating 5q spinal muscular atrophy (SMA) with a bi-allelic mutation in the survival of motor neuron 1 (*SMN1*) gene and a clinical diagnosis of type 1 SMA in babies, only if:
>
> - they are 6 months or younger, or
> - they are aged 7 to 12 months, and their treatment is agreed by the national multidisciplinary team.
>
> It is only recommended for these groups if:
>
> - permanent ventilation for more than 16 hours per day or a tracheostomy is not needed
> - the company provides it according to the commercial arrangement.
>
> 1.2 For babies aged 7 to 12 months, the national multidisciplinary team should develop auditable criteria to enable onasemnogene abeparvovec to be allocated to babies in whom treatment will give them at least a 70% chance of being able to sit independently.
>
> 1.3 Onasemnogene abeparvovec is recommended as an option for treating pre-symptomatic 5q SMA with a bi-allelic mutation in the *SMN1* gene and up to 3 copies of the *SMN2* gene in babies. It is recommended only if the conditions in the managed access agreement (MAA) are followed.

This appraisal is a partial review of HST15,[1] focusing on recommendation 1.3. The company has provided evidence to support the use of onasemnogene abeparvovec as a treatment option for patients with pre-symptomatic 5q SMA with a bi-allelic mutation in the *SMN1* gene and up to three copies of the *SMN2* gene; this evidence was not available at the time of the original appraisal. In this External Assessment Group (EAG) report, references to the company submission (CS) are to the company's Document B, which is the company's full evidence submission.

The company has presented evidence to inform the comparison of:

- providing onasemnogene abeparvovec pre-symptomatically to the pre-symptomatic patient

versus

- best supportive care (BSC) (provided in the CS)

- providing onasemnogene abeparvovec to the patient with a pre-symptomatic diagnosis only at symptom onset if the patient develops type 1 SMA and BSC if they develop type 2 or 3 SMA (the company provided cost effectiveness evidence as part of the clarification response but no clinical effectiveness evidence [other than the information included in the updated economic model])

2.2 Spinal muscular atrophy

Spinal muscular atrophy is a rare genetic neuromuscular disorder characterised by muscle weakness and progressive loss of motor function.[2] This appraisal focuses on the pre-symptomatic treatment of 5q SMA, which is caused by a bi-allelic mutation in *SMN1* located in chromosome 5q and accounts for 95% of SMA cases. In this EAG report, all references to SMA hereafter are to 5q SMA. The bi-allelic mutation results in a lack of the SMN protein, which is necessary for normal motor neuron function, and this leads to motor neuron degeneration.[2] Spinal muscular atrophy causes substantial disability and, in many cases, reduces life expectancy.[2,3]

The *SMN2* gene produces very low levels of functional SMN and this production can partially compensate for a mutated *SMN1* gene. In general, the higher the number of copies of the *SMN2* gene, the less severe the disease phenotype.[4] Clinically, SMA is classified depending on disease severity, which ranges from type 0 SMA (the most severe disease phenotype) to type 4 SMA (the least severe disease phenotype).[5] SMA type can be classified into subtypes based on age of onset and acquired motor milestones.[6,7] A summary of the key features of SMA types is provided in Table 1.

Table 1 Key features of SMA types

SMA type	Description used in CS	Age at symptom onset	Highest motor milestone achievable	Life expectancy (BSC only)
Type 0 SMA				
0	NA	Pre-natal or at birth	• Nil, require respiratory support from birth	Days to weeks
Type 1 SMA				
1	Non-sitter	<6 months[a]	• Unable to sit without support • Over time, lose the ability to swallow and experience respiratory complications, ultimately resulting in death from respiratory failure	<2 years (without ventilatory support)
1A		<1 month (usually by 2 weeks)	• Nil, no head control (similar to type 0 SMA)	<6 months
1B		1 month to 3 months	• Little to no head control	<2 years (without ventilatory support)
1C		3 months to 6 months	• Head control and some babies may roll from supine to prone	
Type 2 SMA				
2	Sitter	6 months to 18 months	• Sit without support (normally outside the normal developmental window) • Some babies may crawl and stand alone but do not achieve walking alone • Upon disease progression, may lose previously achieved motor milestones	20 years to 60 years
2A			• Sit without support but may lose the motor milestone	
2B			• Sit without support and maintains the motor milestone • May stand or walk with assistance	
Type 3 SMA				
3	Walker	1.5 years to 10 years	• Walk alone • May lose the ability to walk alone and stand alone after symptom onset	Normal
3A		18 months to 36 months	• Walk alone • Develop scoliosis • Early loss of walking motor milestone	
3B		>36 months	• Walk alone • Loss of ambulation during adulthood	
Type 4 SMA				
4	NA	>35 years	• Walk alone • May develop reduced mobility after symptom onset	Normal

[a] Clinical advice to the EAG is that babies with type 1 SMA present with symptoms between age 4 weeks and 6 weeks and are normally clinically diagnosed between age 8 weeks and 12 weeks
BSC=best supportive care; CS=company submission; NA=not applicable; SMA=spinal muscular atrophy
Source: CS, Table 3 and pp21-22; Calucho 2018;[4] Farrar 2013;[8] Zerres 1997[9]

Most patients (95.7%) with two copies of the *SMN2* gene develop type 1 SMA, and most patients with three copies of the *SMN2* gene develop type 2 (54.3%) or type 3 (30.9%) SMA (Table 2).

Table 2 Expected SMA type by number of copies of the *SMN2* gene

***SMN2* gene copies**	**SMA type**			
	Type 1 (n=1256)	**Type 2 (n=1160)**	**Type 3 (n=1017)**	**Type 4 (n=26)**
1	95.7%	4.3%	0.0%	0.0%
2	78.9%	16.5%	4.5%	0.1%
3	14.7%	54.3%	30.9%	0.1%
≥4	0.7%	11.5%	83.3%	4.4%

SMA=spinal muscular atrophy; *SMN2*=survival motor neuron 2
Source: Calucho 2018,[4] Table 2

Approximately 60 babies are born with SMA each year in England and approximately 60% of these are clinically diagnosed as having type 1 SMA.[10] A pre-symptomatic diagnosis of SMA requires genetic testing. In current NHS practice, only babies who have a sibling with SMA or a parent with confirmed carrier status are genetically tested for SMA. Approximately two babies with pre-symptomatic SMA and up to three copies of the *SMN2* gene are identified each year via this testing.[11]

Currently (October 2022), there is no UK national screening programme for SMA.[12] However, there is an ongoing UK population-based pilot study[13] to assess the feasibility of using spare capacity from the NHS newborn blood spot (NBS) screening programme to provide national screening for SMA. Clinical advice to the company (Clinical Advisory report)[14] is that the pilot study[13] will identify between one and three additional patients with pre-symptomatic SMA and up to three copies of the *SMN2* gene each year. If UK national screening is implemented, the company estimates that [redacted] babies with pre-symptomatic SMA and up to three copies of the *SMN2* gene will be identified each year.[14]

2.3 Onasemnogene abeparvovec

Onasemnogene abeparvovec is a gene replacement therapy that addresses the underlying genetic cause of SMA. The following bullets provide a summary of the information about onasemnogene abeparvovec provided by the company (CS, Table 2):

- onasemnogene abeparvovec is a non-replicating recombinant adeno-associated virus serotype 9 (AAV9) based vector containing the cDNA of the human *SMN1* gene. The functional *SMN1* gene provides continuous SMN protein expression, thus preventing motor neuron loss
- onasemnogene abeparvovec is administered via a syringe pump as a one-time, single-dose intravenous infusion over approximately 60 minutes at a dose of $1.1x10^{14}$vg/kg; an immunomodulation regimen with corticosteroids is recommended

- in July 2022, the European Medicines Agency (EMA)[15] recommended onasemnogene abeparvovec for full marketing authorisation as follows:
    - patients with SMA with a bi-allelic mutation in the *SMN1* gene and a clinical diagnosis of type 1 SMA, or
    - patients with SMA with a bi-allelic mutation in the *SMN1* gene and up to three copies of the *SMN2* gene
- Medicines and Healthcare products Regulatory Agency approval was expected in September 2022
- prior to treatment with onasemnogene abeparvovec, patients must undergo AAV9 antibody testing using an appropriately validated assay, blood testing for liver function, complete blood count, measurement of creatinine and troponin-I level and screening for symptoms of infectious disease
- liver function, platelet count and troponin-I levels must be closely monitored after administration of onasemnogene abeparvovec to assess immune response to the AAV9 capsid.

2.4 Overview of current service provision

The company's proposed positioning of onasemnogene abeparvovec is as a treatment for NHS patients with genetically identified SMA who have no symptoms of SMA (pre-symptomatic) and have up to three copies of the *SMN2 gene*.

2.4.1 Active treatment options for patients with pre-symptomatic SMA

In addition to onasemnogene abeparvovec, NICE has recommended two other drugs, if provided according to the terms set out in their respective MAAs, for people with pre-symptomatic SMA and 1 to 4 copies of the *SMN2* gene:

- nusinersen (recommended in July 2019)[16]
- risdiplam (recommended in December 2021).[17]

2.4.2 Active treatment options for patients with symptomatic SMA

In addition to onasemnogene abeparvovec, NICE has recommended two treatment options, if provided according to the terms set out in their respective MAAs, for people with symptomatic SMA:

- nusinersen for people with type 1, 2 or 3 SMA (recommended in July 2019)[16]
- risdiplam for people aged 2 months and older with a clinical diagnosis of type 1, 2 or 3 SMA (recommended in December 2021).[17]

2.4.3 Best supportive care for patients with SMA

The aim of BSC is to manage SMA upon symptom onset by minimising disability and improving health-related quality of life (HRQoL). BSC does not prevent disease progression but may extend life.[5,18] Clinical advice to the EAG is that the company has presented an accurate overview of the BSC provided in NHS clinical practice, which can be summarised as follows:

- BSC usually follows the International Standard of Care for Spinal Muscular Atrophy guidelines[5,18]
- BSC is delivered by a multidisciplinary team including respiratory, orthopaedic, nutrition, gastrointestinal and bone health specialists, physiotherapists, rehabilitation services and palliative care[5]
- BSC is resource intensive:
    - the company estimates (CS, p45) show that the annual costs of care for patients with type 1 SMA are high; for example, the estimated annual cost of care for a patient receiving permanent assisted ventilation (PAV) is £283,710, with most of the cost attributable to hospitalisations (77%) and social care (20%)
    - costs decrease as disease severity decreases; for example, the estimated annual cost of care for a delayed walker (patients with type 3 SMA) is £8,333.

Prior to the NICE recommendations for onasemnogene abeparvovec,[1] nusinersen[14] and risdiplam,[15] BSC was the only treatment option for patients with SMA.

3 CRITIQUE OF THE COMPANY'S DEFINITION OF THE DECISION PROBLEM

A summary of the decision problem outlined in the final scope[19] issued by NICE and addressed by the company is presented in Table 3. Each parameter is discussed in more detail in the text following Table 3 (Section 3.1 to Section 3.7).

Table 3 Summary of decision problem

Parameter	Final scope issued by NICE	Decision problem addressed in the company submission with rationale	EAG comment
Population	Patients with pre-symptomatic SMA and up to three copies of the *SMN2* gene	As per scope, but for clarity this population is newborns (as highlighted in Recommendation 1.3)[1]	The company did not present data for patients with pre-symptomatic SMA and one copy of the *SMN2* gene. However, patients with one copy of the *SMN2* gene usually display clinical symptoms of SMA at birth and are therefore not relevant to this appraisal Clinical advice to the EAG is that disease severity differs between patients with two copies of the *SMN2* gene and patients with three copies of the *SMN2* gene. Therefore, patients with two and three copies of the *SMN2* gene should be considered as separate subgroups
Intervention	Onasemnogene abeparvovec	As per scope, but for clarity the intervention is: onasemnogene abeparvovec delivered via a single-dose IV infusion	As per scope
Comparator(s)	BSC	As per scope. For clarity, BSC is the only routinely commissioned treatment available for pre-symptomatic patients at the time of appraisal	The company considers (CS, B.1.2.2.2) that the comparison of onasemnogene abeparvovec for patients with pre-symptomatic SMA versus onasemnogene abeparvovec for patients with symptomatic SMA falls outside the scope of this appraisal. As no active treatment is routinely commissioned in NHS clinical practice (i.e., all active treatments for patients with pre-symptomatic SMA are only available via MAAs), the company considers that BSC is the relevant comparator The EAG considers that the relevant comparison for this appraisal is: • providing onasemnogene abeparvovec pre-symptomatically to the pre-symptomatic patient **versus** • providing onasemnogene abeparvovec to the patient with a pre-symptomatic diagnosis only at symptom onset if the patient develops type 1 SMA and BSC if they develop type 2 or 3 SMA In response to the clarification letter, the company provided cost effectiveness evidence, but no clinical effectiveness evidence, for this comparison
Outcomes	The outcome measures to be considered include: • motor function (including, where applicable, age appropriate motor milestones	As per scope, and a composite endpoint of permanent ventilation-free survival (often termed as event-free survival in the assessment of SMA) is also assessed. Carer HRQoL will be considered	The company did not present outcome measures that assessed: • respiratory function • frequency and duration of hospitalisation • speech and communication

Parameter	Final scope issued by NICE	Decision problem addressed in the company submission with rationale	EAG comment
	such as sitting, standing, walking) • bulbar function (e.g., swallowing and ability to communicate) • frequency and duration of hospitalisation • speech and communication • respiratory function • complications of SMA (e.g., scoliosis and muscle contractures) • need for non-invasive or invasive ventilation • stamina and fatigue • mortality • adverse effects of treatment • health-related quality of life (for patients and carers)	qualitatively in this submission, as previous NICE submissions for SMA treatments have highlighted the paucity of data and lack of robust methods when accounting for carer HRQoL and bereavement disutility in economic modelling	• complications of SMA • stamina and fatigue • health-related quality of life (for patients and carers)
Economic analysis	The reference case stipulates that the cost effectiveness of treatments should be expressed in terms of incremental cost per quality-adjusted life year The reference case stipulates that the time horizon for estimating clinical and cost effectiveness should be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared Costs will be considered from an NHS and Personal Social Services perspective The availability of any	As per scope	As per scope

Parameter	Final scope issued by NICE	Decision problem addressed in the company submission with rationale	EAG comment
	commercial arrangements for the intervention, comparator and subsequent treatment technologies will be considered		
Subgroups to be considered	If the evidence allows, subgroups by number of *SMN2* copies will be considered	The SPR1NT trial was designed with two cohorts of patients with two or three copies of *SMN2* that represent the population in the MAA.[11] The *SMN2* two-copy and *SMN2* three-copy cohorts have different primary and secondary efficacy outcomes and length of follow-up in the trial. Results for the two- and three-copy cohorts are included separately in the submission. In the cost effectiveness analysis, the base case analysis is weighted based on proportions of patients expected to have two or three copies of the *SMN2* gene based on natural history data[6,20]	The company considered that whilst number of copies of the *SMN2* gene is predictive of disease severity, this does not determine disease severity (CS, B.3.11) The company has provided cost effectiveness results (in the CS and in the clarification response) independently for patients with two copies of the *SMN2* gene and for patients with three copies of the *SMN2* gene The EAG considers that it is important to consider patients with two copies of the *SMN2* gene and patients with three copies of the *SMN2* gene separately as outcomes for these two groups differ substantially

BSC=best supportive care; CS=company submission; EAG=External Assessment Group; HRQoL=health-related quality of life; IV=intravenous; MAA=managed access scheme; SMA=spinal muscular atrophy; *SMN2*=survival motor neuron 2
Source: Final scope[19] issued by NICE; CS, Table 1; EAG comment

3.1 Source of direct clinical effectiveness data

Onasemnogene abeparvovec

The primary source of clinical effectiveness evidence presented by the company is the SPR1NT[21,22] trial. The SPR1NT trial was a phase III, open-label, single-arm, multi-centre trial that assessed the clinical effectiveness of onasemnogene abeparvovec as a treatment for patients with pre-symptomatic SMA and two (n=14)[21] or three (n=15) copies of the *SMN2* gene.[22] Follow-up was up to age 18 months for patients with two copies of the *SMN2* gene and up to age 24 months for patients with three copies of the *SMN2* gene.

[redacted] patients from the SPR1NT trial enrolled in the LT-002[23] study ([redacted]). The aim of this study is to collect long-term efficacy and safety data from patients with SMA (follow-up to age 15 years) treated with onasemnogene abeparvovec in clinical trials.

Best supportive care

The company has provided evidence for BSC in the CS (Section B.2.6) and in a report[20] that includes analyses of data from the Pediatric Neuromuscular Clinical Research (PNCR) dataset and NeuroNext study.

For ethical reasons (CS, p81), none of the clinical trials of onasemnogene abeparvovec included a control arm. Therefore, data from the PNCR[20] dataset for patients with two (n=23) or three (n=81) copies of the *SMN2* gene who received BSC were used to generate an external control cohort for the SPR1NT trial. The company reported data at 18 months and 24 months for the outcomes recorded in the PNCR[20] dataset; these time points match the follow-up times for patients with two and three copies of the *SMN2* gene in the SPR1NT trial, respectively.

In addition, CHOP-INTEND outcomes from the SPR1NT trial were analysed post-hoc using data from the NeuroNext[20] study (n=26; patients with two copies of the *SMN2* gene and type 1 SMA) as an external control cohort. CHOP-INTEND outcomes were only exploratory outcomes and so NeuroNext[20] data are not presented in this EAG report.

3.2 Population

Clinical advice to the EAG is that it is difficult to be certain whether patients in the SPR1NT trial are representative of NHS patients with pre-symptomatic SMA and up to three copies of the *SMN2* gene as very few patients with pre-symptomatic SMA have been identified in NHS clinical practice. However, clinical advice to the EAG is that results from the SPR1NT trial are likely to be generalisable to NHS patients with SMA.

The EAG highlights that SMA is a rare genetic disorder and hence the sample sizes of the included trials and natural history studies are small.

3.3 Intervention

The intervention that is the focus of this appraisal is onasemnogene abeparvovec for babies with pre-symptomatic SMA and up to three copies of the *SMN2* gene (see Section 2.3).

Onasemnogene abeparvovec is currently recommended by NICE[1] as a treatment option for symptomatic babies:

- aged ≤6 months with a bi-allelic mutation in *SMN1* and a clinical diagnosis of type 1 SMA
- aged 7 months to 12 months with a clinical diagnosis of type 1 SMA whose treatment is agreed by the national multidisciplinary team.

Onasemnogene abeparvovec is not recommended as a treatment option for babies with symptomatic SMA requiring permanent ventilation for more than 16 hours per day or tracheostomy.

Evidence to support the use of onasemnogene abeparvovec as a treatment for patients with symptomatic SMA (n=67) are available from the START[24] (n=12), STR1VE-US[25] (n=33) and STR1VE-EU[26] (n=22) trials and data for patients with pre-symptomatic SMA (n=29) are available from the SPR1NT[21,22] trial.

3.4 Comparators

The comparator listed in the final scope[19] issued by NICE is BSC. The company has presented clinical effectiveness evidence for BSC from natural history studies[20] for some outcomes (see Section 3.5).

As previously highlighted (see Section 2.4), BSC is no longer the only option for most patients with SMA. In addition to treatment with onasemnogene abeparvovec, nusinersen[16] and risdiplam[17] have been recommended by NICE as treatment options for patients with pre-symptomatic SMA if the conditions set out in their respective MAAs are followed. However, as these active treatments are only available through MAAs, they are not considered established NHS clinical practice and are therefore not relevant comparators for this appraisal.

Following the recommendations made by NICE in HST15,[1] onasemnogene abeparvovec is now considered current NHS clinical practice for patients with symptomatic type 1 SMA. Therefore, the EAG considers that the relevant comparison for this appraisal is:

- providing onasemnogene abeparvovec pre-symptomatically to the pre-symptomatic patient

versus

- providing onasemnogene abeparvovec to the patient with a pre-symptomatic diagnosis only at symptom onset if the patient develops type 1 SMA and BSC if they develop type 2 or 3 SMA.

The company clarification response included cost effectiveness evidence, but no clinical effectiveness evidence (other than the information included in the updated economic model), for this comparison.

3.5 Outcomes

The outcome measures listed in the final scope[19] issued by NICE are reproduced in Table 4.

The company has presented SPR1NT trial results for the following outcomes: motor function, bulbar function, need for non-invasive or invasive ventilation, mortality and adverse effects (AEs) of treatment.

As a proxy for BSC outcome data, the company has presented data from the PNCR dataset and NeuroNext study[20] for the following outcomes:

- motor function
- need for non-invasive or invasive ventilation
- mortality

The CS did not include data on the following patient (and carer) outcomes: frequency and duration of hospitalisation, speech and communication, respiratory function, complications of SMA, stamina and fatigue or HRQoL.

The SPR1NT trial primary and secondary outcomes were also considered during the HST15[27] appraisal.

Table 4 Outcomes: NICE decision problem and SPR1NT trial

Outcome in decision problem	Outcome in SPR1NT trial reported in CS[a]	Note
Motor function (including, where applicable, age appropriate motor milestones such as sitting, standing, walking)	Head control • holds head erect for ≥3 seconds without support (BSID GM item #4)	
	Rolls over • turns from back to both right and left sides (BSID GM item #20)	
	Sits without support • sits without support for ≥30 seconds (BSID GM item #26) • sits up straight with head erect for ≥10 seconds; child does not use arms or hands to balance body or support position (WHO-MGRS definition)	BSID GM subtest item #26 is the primary outcome for patients with two copies of the *SMN2* gene and is used in the company economic model as part of a scenario analysis (two-copy *SMN2* cohort) WHO-MGRS definition is used in the company economic model (two-copy and three-copy *SMN2* cohorts)
	Crawls • crawls forward ≥5 feet on hands and knees (BSID GM item #34) • crawls ≥3 continuous and consecutive movements (alternately moves forward or backward on hands and knees; the stomach does not touch the supporting surface) ≥3) (WHO-MGRS definition)	WHO-MGRS definition is used in the company economic model (two-copy and three-copy *SMN2* cohorts)
	Stands with assistance • supports own weight for ≥2 seconds, using hands for balance only (BSID GM subtest item #33) • 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 (WHO-MGRS definition)	WHO-MGRS definition is used in the company economic model (two-copy and three-copy *SMN2* cohorts)
	Pulls to stand • raises self to standing position using chair or other convenient object for support (BSID GM item #35)	
	Stands alone • stands alone for ≥3 seconds after you release his or her hands (BSID GM subtest item #40) • 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 (WHO-MGRS definition)	BSID GM subtest item #40 is the primary outcome for patients with two copies of the *SMN2* gene and is used in the company economic model (three-copy *SMN2* cohort)

Outcome in decision problem	Outcome in SPR1NT trial reported in CS[a]	Note
	Walks with assistance • walks by making coordinated alternated stepping movements (BSID GM item #37) • upright position with the back straight, child makes sideways or forward steps by holding onto a stable object with one or both hands. One leg moves forward while the other supports part of the body weight. Child takes 5 steps in this manner (WHO-MGRS definition)	WHO-MGRS definition is used in the company economic model (two-copy and three-copy *SMN2* cohorts)
	Walks alone • takes ≥5 steps independently, displaying coordination and balance (BSID GM item #43) • takes ≥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 (WHO-MGRS definition)	BSID GM subtest item #43 is the secondary outcome for patients with three copies of the *SMN2* gene and is used in the company economic model as part of a scenario analysis (three-copy *SMN2* cohort) WHO-MGRS definition is used in the company economic model (two-copy and three-copy *SMN2* cohorts)
	• Proportion of infants achieving an improvement over baseline of ≥15 points on BSID GM and FM subsets (raw score) at any visit	
	• Ability to achieve a scaled score on BSID GM and FM subtests within 1.5 standard deviations of a chronological development reference standard at any visit	
	• Achievement of a CHOP-INTEND motor function scale score ≥40 at any visit	CHOP-INTEND outcomes only measured for patients with two copies of the *SMN2* gene
	• Achievement of CHOP-INTEND score >50 at any visit	
	• Achievement of CHOP-INTEND score ≥58 at any visit	
	• Maintenance of achieved milestones at visits in the absence of acute illness or perioperatively	
Bulbar function (including, for example, swallowing and ability to communicate)	Ability to thrive • able to tolerate thin liquids, does not require nutrition through mechanical support, and maintains weight consistent with age Proportion of infants that maintain weight at or above the third percentile[b] without need for non-oral/mechanical feeding support at any visit	
Frequency and duration of hospitalisation	Not reported	
Speech and communication	Not reported	

Outcome in decision problem	Outcome in SPR1NT trial reported in CS[a]	Note
Respiratory function	Not reported	Need for non-invasive or invasive ventilation reported
Complications of SMA (including, for example, scoliosis and muscle contractures)	Not reported	
Need for non-invasive or invasive ventilation	Proportion of infants alive and without tracheostomy Time to respiratory intervention Requirement for respiratory intervention	Proportion of infants alive and without tracheostomy at age 18 months used in the company economic model (two-copy *SMN2* cohort)
Stamina and fatigue	Not reported	
Mortality	Event-free survival Avoidance of death or the requirement of permanent ventilation[c] in the absence of acute illness or perioperatively	Used in the company economic model (two-copy and three-copy *SMN2* cohorts) Same definition used in the PNCR[20] dataset
Adverse effects of treatment	Patients with at least 1 TEAE TEAEs related to study treatment SAEs SAEs related to study treatment TEAEs causing study discontinuation TEAEs resulting in death AESIs	Additional AEs reported in CSR
Health-related quality of life (for patients and carers)	Not reported	

[a] All outcomes measured up to/at age 18 months (two-copy *SMN2* cohort) or age 24 months (three-copy *SMN2* cohort)
[b] As seen on growth charts, meaning that 3% of children are a lower weight than the child, and 97% of children are the same weight or a greater weight than the child
[c] 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
AE=adverse effect; AESI=adverse event of special interest; BSID=Bayley Scales of Infant and Toddler Development; CHOP-INTEND=Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders; CS=company submission; CSR=clinical study report; FM=fine motor; GM=gross motor; PNCR=Pediatric Neuromuscular Research Network; SAE=serious adverse effect; *SMN2*=survival motor neuron 2; TEAE=treatment-emergent adverse event; WHO-MGRS=World Health Organization Multicentre Growth Reference Study
Source: CS, Table 7, Table 8 and p68

3.6 Economic analysis

As specified in the final scope[19] issued by NICE, the cost effectiveness of treatment was expressed in terms of incremental cost per QALY. Outcomes were assessed over a lifetime horizon and costs were considered from an NHS and Personal Social Services (PSS) perspective.

Onasemnogene abeparvovec is available to the NHS at a discounted Patient Access Scheme (PAS) price. BSC is costed using list prices for all interventions.

3.7 Subgroups

In the final scope[19] issued by NICE, it is stated that, if the evidence allows, subgroups by number of *SMN2* gene copies should be considered. The company assessed and presented separate primary and secondary efficacy outcomes for patients with two copies of the *SMN2* gene and patients with three copies of the *SMN2* gene (CS, Section B.2.6.1.1 to Section B.2.6.1.4) and provided cost effectiveness results from analyses by *SMN2* copy number (CS, Appendix J and company clarification response).

4 CLINICAL EFFECTIVENESS

4.1 Critique of the methods of review(s)

The company conducted two systematic literature reviews (SLRs) of clinical effectiveness evidence:

- a review of the efficacy and safety of onasemnogene abeparvovec for babies with pre-symptomatic SMA
- a review of SMA natural history studies (since no randomised controlled trials have been conducted that compared onasemnogene abeparvovec versus BSC).

Details of the EAG SLR checks are provided in Table 5 and Table 6. The EAG is satisfied that the two company SLRs addressed relevant research questions and that the searches, which focused on relevant major electronic databases, were of good quality.

Table 5 EAG appraisal of the company's clinical efficacy and safety SLR methods

Review process	EAG response	Note
Was the review question clearly defined in terms of population, interventions, comparators, outcomes and study designs?	Yes	The company conducted a SLR to identify clinical evidence that demonstrated the efficacy and safety of onasemnogene abeparvovec as a treatment for babies with pre-symptomatic SMA from a screened population with a confirmed genetic diagnosis of SMA and up to three copies of the *SMN2* gene
Were appropriate sources searched?	Yes	Appropriate sources were searched, including major electronic databases: MEDLINE (via Ovid), Embase (via Ovid), and the Cochrane Library (Evidence Based Medicine Reviews - Cochrane Central Register of Controlled Trials) The company did not search specific conference websites; however, the EMBASE search would have identified conference proceedings indexed in this database
Was the timespan of the searches appropriate?	Yes	The initial search was conducted on 3 March 2020. Incremental searches were conducted on 13 November 2020 and 1 February 2022
Were appropriate search terms used?	Yes	The company conducted comprehensive searches using appropriate search strategies and relevant sources, including search terms relevant to the disease, interventions, comparators, and study types (as detailed in CS, Appendix D, Tables 57 to 65)
Were the eligibility criteria appropriate to the decision problem?	Yes	In response to clarification question C5, the company provided further information about the eligibility criteria used to select studies. The EAG carried out searches; these did not reveal any new relevant studies. The EAG considers that it is unlikely that relevant evidence has been excluded
Was study selection applied by two or more reviewers independently?	Unclear	Not reported
Was data extracted by two or more reviewers independently?	Unclear	Not reported
Were appropriate criteria used to assess the risk of bias and/or quality of the primary studies?	Yes	Although the NOS is most commonly used to appraise the quality of non-RCTs, the CASP checklist, which was used by the company, is also appropriate
Was the quality assessment conducted by two or more reviewers independently?	Unclear	Not reported
Were attempts to synthesise evidence appropriate?	Yes	The company performed simple naïve comparisons of data from the SPR1NT trial with data from the PNCR dataset and NeuroNext study.[20] Indirect comparisons performed using statistical methods are not possible due to limited data and the inability to match patient populations

CASP=Critical Appraisal Skills Programme; NA=not applicable; NOS=Newcastle-Ottawa scale; PNCR=Pediatric Neuromuscular Research Network; RCT=randomised controlled trial; SLR=systematic literature review; SMA=spinal muscular atrophy
Source: LR*i*G in-house checklist

Table 6 EAG appraisal of the company's natural history studies SLR methods

Review process	EAG response	Note
Was the review question clearly defined in terms of population, interventions, comparators, outcomes and study designs?	Yes	The company conducted a SLR to identify natural history studies of people with type 1, 2 or 3 pre-symptomatic or symptomatic SMA
Were appropriate sources searched?	Yes	Appropriate sources were searched, including major electronic databases: MEDLINE (via Ovid), Embase (via Ovid), and the Cochrane Library (Evidence Based Medicine Reviews - Cochrane Central Register of Controlled Trials) The company did not search specific conference websites; however, the EMBASE search would have identified conference proceedings indexed in this database
Was the timespan of the searches appropriate?	Yes	The initial search was conducted on 13 March 2019. Additional searches were conducted on 26 February 2020, 13 November 2020 and 1 February 2022; the latter two searches match the search dates for the clinical efficacy and safety data
Were appropriate search terms used?	Yes	The company conducted comprehensive searches using appropriate search strategies and relevant sources, including search terms relevant to the disease and study types (as detailed in CS, Appendix D, Tables 66 to 77)
Were the eligibility criteria appropriate to the decision problem?	Unclear	The company's approach to selecting natural history studies for inclusion in the SLR is unclear. In the CS (Appendix D, Table 79), the company listed 37 publications of 27 natural history studies as being eligible for inclusion in the SLR. However, data from only the PNCR dataset and NeuroNext study[20] were included and compared with outcome data from the SPR1NT trial. The company did not provide any rationale for excluding the other 25 natural history studies
Was study selection applied by two or more reviewers independently?	Unclear	Not reported
Was data extracted by two or more reviewers independently?	Unclear	Not reported
Were appropriate criteria used to assess the risk of bias and/or quality of the primary studies?	No	No quality assessment of the natural history studies was presented by the company
Was the quality assessment conducted by two or more reviewers independently?	NA	
Were attempts to synthesise evidence appropriate?	Yes	The company performed simple naïve comparisons of data from the SPR1NT trial with data from the PNCR dataset and NeuroNext study.[20] Indirect comparisons performed using statistical methods are not possible due to limited data and the inability to match patient populations

NA=not applicable; PNCR=Pediatric Neuromuscular Research Network; SLR=systematic literature review; SMA=spinal muscular atrophy
Source: LR*i*G in-house checklist

4.2 Critique of trials of the technology of interest, the company's analysis and interpretation

4.2.1 Included efficacy and safety studies

Studies of pre-symptomatic SMA patients

The company identified two single-arm trials that provided clinical effectiveness evidence of onasemnogene abeparvovec for babies with pre-symptomatic SMA (Table 7): the SPR1NT trial, which is the primary source of evidence, and the ongoing LT-002 study[23] (NCT04042025). The EAG considers that both trials[21-23] provide evidence that is relevant to the decision problem for this appraisal.

Table 7 Studies identified by the company efficacy and safety SLR

Study	Population	Study type	Follow-up
SPR1NT[21,22] trial	Babies with pre-symptomatic SMA with two cohorts of patients: (i) two copies of the *SMN2* gene (n=14) and (ii) three copies of the *SMN2* gene (n=15)	Phase III, open-label, single-arm study to measure the efficacy and safety of treatment with onasemnogene abeparvovec	Patients with two copies of the *SMN2* gene: up to age 18 months Patients with three copies of the *SMN2* gene: up to age 24 months
LT-002[23] study	Patients (n=86)[a] with SMA who were treated with onasemnogene abeparvovec in a Novartis-sponsored clinical trial[b] including [redacted] from the SPR1NT trial	Phase IV, observational, long-term follow-up study for continuous monitoring of safety as well as monitoring of continued efficacy and durability of response to treatment with onasemnogene abeparvovec	Up to 15 years

[a] Anticipated number of patients to be enrolled; eligibility criteria does not specify number of *SMN2* gene copies
[b] Patients who received onasemnogene abeparvovec in a Novartis-sponsored clinical study (including, but not limited to the START,[24] STR1VE-US,[25] STR1VE-EU[26] and SPR1NT[21,22] trials)
SLR=systematic literature review; SMA=spinal muscular atrophy; *SMN2*=survival motor neuron 2
Source: CS, Table 9 and Table 19; CS Appendix D, Figure 23; NCT04042025[23]

Studies of symptomatic SMA patients

The company identified three open-label single-arm trials[24-26] of patients treated with onasemnogene abeparvovec after a clinical diagnosis of type 1 (symptomatic) SMA, namely the START,[24] STR1VE-US[25] and STR1VE-EU[26] trials. However, the company considered that these trials[24-26] were not relevant to this appraisal. The EAG considers that these three trials[24-26] are relevant to the EAG's requested comparison: providing onasemnogene abeparvovec pre-symptomatically to the pre-symptomatic patient versus providing onasemnogene abeparvovec to patients with a pre-symptomatic diagnosis only at symptom onset if the patient develops type 1 SMA and BSC if they develop type 2 or 3 SMA. The EAG identified one other relevant trial, the STR1VE-AP trial.[28] However, this trial only included two patients.

4.2.2 Included natural history studies

The company identified two US natural history studies that included patients with type 1, 2 or 3 pre-symptomatic or symptomatic SMA: the PNCR dataset and NeuroNext study.[20] Data from

the PNCR[20] dataset provided an external control cohort, to allow treatment with onasemnogene abeparvovec (SPR1NT trial) to be compared with treatment with BSC.

In the company response to clarification, the company provided the characteristics of patients with three copies of the *SMN2* gene from the PNCR[20] dataset (n=81). [redacted]. The EAG considers that this cohort of patients provides evidence for the EAG's requested comparison: providing onasemnogene abeparvovec to the patient with a pre-symptomatic diagnosis only at symptom onset if the patient develops type 1 SMA and BSC if they develop type 2 or 3 SMA.

The EAG notes that all PNCR[20] dataset patients with two copies of the *SMN2* gene (n=23) had symptomatic type 1 SMA and age of symptom onset ≤6 months. In current NHS clinical practice, these patients would be eligible for, and receive, treatment with onasemnogene abeparvovec. Therefore, the EAG considers that a comparison of data from this cohort of patients to SPR1NT trial data is not relevant to this appraisal.

4.2.3 Characteristics of the SPR1NT trial

The SPR1NT trial was a phase III, open-label, single-arm, multi-centre trial that evaluated the efficacy and safety of a one-time infusion of onasemnogene abeparvovec for patients with genetically diagnosed, pre-symptomatic SMA. The trial included patients with two copies of the *SMN2* gene (n=14) and patients with three copies of the *SMN2* gene (n=15). The key characteristics of the SPR1NT trial are summarised in Table 8.

Table 8 Key characteristics of the SPR1NT trial

Trial parameter	Summary description

Design	• Phase III, open-label, single-arm, multi-centre trial
	• 16 sites in six countries (Australia, Belgium, Canada, Japan, UK, USA)
	• Screening period: Day -30 to Day -2; patients underwent screening procedures to determine study eligibility
	• Dosing: Day -1 to Day 2
	  ○ Day -1: inpatient pre-treatment baseline procedures
	  ○ Day 1: onasemnogene abeparvovec infusion and inpatient safety monitoring for 24 hours
	  ○ Day 2: patients discharged after 24 hours, based on Investigator judgment
	• Follow-up assessments: Days 7, 14, 21, 30, 44, 51 (Japan only), 60, 72, at age 3 months and every 3 months thereafter through to age 18 months for patients with two copies of the *SMN2* gene (end of study) and to age 24 months for patients with three copies of the *SMN2* gene (end of study)
	• Optional enrolment into the long-term follow-up study, LT-002[23]

Patient population	• Babies with pre-symptomatic SMA and two or three copies of the *SMN2 gene* • Age ≤6 weeks (≤42 days) at time of dose • Ability to tolerate thin liquids as demonstrated through a formal bedside swallowing test • CMAP≥2mV at baseline • Gestational age of 35 weeks to 42 weeks • Genetic diagnosis obtained from an acceptable newborn or prenatal screening test method • Up-to-date childhood vaccinations • Excluded patients who required tracheostomy, 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 • Excluded patients receiving any non-oral feeding method
Treatment	• One-time, single-dose intravenous infusion of onasemnogene abeparvovec over approximately 60 minutes at a dose of 1.1x10vg/kg[14] • Patients received prophylactic prednisolone (1mg/kg/day to 2mg/kg/day) from 24 hours before to 48 hours after onasemnogene abeparvovec infusion; 1 mg/kg/day for a minimum of 30 days then tapered
Primary outcome	<u>Cohort with two copies of the *SMN2* gene (n=14)</u> • Child sits alone without support for ≥30 seconds at any visit up to age 18 months (BSID GM item #26) <u>Cohort with three copies of the *SMN2* gene (n=15)</u> • Standing alone for ≥3 seconds at any visit up to age 24 months (BSID GM item #40)
Secondary outcomes	<u>Cohort with two copies of the *SMN2* gene (n=14)</u> • Event-free survival at age 14 months • Ability to maintain weight at or above 3rd percentile (without non-oral/mechanical feeding support) at all visits up to age 18 months <u>Cohort with three copies of the *SMN2* gene (n=15)</u> • Walking alone (≥5 steps, displaying coordination and balance) at any visit up to age 24 months (BSID GM item #43)
Safety outcomes	• Incidence of AEs and/or serious AEs • Change from baseline in clinical laboratory parameters

AE=adverse events; BSID GM=Bayley Scales of Infant and Toddler Development (Version 3) Gross Motor subtest; CMAP=compound motor action potential; SMA=spinal muscular atrophy; *SMN2*=survival motor neuron 2
Source: CS, Table 3 and Table 5, Strauss 2022[21,22]

4.2.4 Characteristics of SPR1NT trial patients

The baseline characteristics of patients participating in the SPR1NT trial are provided in Table 16.

All patients in the SPR1NT trial were diagnosed with pre-symptomatic SMA before the age of 4 weeks and received onasemnogene before the age of 7 weeks. Most patients (22/29, 75.9%) were diagnosed with pre-symptomatic SMA by newborn screening. Six patients (6/29, 20.7%) were diagnosed by prenatal testing and, for one patient (1/29, 3.4%), the method of diagnosis was unspecified.

4.2.5 Quality assessment of the SPR1NT trial

The company assessed the quality of the SPR1NT trial using a subset of questions from the Critical Appraisal Skills Programme (CASP) cohort study checklist. The EAG agrees with the company (CS, Section B.2.12.2, p81) that i) a single-arm trial was necessary for ethical reasons and ii) that the SPR1NT trial was well-designed and well-conducted. The company's assessments, and EAG comments, are presented in Table 9.

Table 9 Quality assessment for the SPR1NT trial (CASP checklist)

Question	Company response	Company assessment	EAG comment
1. Did the study address a clearly focused issue?	NR	NR	Yes, to investigate the efficacy and safety of onasemnogene abeparvovec for pre-symptomatic SMA in patients with biallelic *SMN1* gene mutations and up to three copies of the *SMN2* gene
2. 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	Agree. In addition, extended information on eligibility criteria for the SPR1NT trial are presented in the CS, Appendix D, Table 80
3. Was the exposure accurately measured to minimise bias?	Yes	Details of intervention were fully described	Agree
4. Was the outcome accurately measured to minimise bias?	Yes	Measurements for primary and secondary outcomes were clearly described. Achievement of developmental motor milestones was confirmed by independent central video review	Agree
5a. Have the authors identified all important confounding factors?	Yes	The inclusion criteria were carefully considered by investigators with regard to confounding factors. The protocol specified that all primary and secondary analyses would be performed on the population of patients with bi-allelic *SMN1* deletions with two or three copies of *SMN2* without the c.859G>C genetic modifier in exon 7 of *SMN2* which predicts a milder phenotype of the disease. While they could be enrolled in the study, patients with *SMN1* point mutations or with the c.859G>C mutation would be evaluated separately	Agree
5b. Have the authors taken account of the confounding factors in the design and/or analysis?	Yes	Not applicable, see above	Agree
6a. Was the follow-up of patients complete?	Yes	All patients were alive at the end of the study, and none were lost to follow-up	Agree

Question	Company response	Company assessment	EAG comment
6b. Was the follow up of subjects long enough?	NR	NR	Yes, follow-up was up to age 18 months for patients with two copies of the *SMN2* gene and up to age 24 months for patients with three copies of the *SMN2* gene. These differences in follow-up reflect the time expected to achieve motor milestones based on the number of *SMN2* gene copies
7. What are the results of this study?	NR	NR	Results were appropriately presented in the CS (Section B). The key findings were that (CS, Section B.2.12.1): • all patients enrolled in the SPR1NT trial survived without mechanical or non-oral feeding support, or ventilatory support of any kind, and achieved motor milestones that would never be achieved in patients receiving BSC only • most patients with two copies of the *SMN2* gene (78.6%) and three copies of the *SMN2* gene (93.3%) achieved the primary outcomes (independent sitting and standing for patients with two and three copies of the *SMN2* gene, respectively) within normal developmental windows
8. How precise are the results?	Yes	All statistical analyses were prospectively defined in the protocol and statistical analysis plan, as detailed in CS, Table 12	The EAG considers that it is not possible to assess precision as measures of variability are rarely reported
9. Do you believe the results?	NR	NR	Yes, the trial was well-conducted with clearly pre-defined recruitment processes, eligibility criteria, assessments and outcomes, and analyses
10. Can the results be applied to the local population	NR	NR	Yes, the population included in the SPR1NT trial matches that of the NICE scope
11. Do the results of this study fit with other available evidence?	NR	NR	No other studies of onasemnogene abeparvovec for pre-symptomatic SMA have been conducted
12. What are the implications of this study for practice?	NR	NR	The trial results suggest that onasemnogene abeparvovec is a clinically effective treatment for patients with pre-symptomatic SMA and two or three copies of the *SMN2* gene

BSC=best supportive care; NR=not reported (the company did not address this item); SMA=spinal muscular atrophy
Source: CS, Table 13; CASP checklist;[29] EAG comment

4.2.6 Statistical approach adopted for the analysis of the SPR1NT trial data

The EAG has extracted information relevant to the statistical approach taken by the company to analyse the SPR1NT trial data from the Clinical Study Report (CSR),[30] the trial statistical analysis plan (TSAP),[31] the trial protocol,[32] and the CS. A summary of the EAG checks of the pre-planned statistical approach used by the company to analyse data from the SPR1NT trial is provided in Appendix 1, Section 9.1, Table 45.

The EAG considers that appropriate statistical methods were used to analyse data from the SPR1NT trial. The EAG notes that the statistical tests used to compare data from the SPR1NT trial with data from the PNCR[20] dataset did not account for between-trial differences in patient and trial characteristics that may influence treatment outcome; the EAG has not presented the results of these statistical tests. An EAG naïve comparison of data from the SPR1NT trial, the PNCR[20] dataset, other trials[24-26] evaluating onasemnogene abeparvovec for symptomatic SMA and additional evidence[4,6,33] for patients with type 2, 3 and 4 SMA who received BSC is presented in Section 4.4.3 and 4.4.4.

4.3 Efficacy results from the SPR1NT trial

4.3.1 Primary and secondary efficacy endpoints

Patients with two copies of the *SMN2* gene

All 14 patients with two copies of the *SMN2* gene met the primary efficacy endpoint of functional independent sitting at any visit up to age 18 months, and the secondary endpoint of event-free survival at 14 months (Table 10). The majority (11/14, 78.6%) of patients achieved the primary outcome within the normal development window (as defined by the World Health Organization Multicentre Growth Reference Study [WHO-MGRS]).[34] The company highlighted (CS, p82 and p101) that as motor milestone achievements were assessed in the SPR1NT trial at study visits (every 3 months), there would be a delay in recording milestones achieved by patients between visits. No patients received any feeding support at any point up to the end-of-study visit at 18 months (CS, p65). All except one patient (13/14, 92.9%) maintained their weight at or above the third percentile (without non-oral/mechanical feeding support) up to age 18 months.

Table 10 Results for the primary and secondary efficacy endpoints for patients with two copies of the *SMN2* gene (n=14)

Endpoint		Result
Primary efficacy endpoint		
Sitting without support for ≥30 seconds at any visit up to age 18 months (BSID GM item #26)	n (%)	14 (100%)
	Achieved within normal range, n (%) [a]	11 (78.6%)
	Age (months) when milestone was first demonstrated, mean (SD) [range]	8.21 (1.76) [5.7 to 11.8]
Secondary efficacy endpoints		
Event-free survival at age 14 months, n (%) [b]		14 (100%)
Ability to maintain weight at or above 3rd percentile (without non-oral/mechanical feeding support) at all visits up to age 18 months, n (%)		13 (92.9%)

[a] 99th percentile ≤age 279 days; WHO-MGRS definition[34]
[b] Event-free survival definition provided in EAG report, Table 4
BSID GM=Bayley Scales of Infant and Toddler Development (Version 3) Gross Motor subtest; CS=company submission; SD=standard deviation; WHO-MGRS=World Health Organization Multicentre Growth Reference Study
Source: CS (p57, pp64-65)

Patients with three copies of the *SMN2* gene

All 15 patients with three copies of the *SMN2* gene met the primary efficacy endpoint of standing alone at any visit up to age 24 months, and 14 patients (93.3%) met the secondary efficacy endpoint of walking alone at any visit up to age 24 months (Table 11). A clinical evaluator observed the fifteenth patient walking alone during the assessment at 24 months which was conducted via video call. However, the video was not recorded and, therefore, independent video review could not take place and the patient was recorded as not having achieved this motor milestone. The majority of patients achieved the primary and secondary

endpoint milestones (standing alone: 93.3%; walking alone: 73.3%) within the normal development window (as defined by WHO-MGRS).[34]

Table 11 Results for the primary and secondary efficacy endpoints for patients with three copies of the *SMN2* gene (n=15)

Endpoint		Result
Primary efficacy endpoint		
Standing alone for ≥3 seconds at any visit up to age 24 months (BSID GM item #40)	n (%)	15 (100%)
	Achieved within normal range, n (%) [a]	14 (93.3%)
	Age (months) when milestone was first demonstrated, mean (SD) [range]	13.5 (2.18) [9.5 to 18.3]
Secondary efficacy endpoint		
Walking alone (≥5 steps, displaying coordination and balance) at any visit up to age 24 months (BSID GM item #43)	n (%)	14 (93.3%)
	Achieved within normal range, n (%) [b]	11 (73.3%)
	Age (months) when milestone was first demonstrated, mean (SD) [range]	14.6 (2.48) [12.1 to 18.8]

[a] 99th percentile ≤age 514 days; WHO-MGRS definition[34]
[b] 99th percentile ≤age 534 days; WHO-MGRS definition[34]
BSID GM=Bayley Scales of Infant and Toddler Development (Version 3) Gross Motor subtest; CS=company submission; SD=standard deviation; WHO-MGRS=World Health Organization Multicentre Growth Reference Study
Source: CS (p60 and p65), SDs calculated from Strauss 2022[22] supplementary material, Table 2 data

4.3.2 Exploratory efficacy outcomes

Developmental milestones

A summary of the developmental milestones achieved by patients in the SPR1NT trial with two copies of the *SMN2* gene at any visit up to age 18 months, and by patients with three copies of the *SMN2* gene at any visit up to age 24 months, is presented in Table 12. The company presented the ages at which each patient with two copies of the *SMN2* gene and each patient with three copies of the *SMN2* gene achieved developmental milestones in the CS (Figure 5 and Figure 6). The Bayley Scales of Infant and Toddler Development Version 3 (BSID) Gross Motor (GM) subtest[35] and WHO-MGRS[34] definitions of the developmental milestones, where applicable, are provided in Table 4.

As shown in Table 12, a high proportion of patients in both cohorts achieved motor milestones. More patients with three copies of the *SMN2* gene achieved walking milestones than patients with two copies of the *SMN2* gene. Patients with three copies of the *SMN2* gene achieved motor milestones (with the exception of head control) at earlier ages than patients with two copies of the *SMN2* gene. A larger proportion of patients with three copies of the *SMN2* gene achieved crawling, standing and walking milestones within the normal development window (as defined by WHO-MGRS)[34] than patients with two copies of the *SMN2* gene.

Table 12 Proportions of SPR1NT trial patients demonstrating motor milestones

Milestone achieved		**Two copies of the *SMN2* gene Milestones assessed up to age 18 months**			**Three copies of the *SMN2* gene Milestones assessed up to age 24 months**		
		n/N [a] (%)	**Age (months) at earliest achievement, median (range)**	**Achieved within normal development window, n (%) [b]**	**n/N [a] (%)**	**Age (months) at earliest achievement, median (range)**	**Achieved within normal development window, n (%) [b]**
Head control	≥3 seconds without support BSID GM item #4	9/9 (100.0)	1.9 (1.2 to 3.4)	NR	9/9 (100.0)	2.2 (1.3 to 4.3)	NR
Rolls from back to sides	Turns from back to both right and left BSID GM item #20	13/13 (100.0)	8.9 (3.9 to 18.4)	NR	15/15 (100.0)	7.8 (5.9 to 21.2)	NR
Sits without support	≥30 seconds BSID GM item #26	14/14 (100.0)	8.9 (5.7 to 11.8)	11/14 (78.6)	14/15 (93.3)	7.6 (6.1 to 9.6)	11/15 (73.3)
	≥10 secs WHO-MGRS	14/14 (100.0)	9.0 (6.3 to 18.5)	10/14 (71.4)	14/15 (93.3)	8.8 (6.1 to 9.6)	10/15 (66.7)
Crawls	≥5 feet BSID GM item #34	9/14 (64.3)	14.4 (8.9 to 15.3)	4/14 (28.6)	14/15 (93.3)	10.8 (8.9 to 13.3)	14/15 (93.3)
	≥3 movements WHO-MGRS	10/14 (71.4)	13.4 (10.5 to 14.9)	5/14 (35.7)	14/15 (93.3)	10.8 (8.9 to 16.4)	13/15 (86.7)
Stands with assistance	≥2 seconds BSID GM item #33	14/14 (100.0)	13.7 (6.3 to 18.8)	6/14 (42.9)	14/15 (93.3)	9.3 (6.4 to 12.8)	11/15 (73.3)
	≥10 seconds WHO-MGRS	14/14 (100.0)	13.0 (11.1 to 15.3)	5/14 (35.7)	14/15 (93.3)	9.3 (8.9 to 12.8)	11/15 (73.3)
Pulls to stand	Raises self to standing position using chair/other object BSID GM item #35	11/14 (78.6)	14.9 (8.9 to 18.6)	NR	14/15 (93.3)	10.8 (8.9 to 16.4)	NR
Stands alone	≥2 seconds BSID GM item #40	11/14 (78.6)	15.3 (10.9 to 18.8)	7/14 (50.0)	15/15 (100.0)	12.6 (9.5 to 18.3)	14/15 (93.3)
	≥10 seconds WHO-MGRS	10/14 (71.4)	16.4 (14.6 to 18.0)	5/14 (35.7)	15/15 (100.0)	13.3 (12.0 to 18.3)	13/15 (86.7)

Milestone achieved		Two copies of the *SMN2* gene Milestones assessed up to age 18 months			Three copies of the *SMN2* gene Milestones assessed up to age 24 months		
		n/N [a] (%)	Age (months) at earliest achievement, median (range)	Achieved within normal development window, n (%) [b]	n/N [a] (%)	Age (months) at earliest achievement, median (range)	Achieved within normal development window, n (%) [b]
Walks with assistance	Coordinated alternated stepping movements BSID GM item #37	11/14 (78.6)	12.5 (8.9 to 18.5)	6/14 (42.9)	14/15 (93.3)	12.2 (8.9 to 16.4)	13/15 (86.7)
	Holding onto stable object WHO-MGRS	12/14 (85.7)	14.9 (13.3 to 16.4)	5/14 (35.7)	14/15 (93.3)	12.3 (8.9 to 16.4)	12/15 (80.0)
Walks alone	≥5 steps with coordination and balance BSID GM item #43	9/14 (64.3)	17.5 (12.2 to 18.8)	5/14 (35.7)	14/15 (93.3) [c]	14.1 (12.1 to 18.8)	11/15 (73.3)
	≥5 steps WHO-MGRS	10/14 (71.4)	16.4 (14.4 to 17.9)	6/14 (42.9)	14/15 (93.3)	14.1 (12.1 to 18.3)	13/15 (86.7)

[a] N is the number of patients without milestone prior to dosing
[b] Within 99th percentile of normal development (WHO-MGRS)[34]
[c] A fifteenth patient was observed walking alone by a clinical evaluator during the assessment at 24 months conducted via video call, but video was not recorded and hence per study protocol, in the absence of independent video review, this patient was not recorded as having achieved the motor milestone
BSID GM=Bayley Scales of Infant and Toddler Development (Version 3) Gross Motor subtest; CS=company submission; NR=not reported; WHO-MGRS=World Health Organization Multicentre Growth Reference Study
Source: CS, Table 14 and Table 15

Maintenance of achieved milestones

All 12 patients with two copies of the *SMN2* gene assessed at 18 months maintained the achieved milestone of independent sitting. The remaining two patients could not be assessed at 18 months due to non-compliance. All 15 patients with three copies of the *SMN2* gene cohort maintained the achievement of standing alone at age 24 months (CS, p61).

Event-free survival and ventilatory support

All 14 patients with two copies of the *SMN2* gene met the secondary efficacy endpoint of event-free survival at 14 months (see Section 4.3.1). For patients with three copies of the *SMN2* gene, event-free survival at 24 months was an exploratory endpoint; all 15 patients met this endpoint (CS, p68).

All 14 patients with two copies of the *SMN2* gene remained independent of ventilatory support ([redacted] [CSR, p319 and p321]) at age 18 months (CS, p64), and all 15 patients with three copies of the *SMN2* gene remained independent of ventilatory support at age 24 months (CS, p68). No patient with two or three copies of the *SMN2* gene used ventilatory support (invasive or non-invasive, including cough assist) at any point up to the end-of-study visit, which took place at 18 months for patients with two copies of the *SMN2* gene and at 24 months for patients with three copies of the *SMN2* gene (CS, p64 and p68).

BSID scores

The company presented raw scores for the BSID fine motor (FM) and gross motor (GM) subtests for patients with two copies of the *SMN2* gene (CS, Figure 8 and Figure 9) and for patients with three copies of the *SMN2* gene (CS, Figure 10 and Figure 11). A summary of BSID score exploratory endpoints is provided in Table 13.

Table 13 Summary of BSID FM and BSID GM score exploratory endpoints

Two copies of the *SMN2* gene		Three copies of the *SMN2* gene	
Improvement over baseline of ≥15 points on BSID FM and BSID GM (raw score), n/N (%)			
On at least one visit up to age 18 months	14/14 (100%)	On at least one visit up to age 24 months	[redacted]/14[a] ([redacted])
Achievement of a scaled score on BSID FM and BSID GM ≥5.5,[b] n/N (%)			
On at least one visit up to age 18 months	14/14 (100%)	On at least one visit up to age 24 months	15/15 (100%)
At the age 18 months visit	8/14 (57.1%)	At the age 24 months visit	9/10[c] (90%)
Achievement of a scaled score on BSID FM and BSID GM ≥4,[d] n/N (%)			
On at least one visit up to age 18 months	14/14 (100%)	On at least one visit up to age 24 months	15/15 (100%)
At the age 18 months visit	9/14 (64.3%)	At the age 24 months visit	10/10[c] (100%)

[a] One patient was excluded from the analysis of change from baseline as they had a missing score at baseline. [redacted]

[b] Scores between 5.5 and 14.5 are within 1.5 SDs of the mean scaled score for normally developing children (mean=10, SD=3)
[c] 10 patients had BSID FM and BSID GM assessments at the 24-month study visit
[d] Scores between 4 and 16 are within 2 SDs of the mean scaled score for normally developing children (mean=10, SD=3)
BSID FM=Bayley Scales of Infant and Toddler Development (Version 3) Fine Motor subtest; BSID GM=Bayley Scales of Infant and Toddler Development (Version 3) Gross Motor subtest; CS=company submission; SD=standard deviation
Source: CS, p66 and p68; CSR, 138; Strauss 2022[21]

The analyses of achievement of a scaled score of ≥4 on the BSID FM and BSID GM subtests were not pre-specified in the TSAP. The EAG does not consider the post-hoc addition of this endpoint to be an issue of concern for either cohort as the results were presented as exploratory endpoints. However, the post-hoc nature of these analyses should be considered when interpreting the results.

Weight maintenance

All except one of the patients with two copies of the *SMN2* gene (13/14, 92.9%) met the secondary efficacy endpoint of weight maintenance at or above the third percentile (without the need for non-oral/mechanical feeding support) at all visits up to the age of 18 months (see Section 4.3.1). For patients with three copies of the *SMN2* gene, weight maintenance at or above the third percentile at all visits up to the age of 24 months was an exploratory endpoint; 10/15 patients (66.7%) met this endpoint. The company notes (CSR, p139) that [redacted]. No patients with three copies of the *SMN2* gene received nutrition through mechanical support at any point up to the end-of-study visit at 24 months (CS, p70).

Ability to thrive

An analysis of ability to thrive (defined as the ability to tolerate thin liquids, not requiring nutrition through mechanical support, and maintaining weight consistent with age) at the age of 18 months was only performed for patients with two copies of the *SMN2* gene. Twelve of the 14 patients (85.7%) achieved the endpoint of ability to thrive at age 18 months.

Thirteen of the 14 patients with two copies of the *SMN2* gene were assessed with formal swallowing tests at the age of 18 months and all 13 were found to tolerate thin liquids. One patient was not assessed for toleration of thin or very thin liquids at age 18 months; however, the patient showed a "normal swallow" result for foods of solid consistency at this time.

CHOP-INTEND score

For patients with two copies of the *SMN2* gene, the proportions of patients achieving a CHOP-INTEND score ≥40, ≥50, and ≥58 (at any visit up to the age of 18 months) were exploratory endpoints. The mean baseline CHOP-INTEND score for the cohort was 46.1 (standard deviation [SD]=8.77), and all 14 patients achieved scores ≥58 (at any visit up to the age of 18 months). The company presented the CHOP-INTEND score data by patient in the CS (Figure 7).

4.3.3 Long-term follow up of patients from the SPR1NT trial

The ongoing LT-002[23] study aims to collect long-term efficacy and safety data from patients whose SMA was treated with onasemnogene abeparvovec in clinical trials (including the SPR1NT trial). [redacted] patients from the SPR1NT trial enrolled in the LT-002[23] study ([redacted]) and efficacy results for these patients from the most recent data cut-off date (23 May 2022)[36] are provided in the CS (p78).

[redacted]

4.4 Data to inform the EAG's requested comparison

In response to a clarification request, the company provided an updated model that included cost effectiveness evidence to support the EAG's requested comparison:

- providing onasemnogene abeparvovec pre-symptomatically to the pre-symptomatic patient

versus

- providing onasemnogene abeparvovec to the patient with a pre-symptomatic diagnosis only at symptom onset if the patient develops type 1 SMA and BSC if they develop type 2 or 3 SMA.

However, the company did not provide any clinical effectiveness evidence to support this comparison, other than the information included in the updated company model.

There is no direct clinical effectiveness evidence to inform the EAG's requested comparison. Indirect comparisons of SPR1NT trial data versus data from the START,[24] STR1VE-US[25] and STR1VE-EU[26] trials and PNCR[20] dataset performed using statistical methods are not possible due to limited data and the inability to match patient populations. Therefore, the EAG has carried out simple naïve comparisons of data from the SPR1NT trial versus data from:

- the START,[24] STR1VE-US[25] and STR1VE-EU[26] trials that assessed the clinical effectiveness of onasemnogene abeparvovec as a treatment for patients with type 1 SMA and two copies of the *SMN2* gene
- the PNCR[20] dataset and the Wadman,[33] Wijngaarde,[6] and Calucho[4] studies that followed patients with types 2, 3 or 4 SMA who received BSC.

The characteristics of patients in the START,[24] STR1VE-US[25] and STR1VE-EU[26] trials and PNCR[20] dataset are presented in Section 4.4.2 and the results from the EAG's naïve comparisons are presented in Section 4.4.3.

4.4.1 Characteristics of the START, STR1VE-US and STR1VE-EU trials and PNCR dataset

Clinical trials of patients with type 1 SMA

The key characteristics of the three open-label single-arm trials of patients treated with onasemnogene abeparvovec after a clinical diagnosis of type 1 SMA, namely the START,[24] STR1VE-US[25] and STR1VE-EU[26] trials, are summarised in Table 14.

Table 14 Key characteristics of START, STR1VE-US and STR1VE-EU trials

Study	Population	Study description	Follow-up
START[24]	Patients with type 1 SMA with two copies of the *SMN2* gene, aged ≤6 months, with symptom onset at ≤6 months (n=12)	Phase I/IIa open-label, single-arm study to measure efficacy and safety of treatment with onasemnogene abeparvovec	24 months post dose
STR1VE-US[25]	Patients with type 1 SMA with one or two copies[a] of the *SMN2* gene, aged <6 months at the time of gene replacement therapy (n=22)	Phase III open-label, single-arm study to measure efficacy and safety of treatment with onasemnogene abeparvovec	Up to age 18 months
STR1VE-EU[26]	Patients with symptomatic type 1 or type 2 SMA[b] with one or two copies[a] of the *SMN2* gene, aged <6 months at the time of gene replacement therapy (n=33)	Phase III open-label, single-arm study to measure efficacy and safety of treatment with onasemnogene abeparvovec	Up to age 18 months

[a] Patients with one copy of the *SMN2* gene were eligible for inclusion in the STR1VE-US[25] and STR1VE-EU[26] trials, however, all patients enrolled in both studies had two copies of the *SMN2* gene
[b] Patients with type 2 SMA were eligible for inclusion in the STR1VE-EU[26] trial, however, all patients enrolled had type 1 SMA
SMA=spinal muscular atrophy; *SMN2*=survival motor neuron 2
Source: HST15;[1] CS, Table 4; and EAG report, Table 6 and Table 7

The SPR1NT, START,[24] STR1VE-US[25] and STR1VE-EU[26] trials collected similar efficacy and safety outcomes, albeit with different lengths of follow-up. The EAG has extracted the efficacy outcome data reported by the START,[24] STR1VE-US[25] and STR1VE-EU[26] trials that match the SPR1NT trial primary and secondary efficacy outcomes (see Section 4.4.3).

PNCR dataset

The EAG has only presented data from the PNCR[20] dataset. NeuroNext[20] study data have not been presented as these data were only used by the company to undertake an exploratory comparison of CHOP-INTEND outcomes for patients receiving BSC versus patients enrolled in the SPR1NT trial.

The key characteristics of the PNCR[20] dataset are summarised in Table 15.

Table 15 Key characteristics of the PNCR dataset

Parameter	Summary description
Design	• 337 patients in the US with any form of SMA followed at three tertiary medical centres • Outcomes assessed at baseline, 2, 4, 6, 9, and 12 months, and every 6 months thereafter • Maximum length of follow-up was not reported
Patient population eligibility criteria	Cohort with two copies of the *SMN2* gene (n=23) [a] • Type 1 SMA and two copies of the *SMN2* gene • Age at SMA onset ≤6 months • Age at SMA diagnosis ≤2 years Cohort with three copies of the *SMN2* gene (n=81) [b] • Any type of SMA and three copies of the *SMN2* gene ○ patients with type 1 SMA: [redacted] ○ patients with type 2 SMA: [redacted] ○ patients with type 3 SMA: [redacted] ○ patients with type 4 SMA: [redacted]
Treatment	BSC in accordance with the SMA standard of care guidelines published in 2007[37]
Outcomes [c]	Cohort with type 1 SMA and two copies of the *SMN2* gene (n=23) • Sits without support • Stands without support • Walk alone • Proportion of infants that maintain weight at or above the third percentile without need for non-oral/mechanical feeding support at any visit • Event-free survival, defined as avoidance of death or the requirement of permanent ventilation in the absence of acute illness or perioperatively at 14 months of age • [redacted] Cohort with any type of SMA and three copies of the *SMN2* gene (n=81) • Ability to stand without support for at least 3 seconds ([redacted]) • Walk alone with coordination [redacted] • Event-free survival, defined as avoidance of death or the requirement of permanent ventilation in the absence of acute illness or perioperatively at 14 months of age [d] • Proportion of infants alive and without tracheostomy in the absence of acute illness or perioperatively

[a] The population used as a comparator for patients with type 1 SMA and two copies of the *SMN2* gene (n=23) was also used as an external control to patients in the STR1VE-US[25] and STR1VE-US[25] trials
[b] In response to additional clarification, the company provided the characteristics of patients with three copies of the *SMN2* gene from the PNCR[20] dataset
[c] Additional outcomes measured in the PNCR[20] dataset include: physical examination findings of weight, length/height, head and chest circumference, vital signs, motor function, scoliosis, and joint contractures; serum comprehensive metabolic panel and complete blood count; laboratory abnormalities
[d] Data presented by the company in response to additional clarification
BSC=best supportive care; BSID GM=Bayley Scales of Infant and Toddler Development (Version 3) Gross Motor subtest; [redacted]; SMA=spinal muscular atrophy; *SMN2*=survival motor neuron 2
Source: CS, Appendix D, pp50-51; Novartis report;[20] SPR1NT trial CSR;[30] company response to additional clarification questions

Patients were enrolled in the PNCR[20] dataset prospectively and retrospectively. As noted in Table 15, outcomes were assessed at baseline, 2 months, 4 months, 6 months, 9 months, and 12 months, and every 6 months thereafter. Data from the SPR1NT trial and the PNCR[20]

dataset were compared at 18 months (for patients with two copies of *SMN2* gene) and at 24 months (for patients with three copies of *SMN2* gene). However, it is unclear from the information provided by the company whether data from PNCR[20] dataset were reported for patients at age 18 months and 24 months (meaning that outcomes were reported retrospectively for patients who were older than 18 months or 24 months at enrolment), or whether patients in the PNCR[20] dataset were followed up for 18 months or 24 months from the time of enrolment and data were compared at prospective time points.

For completeness, the EAG has presented data from the PNCR[20] dataset for patients with two copies of the *SMN2* gene and type 1 SMA (n=23), as these data were used by the company to provide an external control cohort versus SPR1NT trial data for the primary and secondary efficacy outcomes. This cohort was also used as an external control for the START,[24] STR1VE-US[25] and STR1VE-EU[26] trials.

4.4.2 Characteristics of patients in the START, STR1VE-US and STR1VE-EU trials and PNCR dataset

The key characteristics of patients in the SPR1NT, START,[24] STR1VE-US[25] and STR1VE-EU[26] trials and PNCR[20] dataset are summarised in Table 16.

Table 16 Characteristics of patients in the SPR1NT, START, STR1VE-EU, STR1VE-US trials and PNCR dataset

Baseline characteristic	Pre-symptomatic SMA		Symptomatic SMA				
			Type 1 SMA			Type 1 SMA	Type 1, 2 and 3 SMA
	Onasemnogene abeparvovec					BSC	
	SPR1NT[21] two-copy *SMN2* cohort (N=14)	SPR1NT[22] three-copy *SMN2* cohort (N=15)	START[24] Cohort 2 [a] (N=12)	STR1VE-US[25] (N=22)	STR1VE-EU[26] (N=33)	PNCR[20] two-copy *SMN2* cohort (N=23)	PNCR[20] three-copy *SMN2* cohort (N=81)
SMN2 copy number	2	3	2	2	2	2	3
Age at treatment, days							
Mean (SD)	20.6 (7.87)	28.7 (11.68)	103.4 (63.9) [b]	112.6 (48.7) [b]	124.7 (39.5) [b]	NA [c]	NA [c]
Median (range)	21 (8 to 34)	31 (9 to 43)	NR (27.4 to 240.3) [b]	106.5 (15.2 to 179.5) [b]	124.7 (54.8 to 182.5) [b]	NA [c]	NA [c]
Sex, n (%)							
Female	10 (71.4)	9 (60.0)	7 (58.3)	12 (55)	19 (57.6)	12 (52.2)	[redacted]
Race, n (%)							
White	7 (50.0)	10 (66.7)	11 (91.7)	11 (50)	NR	16 (69.6)	[redacted]
Other	4 (28.6)	2 (13.3)	1 (8.3)	6 (27)	NR	7 (30.4)	[redacted]
Black or African American	1 (7.1)	0 (0.0)	NR	3 (14)	NR	NR	[redacted]
Asian	2 (14.3)	2 (13.3)	NR	2 (9)	NR	NR	[redacted]
American Indian or Alaska Native	0 (0.0)	1 (6.7)	NR	NR	NR	NR	[redacted]
Weight at baseline, kg							
Mean (SD)	3.6 (0.39)	4.1 (0.52)	5.7 (1.34)	5.8 (NR)	5.8 (1.0)	11.8 (7.8)	[redacted]
Median (range)	3.7 (3.0 to 4.3)	4.1 (3.1 to 5.2)	NR (3.6 to 8.4)	5.8 (3.9 to 7.5)	5.8 (4.2 to 8.4)	NR	[redacted]
Age at symptom onset, months							
Mean (SD)	NA	NA	1.4 (1.0)	1.9 (1.2)	1.6 (0.9)	3.0 (1.6)	[redacted]
Median (range)	NA	NA	NR	1.8 (NR)	1.5 (0.0 to 4.0)	NR (0.5 to 6)	[redacted]

Baseline characteristic	Pre-symptomatic SMA		Symptomatic SMA				
			Type 1 SMA			Type 1 SMA	Type 1, 2 and 3 SMA
	Onasemnogene abeparvovec					BSC	
	SPR1NT[21] two-copy *SMN2* cohort (N=14)	SPR1NT[22] three-copy *SMN2* cohort (N=15)	START[24] Cohort 2 [a] (N=12)	STR1VE-US[25] (N=22)	STR1VE-EU[26] (N=33)	PNCR[20] two-copy *SMN2* cohort (N=23)	PNCR[20] three-copy *SMN2* cohort (N=81)
Age at diagnosis, days							
Mean (range)	7.2 (1 to 14) [d]	9.9 (2 to 26) [e]	67.8 (1 to 137)	56.1 (56 to 126)	81.3 (26 to 156)	152 (30 to 365)	[redacted]
CHOP-INTEND score at baseline							
Mean (SD)	46.1 (8.8)	NR	28.2 (12.3)	32.0 (9.7)	27.9 (8.3)	24.6 (11.6)	[redacted]
Familial history of SMA including affected siblings or parent carriers, n (%)							
Yes	8 (57.1)	10 (66.7)	3 (27.3) [f]	NR	NR	NR	[redacted]
Clinical characteristics at baseline							
Reported swallowing thin liquids, n (%)	14 (100.0)	15 (100.0)	4 (33.3)	22 (100.0)	32 (97.0) [g]	NR	[redacted]
Reported feeding support, n (%)	0 (0.0) [h]	0 (0.0) [h]	5 (41.7)	0 (0.0) [h]	9 (27.3)	18 (78.3)	[redacted]
Reported ventilatory support, n (%)	0 (0.0) [h]	0 (0.0) [h]	1 (8.3)	0 (0.0) [h]	9 (27.3)	12 (52.2)	[redacted]

[a] Patients in cohort 2 of the START[24] trial received the recommended dose of onasemnogene abeparvovec. Patients in cohort 1 received a lower dose of onasemnogene abeparvovec and therefore are not considered in this appraisal
[b] Results were reported as months and were converted to days by multiplying by 30.42
[c] The PNCR [20] study reported mean (SD) age at enrolment for patients with two copies of the *SMN2* gene, days: 882.2 (1268.5); range, days: 60.8 to 5201.8; and for patients with three copies of the *SMN2* gene, days: [redacted]; range, days: [redacted]
[d] Data were available for n=14 patients; age at diagnosis refers to genetic diagnosis
[e] Data were available for n=9 patients; age at diagnosis refers to genetic diagnosis
[f] n=11; the familial history of SMA was unknown for one patient
[g] STR1VE-EU[26] reports the ability to swallow defined as having a normal, functional, or safe for swallowing result during a swallow test and does not specify thin liquids
[h] Patients requiring non-invasive ventilatory support for <12h daily or feeding support were excluded from the SPR1NT and STR1VE-US[25] trials
BSC=best supportive care; CHOP-INTEND=Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders; NA=not applicable; NR=not reported; SD=standard deviation; SMA=spinal muscular atrophy; *SMN2*=survival motor neuron 2 gene
Source: Day 2021[25] for STR1VE-US; Mendell 2017[38] for START; Mercuri 2021[26] for STR1VE-EU; Strauss 2022[21,22] for SPR1NT and PNCR two-copy *SMN2* cohort; Company response to additional clarification for PNCR three-copy *SMN2* cohort

The EAG observes that the main differences between the populations in the PNCR[20] dataset and the onasemnogene abeparvovec trials[21,22,24-26] (Table 16) are that:

- the SPR1NT trial only included patients with pre-symptomatic SMA whereas the PNCR[20] dataset and the START,[24] STR1VE-US[25] and STR1VE-EU[26] trials only included patients with symptomatic type 1 SMA
- the mean age at symptom onset for patients in the PNCR[20] dataset (3.0 months) was greater than for patients in the START[24] (1.4 months), STR1VE-US[25] (1.9 months) and STR1VE-EU[26] (1.6 months) trials
- the mean age for clinical diagnosis of type 1 SMA for patients in the PNCR[20] dataset (152 days) was greater than in the START[24] (67.8 days), STR1VE-US[25] (56.1 days) and STR1VE-EU[26] (81.3 days) trials
- in the SPR1NT trial, patients with two copies of the *SMN2* gene had a greater mean CHOP-INTEND score at baseline (46.1) than patients in the PNCR[20] dataset (24.6) and in the START[24] (28.2), STR1VE-US[25] (32.0) and STR1VE-EU[26] (27.9) trials
- only a third of patients in the START[24] trial (4/12, 33.3%) were able to swallow thin liquids compared to nearly all patients in the SPR1NT, STR1VE-EU[26] and STR1VE-US[25] trials
- the SPR1NT and STR1VE-US[25] trials excluded patients who required feeding or ventilatory support whereas the PNCR[20] dataset and the START[24] and STR1VE-EU[26] trials included patients who required feeding (18/23; 5/12; 9/33, respectively) and/or ventilatory support (12/23; 1/12; 9/33, respectively).

The EAG highlights that:

- the START[24] and STR1VE-US[25] trials included patients with symptomatic type 1 SMA at birth, therefore some patients in the START[24] and STR1VE-US[25] trials received onasemnogene abeparvovec as young as age 27.4 days and 15.2 days, respectively
- the START,[24] STR1VE-US[25] and STR1VE-EU[26] trials did not include patients with three copies of the *SMN2* gene
- in the PNCR[20] dataset, the cohort of patients with three copies of the *SMN2* gene included [redacted] patients with type 1 SMA. In NHS clinical practice, patients with type 1 SMA may be eligible for, and receive, treatment with onasemnogene abeparvovec in addition to BSC.[1]

4.4.3 Efficacy results from the START, STR1VE-US and STR1VE-EU trials and PNCR dataset

Data from the START,[24] STR1VE-US[25] and STR1VE-EU[26] trials and PNCR[20] dataset for the primary and secondary outcomes of the SPR1NT trial are presented in Table 17. Data for all motor milestone outcomes and data for event-free survival (deaths and the use of ventilatory support) are presented in Appendix 2, Section 9.2, Table 46 and Table 47.

Table 17 Comparison of key outcomes from the SPR1NT, STR1VE and START trials and the PNCR dataset

Outcome [a] n (%)		Pre-symptomatic SMA		Symptomatic SMA				
				Type 1			Type 1	Type 1, 2, 3
		Onasemnogene abeparvovec					BSC	
		SPR1NT[21] two-copy *SMN2* cohort (N=14)	SPR1NT[22] three-copy *SMN2* cohort (N=15)	START[24] Cohort 2 (N=12)	STR1VE-US[25] (N=22)	STR1VE-EU[26] (N=33) [b]	PNCR[20] two-copy *SMN2* cohort (N=23)	PNCR[20] three-copy *SMN2* cohort (N=81)
		18 months [c]	24 months [c]	24 months [d]	18 months [c]	18 months [c]	18 months [e]	24 months [e]
Sits without support	≥30 seconds BSID GM item #26	14 (100.0)	14 (93.3)	9 (75.0)	14 (63.6)	16 (48.5)	0	[redacted]
	≥10 secs WHO-MGRS	14 (100.0)	14 (93.3)	10 (83.3)	14 (63.6)	15 [f] (45.5)	[redacted]	[redacted]
Stands alone	≥3 seconds BSID GM item #40	11 (78.6)	15 (100.0)	2 (16.7)	1 (4.5)	1 (3.0)	0	19 (23.5)
Walks alone	≥5 steps with coordination and balance BSID GM item #43	9 (64.3)	14 (93.3)	2 (16.7)	1 (4.5)	1 (3.0)	0	17 (21.0)
Ability to maintain weight [g] without need for non-oral/mechanical feeding support at any visit		13 (92.9)	10 (66.7)	NR	14 (63.6)	15 [h] (65.2)	NR	NR
Event-free survival at age 14 months [i]		14 (100)	15 (100)	NR	20 (90.9)	31 (96.9) [j]	6 (26.1)	[redacted]

[a] Outcome definitions for motor milestones (sits without support, stands alone, walks alone) used in the PNCR[20] dataset differed to those used in the onasemnogene abeparvovec trials; see Table 15
[b] Exploratory motor milestones in the STR1VE-EU[26] study were assessed in the efficacy and safety completers population (N=33).
[c] Age at which the outcomes were measured up to
[d] Time after first dose of onasemnogene abeparvovec
[e] it is unclear whether data from PNCR[20] dataset were reported for patients at age 18 months and 24 months or whether patients in the PNCR[20] dataset were followed up for 18 months or 24 months from the time of enrolment
[f] sits without support (BSID GM item #26) was also reported for the STR1VE-EU[26] intention-to-treat population (n/N=14/32, 43.8%)
[g] Maintained weight consistent with age (above third percentile for age and gender as defined by WHO guidelines) consistent with the patient's age at the assessment
[h] Reported as a proportion of ability to thrive population (n=23); the ability to thrive was defined as: (1) The ability to tolerate thin or very thin liquids as demonstrated through a formal swallowing test with a result of normal swallow, functional swallow, or safe for swallowing; (2) did not receive nutrition through mechanical support (i.e., feeding tube); (3) maintained weight (> third percentile for age and gender as defined by WHO guidelines) consistent with the patient's age at the assessment
[i] Event-free survival defined as avoidance of both death and permanent ventilation through the 14 months of age visit. 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
[j] Assessed in the ITT population (N=32)
BSID GM=Bayley Scales of Infant and Toddler Development (Version 3) Gross Motor subtest; ITT=intention to treat; NR=not reported PNCR=Pediatric Neuromuscular Clinical Research; WHO-MGRS=World Health Organization Multicentre Growth Reference Study
Source: CS, Table 14 and Table 15 for SPR1NT; CS, Sections B.2.6.1.1 to B.2.6.1.3 and Novartis PNCR/NeuroNext Report,[20] Table 2 for PNCR; Al-Zaidy 2019[24] for START; supplementary appendices to most recent publications for STR1VE-US[25] and STR1VE-EU[26]

The EAG considers that the results show:

- outcomes are improved for patients who receive onasemnogene abeparvovec pre-symptomatically versus those who receive onasemnogene abeparvovec upon clinical diagnosis of type 1 SMA
- outcomes for patients treated with onasemnogene abeparvovec are much improved compared to outcomes for patients who only receive BSC; this difference is most marked when comparing those treated pre-symptomatically versus BSC as opposed to those treated symptomatically versus BSC
- in general, outcomes for patients with three copies of the *SMN2* gene treated with onasemnogene abeparvovec appear to be better than for those with two copies of the *SMN2* gene treated with onasemnogene abeparvovec
- [redacted]
- however, many more patients with three copies of the *SMN2* gene treated with onasemnogene abeparvovec achieved the motor milestones of walking and standing alone and were independent of ventilatory support at end of study than patients with three copies of the *SMN2* gene who received BSC.

The EAG cautions that simple naïve comparisons do not account for differences between study populations (see Section 4.4.1).

4.4.4 Additional evidence

The EAG also extracted additional outcome data for patients with types 2, 3 or 4 SMA who received BSC only from three studies;[4,6,33] the company used data from these studies to inform the company model (CS, Table 36 to Table 38):

- **relationship between *SMN2* copies and SMA type** (Table 2): Calucho 2018,[4] a cross-sectional study of 625 Spanish SMA patients alongside an analysis of 2836 patients studied worldwide by other studies in articles published from 1999 onwards
- **key motor milestones** (Table 18): Wadman 2018,[33] a cross-sectional study of 180 patients with SMA aged 1 year to 77.5 years enrolled in the Netherlands between September 2010 and August 2016; patients had a median SMA disease duration of 18 years (range: 0 years to 65.8 years)
- **survival and ventilation outcomes** (Table 19): Wijngaarde 2020,[6] a cross-sectional study of 307 patients with genetically confirmed SMA enrolled in the Netherlands between September 2010 and August 2014; median individual follow-up time was 18.3 years (range: 0.01 years to 81.9 years).

Table 18 Key motor milestone outcomes

Outcomes	SMA type					
	Type 1c (n=18)	Type 2a (n=44)	Type 2b (n=36)	Type 3a (n=40)	Type 3b (n=36)	Type 4 (n=6)
Sit independently [a]						
Acquired, n (%)	0 (0)	44 (100)	36 (100)	40 (100)	36 (100)	6 (100)
Lost, n (%) [b]	NA	16 (38)	3 (9)	7 (20)	0 (0)	0 (0)
Stand with support [a]						
Acquired, n (%)	NA	NA	36 (100)	40 (100)	36 (100)	6 (100)
Lost, n (%)	NA	NA	31 (89)	20 (59)	8 (24)	0 (0)
Walk with support [a]						
Acquired, n (%)	NA	NA	36 (100)	40 (100)	36 (100)	6 (100)
Lost, n (%)	NA	NA	21 (84)	22 (65)	10 (30)	0 (0)
Walk without support [a]						
Acquired, n (%)	NA	NA	NA	40 (95) [c]	36 (100)	6 (100)
Lost, n (%)	NA	NA	NA	23 (68)	16 (47)	0 (0)

[a] Criteria for achieving motor milestones were not explicitly stated
[b] Percentage of patients with available data for analysis
[c] n (%) as reported in the original publication; the EAG notes one of these values must be incorrect
NA=not applicable
Source: Wadman 2018,[33] supplementary appendix, Table S3

Table 19 Survival and ventilation outcomes by SMA type

Outcomes in economic model	SMA type						
	Type 1b (n=35)	Type 1c (n=32)	Type 2a (n=75)	Type 2b (n=51)	Type 3a (n=62)	Type 3b (n=40)	Type 4 (n=9)
Deaths, n (%)	27 (77.1)	10 (31.3)	2 (2.7) [c]	0 (0)	2 (3.2)	2 (5.0)	0 (0)
Reached survival endpoint, n (%) [a]	29 (82.9)	17 (53.1)	9 (12.0) [c]	0 (0)	3 (4.8)	2 (5.0)	0 (0)
Requirement for respiratory intervention, n (%) [b]	3 (8.6)	20 (62.5)	35 (46.7)	5 (9.8)	5 (8.1)	1 (2.5)	0 (0)

[a] The survival endpoint comprised both death and/or mechanical ventilation ≥16 hours per day
[b] Use of mechanical ventilation defined as daily use of any form and duration of non-invasive or invasive (tracheostomal) mechanical ventilation due to SMA-related respiratory insufficiency at the composite endpoint of survival. The authors note that the use of mechanical ventilation in patients with type 1a SMA and type 1b SMA was considered unethical in the Netherlands in the absence of any meaningful therapies to prolong survival and improve motor function (i.e., prior to the availability of nusinersen or clinical trials of *SMN1* gene therapy or small molecules)
[c] One patient who opted for euthanasia at the age of 46 years was not included
Source: Wijngaarde 2020,[6] Table 3 except median survival which is taken from the text of the paper

Key points:

- **relationship between *SMN2* copies and SMA type:** Calucho 2018[4] (see Section 2.2, Table 2) found that most babies with two copies of the *SMN2* gene who received BSC developed type 1 SMA, i.e., were not able to sit alone, and that most patients with three copies of the *SMN2* gene developed type 2 SMA, i.e., achieved sitting alone but did not achieve standing or walking alone. In the SPR1NT trial, patients (Table 17) with two and three copies of the *SMN2* gene who were treated with onasemnogene abeparvovec pre-symptomatically achieved motor milestones associated with type 3a and 3b SMA (Table 18), i.e., able to walk alone.
- **key motor milestones:** Wadman 2018 (Table 18) found that many patients who received BSC lost previously achieved milestones later in life. For standing and walking milestones, loss typically occurred within the first 10 years of life for patients with type 2 SMA,[33] within the first 16 years for patients with type 3a SMA and within the first 35 years for patients with type 3b SMA.[33] To date, no data on loss of motor milestones for patients treated with onasemnogene abeparvovec has been reported. Clinical advice to the EAG is that there remains some uncertainty about the long-term efficacy of onasemnogene abeparvovec in clinical practice as some deterioration may occur
- **survival and ventilation outcomes:** Wijngaarde 2020 (Table 19) found that most patients with type 1b SMA who received BSC had died or required mechanical ventilation ≥16 hours per day 'at the time they were surveyed'. However, meaningful comparisons cannot be made between data from Wijngaarde 2018 and the SPR1NT trial due to the different lengths of follow-up (18.3 years versus maximum 24 months, respectively).

4.5 Health-related quality of life

Patient and carer HRQoL data were not collected as part of the SPR1NT, START,24 STR1VE-US25 and STR1VE-EU26 trials.

4.6 Safety and tolerability results

The company has presented adverse event (AE) data from the SPR1NT trial (CS, Section B.2.10). The provided data includes the proportions of patients with treatment-emergent adverse events (TEAEs; CS, Table 16), serious adverse events (SAEs; CS, Table 16) and adverse events of special interest (AESIs; CS, Table 17). In summary, the data show:

- 29/29 (100%) patients experienced ≥1 TEAE, most frequently pyrexia (18/29, 62.1%) and upper respiratory tract infection (14/29, 48.3%)
- 18/29 (62.1%) patients experienced at least one TEAE that was considered by the investigator to be related to treatment with onasemnogene abeparvovec, most frequently increased aspartate aminotransferase, vomiting and rash
- 8/29 (24.1%) patients experienced [redacted] SAEs, none of which were considered by the investigator to be related to onasemnogene abeparvovec
- 15/29 (51.7%) patients experienced at least one AESI, categorised as hepatotoxicity (7/29, 24.1%), thrombocytopenia (5/29, 17.2%), cardiac AEs (5/29, 17.2%), sensory abnormalities suggestive of ganglionitis (4/29, 13.8%) and thrombotic microangiopathy (TMA) (2/29, 6.9%); two AESIs fell under the category of TMA, these were cases of thrombocytopenia and decreased platelet count
- no patient experienced a TEAE that resulted in death or trial discontinuation.

In addition, the EAG observes that:

- other treatment-related AEs reported at a similar frequency to increased aspartate aminotransferase [redacted], vomiting [redacted] and rash [redacted] were: [redacted] (CSR,[30] Table 14.3.11-2 and Table 14.3.1.11-3)
- the [redacted] SAEs were: [redacted] (CSR,[30] Section 12.2.2, Table 14.3.1-2 and Table 14.3.1.1-3)
- [redacted] patients experienced severe (Grade ≥3) TEAEs as follows: [redacted] (CSR,[30] Section 12.1.2.2, Table 14.3.12-2 and Table 14.3.1.12-3).

Based on the SPR1NT trial data presented in the CS, the EAG considers that AEs tended to be more frequent for patients with two copies of the *SMN2* gene than for patients with three copies of the *SMN2* gene.

Clinical advice to the EAG is that safety data from all onasemnogene abeparvovec trials provides more comprehensive information than safety data collected only from patients with pre-symptomatic SMA. The company provided safety data (CS, Table 21) for [redacted] patients enrolled in the LT-002 study[23] (23 May 2022 data cut-off) who originally received treatment in the SPR1NT, STR1VE-US,[25] STR1VE-EU[26] and STR1VE-AP[28] trials. In summary:

- [redacted] ([redacted]) patients had experienced a TEAE (CS, Table 21)
- [redacted] ([redacted]) patients had experienced an SAE of which [redacted] ([redacted]), a case of [redacted], was considered to be possibly related to treatment (company response to clarification question A4).

The EAG notes that safety data for 99 patients who received onasemnogene abeparvovec as a treatment for pre-symptomatic or symptomatic SMA at the recommended dose are reported in the EMA European Public Assessment Report.[39] The AEs most frequently reported from five open-label trials (the SPR1NT, START,[24] STR1VE-US,[25] STR1VE-EU[26] and STR1VE-AP[28] trials), which are described as very common (>10%) or common (>1%), are:

- increased hepatic enzyme (24/99, 24.2%)
- hepatotoxicity (9/99, 9.1%)
- vomiting (8/99, 8.1%)
- thrombocytopenia (6/99, 6.1%)
- increased troponin (5/99, 5.1%)
- pyrexia (5/99, 5.1%).

It is highlighted in the EPAR (Table 3) that outside clinical studies, including in the post-marketing setting, there have been reports of children:

- experiencing TMA (as opposed to AEs simply falling under the category of TMA, as in the SPR1NT trial) and
- developing signs and symptoms of acute liver failure.

More recently (11 August 2022),[40] two children, one in Russia and one in Kazakhstan, have been reported to have experienced acute liver failure resulting in death. These were reported as being the first deaths from liver failure from over 2,300 patients worldwide who have been treated with onasemnogene abeparvovec. The deaths were reported to occur between 5 and 6 weeks after onasemnogene abeparvovec infusion, and between 1 and 10 days after corticosteroid tapering occurred.

4.7 EAG clinical conclusions

The company has presented clinical effectiveness evidence from the phase III, open-label, single-arm, multi-centre SPRINT trial. This trial assessed the clinical effectiveness of onasemnogene abeparvovec as a treatment for patients with pre-symptomatic SMA and two (n=14)[21] or three copies (n=15)[22] of the *SMN2* gene. Follow-up was up to age 18 months for patients with two copies of the *SMN2* gene and up to age 24 months for patients with three copies of the *SMN2* gene. Data from the PNCR[20] dataset were used by the company to construct an external control cohort of patients with two (n=23) or three copies (n=81) of the *SMN2* gene who received BSC. The EAG considers that the SPR1NT trial results support the company conclusion that onasemnogene abeparvovec is a clinically effective treatment for babies with pre-symptomatic SMA and two or three copies of the *SMN2* gene.

However, the EAG considers that the relevant comparison for this appraisal is:

- providing onasemnogene abeparvovec pre-symptomatically to the pre-symptomatic patient

versus

- providing onasemnogene abeparvovec to the patient with a pre-symptomatic diagnosis only at symptom onset if the patient develops type 1 SMA and BSC if they develop type 2 or 3 SMA.

The EAG has presented naïve comparisons of data from the SPR1NT trial, the PNCR[20] dataset, and other trials[24-26] that evaluated the clinical effectiveness of onasemnogene abeparvovec as a treatment for patients with symptomatic SMA, as well as additional evidence[4,6,33] for patients with type 2, 3 and 4 SMA who received BSC. This evidence suggests that outcomes for patients treated pre-symptomatically with onasemnogene abeparvovec are better than outcomes for patients who receive:

- onasemnogene abeparvovec upon a clinical diagnosis of type 1 SMA
- BSC only for any type of SMA.

The EAG cautions that the simple naïve comparisons are not robust because:

- the different characteristics of the trials and study populations are not accounted for
- the trial and study populations are relatively small, which is expected given the rarity of SMA.

To date, the maximum follow-up for patients treated pre-symptomatically with onasemnogene abeparvovec is [redacted] post-dose and age [redacted] (ongoing LT-002[23] study). It is therefore not known whether patients treated pre-symptomatically with onasemnogene abeparvovec will maintain their achieved motor milestones for life.

5 COST EFFECTIVENESS EVIDENCE

This section provides a structured critique of the economic evidence submitted by the company in support of onasemnogene abeparvovec as a treatment option for patients with pre-symptomatic 5q SMA with a bi-allelic mutation in *SMN1* and up to three copies of *SMN2*. The two key components of the economic evidence presented in the CS are (i) a systematic review of the relevant literature and (ii) a report of the company's de novo economic evaluation. The company provided an electronic copy of their economic model, which was developed in Microsoft Excel.

5.1 Published cost effectiveness evidence

Summary details of the company economic burden systematic review are presented in the CS. Full details were provided to the EAG in response to clarification question C7.

5.1.1 Objective of the company's literature searches

The objective of the company review was to describe the current evidence relating to HRQoL, utilities, and economic burden of onasemnogene abeparvovec versus competing interventions for type 1, 2 and 3 SMA.

5.1.2 EAG critique of the company's literature review methods

A summary of the EAG's critique of the company's economic burden literature review methods is provided in Table 20.

Table 20 EAG appraisal of systematic review methods (cost effectiveness)

Review process	EAG response
Was the review question clearly defined in terms of population, interventions, comparators, outcomes and study designs?	Review question was very broad
Were appropriate sources searched?	Yes – CS, Appendix G
Was the timespan of the searches appropriate?	Yes – searches were conducted between March 2019 and February 2022
Were appropriate search terms used?	Yes
Were the eligibility criteria appropriate to the decision problem?	Yes – inclusion/exclusion criteria are provided in the main body of the CS (p84-85)
Was study selection applied by two or more reviewers independently?	Yes
Was data extracted by two or more reviewers independently?	Yes
Were appropriate criteria used to assess the quality of the primary studies?	Yes
Was the quality assessment conducted by two or more reviewers independently?	Yes
Were any relevant studies identified?	72 unique relevant studies were included, of which 31 were full economic evaluations

CS=company submission; NR=not reported
Source: LRiG in-house checklist

5.1.3 Company literature review results

The company economic burden systematic review identified 26 cost analyses, 31 cost effectiveness analyses (including 13 Health Technology Assessment documents), six studies reporting HRQoL outcomes and nine SLRs.

Results from the review indicated substantial heterogeneity in data sources and study design which made comparisons between studies difficult. Nevertheless, the literature suggested that SMA is associated with a substantial economic burden. The company considered that the cost effectiveness of novel therapies to treat SMA has not been conclusively established and that gaps in clinical evidence meant that long-term models had to use assumptions to extrapolate available (short-term) clinical effectiveness data. In summary, results suggested that treatment with onasemnogene abeparvovec and treatment with nusinersen led to higher QALYs than with BSC and, in all studies comparing treatment with onasemnogene abeparvovec versus nusinersen, treatment with onasemnogene abeparvovec was shown to be cost effective.

5.2 EAG comments on company literature review

The EAG considers that the searches carried out by the company were comprehensive. However, no details have been provided about how inclusion/exclusion criteria were applied, data extraction methods, or quality assessment.

The company reviewed a large number of studies. However, the combination of the very wide focus of the review, and provision of only narrative summaries for individual studies, means that it is difficult to identify the findings that are important to this appraisal.

5.3 EAG summary of the company's submitted economic evaluation

5.3.1 NICE Reference Case checklist and Drummond checklist

Table 21 NICE Reference Case checklist

Element of health technology assessment	Reference case	EAG comment on company submission
Defining the decision problem	The scope developed by NICE	Yes
Comparator(s)	As listed in the scope developed by NICE	Yes (post company clarification response)
Perspective on outcomes	All direct health effects, whether for patients or, when relevant, carers	Yes
Perspective on costs	NHS and PSS	Yes
Type of economic evaluation	Cost utility analysis with fully incremental analysis Cost comparison analysis	Cost utility analysis
Time horizon	Long enough to reflect all important differences in costs or outcomes between the technologies being compared	Yes
Synthesis of evidence on health effects	Based on systematic review	Narrative synthesis of health effects
Measuring and valuing health effects	Health effects should be expressed in QALYs. The EQ-5D is the preferred measure of health-related quality of life in adults	Yes
Source of data for measurement of health-related quality of life	Reported directly by patients or carers, or both	The company used values accepted during HST15[1]
Source of preference data for valuation of changes in health-related quality of life	Representative sample of the UK population	The company used values accepted during HST15[1]
Equity considerations	An additional QALY has the same weight regardless of the other characteristics of the individuals receiving the health benefit, except in specific circumstances	Yes
Evidence on resource use and costs	Costs should relate to NHS and PSS resources and should be valued using the prices relevant to the NHS and PSS	Yes
Discounting	The same annual rate for both costs and health effects (currently 3.5%)	Yes

EAG=External Assessment Group; EQ-5D=EuroQol-5 dimensions; HST=Highly Specialised Technology; NICE=National Institute for Health and Care Excellence PSS=personal social services; QALY=quality adjusted life year
Source: NICE Reference Case

Table 22 Critical appraisal checklist for the economic analysis completed by the EAG

Question	Critical appraisal	EAG comment
Was a well-defined question posed in answerable form?	Yes	
Was a comprehensive description of the competing alternatives given?	No	Up to date published micro-resource use data are not available
Was the effectiveness of the programme or services established?	Partial	Samples sizes are small
Were all the important and relevant costs and consequences for each alternative identified?	Yes	
Were costs and consequences measured accurately in appropriate physical units?	Partial	The methods used by the company to calculate care costs are unclear
Were the cost and consequences valued credibly?		
Were costs and consequences adjusted for differential timing?	Yes	
Was an incremental analysis of costs and consequences of alternatives performed?	Yes	
Was allowance made for uncertainty in the estimates of costs and consequences?	Yes	Scenario and sensitivity analyses were carried out
Did the presentation and discussion of study results include all issues of concern to users?	Yes	

EAG=External Assessment Group
Source: Drummond and Jefferson 1996[41] and EAG comment

5.3.2 Model structure

The company has provided a cohort Markov state-transition model. The structure of the model is shown in Figure 1. The health states differ based on:

- the highest motor function milestones achieved by the patient
- the need for PAV
- time to death.

Each health state captures the likely associated SMA symptoms and complications (full details provided in the CS, Table 24). Infant milestone achievement is used as a proxy for SMA severity (type) and prognosis. Costs and health outcomes for patients with type 1, 2 and 3 SMA are used as proxies for each health state:

- HS1 (non-sitter, PAV): type 1 SMA used as a proxy
- HS1 (non-sitter, no PAV): type 1 SMA used as a proxy
- HS2 (sitter): type 2 SMA used as a proxy
- HS3a (delayed walker): type 3 SMA used as a proxy
- HS3b (experiences later onset SMA): type 3 SMA used as a proxy.

The company highlights (CS, p92) other motor function milestones and ‘intra-health state’ clinical benefits are not formally modelled.

Transitions between model health states

If patients do not meet developmental milestones, they are moved to lower functioning health states. Lower functioning health states are associated with poorer survival, lower HRQoL, and higher healthcare resource use (HCRU) costs. Patients can only be in one health state at a time (mutually exclusive) and all patients must be in a health state (mutually exhaustive). Patients can progress to death from any health state. The data used to inform the model are observed and extrapolated data from the phase III SPR1NT trial and from the LT-002 study[23] (observed data up to 23 May 2022 data cut).

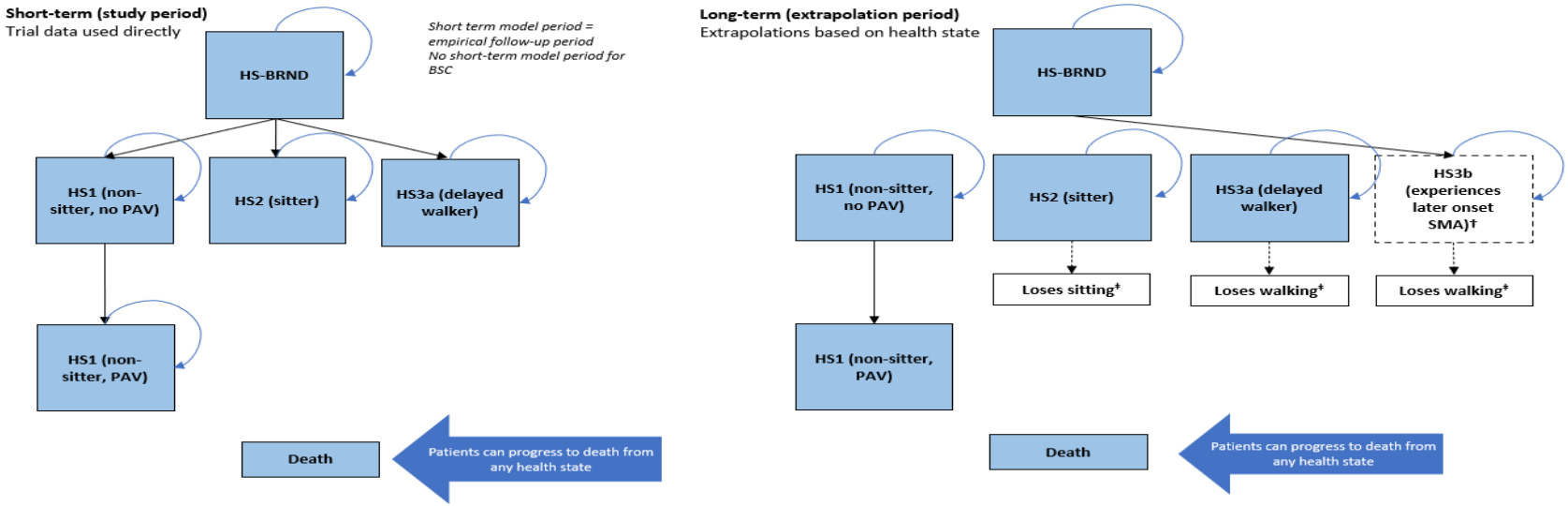
The onasemnogene abeparvovec arm of the model consists of two parts: 1) a short-term model, and 2) a long-term extrapolation model. After the short-term phase, which reflects the empirical period, patients enter the long-term extrapolation phase in the same health state that was assigned to them in the short-term model (based on motor function milestones achieved at the end of the SPR1NT trial follow-up period and the latest available interim data from the LT-002 study),[23] where they remain until death.

The BSC arm of the model only comprises a long-term extrapolation model as the SPR1NT trial was a single-arm trial. Patients in the BSC arm enter the long-term model in any of the SMA onset health states according to their highest achieved motor milestone. They accrue health state associated costs and utilities according to the average age at symptom onset; general age-related utilities and no costs are applied prior to symptom onset. Estimates for the proportions of untreated non-sitter patients requiring PAV (Table 23) were derived from the NeuroNext[20] study (*SMN2* gene two-copy sitter cohort data) and from Wijngaarde 2020[6] (type 1c SMA cohort used as a proxy for *SMN2* gene three-copy cohort).

Table 23 Proportion of untreated non-sitter patients requiring permanent assisted ventilation

Number of copies of the *SMN2* gene	Proportion of non-sitters receiving PAV	Age by which non-sitters received PAV
Two copies	12.5%	18.4 months
Three copies	21.9%	4.8 years

PAV=permanent assisted ventilation; SMN=survival motor neuron
Source: CS, Table 25



Health state	Criteria
HS-BRND	Individual sits and walks independently within normal motor development† + no gastrostomy + no PAV
HS1 (non-sitter, no PAV)	Individual does not sit independently and does not require permanent assisted ventilation
HS1 (non-sitter, PAV)	Individual does not sit independently and requires permanent assisted ventilation
HS2 (sitter)	Individual sits independently but does not walk independently
HS3a (delayed walker)	Individual sits and walks independently but outside normal motor development† i.e. delayed milestones indicative of late onset SMA
HS3b (experiences later onset SMA)*	Proportion of "Broad Range of Normal Development" projected to experience late onset SMA; only applicable to the BSC arm in the base case analysis

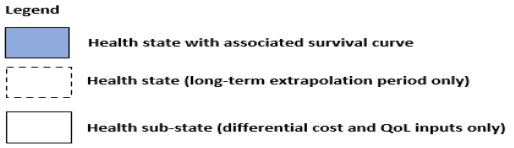


Figure 1 Structure of the company model

† Normal motor development: ages defined by user. Default milestone threshold inputs: 286 days for sitting, 547 days for walking. These are the WHO[34] 99th percentiles, upper 95% confidence limit. An allowance for intermittent visits of 21 days is added to account for first observed milestones at ages slightly above the threshold. This is to account for the fact that individuals will have first presented with the milestone before the clinically confirmed date. The allowance for intermittent visits applies to all treatment arms
‡ Only applicable to the BSC arm in the base case analysis
BRND=broad range of normal development; BSC=best supportive care; HS=health state; PAV=Permanent Assisted Ventilation; SMA=spinal muscular atrophy; WHO=World Health Organization
Source: CS, Figure 13

5.3.3 Population

The population considered by the company is patients with genetically confirmed, pre-symptomatic SMA with two or three copies of the *SMN2* gene who were aged ≤6 weeks (≤42 days) at the time of treatment. The company considered the population as a whole (the combined cohort) with results weighted by number of copies of the *SMN2* gene. The weighting was based on proportions of patients in seven (non-UK) studies[42-48] who had two or three copies of the *SMN2* gene (65.15% and 34.85% respectively). Separate analyses for the cohorts with two and three copies of the *SMN2* gene were also carried out.

5.3.4 Interventions and comparators

Intervention

The intervention is onasemnogene abeparvovec. Onasemnogene abeparvovec is administered once only by intravenous infusion via a syringe driver over approximately 60 minutes, at a dose of $1.1x10^{14}$ vg/kg.

Comparator

The comparator is BSC, defined as standard respiratory, gastrointestinal and nutritional care delivered via a multi-disciplinary team.

5.3.5 Perspective, time horizon and discounting

The company reported that the model perspective was that of the NHS and Personal Social Services. The model time horizon was 100 years, and the cycle length was 1 month (a half-cycle correction was applied).

Costs and outcomes were discounted at a rate of 3.5% per annum. The company highlighted (CS, p97) that during the HST15[1] evaluation, the NICE AC concluded that a 1.5% discount rate was applicable as onasemnogene abeparvovec had a high one-off cost, benefits were accrued over a lifetime, it was transformative (patients would die without treatment), and it offered the potential for substantial long-term gains that enable a high HRQoL for those patients with type 1 SMA and pre-symptomatic SMA with up to three copies of the *SMN2* gene. The company considered that all these criteria had also been met for this evaluation and carried out a scenario analysis using a discount rate of 1.5%.

5.3.6 Treatment effectiveness and extrapolation

Motor function milestone achievement

Onasemnogene abeparvovec

SPR1NT trial and LT-002[23] study (23 May 2022 data cut) motor milestone attainment data inputs are used directly in the model to capture the proportions of the patients treated with onasemnogene abeparvovec in the different health states. WHO-MGRS definitions for assessments of achieving sitting and walking (Table 24) were used as data relating to this definition were collected as part of the SPR1NT trial and as part of the LT-002[23] study.

Table 24 Proportions of SPR1NT trial patients who achieved sitting and walking without support

Patients achieving milestone	Sitting without support	Walking without support
	WHO-MGRS [a]	WHO-MGRS [b]
Two copies of the *SMN2* gene ([redacted])	[redacted]	[redacted]
Three copies of the *SMN2* gene (n=15)	100%	100%

[a] Child sits up straight with head erect for ≥10 seconds; child does not use hands or arms to balance body or support position
[b] 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.
[c] [redacted]

WHO-MGRS=World Health Organization Multicentre Growth Reference Study
Source: CS, Table 26 and Table 27

In the company model, patients accrue costs and QALYs from when they enter a health state. The time point at which patients enter a health state is estimated using the average age of symptom onset associated with SMA severity type (proxied by highest milestone achievement). Ages at symptom onset for SMA severity types 1 to 3 that are applied for each health state are provided in Table 25. The age thresholds used in the model were estimated using the WHO[34] thresholds for sitting and walking (upper 95% CI of the 99th percentile) plus an additional 21-day allowance to account for the fact that, in the SPR1NT trial, motor function assessments were only made at study visits, and the fact that it is inherently difficult to determine windows of development (Table 25).

Table 25 Age of SMA symptom onset in the company short- and long-term model periods

Model period	Health state	Age (months)
Short-term model	HS1 (non-sitter, no PAV)	6
	HS2 (sitter)	10
	HS3a (delayed walker)	18
Long-term model	HS3b (experiences later onset SMA) (age range)	3 to 24

HS=health state; PAV=permanent assisted ventilation; SMA=spinal muscular atrophy
Source: CS, Table 31

The time at which patients are transitioned to lower functioning health states is informed by the average age at symptom onset associated with the SMA severity type, proxied by their highest milestone achievement (CS, Section B.3.2.4). The proportions of patients in each health state by month are shown in Table 26.

Table 26 Proportions of patients in each health state

SMN2 copies	Month	HS-BRND	HS1 (non-sitter, PAV)	HS1 (non-sitter, no PAV)	HS2 (sitter)	HS3a (delayed walker)	Death
Two	0–9	100%	0	0	0	0	0
	10–17	93%	0	0	7%	0	0
	18–26	71%	0	0	7%	21%	0
Three	0–17	100%	0	0	0	0	0
	18–24	93%	0	0	0	7%	0

BRND=broad range of normal development; HS=health state; PAV=permanent assisted ventilation; *SMN2*=survival motor neuron 2
Source: CS, Table 32 and Table 33

Best supportive care

The distribution of patients receiving BSC between initial health states (Table 27) was informed by the distribution of patients across SMA severity type reported by Calucho 2018[4] (n=3,459), based on the proxy relationship between SMA severity type and motor milestone achievement that is outlined in the CS (Section B.3.2.4). Patients are allocated to health states from the first model cycle.

Table 27 Health state distributions of patients in the BSC arm of the company model

SMN2 copies	Health state	Proxy	Percentage
Two copies	HS1 (non-sitter, no PAV)	Type 1 SMA	79%
	HS2 (sitter)	Type 2 SMA	16%
	HS3a (delayed walker)	Type 3a SMA	5%
	HS3b (experiences later onset SMA)	Type 3b SMA	0%
Three copies	HS1 (non-sitter, no PAV)	Type 1 SMA	15%
	HS2 (sitter)	Type 2 SMA	54%
	HS3a (delayed walker)	Type 3a SMA	16%
	HS3b (experiences later onset SMA)	Type 3b SMA	15%

BSC=best supportive care; HS=health state; PAV=permanent assisted ventilation; SMA=spinal muscular atrophy; *SMN2*=survival motor neuron 2
Source: CS, Table 34 and Table 35

Motor function milestone loss

Onasemnogene abeparvovec

Patients treated with onasemnogene abeparvovec are assumed to maintain their achieved milestones. This assumption is in line with available study results (LT-001[49] and LT-002)[23] and the NICE AC preferred assumptions during HST15.[1]

Best supportive care

Milestone losses for patients in the BSC arm were estimated using data published by Wadman 2018[33] and are presented in Table 28. There is a lack of data available by copy number and therefore the same milestone loss data were applied for the *SMN2* gene two-copy and three-copy cohorts. The company assumed that milestone losses happened between the ages at which they were reported using a linear increase from minimum to maximum age.

Table 28 Proportions of patients in the BSC arm of the company model with two or three copies of the *SMN2* gene who experience milestone losses

Transition	Percentage
Infants from HS2 (sitter) who lose sitting	25%
Infants from HS3a (delayed walker) who lose independent walking	68%
Infants from HS3b (experiences later onset SMA) who lose independent walking	47%

HS=health state; SMA=spinal muscular atrophy
Source: CS, Table 37 and Table 38

Survival

Short-term model (onasemnogene abeparvovec only)

The data sources used to populate the short-term model are listed in Table 29. The EAG highlights that the SPR1NT trial provides 18-month follow-up data for the cohort of patients with two copies of the *SMN2* gene and 24-month follow-up data for the cohort of patients with three copies of the *SMN2* gene. No SPR1NT trial patients died, or received PAV.

Table 29 Sources of survival data used to populate the company short-term model (onasemnogene abeparvovec) for the *SMN2* gene two- and three-copy cohorts

Health state	Data source
HS1 (non-sitter, no PAV)	NA
HS2 (sitter)	Survival data from SPR1NT and LT-002[23] (23 May 2022 data cut)
HS3a (delayed walker)	General population survival (from 2018–2020 UK National Life tables)[50] data
HS3b (experiences later onset SMA)	NA – Given the assumption of no treated patients enter this health state (as development of symptoms later in life has not been observed in SPR1NT or LT-002)[23]
HS-BRND	General population survival (from 2018–2020 UK National Life tables)[50] data

BRND=broad range of normal development; HS=health state; NA=not applicable; SMA=spinal muscular atrophy; *SMN2*=survival motor neuron 2
Source: CS, Table 38

Long-term model

The company long term model was populated using data from natural history studies and UK National life table data (Table 30).

Table 30 Sources of survival data used to populate the company long-term model (BSC) for the *SMN2* two- and three-copy cohorts

Health state	*SMN2* two-copy cohort	*SMN2* three-copy cohort
HS1 (non-sitter, PAV)	Parametric survival curve fitted to longitudinal overall survival K-M data for non-invasive ventilation from the Italian natural history study[51]	
HS1 (non-sitter, no PAV)	Projected permanent ventilation-free survival using fitted parametric curve to observed data from the NeuroNext/Kolb 2017[3,20] study [a]	Projected permanent ventilation-free survival using fitted parametric curve to observed data from Wijngaarde 2020[6]
HS2 (sitter)	General population survival (from 2018–2020 UK National Life tables)[50] data adjusted by hazard ratio obtained from the best fitting parametric survival curve to the longitudinal overall survival K-M data from Wijngaarde 2020[6]	
HS3a (delayed walker)	General population survival (from 2018–2020 UK National Life tables)[50] data	
HS3b (experiences later onset SMA)	General population survival (from 2018–2020 UK National Life tables)[50] data	
HS-BRND	NA – patients on BSC never reside in the within BRND health state	

BSC=best supportive care; BRND=broad range of normal development; K-M=Kaplan-Meier; NA=not applicable; PAV=permanent assisted ventilation; SMA=spinal muscular atrophy; *SMN2*=survival motor neuron 2; UK=United Kingdom
[a] NeuroNext/Kolb 2017[3,20] cohort as reported in Novartis Gene Therapies external control database
Source: CS, Table 38

The company used standard methods to fit parametric distributions to available data. To avoid clinically implausible survival estimates (long tails), curves were terminated based on observed life expectancy, input from clinical expert opinion or HST15[27] 'ERG-preferred base case' assumptions. The parametric distributions used in the company base case are presented in Table 31.

Table 31 Distributions used to model survival (company base case)

Survival curve	Parametric curve	Survival limit
HS1 (non-sitter, PAV)	Exponential ('NRA' group) [a]	16 years
HS1 (non-sitter, no PAV)	Weibull – 2-copy cohort [b] Gamma – 3-copy cohort	4 years – two-copy cohort 100 years (lifetime time horizon) – three-copy cohort
HS2 (sitter)	Exponential	100 years (lifetime time horizon)
HS3a (delayed walker), HS3b (experiences later onset SMA) HS-BRND	National Life Tables[50]	100 years (lifetime time horizon)

BRND=broad range of normal development; BSC=best supportive care; SMA=spinal muscular atrophy
[a] Defined as continuous non-invasive respiratory muscle aid, including non-invasive ventilation; and mechanically assisted cough ('NRA' group in publication)[51]
[b] In HST15 (type 1 SMA) economic model submitted to NICE in the UK, the ERG-preferred base case used the Weibull distribution for the non-sitter health state. This preference is reflected in the base case of this model when using the NeuroNext[20] data source
Source: CS, Table 40

5.3.7 Health-related quality of life

The company carried out a SLR using the following criteria to select base case utility values:

- those considered most appropriate by the US ICER independent assessment group[52] and/or the clinical experts advising the HST15 ERG report[27]
- conformed to the NHS Reference Case
- deemed plausible by a UK Advisory Board
- parent-proxy (rather than healthcare professional-proxy) EQ-5D values.

The company base case utility values are presented in Table 32.

Table 32 Company model base case utility values

Health state	Utility value	Reference
HS1 (non-sitter, PAV)	0	Interim ERG report; Edwards 2020[53] Thompson 2017[54]
HS1 (non-sitter, no PAV) and HS2 (sitter, loses sitting)	0.190	
HS2 (sitter)	0.600	Tappenden 2018[55]
HS3a (delayed walker)	General population	Ara and Brazier 2010[56]
HS3b (experiences later onset SMA)		
HS3a (delayed walker, loses walking) and HS3b (experiences later onset SMA, loses walking)	0.774	Thompson 2017[54]
HS-BRND	General population	Ara and Brazier 2010[56]

BRND=broad range of normal development; ERG=Evidence Review Group; PAV=permanent assisted ventilation; SMA=spinal muscular atrophy
Source: CS, Table 42

In the company model, age and gender adjustments were applied to utility values to reflect decreases in HRQoL seen over time and to ensure model values did not exceed general population values. The Ara and Brazier[56] approach was used to implement this adjustment (CS, Table 43).

Disutilities associated with AEs were not included in the company model. Additional 'on-treatment utilities' were not applied for patients in the onasemnogene abeparvovec arm, although these utility increments were applied in the US ICER[52] and accepted during HST15.[1]

5.3.8 Resources and costs

Cost of onasemnogene abeparvovec

Onasemnogene abeparvovec is available to the NHS at a confidential PAS price. The company estimated that the administration cost was £3,139. This administrative cost is the weighted average of NHS Reference Costs 2019-20[57] health care resource codes relating to paediatric nervous system disorders and cerebral degenerations or miscellaneous disorders of nervous system (EL- PR01A-E and EL - AA25C-G), inflated to 2021 prices.[58]

Health state costs

The company sourced health state costs from NHS Reference Costs 2019-2020,[57] the NHS Business Services Authority prescription cost analysis 2021/22[59] and the literature. Where appropriate, costs were inflated to 2021 prices using Personal Social Services Resource Use (PSSRU) National Health Service Cost Inflation Index (NHSCII).[58] The health state costs used in the company model are presented in Table 33 with further details provided in Appendix 3, Section 9.3, Table 48.

Table 33 Company model health state costs

Health state	SMA proxy applied	Total value
HS1 (non-sitter, PAV)	Type 1 SMA	£283,710
HS1 (non-sitter, no PAV)	Type 1 SMA	£112,500
HS2 (sitter)	Type 2 SMA	£67,567
HS2 (sitter, loses sitting)	Type 1 SMA	£112,500
HS3a (delayed walker)	Type 3 SMA	£8,333
HS3a (delayed walker, loses walking)	Type 2 SMA	£67,567
HS3b (experiences later onset SMA)	Type 3 SMA	£8,333
HS3b (experiences later onset SMA, loses walking)	Type 2 SMA	£67,567
HS-BRND	Type 3 SMA	£8,333

BRND=broad range of normal development; PAV=permanent assisted ventilation; SMA=spinal muscular atrophy
Source: CS, Table 45

Adverse events

The costs associated with AEs were not included in the company model due to difficulties separating AEs due to treatment from SMA complications.

5.4 Additional analyses

In response to a concern raised by the EAG in the clarification letter, the company provided model cost effectiveness results for the scenario in which onasemnogene abeparvovec is provided at symptom onset to patients with a pre-symptomatic SMA diagnosis if the patient develops type 1 SMA and BSC if the patient develops type 2 or type 3 SMA.

5.4.1 Quantifying outcomes

The probabilities (by number of copies of the *SMN2* gene) of a patient untreated pre-symptomatically will develop type 1, type 2 or type 3 SMA are key model inputs (Table 34).

Table 34 Probabilities of developing different SMA types

SMA type	Probability		Highest motor milestone achievement
	Two copies of the *SMN2* gene	Three copies of the *SMN2* gene	
Type 1	79%	15%	Non-sitter
Type 2	16%	54%	Sitter
Type 3	5%	31%	Delayed walker/experience late SMA onset [a]

SMA=spinal muscular atrophy; *SMN2*=survivor motor neuron 2
[a] Calucho 2018[4] data suggest that patients with two copies of the *SMN2* gene and type 3 SMA will all be delayed walkers but that patients with three copies of the *SMN2* gene will have an equal chance of being a delayed walker or to experience late SMA onset
Source: Company response to clarification, Table 1

Patients (not treated pre-symptomatically) who are treated with onasemnogene abeparvovec on symptom onset

The company's short-term model (up to 60 months of age) is informed by pooled clinical trial data for patents with type 1 SMA and two copies of the *SMN2* gene from the START,[24] STR1VE-US[25] and STR1VE-EU[26] trials. All patients enter the long-term model in the 'non-sitter' health state.

In the absence of data demonstrating the efficacy of onasemnogene abeparvovec for treating patients with type 1 SMA who have three copies of the *SMN2* gene, the company assumed that the efficacy of onasemnogene abeparvovec was the same as for patients with type 1 SMA and either two or three copies of the *SMN2* gene.

From the age of 61 months onwards, patients enter the long-term model until death. They are assumed to stay in the health state they reached at the end of the short-term model for the duration of long-term model time horizon. Survival was modelled using parametric curves for each SMA severity type; the curves were selected based on data from natural history studies.[3,6,20]

Patients (not treated pre-symptomatically) who develop type 2 and type 3 SMA and remain on BSC

The company modelled outcomes for patients who develop type 2 SMA by assuming that all patients in the BSC arm were sitters.

The company modelled outcomes for patients who develop type 3 SMA by assuming that all patients in the BSC arm were either delayed walkers or experienced late SMA onset. Based on epidemiological evidence, all patients with type 3 SMA and two copies of the *SNM2* gene were assumed to be delayed walkers; 50% of patients with type 3 SMA and three copies of

the *SMN2* gene were assumed to be delayed walkers and the other 50% were assumed to experience late SMA onset.

The company estimated survival for sitters by adjusting general UK population data[50] using a hazard ratio obtained by comparing survival statistics in the general population with survival of the population of sitters.[6] Survival for delayed walkers and for those who experience late SMA onset was assumed to be the same as that of the general population.

6 COST EFFECTIVENESS RESULTS

6.1 Base case analysis

Company base case results for the combined cohort of patients with two and three copies of the *SMN2* gene (65.15%:34.85%) who are treated pre-symptomatically with onasemnogene abeparvovec are provided in the main body of the CS; results by *SMN2* gene copy number are provided in CS, Appendix J.

Base case company analysis results (reproduced in Table 35) show that compared with BSC, and using the PAS price of onasemnogene abeparvovec, treatment with onasemnogene abeparvovec generates [redacted] more QALYs at an increased cost of [redacted], leading to an ICER of [redacted] per QALY gained. The base case ICERs for the patients with two and three copies of the *SMN2 gene* are [redacted] and [redacted] per QALY gained respectively.

Table 35 Base case results for the combined cohort of patients with two and three copies of the *SMN2* gene who are treated pre-symptomatically with onasemnogene abeparvovec (PAS price)

Technology	Total			Incremental			ICER (£/QALY)
	Costs	Life years	QALY	Costs	Life years	QALY	
BSC	£882,564	[redacted]	[redacted]	-	-	-	-
Onasemnogene abeparvovec	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

BSC=best supportive care; ICER=incremental cost effectiveness ratio; PAS=Patient Access Scheme; QALY=quality adjusted life year; *SMN2*=survival motor neuron 2
Source: CS, Table 49

The company notes (clarification response, p15) that pre-symptomatic treatment with onasemnogene abeparvovec provides [redacted] more (undiscounted) QALYs than treatment with BSC and, therefore, the maximum weighting of three applies to the standard willingness-to-pay (WTP) threshold of £100,000 per QALY. Using a weighting of three results in a WTP threshold value of [redacted] per QALY. Incremental net monetary benefit results are shown in Table 36.

Table 36 Incremental net health benefit and incremental net monetary benefit results for the combined cohort with two and three copies of the *SMN2* gene who are treated pre-symptomatically with onasemnogene abeparvovec (PAS price)

	Combined cohort
Incremental net health benefit (undiscounted QALY)	49.9
Incremental net monetary benefit at £100,000/QALY	[redacted]
Incremental net monetary benefit at £300,000/QALY	[redacted]

PAS=Patient Access Scheme; QALY=quality adjusted life year; *SMN2*=survival motor neuron 2
Source: Company response to clarification, Table 7

6.2 Probabilistic sensitivity analysis

The company assigned distributions to parameters according to standard practice (see CS, Table 46) and ran 1,000 iterations of the model. Company probabilistic sensitivity analysis results are presented in Table 37.

Table 37 PSA results from 1,000 simulations: combined cohort of patients (onasemnogene abeparvovec PAS discounted price)

	Costs		Life years		QALYs		ICER/QALY	
	Min	Max	Min	Max	Min	Max	Min	Max
BSC	£442,806	£1,455,106	[redacted]	[redacted]	[redacted]	[redacted]		
Onasemnogene abeparvovec [a]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

BSC=best supportive care; ICER=incremental cost effectiveness ratio; PAS=Patient Access Scheme; PSA=probabilistic sensitivity analysis; QALY=quality adjusted life years

[a] Variation between the minimum and maximum life years for onasemnogene abeparvovec is minimal as the most patients in the onasemnogene abeparvovec arm are in the HS3a (delayed walker) and HS-BRND health states, in which patients are assumed to follow the survival of the general population. For the general population survival estimates, no uncertainty is applied in the model.

Source: CS, Table 51

6.3 Deterministic sensitivity analyses

The company varied parameter values by ±20%. The model parameters that had the largest impact on results were:

- onasemnogene abeparvovec acquisition costs
- the proportion of patients with two copies of the *SMN2* gene in the population
- the proportion of patients treated with BSC with two copies of the *SMN2* gene who reside in the HS1 (non-sitter) health state
- the SMA care costs for patients in the HS2 (sitter) health state.

For the combined cohort, the parameter that, when varied, had the biggest effect on cost effectiveness results was the cost of onasemnogene abeparvovec; using the PAS price for onasemnogene abeparvovec, the ICER per QALY gained changed by approximately plus or minus £[redacted].

The parameter that, when varied, had the largest impact on the cost effectiveness results generated for the cohorts with two and three copies of the *SMN2* gene was also the cost of onasemnogene abeparvovec.

6.4 Scenario analyses

The company also carried out 16 scenario analyses. The five scenarios that had the greatest effect on company base case results are presented in Table 38.

Table 38 Scenario analyses that had the largest effect on the company base case results: combined cohort of patients (onasemnogene abeparvovec PAS discounted price)

Scenario	Arm	Total		Incremental		ICER (£/QALY)
		Costs	QALYs	Costs	QALYs	
Base case results	BSC	£882,564	[redacted]	-	-	-
	Onasemnogene abeparvovec	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Scenarios						
Costs and effects discounted at 0%	BSC	£2,341,482	[redacted]	-	-	-
	Onasemnogene abeparvovec	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Costs and effects discounted at 1.5%	BSC	£1,428,660	[redacted]	-	-	-
	Onasemnogene abeparvovec	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Costs and effects discounted at 5%	BSC	£678,696	[redacted]	-	-	-
	Onasemnogene abeparvovec	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
NICE TA588[16] - RWE values for SMA care costs	BSC	£1,012,284	[redacted]	-	-	-
	Onasemnogene abeparvovec	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
No cost in HS-BRND health state	BSC	£872,941	[redacted]	-	-	-
	Onasemnogene abeparvovec	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

BRND=broad range of normal development; BSC=best supportive care; HS=health state; ICER=incremental cost effectiveness ratio; NICE=National Institute for Health and Care Excellence; PAS=Patient Access Scheme; QALY=quality-adjusted life year; RWE=real world evidence; TA=technology appraisal
Source: CS, Table 54

6.5 Additional analysis results provided by the company at clarification

Company results for the combined cohort show that providing onasemnogene abeparvovec pre-symptomatically to patients with two and three copies of the *SMN2* gene dominates the alternative strategy of providing onasemnogene abeparvovec at symptom onset to patients when, and if, the patient develops type 1 SMA and providing BSC if the patient develops type 2 or type 3 SMA (Table 39).

Table 39 Combined cohort of patients (onasemnogene abeparvovec PAS discounted price)

Technology	Total			Incremental			ICER (£/QALY)
	Costs	Life years	QALY	Costs	Life years	QALY	
OA as pre-symptomatic treatment	[redacted]	[redacted]	[redacted]	-	-	-	-
OA at symptom-onset if patient develops type 1 SMA and BSC otherwise	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	OA as pre-symptomatic treatment is dominant

BSC=best supportive care; ICER=incremental cost effectiveness ratio; OA=onasemnogene abeparvovec; PAS=Patient Access Scheme; QALY=quality-adjusted life year; SMA=spinal muscular atrophy
Source: Company response to clarification, Table 4

6.6 Model validation and face validity check

Face validation of the conceptual model was performed by clinical experts. The validity of the model was assessed through examination of Markov traces and by comparing modelled mortality and disease progression probabilities with the data used to populate the model. The company also undertook testing by implementing extreme parameter values.

7 EAG CRITIQUE OF COMPANY ECONOMIC MODEL

7.1 Introduction

7.1.1 Comparators

In the CS, the company provided results for the comparison of pre-symptomatic delivery of onasemnogene abeparvovec versus BSC for patients with two and three copies of the *SMN2* gene. However, following HST15,[1] onasemnogene abeparvovec was recommended as an option for treating SMA with a bi-allelic mutation in the *SMN1* gene and a clinical diagnosis of type 1 SMA in babies, only if:

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

It is only recommended for these groups if:

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

Thus, the EAG considers that onasemnogene abeparvovec treatment for patients with pre-symptomatic SMA and up to three copies of the *SMN2* gene should be compared with:

- onasemnogene abeparvovec provided to the patient with a pre-symptomatic diagnosis only at symptom onset if the patient develops type 1 SMA and BSC if they develop type 2 or 3 SMA.

The company clarification response included an updated model that generated results for this comparison.

7.1.2 Population

Company base case results have been generated for the combined cohort of patients with two and three copies of the *SMN2* gene; however, the company model is able to generate results separately for patients with two copies and those with three copies of the *SMN2* gene. The EAG considers that cost effectiveness decisions should be made depending on *SMN2* gene copy number because:

- outcomes (mortality, HRQoL and costs) differ substantially by number of copies of the *SMN2* gene. Patients with two copies of the *SMN2* gene have a higher likelihood of having type 1 SMA than patients with three copies of the *SMN2* gene. Further, patients with type 1 SMA with three copies of the *SMN2* gene tend to have longer expected survival than those with two copies of the *SMN2* gene (CS, B.3.3.3, Figure 15 and Figure 16)
- it is possible to differentiate between patients with two copies of the *SMN2* gene and those with three copies of the *SMN2* gene
- approximately 85% of patients with three copies of the *SMN2* gene have type 2 SMA (54.3%) or type 3 SMA (30.9%), not type 1 SMA (14.7%), and so are not eligible for

treatment with onasemnogene abeparvovec following the development of symptoms based on the recommendations made by NICE in HST15.[1]

7.1.3 EAG model checks

The EAG has undertaken a comprehensive check of the company model and is satisfied that the model algorithms are accurate. The EAG is satisfied that the issues described in Table 40 are of no importance in terms of drawing conclusions from model cost effectiveness results.

Table 40 Elements of the company model that do not raise concerns for the EAG

Element	EAG comment
Population	The EAG considers that decisions should be made separately for patients with two copies of the *SMN2* gene and patients with three copies of the *SMN2* gene, rather than for the combined cohort of patients with two and three copies of the *SMN2* gene. The company model allows results to be generated by copy number
Modelled treatment pathway(s)	The company has provided aggregated results, and results disaggregated by number of copies of the *SMN2* gene (two copies and three copies), for the comparison of pre-symptomatic treatment with onasemnogene abeparvovec versus: • BSC • onasemnogene abeparvovec provided to the patient with a pre-symptomatic diagnosis only at symptom onset if the patient develops type 1 SMA and BSC if they develop type 2 or 3 SMA
Utility values	The health state utility values used in the company model are those that were used to generate HST15[1] cost effectiveness results. The NICE AC[1] considered that these values were uncertain but recognised that identifying robust utility values for young children was problematic In the company model, patients who receive PAV are assigned a utility value of zero, which appears pessimistic. The EAG explored the impact of setting the utility value for these patients to 0.19, the utility value assigned to patients in the HS1 non-sitter, no PAV health state. The effect of using this parameter value was to change the ICER per QALY gained for the comparison of OA given pre-symptomatically versus OA given when symptoms emerge by less than 1%
Survival	The EAG is satisfied with the company approach to modelling survival. The company's choices of parametric distributions used to represent survival for patients who did not achieve a BRND may be optimistic and, therefore, company OA QALY gains are likely to be underestimated in the company base case
Non-sitters treated with onasemnogene abeparvovec on emergence of symptoms	The company has assumed that non-sitters do not survive beyond 60 months. The long-term model, therefore, does not include any non-sitters and the [redacted]% of patients who are in the non-sitting health state at 59 months are moved to the 'dead' health state at 60 months It is likely that some non-sitters may live longer than 60 months. However, due to the low utility value (0.19) and high annual costs ([redacted]) for patients in this health state, if patients remain alive beyond 60 months it would only improve the cost effectiveness of OA given pre-symptomatically versus OA given when symptoms emerge
Definitions	<u>Walking</u> There are differences between the definitions of walking used in the two sources of data used to populate the company model (STR1VE-US[25] and STR1VE-EU[26]). In both trials outcomes were assessed using BSID definitions; however, the company has pooled the STR1VE-US[25] trial 'walking alone' data and the STR1VE-EU[26] trial 'walking assisted' data. Populating the model using pooled data collected using the same definition had negligible impact on company base case cost effectiveness results <u>Sitting</u> The company model is populated with sitting for 5 seconds outcome data from the START[24] trial and sitting for 30 seconds outcome data from the STR1VE-EU[26] and STR1VE-US[25] trials. These data are pooled to estimate the proportion of patients who, following the development of symptoms, can sit after being treated with onasemnogene abeparvovec. The EAG tested the impact on cost effectiveness results of using pooled sitting for 30 seconds outcome data from the START,[24] STR1VE-US[25] and STR1VE-EU[26] data. This change had a negligible impact on cost effectiveness results

Delayed walker: onasemnogene abeparvovec model arm	Data presented in the CS (Table 27) shows that all patients in the SPR1NT trial who had three copies of *the SMN2* gene achieved the 'walking without support' milestone. However not all patients with three copies of the *SMN2* gene are recorded as achieving 'walking without support' (CS, Table 15). The company explained that although one patient was observed walking on a video call, as the call was not recorded, the observation could not be independently verified and therefore did not meet the SPR1NT trial protocol criteria. This patient is modelled as a 'delayed walker'. The EAG considers that this is a conservative approach
Costs	The EAG is satisfied that the company has used appropriate approaches to estimate drug and health care costs
Discounting	The company has carried out discounting correctly. The EAG agrees with the company that a discount rate of 1.5% is likely to be appropriate
PSA	The EAG has checked that PSA parameter values are reasonable and has re-run the PSA. The EAG considers that the company PSAs have been carried out appropriately
QALY weighting	The EAG is satisfied that, for the comparison of onasemnogene abeparvovec given pre-symptomatically versus BSC, a QALY weighting of 3 is appropriate As the EAG is satisfied that for the comparison of onasemnogene abeparvovec given pre-symptomatically dominates onasemnogene abeparvovec given to patients with type 1 SMA patients on symptom development and BSC otherwise, a QALY weighting is not necessary
Stress testing - extreme values	The company model generates appropriate results when extreme parameter values are used

AC=Appraisal Committee; BSC=best supportive care; BRND=broad range of normal development; BSID=Bayley Scales of Infant and Toddler development; CS=company submission; EAG=External Assessment Group; HST=Highly Specialised Technology; ICER=incremental cost effectiveness ratio; NICE=National Institute for Health and Care Excellence; PAV=permanent assisted ventilation; PSA=probabilistic sensitivity analysis; QALY=quality adjusted life year
Source: EAG comment

The EAG is satisfied that the cost effectiveness results provided by the company, for providing onasemnogene abeparvovec pre-symptomatically versus BSC and for providing onasemnogene abeparvovec pre-symptomatically versus providing onasemnogene abeparvovec only at symptom onset if the patient develops type 1 SMA and BSC for all other SMA types, are robust and suitable for decision making. The EAG considers that the assumptions used by the company to model survival for patients who do not achieve broad range of normal development (BRND) milestones may underestimate the size of the QALY gains associated with pre-symptomatic onasemnogene abeparvovec treatment. The EAG has explored two areas of uncertainty, namely loss of milestones achieved and social care costs; these are explored in Section 7.2.

7.2 Exploratory analyses undertaken by the EAG

7.2.1 Loss of milestones previously achieved (Scenario 1)

In the company model, patients in the onasemnogene abeparvovec arm are modelled to maintain the best milestone they achieved whilst, over time, patients in the BSC arm may lose milestones previously achieved.

Milestone data are available from the SPR1NT trial for a maximum follow-up of 24 months, and from the phase I START[24] trial for 6.2 years. These data show no loss of milestones

previously achieved for patients treated with onasemnogene abeparvovec. This means that there is still uncertainty whether, over a lifetime, patients treated with OA would lose a previously achieved milestone. To explore the impact of this uncertainty on company cost effectiveness results, the EAG has run a scenario applying the company base case loss of milestone assumptions for the BSC arm of the long-term model to patients in the OA arm of the long-term model. These are:

- BRND health state: no loss of milestones achieved
- Non-sitter health states (PAV and no PAV): no loss of milestones achieved (as no milestone achieved)
- All other health states: lose milestones in the same proportions and over the same time frame as for patients in the BSC arm.

The EAG's revised cost effectiveness results are presented in Section 7.3.

7.2.2 Social care costs (Scenario 2)

In the company model, social care costs have been calculated using resource use estimates suggested by Noyes 2006.[60] The company provided further information about costs in response to clarification question B1. However, it is not clear how the company calculated social care costs as the value in the model does not match the costs presented in the publication by Noyes 2006.[60]

In the company model, social care costs account for the largest proportion of total costs after hospitalisations. To test the impact of these costs on company cost effectiveness results, the EAG has carried out a scenario in which the costs of social care are set to zero. The EAG considers that patients with SMA are likely to rely heavily on social care and accepts that this is an extreme scenario; however, it has been undertaken to highlight whether reducing social care costs would change the conclusions that can be drawn from model cost effectiveness results.

The EAG's revised cost effectiveness results are presented in Section 7.3.

7.3 Impact on the ICER per QALY gained of additional clinical and economic analyses presented by the EAG

The EAG has generated cost effectiveness results separately for patients with two and three copies of the *SMN2* gene. These results have been generated for the comparison of pre-symptomatic treatment with onasemnogene abeparvovec versus two comparators:

- BSC
- onasemnogene abeparvovec provided to the patient with a pre-symptomatic diagnosis only at symptom onset if the patient develops type 1 SMA and BSC if they develop type 2 or 3 SMA.

Using the model provided as part of the company response to clarification, the EAG has run two scenario analyses:

- Scenario 1: milestone loss is equal to that of patients in the BSC arm for patients who did not reach a broad range of normal development

  Scenario 2: social care costs set to zero.

Details of how to implement the EAG scenarios in the updated company model are presented in Appendix 4, Section 9.4, Table 49.

7.3.1 EAG scenario analysis results for pre-symptomatic treatment with onasemnogene abeparvovec versus BSC

Table 41 EAG scenarios: patients with **two copies** of the *SMN2* gene (PAS price for onasemnogene abeparvovec)

EAG scenarios	Pre-symptomatic OA		BSC		Incremental		ICER
	Cost	QALYs	Cost	QALYs	Cost	QALYs	£/QALY
A1: Company base case (deterministic)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Scenario 1: Milestone loss is equal to that of patients in the BSC arm	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Scenario 2: Social care costs set to zero	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

BSC=best supportive care; EAG=External Assessment Group; ICER=incremental cost effectiveness ratio; OA=onasemnogene abeparvovec; PAS=Patient Access Scheme; QALY=quality adjusted life year

Table 42 EAG scenarios: patients with **three copies** of the *SMN2* gene (PAS price for onasemnogene abeparvovec)

EAG scenarios	Pre-symptomatic OA		BSC		Incremental		ICER
	Cost	QALYs	Cost	QALYs	Cost	QALYs	£/QALY
A1: Company base case (deterministic)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Scenario 1: Milestone loss is equal to that of patients in the BSC arm	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Scenario 2: Social care costs set to zero	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

BSC=best supportive care; EAG=External Assessment Group; ICER=incremental cost effectiveness ratio; OA=onasemnogene abeparvovec; PAS=Patient Access Scheme; QALY=quality adjusted life year

7.3.2 EAG scenario analysis results for pre-symptomatic treatment with onasemnogene abeparvovec versus onasemnogene abeparvovec administered on symptom development for patients with type 1 SMA and BSC for all other patients

Table 43 EAG scenarios: patients with **two copies** of the *SMN2* gene (PAS price for onasemnogene abeparvovec)

EAG scenarios	Pre-symptomatic OA		OA on symptom development/BSC		Incremental		ICER
	Cost	QALYs	Cost	QALYs	Cost	QALYs	£/QALY
A1: Company base case (deterministic)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Scenario 1: Milestone loss is equal to that of patients in the BSC arm	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Scenario 2: Social care costs set to zero	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

BSC=best supportive care; EAG=External Assessment Group; ICER=incremental cost effectiveness ratio; OA=onasemnogene abeparvovec; PAS=Patient Access Scheme; QALY=quality adjusted life year

Table 44 EAG scenarios: patients with **three copies** of the *SMN2* gene (PAS price for onasemnogene abeparvovec)

EAG scenarios	Pre-symptomatic OA		OA on symptom development/BSC		Incremental		ICER
	Cost	QALYs	Cost	QALYs	Cost	QALYs	£/QALY
A1: Company base case (deterministic)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Scenario 1: Milestone loss is equal to that of patients in the BSC arm	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Scenario 2: Social care costs set to zero	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

BSC=best supportive care; EAG=External Assessment Group; ICER=incremental cost effectiveness ratio; OA=onasemnogene abeparvovec; PAS=Patient Access Scheme; QALY=quality adjusted life year

7.4 EAG summary of cost effectiveness results and conclusions

The EAG is satisfied that the cost effectiveness results provided by the company, for providing onasemnogene abeparvovec pre-symptomatically versus BSC and for providing onasemnogene abeparvovec pre-symptomatically versus providing onasemnogene abeparvovec only at symptom onset if the patient develops type 1 SMA and BSC for all other SMA types, are robust and suitable for decision making. Although uncertainty remains around long-term efficacy of onasemnogene abeparvovec and the costs associated with social care provision to children with SMA, these uncertainties are unlikely to change the conclusions that could be drawn on the cost effectiveness of onasemnogene abeparvovec given pre-symptomatically.

For the comparison of pre-symptomatic onasemnogene abeparvovec versus BSC, the ICER per QALY gained is likely to be <£100,000.

For the comparison of pre-symptomatic onasemnogene abeparvovec versus onasemnogene abeparvovec on development of symptoms of type 1 SMA and BSC for all other types of SMA, pre-symptomatic treatment with onasemnogene abeparvovec is likely to be dominant.

The EAG highlights that model results show that patients with two copies of the *SMN2* gene and patients with three copies of the *SMN2* gene have substantially different QALYs and BSC costs. Patients with two copies of the *SMN2* gene tend to have poorer HRQoL, lower life-expectancy and therefore substantially lower QALYs than patients with three copies of the *SMN2* gene. However, the lower life expectancy of patients with two copies of the *SMN2* gene compared to patients with three copies of the *SMN2* gene results in BSC costs for patients with two copies of the *SMN2* gene being lower than BSC costs for patients with three copies of the *SMN2* gene.

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9 APPENDICES

9.1 Appendix 1 – EAG assessment of the statistical approaches used in the SPR1NT trial

Table 45 EAG assessment of the statistical approaches used in the SPR1NT trial

Item	EAG assessment	Statistical approach and EAG comments
Were all analysis populations clearly defined and pre-specified?	Yes	All efficacy analyses were carried out using data from the ITT population (all enrolled patients with bi-allelic *SMN1* gene deletions and two or three copies of the *SMN2* gene without the *SMN2* gene modifier mutation c.859G>C who received onasemnogene abeparvovec). Safety analyses were carried out using data from the safety population (all patients who received an onasemnogene abeparvovec injection, including patients with *SMN1* gene point mutations and patients who were positive for the *SMN2* gene modifier mutation c.859G>C). The EAG is satisfied that these populations were clearly defined and pre-specified in the TSAP (p33)
Was an appropriate sample size calculation pre-specified?	Yes	Study sample size calculations for the cohort of patients with two copies of the *SMN2* gene and the cohort of patients with three copies of the *SMN2* gene were pre-specified in the TSAP (pp23-24); the EAG is satisfied that these sample size calculations were appropriate
Were all changes in the conduct of the study or planned analysis made prior to analysis?	Partial	Changes in the conduct of the study or planned analyses are listed in the CSR (pp80-84). [redacted]; however, the EAG considers that these changes were reasonable and well justified
Were all primary and secondary efficacy endpoints pre-defined and analysed appropriately?	Yes	The primary and secondary efficacy endpoints for the two-copy and the three-copy *SMN2* gene cohorts are listed in the CS (Table 7). Definitions and analysis approaches for these endpoints were pre-specified in the TSAP (pp17-21, 56-61). The company conducted statistical tests to compare SPR1NT trial primary and secondary efficacy endpoint results with results from the PNCR[20] dataset, and used a hierarchical testing method to strongly protect against Type I errors within the cohort of patients with two copies of the *SMN2* gene and within the cohort of patients with three copies of the *SMN2* gene separately. The EAG is satisfied that all primary and secondary efficacy endpoints were pre-defined and analysed appropriately
Was the analysis approach for PROs appropriate and pre-specified?	NA	PROs were not assessed in the SPR1NT trial
Was the analysis approach for AEs appropriate and pre-specified?	Yes	Proportions of patients with TEAEs, SAEs and AESIs are presented in the CS (Table 16 and Table 17). The safety analyses were descriptive only and were pre-specified in the TSAP (pp73-76)
Was a suitable approach employed for handling missing data?	Yes	The company's approach to handling missing data is outlined in the TSAP (pp37-38). The EAG is satisfied that the approach described was appropriate
Were all subgroup and sensitivity analyses pre-specified?	Yes	Results are presented in the CS by *SMN2* gene copy number, as pre-specified in the trial protocol (p5). No other subgroup analyses or sensitivity analyses are presented in the CS

AESI=adverse event of special interest; CS=company submission; CSR=clinical study report; EAG=External Assessment Group, ITT=intention-to-treat; NA=not applicable; PNCR=Pediatric Neuromuscular Clinical Research; PRO=patient-reported outcome; SAE=serious adverse event; SMN=survival motor neuron; TEAE=treatment-emergent adverse event; TSAP=trial statistical analysis plan
Source: CS, CSR,[30] trial protocol,[32] TSAP[31] and EAG comment

9.2 Appendix 2 - Efficacy results from the START, STR1VE-US and STR1VE-EU trials and PNCR dataset

Table 46 Comparison of key motor milestone outcomes from the SPR1NT, STR1VE and START trials and PNCR dataset

Milestone, [a] n/N (%) [b]		Pre-symptomatic SMA		Symptomatic SMA				
				Type 1 SMA			Type 1 SMA	Type 1, 2 and 3 SMA
		Onasemnogene abeparvovec					BSC	
		SPR1NT[21] two-copy *SMN2*	SPR1NT[22] three-copy *SMN2*	START[24] two-copy *SMN2*	STR1VE-US[25] two-copy *SMN2*	STR1VE-EU[26] two-copy *SMN2* [c]	PNCR[20] two-copy *SMN2*	PNCR[20] three-copy *SMN2*
		18 months [d]	24 months [d]	24 months [e]	18 months [d]	18 months [d]	18 months [f]	24 months [f]
Head control	≥3 seconds without support BSID GM item #4	9/9 (100)	9/9 (100)	11/12 (91.7)	17/20 (85.0)	23/33 (69.7%)	NR	NR
Rolls from back to sides	Turns from back to both right and left BSID GM item #20	13/13 (100)	15/15 (100)	9/12 (75.0)	13/22 (59.1)	19/33 (57.6)	NR	NR
Sits without support	≥30 seconds BSID GM item #26	14/14 (100.0)	14/15 (93.3)	9/12 (75.0)	14/22 (63.6)	16/33 (48.5)	0/23	[redacted]
	≥10 secs WHO-MGRS	14/14 (100.0)	14/15 (93.3)	10/12 (83.3)	14/22 (63.6)	15/33 [g] (45.5)	[redacted]	[redacted]
Crawls	≥5 feet BSID GM item #34	9/14 (64.3)	14/15 (93.3)	2/12 (16.7)	1/22 [h] (4.5)	1/33 [i] (3.0)	NR	NR
	≥3 movements WHO-MGRS	10/14 (71.4)	14/15 (93.3)	NR	NR	1/33 [i] (3.0)	NR	NR
Stands with assistance	≥2 seconds BSID GM item #33	14/14 (100)	14/15 (93.3)	2/12 (16.7)	1/22 [h] (4.5)	2/33 (6.1)	NR	NR
	≥10 seconds WHO-MGRS	14/14 (100)	14/15 (93.3)	NR	NR	2/33 (6.1)	NR	NR
Pulls to stand	Raises self to standing position using chair/other object BSID GM item #35	11/14 (78.6)	14/15 (93.3)	2/12 (16.7)	1/22 [h] (4.5)	1/33 [i] (3.0)	NR	NR

Milestone, [a] n/N (%) [b]		Pre-symptomatic SMA		Symptomatic SMA				
				Type 1 SMA			Type 1 SMA	Type 1, 2 and 3 SMA
		Onasemnogene abeparvovec					BSC	
		SPR1NT[21] two-copy *SMN2*	SPR1NT[22] three-copy *SMN2*	START[24] two-copy *SMN2*	STR1VE-US[25] two-copy *SMN2*	STR1VE-EU[26] two-copy *SMN2* [c]	PNCR[20] two-copy *SMN2*	PNCR[20] three-copy *SMN2*
		18 months [d]	24 months [d]	24 months [e]	18 months [d]	18 months [d]	18 months [f]	24 months [f]
Stands alone	≥3 seconds BSID GM item #40	11/14 (78.6)	15/15 (100.0)	2/12 (16.7)	1/22 [h] (4.5)	1/33 [i] (3.0)	0/23	19/81 (23.5)
	≥10 seconds WHO-MGRS	10/14 (71.4)	15/15 (100.0)	NR	NR	1/33 [i] (3.0)	NR	NR
Walks with assistance	Coordinated alternated stepping movements BSID GM item #37	11/14 (78.6)	14/15 (93.3)	2/12 (16.7)	1/22 [h] (4.5)	1/33 [i] (3.0)	NR	NR
	Holding onto stable object WHO-MGRS	12/14 (85.7)	14/15 (93.3)	NR	NR	1/33 [i] (3.0)	NR	NR
Walks alone	≥5 steps with coordination and balance BSID GM item #43	9/14 (64.3)	14/15 (93.3)	2/12 (16.7)	1/22 [h] (4.5)	1/33 [i] (3.0)	0/23	17/81 (21.0)
	≥5 steps WHO-MGRS	10/14 (71.4)	14/15 (93.3)	NR	NR	1/33 [i] (3.0)	NR	NR

[a] Outcome definitions for motor milestones differed in the PNCR cohorts to those used in the onasemnogene abeparvovec trials; see Table 15
[b] N is the number of patients without milestone prior to dosing
[c] Exploratory motor milestones in the STR1VE-EU[26] study were assessed in the efficacy and safety completers population (N=33).
[d] Age at which the outcomes were measured up to
[e] Time after first dose of onasemnogene abeparvovec
[f] it is unclear whether data from PNCR[20] dataset were reported for patients at age 18 months and 24 months or whether patients in the PNCR[20] dataset were followed up for 18 months or 24 months from the time of enrolment
[g] sits without support (BSID GM item #26) was also reported for the STR1VE-EU[26] intention-to-treat population (n/N=14/32, 43.8%)
[h] The milestones of crawls, pulls to stand, stands with assistance, stands alone, walks with assistance, and walks alone were all achieved by the same patient
[i] The milestones of crawls, pulls to stand, stands with assistance, stands alone, walks with assistance, and walks alone were all achieved by the same patient
BSC=best supportive care; BSID GM=Bayley Scales of Infant and Toddler Development (Version 3) Gross Motor subtest; NR=not reported PNCR=Pediatric Neuromuscular Clinical Research; WHO-MGRS=World Health Organization Multicentre Growth Reference Study
Source: CS, Table 14 and Table 15 for SPR1NT; CS, Sections B.2.6.1.1 to B.2.6.1.3 and Novartis PNCR/NeuroNext Report,[20] Table 2 for PNCR; Al-Zaidy 2019[24] and CS for HST15,[27] Table 30 and Table 33 for START; supplementary appendices to most recent publications for STR1VE-US[25] and STR1VE-EU[26]

Table 47 Comparison of weight, survival and ventilation outcomes from the SPR1NT, STR1VE and START trials

Outcome, n/N (%) [a]	Pre-symptomatic SMA		Symptomatic SMA				
	Unknown		Type 1 SMA			Type 1 SMA	Type 1, 2 and 3 SMA
	Onasemnogene abeparvovec					BSC	
	SPR1NT[21] two-copy *SMN2*	SPR1NT[22] three-copy *SMN2*	START[24] two-copy *SMN2*	STR1VE-US[25] two-copy *SMN2*	STR1VE-EU[26] two-copy *SMN2* [d]	PNCR[20] two-copy *SMN2*	PNCR[20] three-copy *SMN2*
	18 months [b]	24 months [b]	24 months [c]	18 months [b]	18 months [b]	18 months [d]	24 months [d]
Ability to maintain weight [e] without need for non-oral/mechanical feeding support at any visit	13/14 (92.9)	10/15 (66.7)	NR	14/22 (63.6)	15/23 (65.2) [f]	NR	NR
Deaths at any point during the study, n (%)	0	0	0	1/22 (4.5)	1/33 (3.0)	[redacted]	[redacted]
Event-free survival at age 14 months,[g]	14/14 (100)	15/15 (100)	NR	20/22 (90.9)	31/32 (96.9) [h]	6/23 (26.1)	[redacted]
Independent of ventilatory support at end of study	14/14 (100)	15/15 (100)	7/12 (58.3%)	18/22 (81.8)	18/33 (54.5) [i]	0/23	3/81 (3.7) [j]
Used ventilatory support at any point in the study	0	0	5/12 (41.7)	7/22 (31.8)	NR	23 (100)	NR

[a] N is the number of patients without milestone prior to dosing
[b] Age at which the outcomes were measured up to
[c] Time after first dose of onasemnogene abeparvovec
[d] it is unclear whether data from PNCR[20] dataset were reported for patients at age 18 months and 24 months or whether patients in the PNCR[20] dataset were followed up for 18 months or 24 months from the time of enrolment
[e] At or Maintained weight consistent with age (above third percentile for age and gender as defined by WHO guidelines) consistent with the patient's age at the assessment
[f] Reported as a proportion of ability to thrive population (n=23); the ability to thrive was defined as: (1) The ability to tolerate thin or very thin liquids as demonstrated through a formal swallowing test with a result of normal swallow, functional swallow, or safe for swallowing; (2) did not receive nutrition through mechanical support (i.e., feeding tube); (3) maintained weight (> third percentile for age and gender as defined by WHO guidelines) consistent with the patient's age at the assessment
[g] Event-free survival defined as avoidance of both death and permanent ventilation through the 14 months of age visit. 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
[h] Assessed in the ITT population (N=32)
[i] 7/9 patients who required non-invasive ventilatory support at baseline still required support at the end of this study;16/24 patients who did not require ventilatory support at baseline remained independent of ventilatory support at the end of the study
[j] The company report that 96.3% of patients in the PNCR[20] cohort survived without tracheostomy at 24 months
BSC=best supportive care; NR=not reported
Source: CS, Section B.2.6.1.3 for SPR1NT; CS, Section B.2.6.1.3, Novartis PNCR/NeuroNext Report,[20] Table 3 and most recent publications for STR1VE-EU[26] for PNCR and company response to additional clarification for PNCR three-copy *SMN2* cohort; Al-Zaidy 2019[24] and CS for HST15,[27] pp139-140 for START; most recent publications for STR1VE-US[25] and STR1VE-EU

9.3 Appendix 3 - model health state costs

Table 48 Model health state costs

Cost Category	Broad Range of Normal Development	1. Non-Sitter (PAV)	1. Non-Sitter	2. Sitter	2. Sitter - Lost Sitting	3a. Delayed Walker	3a. Delayed Walker - Lost Walking	3b. Experiences later onset SMA	3b. Experiences later onset SMA - Lost Walking
Drugs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Medical tests	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Medical visits	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Hospitalisations	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
GP & Emergency	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Health material	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Social Services	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Monthly Total	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

PAV=permanent assisted ventilation; SMA=spinal muscular atrophy
Source: company model

9.4 Appendix 4 - Microsoft Excel revisions made by the EAG to the company model

Table 49 EAG revisions to company model

EAG revisions	Implementation instructions
Scenario 1: Loss of response in OA equal to that in BSC	In Sheet 'Parameters' Name cell B3 'EAG_Mod_A' Set cell B3=1 Change cell H76 to =IF(EAG_Mod_A=1,H60,Intervention_Inputs!$O$75) Change cell H77 to =IF(EAG_Mod_A=1,H61,Intervention_Inputs!$O$77) Change cell H78 to =IF(EAG_Mod_A=1,H62,Intervention_Inputs!$O$78) Change cell H80 to =IF(EAG_Mod_A=1,H64,Intervention_Inputs!$T$75) Change cell H81 to =IF(EAG_Mod_A=1,H65,Intervention_Inputs!$T$77) Change cell H82 to =IF(EAG_Mod_A=1,H66,Intervention_Inputs!$T$78) Change cell H84 to =IF(EAG_Mod_A=1,H68,Intervention_Inputs!$X$77) Change cell H85 to =IF(EAG_Mod_A=1,H69,Intervention_Inputs!$X$79) Change cell H86 to =IF(EAG_Mod_A=1,H70,Intervention_Inputs!$X$80) Change cell H93 to =IF(EAG_Mod_A=1,H60,Intervention_Inputs!$P$75) Change cell H94 to =IF(EAG_Mod_A=1,H61,Intervention_Inputs!$P$77) Change cell H95 to =IF(EAG_Mod_A=1,H62,Intervention_Inputs!$P$78) Change cell H97 to =IF(EAG_Mod_A=1,H64,Intervention_Inputs!$U$75) Change cell H98 to =IF(EAG_Mod_A=1,H65,Intervention_Inputs!$U$77) Change cell H99 to =IF(EAG_Mod_A=1,H66,Intervention_Inputs!$U$78) Change cell H101 to =IF(EAG_Mod_A=1,H68,Intervention_Inputs!$Y$77) Change cell H102 to =IF(EAG_Mod_A=1,H69,Intervention_Inputs!$Y$79) Change cell H103 to =IF(EAG_Mod_A=1,H70,Intervention_Inputs!$Y$80)

EAG revisions	Implementation instructions
Scenario 2: Social care costs set to zero	In Sheet 'MedicalCostsCalculator' Name cell J1 'EAG_Mod_B' Set cell J1=1 Change cell X24 to =IF(EAG_Mod_B=1,0,SUM(U24:W24)) Change cell X39 to =IF(EAG_Mod_B=1,0,SUM(U39:W39)) Change cell X54 to =IF(EAG_Mod_B=1,0,SUM(U54:W54)) Change cell X69 to =IF(EAG_Mod_B=1,0,SUM(U69:W69))

National Institute for Health and Care Excellence

Centre for Health Technology Evaluation

EAG report – factual accuracy check and confidential information check

Onasemnogene abeparvovec for treating pre-symptomatic spinal muscular atrophy (MAA partial review of HST 15) [ID4051]

"Data owners may be asked to check that confidential information is correctly marked in documents created by others in the evaluation before release." (Section 5.4.9, NICE health technology evaluations: the manual).

You are asked to check the EAG report to ensure there are no factual inaccuracies or errors in the marking of confidential information contained within it. The document should act as a method of detailing any inaccuracies found and how they should be corrected.

If you do identify any factual inaccuracies or errors in the marking of confidential information, you must inform NICE by **5pm on Friday 28 October** using the below 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 committee papers.

Please underline all confidential information, and separately highlight information that is submitted as '[redacted]' in turquoise, all information submitted as '[redacted]' in yellow, and all information submitted as '[redacted]' in pink.

Issue 1 Reporting of maximum follow-up

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Page 10 of EAG report states that: Motor milestone data for patients treated pre-symptomatically with onasemnogene abeparvovec are available from the SPR1NT trial for a maximum follow-up of up to age 24 months, and from the LT-002 study for a maximum follow-up of [redacted].	Please change the statement to: Motor milestone data for patients treated pre-symptomatically with onasemnogene abeparvovec are available from the SPR1NT trial for a maximum follow-up of up to age 24 months, and from the LT-002 study for a maximum follow-up of [redacted] post-dose and [redacted] of age.	It is not clear from the statement whether the [redacted] refers to age or time after dosing. Therefore, this should be clarified. Further details can be found in Table 20 (page 78) of the company submission.	Thank you for clarifying this information. Updated text: a maximum follow-up of [redacted] post-dose and age [redacted]
Page 61 of EAG report states that: To date, the maximum follow-up for any of the clinical trials[21-26] of onasemnogene abeparvovec is [redacted] months (ongoing LT-002[23] study).	Please change the statement to: To date, the maximum follow-up for any patient treated pre-symptomatically with onasemnogene abeparvovec is [redacted] months post-dose and [redacted] of age (ongoing LT-002[23] study).	The figure of [redacted] refers to follow-up after dosing specifically in patients enrolled in LT-002 who were treated with onasemnogene abeparvovec in SPR1NT (the pre-symptomatic trial). This does not refer to patients included in LT-002 from other parent trials, and does not take into account patients enrolled in the long-term extension study for START (LT-001). This should be clarified in the statement.	Thank you for clarifying this information. Updated text: To date, the maximum follow-up for patients treated pre-symptomatically with onasemnogene abeparvovec is [redacted] post-dose and age [redacted] (ongoing LT-002[23] study).

Issue 2 Wording around severity of disease within SMA type 1

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Pages 11 and 81 of EAG report include the following statement: Further, patients with type 1 SMA with three copies of the *SMN2* gene tend to have less severe disease than those with two copies of the *SMN2* gene.	Please remove this statement on both pages 11 and 81.	The statement is not referenced on either page 11 or page 81 of the EAG report. The company is not aware of any published evidence to suggest that *SMN2* copy number has any impact on the severity of disease among those with type 1 SMA. The statement should be removed as it is not supported by evidence.	Thank you for identifying this error. Updated text: **EAG report, p11** Further, patients with type 1 SMA with three copies of the *SMN2* gene tend to have longer expected survival than those with two copies of the *SMN2* gene **EAG report, p82** Further, patients with type 1 SMA with three copies of the *SMN2* gene tend to have longer expected survival than those with two copies of the *SMN2* gene (CS, B.3.3.3, Figure 15 and Figure 16)

Issue 3 Wording around eligibility for people with SMA types 2 and 3

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Page 11 of the EAG report includes the following statement: approximately 85% of patients with three copies of the *SMN2* gene have type 2 SMA (54.3%) or type 3 SMA (30.9%), not type 1 SMA (14.7%), and so are not eligible for treatment with onasemnogene abeparvovec following the development of symptoms	Please change the statement to: approximately 85% of patients with three copies of the *SMN2* gene have type 2 SMA (54.3%) or type 3 SMA (30.9%), not type 1 SMA (14.7%), and so are not eligible for treatment with onasemnogene abeparvovec following the development of symptoms based on the recommendations from HST15	Onasemnogene abeparvovec is indicated 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' Therefore, it is misleading to state that patients with three copies of the *SMN2* gene and type 2 or type 3 SMA are not eligible for treatment, without indicating that this eligibility refers to the previous NICE appraisal (HST15) rather than the licensed indication.	Thank you for this suggestion. Updated text on p11 and p83 of the EAG report: approximately 85% of patients with three copies of the *SMN2* gene have type 2 SMA (54.3%) or type 3 SMA (30.9%), not type 1 SMA (14.7%), and so are not eligible for treatment with onasemnogene abeparvovec following the development of symptoms based on the recommendations made by NICE in HST15

Issue 4 Description of disease mechanism (lack of SMN protein)

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Page 15 of the EAG report includes the following statement: The bi-allelic mutation results in the loss of the SMN protein, which is necessary for normal motor neuron function, and this leads to motor neuron degeneration	Please change the statement to: The bi-allelic mutation results in a lack of SMN protein, which is necessary for normal motor neuron function, and this leads to motor neuron degeneration	The statement refers to a loss of SMN protein. However, this suggests that SMN protein is produced normally and then lost, whereas, in people with SMA, production of SMN protein is affected. Therefore, it is more accurate to refer to a 'lack of' SMN protein than 'the loss of' SMN protein.	Thank you for this suggestion. Updated text as suggested

Issue 5 Description of disease mechanism (functional SMN protein)

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Page 15 of the EAG report includes the following statement: The *SMN2* gene produces very low levels of SMN	Please change the statement to: The *SMN2* gene produces very low levels of functional SMN	A large proportion of the SMN protein produced as a result of the *SMN2* gene is a truncated, non-functional variant, although some functional SMN protein is produced. Therefore, it is more accurate to describe low levels of 'functional SMN' than low levels of SMN more generally.	Thank you for this suggestion. Updated text as suggested

Issue 6 Estimated patient numbers

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Page 17 of the EAG report includes the following statement: Approximately 65 babies are born with SMA each year in England and approximately 60% of these are clinically diagnosed as having type 1 SMA.	Please change the statement to: Approximately 60 babies are born with SMA each year in England and approximately 60% of these are clinically diagnosed as having type 1 SMA.	Per the company submission and budget impact analysis: It is estimated that 60 infants (more precisely 59.5 if we apply the incidence rate of 1:10,000 to the 595,239 live births in England in 2021) are born with SMA in England each year. The reference used for the 65 babies in the EAG report includes the incidence rate of 1:10,000 as reported in the company submission. Since when applying such incidence rate to the number of live births we reach a total of 60, the source for the 65 babies in the EAG report is unclear.	Thank you for this suggestion. Updated text as suggested
Page 17 of the EAG report includes the following statement: If UK national screening is implemented, the company estimates that [redacted] babies with pre-symptomatic SMA and up to three copies of the *SMN2* gene will be identified each year.[14]	Please change the statement to: If UK national screening is implemented, the company estimates that [redacted] babies with pre-symptomatic SMA and up to three copies of the *SMN2* gene will be identified each year.[14]	The company cannot identify the source of the estimated [redacted] babies in any of the submission documents. Per the scenario in which national screening was included in the budget impact template, NICE estimate was [redacted]	Thank you for identifying this error. Updated text as suggested

Issue 7 Incorrect value reported

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Page 42 of the EAG report includes the following statement: The majority of patients achieved the primary and secondary endpoint milestones (standing alone: 93.6%; walking alone: 73.3%)	Please change the statement to: The majority of patients achieved the primary and secondary endpoint milestones (standing alone: 93.3%; walking alone: 73.3%)	The 93.6% for standing alone is incorrect and should be 93.3%. The value shown in Table 11 below is correct.	Thank you for identifying this error. Updated text as suggested

Issue 8 Reporting of maintenance of motor milestones

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Page 47 of the EAG report includes the following statement: [redacted]	Please change the statement to: [redacted]	The statement is incorrect as, on page 79 of the company submission, the following statement is made: [redacted]	Thank you for clarifying this information. Updated text to: [redacted]
Page 61 of the EAG report includes the following statement: The company has not provided information about whether	Please remove the statement.	The statement is incorrect as, on page 79 of the company submission, the following statement is made: [redacted]	Thank you for clarifying this information. Text has been removed

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
patients in the onasemnogene abeparvovec trials[21-26] lost any achieved motor milestones.			

Issue 9 Incremental cost of onsasemnogene abeparvovec (OA) at PAS price versus BSC – combined cohort

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Table 35 pp 77 of the report, the incremental cost of onsasemnogene abeparvovec (OA) at PAS price versus BSC for the combined patient 'cohort' should be [redacted] (in line with the reported costs of [redacted] for OA and £882,564 for BSC) instead of currently [redacted]. All other outcome and incremental outcome values reported in table 35 and in table 36 are correct.	Replacing the incremental cost value of [redacted] with the value of [redacted] in table 35 pp 77 of the report.	The value should be updated for correctness and consistency with the costs reported for OA and BSC.	Thank you for identifying this error. Updated table

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
This error come from a mistake in table 49 of document B.			

Location of incorrect marking	Description of incorrect marking	Amended marking
Not applicable	Not applicable	Not applicable

Onasemnogene abeparvovec for treating pre-symptomatic spinal muscular atrophy (MAA partial review of HST 15) [ID4051]

Additional analyses proposed to address the latest request from NICE dated 12th Dec 2022

'Commercial in confidence' in turquoise.

NICE Request:

The panel therefore requests that the company provides further analysis by adjusting the model to provide results which assume a diagnosis at 1 year of age.

This should reflect that;

- those diagnosed with presymptomatic SMA at 1 year of age in the comparator arm would not develop SMA type 1, will have a lower chance of developing SMA type 2 and a higher chance of developing SMA type 3 (both "delayed walkers" and "late onset SMA"),
- those diagnosed with presymptomatic SMA at 1 year of age are likely to have a different ratio in terms of SMN2 copy numbers,
- The likelihood of developing different types of SMA in the modelled scenario should ideally be based on clinical evidence. If no evidence can be found to inform this, then clinical expert input/other assumptions should be used.

Other analysis which may be useful to the committee would be to also consider a diagnosis at 6 months of age (where it is known that SMA type 1 cannot occur in best supportive care arm).

Novartis response:

The company acknowledges that currently available data for onasemnogene abeparvovec in presymptomatic patients with SMA are limited to those treated by 6 weeks of age and understands that there are two elements to the request:

1. Understanding the cost-effectiveness of treating patients with presymptomatic SMA with onasemnogene abeparvovec diagnosed later than 6 weeks, at up to 1 year of age
2. Assessing the cost-effectiveness of treating patients with presymptomatic SMA with onasemnogene abeparvovec diagnosed by 6 weeks of age but not receiving treatment until after this timepoint

The company has attempted to address the request, but would like to note that, in clinical practice in England, very few patients are likely to be diagnosed with presymptomatic SMA and treated later than 6 weeks of age. Furthermore, there is a lack of data available to support the requested analyses and, as a result, there is considerable uncertainty in these analyses, although, where possible, assumptions have been made and validated with clinical experts in SMA.

Scenario 1: Understanding the cost-effectiveness of treating patients with presymptomatic SMA with onasemnogene abeparvovec diagnosed later than 6 weeks, at up to 1 year of age

1. Context:

While it is theoretically possible that some patients may be diagnosed with presymptomatic SMA after 6 weeks of age, diagnosis of presymptomatic SMA at up to 1 year of age is highly unlikely. By 1 year of age, all patients with two copies of *SMN2* and the majority of patients with three copies of *SMN2* would be expected to develop symptomatic SMA. Therefore, only a small minority of patients with three copies of *SMN2* would remain presymptomatic. In the absence of a newborn blood spot (NBS) screening programme in England, those with presymptomatic SMA are identified through genetic testing referrals due to a sibling history of SMA or a parent with confirmed carrier status (family screening). The only scenario in which a presymptomatic patient would be identified at up to 1 year of age would be through identification of a younger sibling who presents with symptoms of SMA at a younger age than the older sibling with presymptomatic SMA, which is expected to be extremely rare.

In addition, while we know that the longer a patient with SMA remains presymptomatic, the more likely they would have SMA type 3 (owing to the rarity of the situation described above), we do not know the probability of the patient having type 3 vs type 2 if they were untreated presymptomatically.

As we do not have precise information on the SMA type that patients would develop without presymptomatic treatment, we propose evaluation of economic outcomes for a population of presymptomatic patients who are diagnosed and treated at an age when the possibility of the patient having SMA type 1 (≥6 months) can be ruled out, instead of evaluating patient outcomes at a specific age at diagnosis (e.g. at 6 or 12 months).

This approach can be informed by probabilities of being type 2 and type 3 for each *SMN2* group obtained by rescaling the probabilities used for our base case analysis after setting the probability of being type 1 to zero (see detailed information below), instead of relying on additional assumptions.

2. Analysis implementation

2.1. Characterising outcomes for patients of the population P* who receive BSC

We hereafter refer to patients diagnosed pre-symptomatically at an age of 6 months or older when SMA type 1 can be ruled out, as '**Patient population P***'.

Implementation of the analysis requires, as clearly laid out in the request, to assess the probabilities that the patients of population P* would: (i) have 2 or 3 copies of *SMN2* and (ii) develop SMA type 2 or SMA type 3 (based on their *SMN2* copy-phenotype) if they only receive BSC.

2.1.1. *SMN2* copy-split

The clinical experts consulted suggested that only a minority of 2-copy patients would still be asymptomatic at 6 months of age, which reflects the fact that a large majority of patients are expected to be SMA type 1. On this basis, we assume that 5% of patients of population P* would have 2 copies of *SMN2* and 95% would have 3 copies.

2.1.2. Probabilities of developing SMA type 2 and type 3 if untreated presymptomatically

For each *SMN2* copy group, the probabilities of developing SMA type 2 and SMA type 3 for P* patients were derived based on the ratio of patients with SMA type 2 (SMA type 3) within the pool of patients with SMA type 2 or 3 in the overall presymptomatic patient population that underpins the base case analysis (see Table 1 and Table 2 below).

2.1.2.1. Probabilities calculation in the 2-copy group of the patient population P*

Table 1: **Extract of Table 34 from document B: SMA severity type distribution among 2-copy group of the overall pre-symptomatic population**

Proxy	%	Source
SMA type 1	79	Calucho et al. 2018
SMA type 2	16	
SMA type 3a	5	
SMA type 3b	0	

Abbreviations: SMA, spinal muscular atrophy.

Therefore, in the 2-copy group of the patient population P*:

Pr(T2)/Pr(T2or3) = 16/21=76.19%

Pr(T3)/Pr(T2or3) = 5/21=23.81%

Consequently**, in the 2-copy group** of the patient population P***, we would expect 76.19% of untreated patients to develop SMA type 2 and 23.81% to develop SMA type 3 (3a)**.

2.1.2.2. Probabilities calculation in the 3-copy group of the patient population P*

Table 2: Extract of Table 35 from document B: SMA severity type distribution among 3-copy group of the overall presymptomatic population

Proxy	%	Source
SMA type 1	15	Calucho et al. 2018[1]
SMA type 2	54	
SMA type 3a	16	
SMA type 3b	15	

Abbreviations: SMA, spinal muscular atrophy.

Therefore, in the 3-copy group of the patient population P*:

Pr(T2)/Pr(T2or3) = 54/85=63.53%

Pr(T3)/Pr(T2or3) = 31/85=36.47%

Pr(T3a)/Pr(T3) = 16/31=51.6%

Consequently, **in the 3-copy group** of the patient population P***, we would expect 63.53% of untreated patients to develop SMA type 2 and 36.47% to develop SMA type 3** (51.6% of which would be expected to be of type 3a and 48.4% of type 3b).

2.1.3. P* with equal type 2 and type 3 split

Since the true probability that a patient diagnosed at 6 months of age or older would develop SMA type 2 or type 3 if untreated presymptomatically is unknown, to 'stress-test' our findings, we also evaluated outcomes for P* patients assuming that the latter are even more likely to develop SMA type 3 (if untreated) than our calculations suggest based on data from Calucho (2018) (and setting the probability of SMA type 1 to zero). In this patient population, hereafter referred to as 'P* with equal T2/T3 split', 50% of patients are assumed to develop SMA type 2 and 50% to develop SMA type 3 if they are untreated presymptomatically. All patients in this additional specific patient population are assumed to have 3 copies of *SMN2*.

Comparison of the probabilities of developing SMA type 2 and type 3 between: (i) the overall pre-symptomatic population used for base case analysis; (ii) P* population described in the previous sections and (iii) P* with equal T2/T3 split, is provided in Table 3.

2.1.4. Summary of input for characterizing outcomes in BSC patients

Table 3: SMA severity type in patients of the overall pre-symptomatic population, P* population and P* with equal T2/T3 split population

	Overall pre-symptomatic population (base case) (%)		P* population (%)		P* with equal T2/T3 split population (%)	
	2-copy =65.15%	3-copy =34.85%	2-copy =5%	3-copy =95%	2-copy =0%	3-copy =100%
SMA type 1	79	15	0	0	NA	0
SMA type 2	16	54	76.2	63.5	NA	50
SMA type 3a	5	16	23.8	18.8	NA	25
SMA type 3b	0	15	0	17.7	NA	25

Abbreviations: NA, not applicable; SMA, spinal muscular atrophy.

2.2. Characterising the impact of diagnosis and treatment delay until 6 months of age or older on the efficacy of onasemnogene abeparvovec

2.2.1. Scenario description

Since presymptomatic patients do not show symptoms, it is possible that many of their motor neurons could have been preserved. In this case, given the relationship between motor neuron preservation and efficacy of treatment, it seems plausible to assume that the efficacy of onasemnogene abeparvovec in this specific patient population would be similar to the efficacy reported in SPR1NT conducted in presymptomatic patients treated up to 6 weeks of age.

However, since irreversible neuron loss could nevertheless have occurred despite the absence of symptoms, [2] we also provide results when a reduction in efficacy is applied. A reduction in treatment efficacy corresponds to a reduction in the number of patients who either achieve broad range of normal development (BRND) or 'Delayed walker' and a corresponding increase in the number of patients achieving sitting as highest motor milestone.

Please note that patients achieving BRND and Delayed walker are pulled together within all the analyses provided in this document since, in the base case analysis, these patients benefit from the same survival probabilities and utilities as the general population and incur the same SMA care costs.

Given the lack of data, it is very difficult to assess the reduction in efficacy associated with treating patients after 6 months of age. Clinicians suggested that since 2-copy patients have a greater propensity of having SMA type 2 and that patients with SMA type 2 would most likely suffer from a greater amount of motor neuron loss, a ballpark estimate of the reduction in the number of patients who would achieve BRND or become a Delayed walker could be up to 20% for patients with 2 copies and up to 10% for patients with 3 copies.

2.2.2. Patient distribution across health states (onasemnogene abeparvovec arm) under the base case efficacy (informed by the SPR1NT trial) and under the scenario of reduced efficacy

Table 4: Patient distribution across the cost-effectiveness model's health states under the base case and the scenario of reduced efficacy

Empirical data	2-copy patients		3-copy patients	
	Base case efficacy	Efficacy reduction scenario	Base case efficacy	Efficacy reduction scenario
BRND	71%	57%	93%	84%
1. Non-Sitter (PAV)	0%	0%	0%	0%
1. Non-Sitter	0%	0%	0%	0%
2. Sitter	7%	26%	0%	10%
3a. Delayed Walker	21%	17%	7%	6%
Dead	0%	0%	0%	0%
Total	100%	100%	100%	100%

Abbreviations: BRND, Broad Range of Normal Development; PAV, permanent assisted ventilation.

3. Results

3.1. Results for patients of the population P* assuming no loss of efficacy

Table 5: Economic analysis results for the full cohort of Population P* (weighted results)

	Costs (£)†	QALYs (Undisc)	LYs†	QALYs†			
BSC	1,470,163	[redacted]	[redacted]	[redacted]	-	-	-
Onasemnogene abeparvovec	[redacted]	[redacted]	[redacted]	[redacted]	-	-	-

Incremental outcomes (onasemnogene abeparvovec vs BSC)							
	Costs (£)†	**QALYs (Undisc)**	**LYs†**	**QALYs†**	**INMB at £100,000 /QALY**	**INMB at £300,000 /QALY**	**ICER**
Onasemnogene abeparvovec vs BSC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: Undisc. undiscounted; BSC, best supportive care; ICER, incremental cost-effectiveness ratio; LYs, life years; QALYs, quality-adjusted life years; INMB, Incremental Net Monetary Benefit.
†Values presented are based on a discount rate of 3.5%.

Table 6: Economic analysis results for the 2-copy cohort (5% of population P*)

	Costs (£)†	**QALYs (Undisc)**	**LYs†**	**QALYs†**			
BSC	1,661,003	[redacted]	[redacted]	[redacted]	-	-	-
Onasemnogene abeparvovec	[redacted]	[redacted]	[redacted]	[redacted]	-	-	-
Incremental outcomes (onasemnogene abeparvovec vs BSC)							
	Costs (£)†	**QALYs (Undisc)**	**LYs†**	**QALYs†**	**INMB at £100,000 /QALY**	**INMB at £300,000 /QALY**	**ICER**
Onasemnogene abeparvovec vs BSC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: Undisc. undiscounted; BSC, best supportive care; ICER, incremental cost-effectiveness ratio; LYs, life years; QALYs, quality-adjusted life years; INMB, Incremental Net Monetary Benefit.
†Values presented are based on a discount rate of 3.5%.

Table 7: Economic analysis results for the 3-copy cohort (95% of population P*)

	Costs (£)†	QALYs (Undisc)	LYs†	QALYs†			
BSC	1,460,118	[redacted]	[redacted]	[redacted]	-	-	-
Onasemnogene abeparvovec	[redacted]	[redacted]	[redacted]	[redacted]	-	-	-
Incremental outcomes (onasemnogene abeparvovec vs BSC)							
	Costs (£)†	**QALYs (Undisc)**	**LYs†**	**QALYs†**	**INMB at £100,000 /QALY**	**INMB at £300,000 /QALY**	**ICER**
Onasemnogene abeparvovec vs BSC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: Undisc. undiscounted; BSC, best supportive care; ICER, incremental cost-effectiveness ratio; LYs, life years; QALYs, quality-adjusted life years; INMB, Incremental Net Monetary Benefit.
†Values presented are based on a discount rate of 3.5%.

3.2. Results for patients of the population P* assuming loss in efficacy (20% efficacy reduction in 2-copy patients and 10% efficacy reduction in 3-copy patients)

Table 8: Economic analysis results (efficacy loss scenario) for the full cohort of Population P* (weighted results)

	Costs (£)†	QALYs (Undisc)	LYs†	QALYs†			
BSC	1,470,163	[redacted]	[redacted]	[redacted]	-	-	-
Onasemnogene abeparvovec	[redacted]	[redacted]	[redacted]	[redacted]	-	-	-
Incremental outcomes (onasemnogene abeparvovec vs BSC)							
	Costs (£)†	**QALYs (Undisc)**	**LYs†**	**QALYs†**	**INMB at £100,000 /QALY**	**INMB at £300,000 /QALY**	**ICER**
Onasemnogene abeparvovec vs BSC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: Undisc. undiscounted; BSC, best supportive care; ICER, incremental cost-effectiveness ratio; LYs, life years; QALYs, quality-adjusted life years; INMB, Incremental Net Monetary Benefit.
†Values presented are based on a discount rate of 3.5%.

Table 9: Economic analysis results (efficacy loss scenario) for the 2-copy cohort (5% of population P*)

	Costs (£)†	QALYs (Undisc)	LYs†	QALYs†			
BSC	1,661,003	[redacted]	[redacted]	[redacted]	-	-	-
Onasemnogene abeparvovec	[redacted]	[redacted]	[redacted]	[redacted]	-	-	-
Incremental outcomes (onasemnogene abeparvovec vs BSC)							
	Costs (£)†	**QALYs (Undisc)**	**LYs†**	**QALYs†**	**INMB at £100,000 /QALY**	**INMB at £300,000 /QALY**	**ICER**
Onasemnogene abeparvovec vs BSC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: Undisc. undiscounted; BSC, best supportive care; ICER, incremental cost-effectiveness ratio; LYs, life years; QALYs, quality-adjusted life years; INMB, Incremental Net Monetary Benefit.
†Values presented are based on a discount rate of 3.5%.

Table 10: Economic analysis results (efficacy loss scenario) for the 3-copy cohort (95% of population P*)

	Costs (£)†	QALYs (Undisc)	LYs†	QALYs†			
BSC	1,460,118	[redacted]	[redacted]	[redacted]	-	-	-
Onasemnogene abeparvovec	[redacted]	[redacted]	[redacted]	[redacted]	-	-	-
Incremental outcomes (onasemnogene abeparvovec vs BSC)							
	Costs (£)†	**QALYs (Undisc)**	**LYs†**	**QALYs†**	**INMB at £100,000 /QALY**	**INMB at £300,000 /QALY**	**ICER**
Onasemnogene abeparvovec vs BSC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: Undisc. undiscounted; BSC, best supportive care; ICER, incremental cost-effectiveness ratio; LYs, life years; QALYs, quality-adjusted life years; INMB, Incremental Net Monetary Benefit.
†Values presented are based on a discount rate of 3.5%.

3.3. Results for patients of the population P* with equal T2/T3 split assuming no loss of efficacy

Table 11: Economic analysis results for 3-copy cohort (= whole patient cohort)

	Costs (£)†	QALYs (Undisc)	LYs†	QALYs†			
BSC	1,291,735	[redacted]	[redacted]	[redacted]	-	-	-
Onasemnogene abeparvovec	[redacted]	[redacted]	[redacted]	[redacted]	-	-	-
Incremental outcomes (onasemnogene abeparvovec vs BSC)							
	Costs (£)†	**QALYs (Undisc)**	**LYs†**	**QALYs†**	**INMB at £100,000 /QALY**	**INMB at £300,000 /QALY**	**ICER**
Onasemnogene abeparvovec vs BSC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: Undisc. undiscounted; BSC, best supportive care; ICER, incremental cost-effectiveness ratio; LYs, life years; QALYs, quality-adjusted life years; INMB, Incremental Net Monetary Benefit.
†Values presented are based on a discount rate of 3.5%.
NB: All patients of population P* with equal T2/T3 split are assumed to have three *SMN2* copies.

3.4. Results for patients of the population P* with equal T2T3 split assuming a 10% reduction in efficacy

Table 12: Economic analysis results (efficacy loss scenario) for 3-copy cohort (= whole patient cohort)

	Costs (£)†	QALYs (Undisc)	LYs†	QALYs†			
BSC	1,291,735	[redacted]	[redacted]	[redacted]	-	-	-
Onasemnogene abeparvovec	[redacted]	[redacted]	[redacted]	[redacted]	-	-	-
Incremental outcomes (onasemnogene abeparvovec vs BSC)							
	Costs (£)†	**QALYs (Undisc)**	**LYs†**	**QALYs†**	**INMB at £100,000 /QALY**	**INMB at £300,000 /QALY**	**ICER**
Onasemnogene abeparvovec vs BSC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: Undisc. undiscounted; BSC, best supportive care; ICER, incremental cost-effectiveness ratio; LYs, life years; QALYs, quality-adjusted life years; INMB, Incremental Net Monetary Benefit.
†Values presented are based on a discount rate of 3.5%.
NB: All patients of population P* with equal T2/T3 split are assumed to have three *SMN2* copies.

4. Conclusions

It should be noted that all clinical experts consulted by the company expressed the opinion that the patient population P* – constituted by presymptomatic patients with SMA who are diagnosed and treated at 6 months of age or older when the possibility that they have SMA type 1 can be ruled out – is expected to be extremely small in practice.

The rarity of such patients has two implications. First, the economic analyses for this patient population are underpinned by input data that are highly uncertain and their results should be interpreted with caution. Second, the cost-effectiveness results for this extremely small subgroup of presymptomatic patients are not expected to have any major influence on the cost-effectiveness results for the overall presymptomatic SMA patient population.

Patients of P* population have a much greater baseline probability of survival than patients of the base case population ([redacted] vs [redacted] expected discounted life years in the BSC arm). Consequently, treating these patients presymptomatically with onasemnogene abeparvovec results in a lower discounted QALY gain, namely [redacted] discounted QALY gain per patient of the P* population under full efficacy maintenance and

[redacted] discounted QALY gain when applying a speculative 20% efficacy reduction for 2-copy patients and a speculative 10% reduction for 3-copy patients, than when treating the average patient of the overall presymptomatic population i.e., our base case population ([redacted] discounted QALY gain).

However, since patients of scenario P* population have a much greater probability of survival, their SMA costs over their lifetime in the absence of active treatment is very high ([redacted] per patient of P* population vs [redacted] per patient of the overall pre-symptomatic population). In contrast, by enabling a majority of patients to achieve BRND/Delayed walker, onasemnogene abeparvovec treatment leads to a substantial reduction in SMA care costs of patients.

As a result, even when under scenarios of speculative reduction in treatment efficacy, onasemnogene abeparvovec is expected to remain cost-effective, with ICERs for the combined cohort being respectively [redacted] under no efficacy reduction and [redacted] assuming a 20% efficacy reduction in patients with 2 copies and a 10% efficacy reduction in patients with 3 copies.

Importantly, even when assuming relatively optimistic projections of SMA severity type for untreated patients (as modelled via the P* 'T2/T3 equal split' patient population for whom probabilities of developing SMA Type 2 and Type 3 are even more speculative than for P* patients for whom these probabilities were derived using available data) and combining them with a reduction in efficacy, the ICER of onasemnogene abeparvovec remains below £100,000/QALY.

Scenario 2: Addressing the cost-effectiveness of treating patients with presymptomatic SMA with onasemnogene abeparvovec diagnosed by 6 weeks of age but not receiving treatment until after this timepoint

1. Context

Objective: Modelling the impact of presymptomatic patients with SMA being treated after more than 6 weeks of age

SMA is characterised by irreversible motor neuron loss and, by the time that symptoms of SMA develop, significant motor neuron loss has already occurred. Early initiation of disease-modifying treatment for SMA, ideally before symptoms become apparent, can halt this irreversible motor neuron loss, improve neuromuscular function, and prevent disease progression. Therefore, both clinical experts[3-8] and the company support immediate treatment following diagnosis, and clinical trials have shown that administration of therapy early in the disease course has a positive impact on outcomes.[2] As such, it would be unethical to wait to treat SMA once a genetic diagnosis has been made.

It is possible that some patients diagnosed with presymptomatic SMA by 6 weeks of age may not receive treatment until after this timepoint. As treatment with onasemnogene abeparvovec results in preservation of remaining motor neurons, the extent to which a patient may benefit from treatment will depend on the

extent of motor neuron loss at treatment. However, there are currently no data available to characterise the rate of motor neuron loss in patients with SMA or level of motor neuron loss at which symptoms become apparent.[2] As such, it cannot be assumed that, in patients who remain presymptomatic after 6 weeks of age, treatment efficacy will decline based on arbitrary age thresholds. Therefore, while the company has attempted to address the request, the scenario provided below should be interpreted with caution.

In the absence of data to characterise any possible efficacy loss in patients treated after 6 weeks of age, the company has provided a scenario (below), making broad assumptions based on a linear decline in efficacy from 6 weeks of age to the point at which all patients (based on their *SMN2* copy number) would be expected to lose all potential to achieve ambulation. The assumptions made have been validated by clinical experts in SMA and were deemed to be reasonable. However, it should be noted that, even with clinical validation, there is considerable uncertainty in this approach and that there are currently no data available to suggest that efficacy is reduced in presymptomatic patients treated after 6 weeks of age.

2. Analysis implementation

The present analysis aims to evaluate the effect on economic outcomes of a potential reduction in treatment efficacy due to treatment delay. It is important to underline that for this analysis, the patient population is the same as for the base case analysis i.e., it is the overall pre-symptomatic population, such that the expected patient distribution across SMA severity types (conditional on *SMN2* copy number) that drives the outcomes of patients under BSC will be the same as in the base case analysis.

Calculation of the weekly percentage reduction in efficacy (% reduction) was undertaken assuming a constant linear decline from the level of efficacy shown in the SPR1NT trial in patients treated up to 6 weeks of age to the point in time (T*) at which treatment is provided and the treated patients could no longer expect to achieve ambulation later in life.

Expert clinicians consulted expressed the opinion that a 2-copy patient and a 3-copy patient would no longer be able to achieve ambulation through treatment if treated after 22 weeks and 78 weeks respectively. In other words, T* equates to 22 weeks for 2-copy patients and to 78 weeks for 3-copy patients.

For 2 copy-patients, where 93% of patients either achieved BRND or Delayed walker if treated within 6 weeks of age, the weekly % reduction in efficacy is therefore derived as:

93% / (22-6) = 5.8% per week

For 3 copy-patients, where 100% of patients either achieved BRND or Delayed walker if treated within 6 weeks of age, the weekly % reduction in efficacy is therefore derived as:

100% / (78-6) = 1.4% per week

Table 13 summarises the % reduction in the number of patients achieving either BRND or Delayed walker in each *SMN2* copy group for three scenarios of delay duration i.e., a 2-week, 4-week and 6-week delay.

Table 13: Percentage reduction in number of patients achieving BRND/Delayed Walker post treatment under each scenario of delay duration

Scenario name	Delay duration	Age at treatment	% reduction in efficacy*	
			2-copy cohort	3 copy cohort
D2	2-week delay	8 weeks	11.6%	2.8%
D4	4-week delay	10 weeks	23.2%	5.6%
D6	6-week delay	12 weeks	34.8%	8.4%

* rounded % reduction in the number of patients achieving either BRND or Delayed Walker post treatment – compensated by an equivalent increase in the number of patients achieving sitting as highest motor milestone.

Economic results for scenarios D2, D4 and D6 are provided for the full cohort and each *SMN2* group in Table 14 to Table 22. Importantly, results for the full cohort under each delay scenario were based on the same split of copy number used for base case analysis at up to 6 weeks of age, namely 65.15 % with 2 copies and 34.85% with 3 copies. However, since 2-copy patients are more likely to show symptoms at an earlier age than 3-copy patients, the patient copy-split of presymptomatic patients at 8, 10 and 12 weeks of age is expected to be different from the copy split at 6 weeks of age. More specifically, as the delay duration lengthens, the proportion of 3-copy patients is expected to be larger than the proportion of 2-copy patients. This means that as delay duration lengthens, the results for the full cohort are expected to be more heavily influenced by the economic results for the 3-copy cohort than what Table 14, Table 17, and Table 20 (that use the 65.15/34.85% split) currently show.

3. Results

3.1. Results under scenario D2 (2-week treatment delay)

Table 14: Economic analysis results for the full cohort (Scenario D2)

	Costs (£)†	QALYs (Undisc)	LYs†	QALYs†			
BSC	882,564	[redacted]	[redacted]	[redacted]	-	-	-
Onasemnogene abeparvovec	[redacted]	[redacted]	[redacted]	[redacted]	-	-	-
Incremental outcomes (onasemnogene abeparvovec vs BSC)							
	Costs (£)†	**QALYs (Undisc)**	**LYs†**	**QALYs†**	**INMB at £100,000 /QALY**	**INMB at £300,000 /QALY**	**ICER**
Onasemnogene abeparvovec vs BSC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: Undisc. undiscounted; BSC, best supportive care; ICER, incremental cost-effectiveness ratio; LYs, life years; QALYs, quality-adjusted life years; INMB, Incremental Net Monetary Benefit.
†Values presented are based on a discount rate of 3.5%.

Table 15: Economic analysis results for the 2-copy cohort (Scenario D2)

	Costs (£)†	QALYs (Undisc)	LYs†	QALYs†			
BSC	538,617	[redacted]	[redacted]	[redacted]	-	-	-
Onasemnogene abeparvovec	[redacted]	[redacted]	[redacted]	[redacted]	-	-	-
Incremental outcomes (onasemnogene abeparvovec vs BSC)							
	Costs (£)†	**QALYs (Undisc)**	**LYs†**	**QALYs†**	**INMB at £100,000 /QALY**	**INMB at £300,000 /QALY**	**ICER**
Onasemnogene abeparvovec vs BSC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: Undisc. undiscounted; BSC, best supportive care; ICER, incremental cost-effectiveness ratio; LYs, life years; QALYs, quality-adjusted life years; INMB, Incremental Net Monetary Benefit.
†Values presented are based on a discount rate of 3.5%.

Table 16: Economic analysis results for the 3-copy cohort (Scenario D2)

	Costs (£)†	QALYs (Undisc)	LYs†	QALYs†			
BSC	1,525,551	[redacted]	[redacted]	[redacted]	-	-	-
Onasemnogene abeparvovec	[redacted]	[redacted]	[redacted]	[redacted]	-	-	-
Incremental outcomes (onasemnogene abeparvovec vs BSC)							
	Costs (£)†	**QALYs (Undisc)**	**LYs†**	**QALYs†**	**INMB at £100,000 /QALY**	**INMB at £300,000 /QALY**	**ICER**
Onasemnogene abeparvovec vs BSC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: Undisc. undiscounted; BSC, best supportive care; ICER, incremental cost-effectiveness ratio; LYs, life years; QALYs, quality-adjusted life years; INMB, Incremental Net Monetary Benefit.
†Values presented are based on a discount rate of 3.5%.

3.2. Results under scenario D4 (4-week treatment delay)

Table 17: Economic analysis results for the full cohort (Scenario D4)

	Costs (£)†	QALYs (Undisc)	LYs†	QALYs†			
BSC	882,564	[redacted]	[redacted]	[redacted]	-	-	-
Onasemnogene abeparvovec	[redacted]	[redacted]	[redacted]	[redacted]	-	-	-
Incremental outcomes (onasemnogene abeparvovec vs BSC)							
	Costs (£)†	**QALYs (Undisc)**	**LYs†**	**QALYs†**	**INMB at £100,000 /QALY**	**INMB at £300,000 /QALY**	**ICER**
Onasemnogene abeparvovec vs BSC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: Undisc. undiscounted; BSC, best supportive care; ICER, incremental cost-effectiveness ratio; LYs, life years; QALYs, quality-adjusted life years; INMB, Incremental Net Monetary Benefit.
†Values presented are based on a discount rate of 3.5%.

Table 18: Economic analysis results for the 2-copy cohort (Scenario D4)

	Costs (£)†	QALYs (Undisc)	LYs†	QALYs†			
BSC	538,617	[redacted]	[redacted]	[redacted]	-	-	-
Onasemnogene abeparvovec	[redacted]	[redacted]	[redacted]	[redacted]	-	-	-
Incremental outcomes (onasemnogene abeparvovec vs BSC)							
	Costs (£)†	**QALYs (Undisc)**	**LYs†**	**QALYs†**	**INMB at £100,000 /QALY**	**INMB at £300,000 /QALY**	**ICER**
Onasemnogene abeparvovec vs BSC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: Undisc. undiscounted; BSC, best supportive care; ICER, incremental cost-effectiveness ratio; LYs, life years; QALYs, quality-adjusted life years; INMB, Incremental Net Monetary Benefit.
†Values presented are based on a discount rate of 3.5%.

Table 19: Economic analysis results for the 3-copy cohort (Scenario D4)

	Costs (£)†	QALYs (Undisc)	LYs†	QALYs†			
BSC	1,525,551	[redacted]	[redacted]	[redacted]	-	-	-
Onasemnogene abeparvovec	[redacted]	[redacted]	[redacted]	[redacted]	-	-	-
Incremental outcomes (onasemnogene abeparvovec vs BSC)							
	Costs (£)†	**QALYs (Undisc)**	**LYs†**	**QALYs†**	**INMB at £100,000 /QALY**	**INMB at £300,000 /QALY**	**ICER**
Onasemnogene abeparvovec vs BSC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: Undisc. undiscounted; BSC, best supportive care; ICER, incremental cost-effectiveness ratio; LYs, life years; QALYs, quality-adjusted life years; INMB, Incremental Net Monetary Benefit.
†Values presented are based on a discount rate of 3.5%.

3.3. Results under scenario D6 (6-week treatment delay)

Table 20: Economic analysis results for the full cohort (Scenario D6)

	Costs (£)†	QALYs (Undisc)	LYs†	QALYs†			
BSC	882,564	[redacted]	[redacted]	[redacted]	-	-	-
Onasemnogene abeparvovec	[redacted]	[redacted]	[redacted]	[redacted]	-	-	-
Incremental outcomes (onasemnogene abeparvovec vs BSC)							
	Costs (£)†	**QALYs (Undisc)**	**LYs†**	**QALYs†**	**INMB at £100,000 /QALY**	**INMB at £300,000 /QALY**	**ICER**
Onasemnogene abeparvovec vs BSC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: Undisc. undiscounted; BSC, best supportive care; ICER, incremental cost-effectiveness ratio; LYs, life years; QALYs, quality-adjusted life years; INMB, Incremental Net Monetary Benefit.
†Values presented are based on a discount rate of 3.5%.

Table 21: Economic analysis results for the 2-copy cohort (Scenario D6)

	Costs (£)†	QALYs (Undisc)	LYs†	QALYs†			
BSC	538,617	[redacted]	[redacted]	[redacted]	-	-	-
Onasemnogene abeparvovec	[redacted]	[redacted]	[redacted]	[redacted]	-	-	-
Incremental outcomes (onasemnogene abeparvovec vs BSC)							
	Costs (£)†	**QALYs (Undisc)**	**LYs†**	**QALYs†**	**INMB at £100,000 /QALY**	**INMB at £300,000 /QALY**	**ICER**
Onasemnogene abeparvovec vs BSC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: Undisc. undiscounted; BSC, best supportive care; ICER, incremental cost-effectiveness ratio; LYs, life years; QALYs, quality-adjusted life years; INMB, Incremental Net Monetary Benefit.
†Values presented are based on a discount rate of 3.5%.

Table 22: Economic analysis results for the 3-copy cohort (Scenario D6)

	Costs (£)†	QALYs (Undisc)	LYs†	QALYs†			
BSC	1,525,551	[redacted]	[redacted]	[redacted]	-	-	-
Onasemnogene abeparvovec	[redacted]	[redacted]	[redacted]	[redacted]	-	-	-
Incremental outcomes (onasemnogene abeparvovec vs BSC)							
	Costs (£)†	**QALYs (Undisc)**	**LYs†**	**QALYs†**	**INMB at £100,000 /QALY**	**INMB at £300,000 /QALY**	**ICER**
Onasemnogene abeparvovec vs BSC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: Undisc. undiscounted; BSC, best supportive care; ICER, incremental cost-effectiveness ratio; LYs, life years; QALYs, quality-adjusted life years; INMB, Incremental Net Monetary Benefit.
†Values presented are based on a discount rate of 3.5%.

4. Conclusions

Early initiation of disease-modifying treatment for SMA, ideally presymptomatically, can halt the irreversible motor neuron loss and improve outcomes for patients with SMA. However, in the unlikely event that a presymptomatic patient with 2 or 3 copies of *SMN2* is treated after 6 weeks of age, the present analysis shows that treatment with onasemnogene abeparvovec remains cost-effective.

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EAG response to company additional analyses

LIVERPOOL REVIEWS AND IMPLEMENTATION GROUP (LRiG)

Onasemnogene abeparvovec for treating pre-symptomatic spinal muscular atrophy (MAA partial review of HST 15) [ID4051]

EAG response to company additional OA analyses: cost effectiveness results generated using discounted price for onasemnogene abeparvovec

This report was commissioned by the NIHR Evidence Synthesis Programme as project number NIHR135653

Completed 23 January 2023

CONTAINS COMMERCIAL IN CONFIDENCE DATA

UNIVERSITY OF LIVERPOOL | LIVERPOOL REVIEWS AND IMPLEMENTATION GROUP

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ALL TABLES AND FIGURES IN THIS APPENDIX ARE CONFIDENTIAL

1 INTRODUCTION

To inform the National Institute for Health and Care Excellence Single Technology Appraisal process for the clinical and cost effectiveness of onasemnogene abeparvovec for treating pre-symptomatic spinal muscular atrophy, the company has provided additional cost effectiveness analyses at the request of the Committee. The company has generated cost effectiveness results, using the Patient Access Scheme price, for onasemnogene abeparvovec for the following two scenarios:

Company Scenario 1: Understanding the cost-effectiveness of treating patients with pre-symptomatic SMA with onasemnogene abeparvovec diagnosed later than 6 weeks, at up to 1 year of age

Company Scenario 2: Addressing the cost-effectiveness of treating patients with pre-symptomatic SMA with onasemnogene abeparvovec diagnosed by 6 weeks of age but not receiving treatment until after this timepoint

The EAG is satisfied with the company's approach to both scenarios, recognising the lack of clinical effectiveness evidence to support both scenarios. The EAG considers Company Scenario 2 cost effectiveness results to be pessimistic. In this scenario, the delay in administering onasemnogene abeparvovec means that, if treatment does not commence by 22 weeks for 2-copy patients, then a child will never walk (i.e., be Type 2 SMA). The evidence presented in HST 15 was that a proportion of symptomatic 2-copy patients, if treated before 6-months, would be able to walk.

The EAG has re-run the cost effectiveness results for Company Scenario 1 and Company Scenario 2. The EAG identified several minor discrepancies in results that are unlikely to affect decision making. For clarity, where there is a minor discrepancy, the EAG has presented the company's own cost effectiveness table, as presented in the additional analyses report submitted to NICE on 13th January 2023, using EAG revised values where appropriate.

2 HEADINGS AND TABLES TAKEN FROM COMPANY NEW ANALYSES SUBMITTED ON JANUARY 13TH 1-23

3.2. Results for patients of the population P* assuming loss in efficacy (20% efficacy reduction in 2-copy patients and 10% efficacy reduction in 3-copy patients)

Table 1: Economic analysis results (efficacy loss scenario) for the full cohort of Population P* (weighted results) (PAS price)

	Costs (£)†	**QALYs (Undisc)**	**LYs†**	**QALYs†**			
BSC	1,470,163	[redacted]	[redacted]	[redacted]	-	-	-
Onasemnogene abeparvovec	[redacted]	[redacted]	[redacted]	[redacted]	-	-	-
Incremental outcomes (onasemnogene abeparvovec vs BSC)							
	Costs (£)†	**QALYs (Undisc)**	**LYs†**	**QALYs†**	**INMB at £100,000 /QALY**	**INMB at £300,000 /QALY**	**ICER**
Onasemnogene abeparvovec vs BSC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: Undisc. undiscounted; BSC, best supportive care; ICER, incremental cost-effectiveness ratio; LYs, life years; QALYs, quality-adjusted life years; INMB, Incremental Net Monetary Benefit.
†Values presented are based on a discount rate of 3.5%.

Table 2: Economic analysis results (efficacy loss scenario) for the 2-copy cohort (5% of population P*) (PAS price)

	Costs (£)†	**QALYs (Undisc)**	**LYs†**	**QALYs†**			
BSC	1,661,003	[redacted]	[redacted]	[redacted]	-	-	-
Onasemnogene abeparvovec	[redacted]	[redacted]	[redacted]	[redacted]	-	-	-
Incremental outcomes (onasemnogene abeparvovec vs BSC)							
	Costs (£)†	**QALYs (Undisc)**	**LYs†**	**QALYs†**	**INMB at £100,000 /QALY**	**INMB at £300,000 /QALY**	**ICER**
Onasemnogene abeparvovec vs BSC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: Undisc. undiscounted; BSC, best supportive care; ICER, incremental cost-effectiveness ratio; LYs, life years; QALYs, quality-adjusted life years; INMB, Incremental Net Monetary Benefit.
†Values presented are based on a discount rate of 3.5%.

3.1. Results under scenario D2 (2-week treatment delay)

Table 3: Economic analysis results for the full cohort (Scenario D2) (PAS price)

	Costs (£)†	**QALYs (Undisc)**	**LYs†**	**QALYs†**			
BSC	882,564	[redacted]	[redacted]	[redacted]	-	-	-
Onasemnogene abeparvovec	[redacted]	[redacted]	[redacted]	[redacted]	-	-	-
Incremental outcomes (onasemnogene abeparvovec vs BSC)							
	Costs (£)†	**QALYs (Undisc)**	**LYs†**	**QALYs†**	**INMB at £100,000 /QALY**	**INMB at £300,000 /QALY**	**ICER**
Onasemnogene abeparvovec vs BSC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: Undisc. undiscounted; BSC, best supportive care; ICER, incremental cost-effectiveness ratio; LYs, life years; QALYs, quality-adjusted life years; INMB, Incremental Net Monetary Benefit.
†Values presented are based on a discount rate of 3.5%.

Table 4: Economic analysis results for the 2-copy cohort (Scenario D2) (PAS price)

	Costs (£)†	QALYs (Undisc)	LYs†	QALYs†			
BSC	538,617	[redacted]	[redacted]	[redacted]	-	-	-
Onasemnogene abeparvovec	[redacted]	[redacted]	[redacted]	[redacted]	-	-	-
Incremental outcomes (onasemnogene abeparvovec vs BSC)							
	Costs (£)†	**QALYs (Undisc)**	**LYs†**	**QALYs†**	**INMB at £100,000 /QALY**	**INMB at £300,000 /QALY**	**ICER**
Onasemnogene abeparvovec vs BSC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: Undisc. undiscounted; BSC, best supportive care; ICER, incremental cost-effectiveness ratio; LYs, life years; QALYs, quality-adjusted life years; INMB, Incremental Net Monetary Benefit.
†Values presented are based on a discount rate of 3.5%.

3.2. Results under scenario D4 (4-week treatment delay)

Table 5: Economic analysis results for the full cohort (Scenario D4) (PAS price)

	Costs (£)†	QALYs (Undisc)	LYs†	QALYs†			
BSC	882,564	[redacted]	[redacted]	[redacted]	-	-	-
Onasemnogene abeparvovec	[redacted]	[redacted]	[redacted]	[redacted]	-	-	-
Incremental outcomes (onasemnogene abeparvovec vs BSC)							
	Costs (£)†	**QALYs (Undisc)**	**LYs†**	**QALYs†**	**INMB at £100,000 /QALY**	**INMB at £300,000 /QALY**	**ICER**
Onasemnogene abeparvovec vs BSC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: Undisc. undiscounted; BSC, best supportive care; ICER, incremental cost-effectiveness ratio; LYs, life years; QALYs, quality-adjusted life years; INMB, Incremental Net Monetary Benefit.
†Values presented are based on a discount rate of 3.5%.

Table 6: Economic analysis results for the 2-copy cohort (Scenario D4) (PAS price)

	Costs (£)†	QALYs (Undisc)	LYs†	QALYs†			
BSC	538,617	[redacted]	[redacted]	[redacted]	-	-	-
Onasemnogene abeparvovec	[redacted]	[redacted]	[redacted]	[redacted]	-	-	-
Incremental outcomes (onasemnogene abeparvovec vs BSC)							
	Costs (£)†	**QALYs (Undisc)**	**LYs†**	**QALYs†**	**INMB at £100,000 /QALY**	**INMB at £300,000 /QALY**	**ICER**
Onasemnogene abeparvovec vs BSC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: Undisc. undiscounted; BSC, best supportive care; ICER, incremental cost-effectiveness ratio; LYs, life years; QALYs, quality-adjusted life years; INMB, Incremental Net Monetary Benefit.
†Values presented are based on a discount rate of 3.5%.

3.3. Results under scenario D6 (6-week treatment delay)

Table 7: Economic analysis results for the full cohort (Scenario D6) (PAS price)

	Costs (£)†	QALYs (Undisc)	LYs†	QALYs†			
BSC	882,564	[redacted]	[redacted]	[redacted]	-	-	-
Onasemnogene abeparvovec	[redacted]	[redacted]	[redacted]	[redacted]	-	-	-
Incremental outcomes (onasemnogene abeparvovec vs BSC)							
	Costs (£)†	**QALYs (Undisc)**	**LYs†**	**QALYs†**	**INMB at £100,000 /QALY**	**INMB at £300,000 /QALY**	**ICER**
Onasemnogene abeparvovec vs BSC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: Undisc. undiscounted; BSC, best supportive care; ICER, incremental cost-effectiveness ratio; LYs, life years; QALYs, quality-adjusted life years; INMB, Incremental Net Monetary Benefit.
†Values presented are based on a discount rate of 3.5%.

Table 8: Economic analysis results for the 2-copy cohort (Scenario D6) (PAS price)

	Costs (£)†	QALYs (Undisc)	LYs†	QALYs†			
BSC	538,617	[redacted]	[redacted]	[redacted]	-	-	-
Onasemnogene abeparvovec	[redacted]	[redacted]	[redacted]	[redacted]	-	-	-
Incremental outcomes (onasemnogene abeparvovec vs BSC)							
	Costs (£)†	**QALYs (Undisc)**	**LYs†**	**QALYs†**	**INMB at £100,000 /QALY**	**INMB at £300,000 /QALY**	**ICER**
Onasemnogene abeparvovec vs BSC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: Undisc. undiscounted; BSC, best supportive care; ICER, incremental cost-effectiveness ratio; LYs, life years; QALYs, quality-adjusted life years; INMB, Incremental Net Monetary Benefit.
†Values presented are based on a discount rate of 3.5%.