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]

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A MEMBER OF THE RUSSELL GROUP

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

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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).

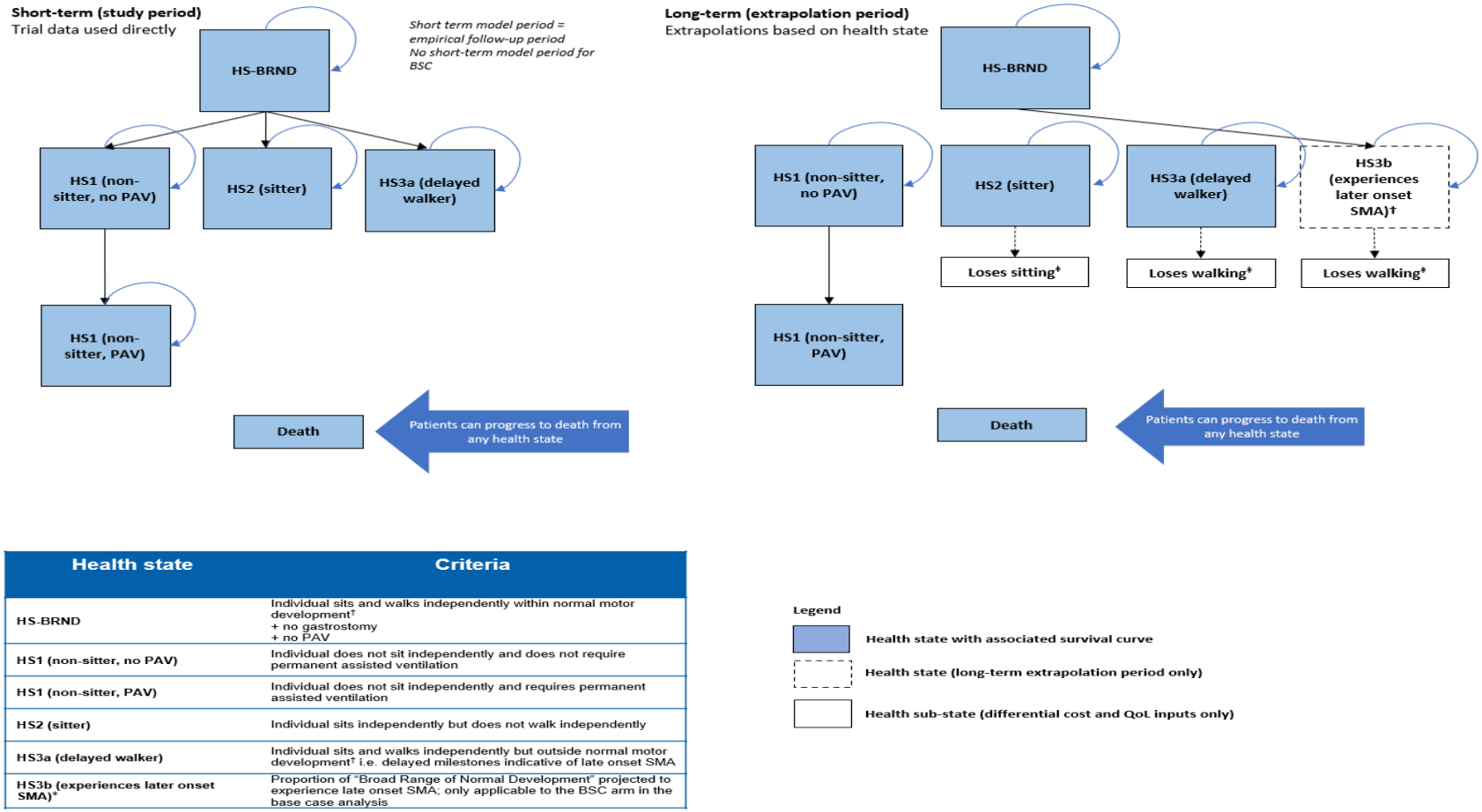
The onasemnogene abeparvovec arm of the model consists of two parts: 1) a short-term model, and 2) a long-term extrapolation model. After the short-term phase, which reflects the empirical period, patients enter the long-term extrapolation phase in the same health state that was assigned to them in the 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))