For the public: contains no confidential information

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

Highly Specialised Technology 1ST Committee Meeting [9th February 2023]

Chair: Peter Jackson

Lead team: Paul Arundel, Sarah Davies and Karen Whitehead

Evidence assessment group: Liverpool Reviews and Implementation Group (LRiG)

NICE technical team: Alan Moore, Sally Doss and Jasdeep Hayre

Company: Novartis gene therapies

Key issues

The key issues as outlined in the External Assessment Group (EAG) report

Issue	ICER impact
Generalisability of SPR1NT trial to NHS practice [NICE lead team identified issue]	High
What is the most relevant comparator?	High
Long-term clinical effectiveness of onasemnogene abeparvovec administered pre-symptomatically is not known	Unknown
Clinical effectiveness evidence of onasemnogene abeparvovec is only available from trials with small sample sizes	Unknown
Population should be considered by number of copies of the *SMN2* gene	Medium
EAG exploration of areas of uncertainty	Medium

Overview of condition

Pre-symptomatic SMA develops into a range of SMA types with different severity if untreated

- **SMA:** a genetic, progressive neuromuscular disease most commonly caused by mutations in the *SMN1* gene on chromosome 5q. *SMN1* gene encodes the "survival motor neurone" (SMN) protein and lack of SMN protein causes motor neurones to malfunction, deteriorate and die. *SMN2* gene also produces SMN protein
- SMA causes muscle weakness and progressive loss of movement. Motor neurones control walking, crawling, arm movement, head and neck movement, swallowing and breathing
- SMA is a heterogeneous condition, often grouped into 5 main types (0 to 4), based on age of onset of symptoms and level of motor function. Some people can be diagnosed pre-symptomatically if they have a sibling with SMA. New-born screening for SMA is not routinely done in clinical practice in England

SMA classification system			
Type	Age at symptom onset	Maximum Motor Function	Life Expectancy
0*	Foetal	Nil	Days to weeks
1	less than 6 months	Never sits	Less than 2 years
2	6 – 18 months	Never walks	20 – 60 years
3	1.5 – 10 years	Walks, regression	As per general population
4*	more than 35 years	Slow decline	

*SMA type 0 and 4 are rarely diagnosed

Onasemnogene Abeparvovec (Zolgensma)

Novartis Gene Therapies

Conditional Marketing authorisation	Indicated for the treatment of people: • with 5q spinal muscular atrophy (SMA) with a bi-allelic mutation in the *SMN1* gene and a clinical diagnosis of SMA Type 1, or • 5q SMA with a bi-allelic mutation in the *SMN1* gene and up to 3 copies of the *SMN2* gene
Mechanism of action	Gene replacement therapy made of a viral vector modified to contain the primary gene for human survival motor neuron (SMN) protein When infused, the vector is expected to carry the gene into the nerve cells, enabling production of sufficient amounts of SMN protein
Administration & dose	• Single peripheral intravenous (IV) infusion • Weight based dosing: 1.1 x 10^{14} vector genome copies per kg (vg/kg) • SmPC gives dosing schedule up to 21 kg
List price and PAS discount	• List price for onasemnogene aberparvovec is £1,795,000 for one-off dose • Simple discount patient access scheme (PAS) approved

SmPC states that there is limited experience in patients 2 years of age and older or with body weight above 13.5 kg. Safety and efficacy in these patients has not been established

NICE

SmPC: Summary of Product Characteristics, PAS: Patient Access Scheme

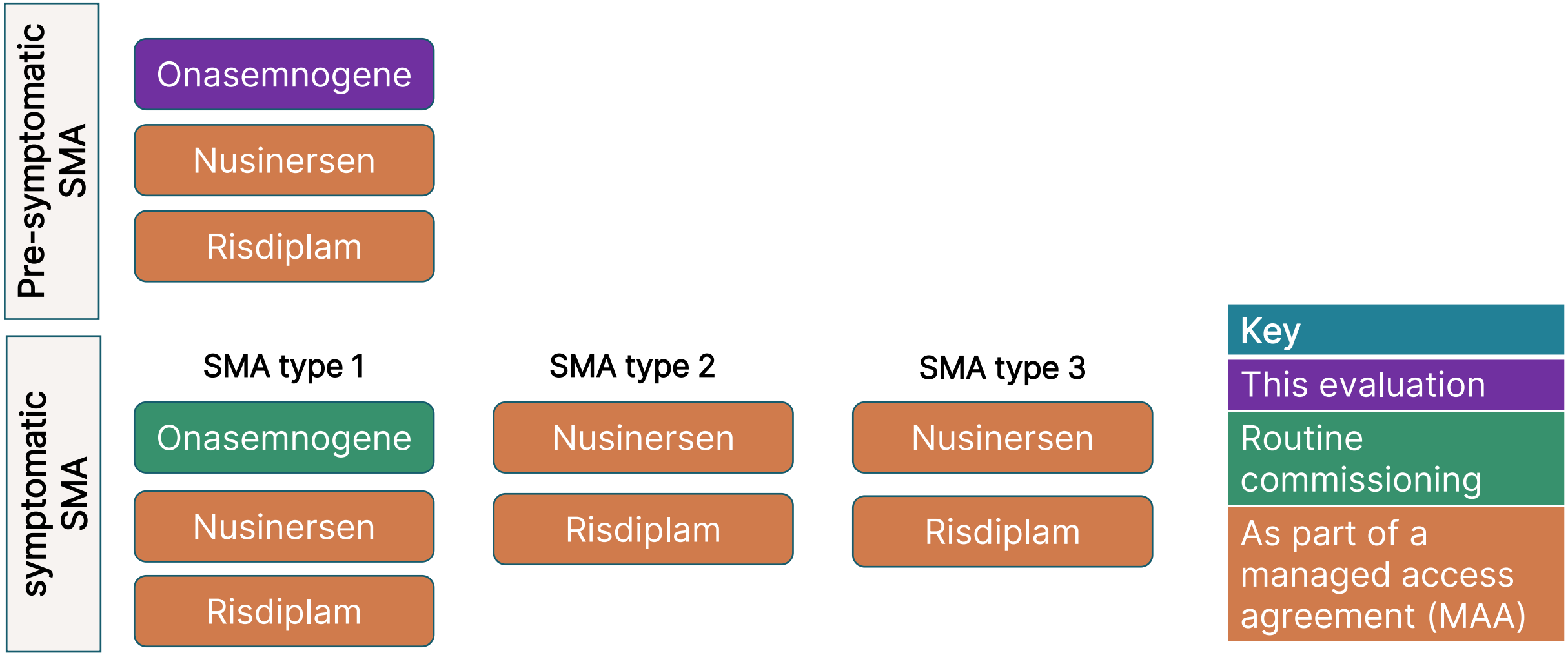
HST 15 recommendations

HST15 recommended onasemnogene for SMA type 1 and within a managed access agreement (MAA) for pre-symptomatic SMA

- **1.1** Onasemnogene abeparvovec is recommended as an option for treating 5q spinal muscular atrophy (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
- **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 presymptomatic 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 are followed. **[Focus of this review]**

Treatment pathway (SMA)

There are no treatments in routine commissioning for pre-symptomatic SMA



In current NHS clinical practice, pre-symptomatic SMA is diagnosed by testing siblings of patients with symptomatic SMA (there is no new-born screening currently for SMA)

Clinical expert perspectives

Input received from 2 clinical experts

Theme	Overview of comments
Treating pre-symptomatic SMA	• New-born screening (NBS) should be implemented (many European countries have NBS – England does not) • Earlier treatment associated with better outcomes
SPR1NT inclusion criteria vs NHS clinical practice	• Treatment delays may occur which may mean treating at <6weeks of age isn't always possible – important not to exclude treatment in such cases • Possible for pre-symptomatic diagnosis much older than 6 weeks (e.g at 2 years of age) – reasonable limit of 2 months should be set for treatment • Trial inclusion criteria of CMAP ≥2mV – CMAP not routinely measured in NHS clinical practice and possible some infants have CMAP < 2mV • Trial inclusion criteria of gestational age 35-42 weeks - important to consider how to treat those born at less than 35 weeks gestation
The technology	• Similar effect to nusinersen or risdiplam but benefits of a one-off treatment. Benefits compared to BSC are very high
Other comments	• Onasemnogene has been administered to a much too broad population

BSC: Best supportive care, CMAP: Compound muscle action potential

Patient Perspective

Patient organisations and patient experts submissions

Summary of patient organisation and patient expert input

Theme	Overview of comments
The technology	• Benefits of one-off treatment – other treatments can be withdrawn with declining function. Other treatments can be invasive • Better outcomes seen in pre-symptomatic SMA. Unethical to wait until symptoms appear • Potential cost-savings with improved outcomes in pre-symptomatic treatment
Diagnosis of SMA	• Without new-born screening, it is very difficult to diagnosis pre-symptomatic SMA. New-born screening is needed to achieve best outcomes • Delays in diagnosing symptomatic SMA can occur in NHS clinical practice – leads to poorer prognosis
Impact of SMA	• Severe forms of SMA have a huge effect on patients and caregivers • Impacts all aspects of life, e.g schooling, socialising, feeding and daily tasks • Frequent hospitalisations and ongoing treatments • Caregivers have constant anxiety and limited social life. Caregivers may have to give up employment to care for their child

Patient expert submissions

Quotes from patient expert submissions

"We were constantly alert for any signs of sudden deterioration, he could be playing happily in the morning and then admitted to PICU the same evening."

Parent of a child with SMA type 1 on impact of SMA type 1

"The 24 hour-a-day responsibility of caring for a child with complex medical needs that follows is physically, emotionally and psychologically exhausting: constant re-positioning and care, large amounts of medical equipment ."

SMA UK and MDUK submission on impact of SMA type 1 on caregivers

Onasemnogene clinical effectiveness (pre-symptomatic)

The SPR1NT trial is now complete

SPR1NT trial	
Description	SPR1NT is a Phase III, open-label, single-arm, multi-centre trial, six countries (Australia, Belgium, Canada, Japan, UK, USA)
Key inclusion criteria	Babies with pre-symptomatic SMA defined by bi-allelic deletion of *SMN1* and two or three copies of the *SMN2* gene and age ≤6 weeks (≤42 days) at time of dose
Primary outcomes	• Cohort with two copies of the *SMN2* gene (n=14) Child sits alone without support for ≥30 seconds up to age 18 months • Cohort with three copies of the *SMN2* gene (n=15) Standing alone for ≥3 seconds at up to age 24 months
Secondary outcomes	Cohort with two copies of the *SMN2* gene (n=14) • Event-free survival at age 14 months + ability to maintain weight at or above 3rd percentile (without non-oral/mechanical feeding support) at visits to age 18 months Cohort with three copies of the *SMN2* gene (n=15) • Walking alone (≥5 steps, displaying coordination + balance) to age 24 months

Onasemnogene clinical effectiveness (pre-symptomatic)

The SPR1NT trial is now complete

Results: 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 up to age 18 months	n (%)	14 **(100%)**
	Achieved within normal range, n (%)*	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 (%)		14 **(100%)**
Ability to maintain weight at or above 3rd percentile (without non-oral/mechanical feeding support) up to age 18 months, n (%)		13 **(92.9%)**

NICE *99th percentile ≤279 days of age (sitting without support); World Health Organisation definition

Onasemnogene clinical effectiveness (pre-symptomatic)

The SPR1NT trial is now complete

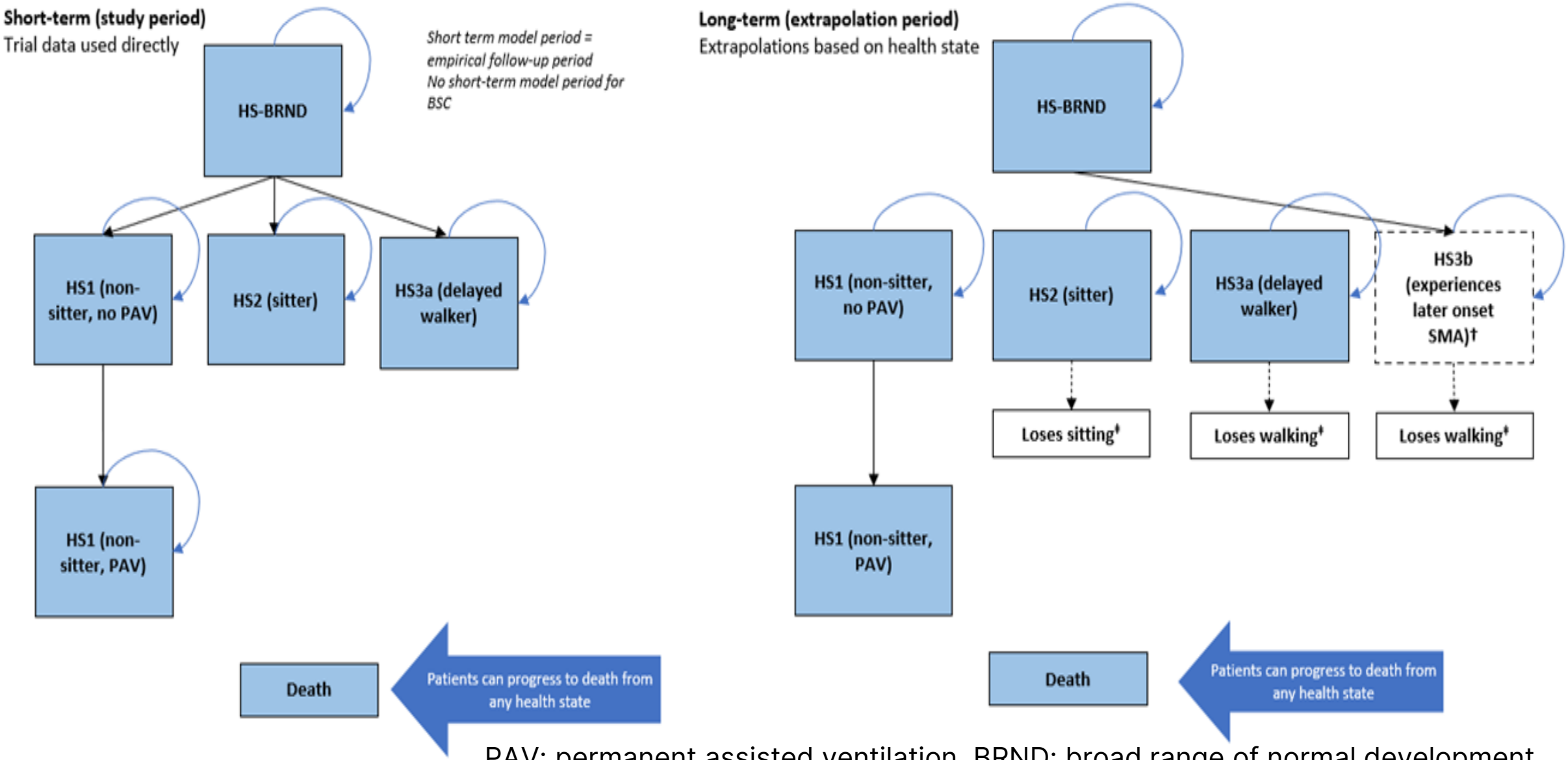
Results: primary and secondary efficacy endpoints for patients with three copies of the *SMN2* gene (n=15)

Endpoint		Result
Primary efficacy endpoint		
Standing alone for ≥3 seconds up to age 24 months	n (%)	15 **(100%)**
	Achieved within normal range, n (%)*	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	n (%)	14 **(93.3%)**
	Achieved within normal range, n (%)*	11 **(73.3%)**
	Age (months) when milestone was first demonstrated, mean (SD) [range]	14.6 (2.48) [12.1 to 18.8]

*99th percentile ≤514 days of age (standing alone), ≤534 days of age (walking alone); World Health Organisation definition

Economic model summary

The company's model consists of a short term part (informed by clinical trial results) and a longer term part (informed by assumptions/extrapolations)



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

Economic model summary (2)

Summary of key assumptions in company analysis

Parameter	
Model description and health states	Cohort Markov state-transition model based on motor milestones. Health states: **HS1**; non-sitter permanent assisted ventilation (PAV), and non-sitter no PAV [SMA type 1 proxy], **HS2**; sitter [SMA type 2 proxy], **H3a/b**; delayed walker/later onset [SMA type 3 proxy], BRND: broad range of normal development
Transitions in short term model	Informed by clinical trial data (SPR1NT + LT-002) in onasemnogene arm. BSC arm informed by natural history studies (PNCR, NeuroNext and Wijngaarde et al, 2020)
Long-term effectiveness assumptions	Motor milestones achieved in short term model assumed to be retained overtime in onasemnogene arm. In BSC arm, milestone loss assumed to occur in % of patients (based on Wadman 2018)
Health state utilities	Walking (**General population**), Loss of walking* (**0.774**), Sitting (**0.60**), Loss of sitting* (**0.19**) Non-sitting + no PAV (**0.19**), Non-sitting PAV (**0.0**)
Health state costs	Based on HST15: HS1 no PAV (£112,500), HS1 PAV (£283,710), HS2 (£67,567), HS3 (£8,333)
Additional information	3.5% discount rate used in base case, 1.5% discount rate accepted in HST15

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*Only applicable to best supportive care arm, PNCR: Pediatric Neuromuscular Clinical Research, BRND: broad range of normal development

NHS England statement on onasemnogene adverse events

NHS England has informed the public on reported onasemnogene adverse events in NHS clinical practice

NHS England statement:

- Following discussion with the National MDT (NMDT), there will be a temporary change to eligibility for NHS funded onasemnogene in England
- A small number of children, particularly those who are older and weighing more than 13.5 kg, have had suspected significant adverse drug reactions affecting the liver following administration
- Considering these adverse events, and noting there are 2 other disease-modifying drugs available [within Managed Access], NHS funded treatment with onasemnogene in England should be temporarily paused in children older than 12 completed months (as per NICE guidance)
- The MHRA are reviewing data including information and adverse incident reports

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Key Issues

Key issue: Generalisability of SPR1NT to NHS practice

SPR1NT inclusion criteria included restrictions on age at treatment

Background

- The SPR1NT trial included babies with pre-symptomatic SMA treated with onasemnogene at 6 weeks of age or younger - NICE lead team were concerned that this may not be reflective of the population in NHS clinical practice
- The marketing authorisation for onasemnogene does not mention age but does state that *"There is limited experience in patients 2 years of age and older or with body weight above 13.5 kg"*
- Clinical expert input received by NICE stated that diagnosis and treatment of pre-symptomatic can occur after 6 weeks of age

NICE requested additional company analysis on effect of age at treatment; specifically to consider adjusting the economic model to account for a scenario assuming treatment at 1 year of age (NICE defines babies as 1 year and younger). Analysis should reflect:

- that those in the comparator arm would not develop type 1, have a lower chance of developing type 2 and higher chance of type 3 SMA
- they would have a different ratio in terms of *SMN2* copy number

NICE also suggested analysis assuming treatment at 6 months of age may also be useful

Company response to NICE further analysis request

Company provide additional analysis around age at treatment

Company provided 2 scenario analysis in response to NICE's request. Company note diagnosis of pre-symptomatic SMA after 6 weeks of age is rare. Also highlight lack of data to inform requested analysis – assumptions validated with experts but are highly uncertain

Scenario 1 – cost-effectiveness of treatment later than 6 weeks, up to 1 year

Background:

- Diagnosis at 1 year highly unlikely – all patients with 2 *SMN2* copies and majority with 3 copies expected to develop symptoms by this timepoint
- Propose economic evaluation of those aged ≥6 months at treatment (when SMA type 1 not possible)

Analysis:

- Analysis informed by rescaling probabilities of developing SMA types 2 and 3 used in base case (based on Calucho et al 2018)
- Clinical expert advice: at 6 months of age 5% would have 2 *SMN2* copies and 95% would have 3 *SMN2* copies in the pre-symptomatic population
- Company also run conservative analysis which assumes equal probability of developing SMA type 2 and SMA type 3, and an analysis which assumes treatment efficacy reduction based on clinical expert input

Company response to NICE further analysis request (2)

Summary of input for characterizing outcomes in BSC patients

Table 3 from company additional analysis: SMA severity type in patients of overall pre-symptomatic population, P* population and P* with equal SMA Type 2/Type 3 split

	Overall pre-symptomatic population (base case) (%)		P* population (%)		P* with equal T2/T3 split population (%)	
	2-copy =65.15%	3-copy =34.85%	2-copy =5%	3-copy =95%	2-copy =0%	3-copy =100%
SMA type 1	79	15	0	0	NA	0
SMA type 2	16	54	76.2	63.5	NA	50
SMA type 3a	5	16	23.8	18.8	NA	25
SMA type 3b	0	15	0	17.7	NA	25

Reduced efficacy scenario – treating patients 6 months and older

- Possible that many motor neurones preserved due to asymptomatic population – plausible to assume similar efficacy as in base case
- However, irreversible neuron loss could occur despite absence of symptoms – therefore company provide results assuming efficacy reduction
- Based on clinical expert input, rough estimate of up to 20% reduction for patients with 2 *SMN2* copies and up to 10% for patients with 3 copies – for those treated after 6 months of age

NICE

***P population** = population aged 6 months and over at treatment

Company response to NICE further analysis request (3)

Scenario 2 – cost-effectiveness of treating patients diagnosed by 6 weeks of age, but treated after this timepoint

Background:

- May be possible that babies diagnosed before 6 weeks receive delayed treatment

Analysis:

- In absence of data, company provided a scenario which assumes a linear decline in onasemnogene efficacy in babies older than 6 weeks to a timepoint at which they would no longer be expected to achieve ambulation – based on clinical expert input
  - Timepoint: 2 *SMN2* copies =22 weeks, 3 *SMN2* copies =78 weeks
- Based on SPR1NT results and clinical expert input an efficacy decline of 5.8% per week is modelled (93%/(22-6)) for 2 *SMN2* copies and 1.4% per week for 3 *SMN2* copies (100%/(78-6)) – company provided analysis for 2,4 and 6 week treatment delays

Percentage reduction in achieving milestones of ambulation by treatment delay

Scenario name	Delay duration	Age at treatment	% reduction in efficacy	
			2-copy cohort	3 copy cohort
D2	2-week delay	8 weeks	11.6%	2.8%
D4	4-week delay	10 weeks	23.2%	5.6%
D6	6-week delay	12 weeks	34.8%	8.4%

EAG critique of company's additional analysis

EAG is satisfied with the company's additional scenarios

- EAG has re-run the company's additional scenarios and identified minor discrepancies but do not believe these impact on decision-making
- EAG believe that company's scenario 2 cost-effectiveness results to be pessimistic – as it assumes walking is not possible if treatment occurs after 22 weeks for those with 2 *SMN2* copies
  - trial results from HST15 shows a proportion of symptomatic patients with 2 *SMN2* copies were able to walk
- EAG is satisfied with the company's approach, recognising the lack of clinical effectiveness evidence to support both scenarios

NICE

Is the panel satisfied that onasemnogene clinical evidence is generalisable to the NHS? Should an age restriction be included in any recommendation?

Key issue: Relevant comparator

HST15 recommended onasemnogene for SMA type 1

Background

- Currently no routinely available treatments for pre-symptomatic SMA
- Pre-symptomatic SMA can develop into a range of SMA types (1-3) if untreated
- If pre-symptomatic SMA develops into SMA type 1, HST15 recommends onasemnogene as a treatment option
- The company consider best supportive care to be the relevant comparator – but also provide a comparison where onasemnogene is in the comparator arm

EAG

- EAG believe that the relevant comparator is onasemnogene for SMA type 1 and best-supportive care for SMA types 2 and 3

What is the most relevant comparator?

Key issues: Limited long term evidence and small numbers in pivotal trial

Company assume no loss of motor milestones gained in SPR1NT– there is limited long-term evidence to support this assumption

Background

- Clinical evidence comes from SPR1NT – which included 14 babies with 2 *SMN2* copies and 15 babies with 3 *SMN2* copies
- Company model assumes motor milestones gained in clinical trial period are maintained over a lifetime
- Limited long term evidence from LT-002 is available (long term follow up trial; data available to maximum follow-up to age [redacted]) – no loss in motor milestones in data and some new milestones achieved

EAG

- Keep assumption of no motor milestone loss in their base case analysis but state if motor milestones are lost then cost-effectiveness decreases

Key issues: Results by *SMN2* copy number and additional EAG scenario analysis

EAG prefer to consider results by *SMN2* copy number and provide additional analysis

Background

- *SMN2* gene copies can compensate to some degree for lack of *SMN1* gene
- Babies with pre-symptomatic SMA and 2 *SMN2* gene copies are more likely to develop severe SMA types if untreated compared to babies with 3 *SMN2* gene copies
- SPR1NT trial included different outcomes and follow-up by number of *SMN2* gene copies
- Company state full population should be considered together
- While the EAG base case mirrors that of the company, they also provided 2 additional scenario analysis to test impact of assuming no motor milestone loss and social care costs (2nd largest cost category and EAG report company's sourcing of this cost to be unclear)

EAG

- Believe that results should be considered by *SMN2* copy number
- The ICER estimates stays below £100,000 per QALY gained across alternative EAG scenarios, and across *SMN2* subgroups

Should results be considered by *SMN2* gene copy number?

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Cost-effectiveness results - Base case

Summary of cost-effectiveness results

Analysis	Description	Carried out by
Base case analysis in company submission and EAG report		
Base case v BSC	Base case analysis comparing onasemnogene to best supportive care	Company+ EAG
Base case v BSC/ onasemnogene	Base case analysis comparing onasemnogene to best supportive care and onasemnogne (SMA type 1)	Company+ EAG
SMN2 subgroups	Results by 2 and 3 *SMN2* gene copies	Company+ EAG
Motor milestone loss scenario	Assuming the same motor milestone loss over time in both arms of the model	EAG
Social care costs scenario	Setting social care costs to zero	EAG
Company additional scenario analysis in response to NICE request		
Age ≥6 months	% expected to develop SMA types 2 and 3 recalculated. Reduced efficacy scenario also provided	Company
Treatment delayed	Reduction in efficacy estimated by length of treatment delay (2,4 and 6 week delay modelled)	Company

BSC: best supportive care

Cost-effectiveness results

Both the company and EAG base case analysis align

Company and EAG results: full cohort

Technology	Incremental (OA v BSC)			ICER (£/QALY)
	Costs	Life years	QALY	
BSC	-	-	-	-
Onasemnogene	[redacted]	[redacted]	[redacted]	[redacted]

Analysis results in [redacted] incremental undiscounted QALYs

Company and EAG results with onasemnogene in comparator arm

Technology	Incremental (OA v OA/BSC)			ICER (£/QALY)
	Costs	Life years	QALY	
OA as pre-symptomatic treatment	-	-	-	-
OA at symptom-onset if patient develops type 1 SMA and BSC otherwise	[redacted]	[redacted]	[redacted]	OA pre-symptomatic is dominant

Results do not include a QALY weighting and assume a 3.5% discount rate (1.5% was used in HST15)

OA: onasemnogene abeparvovec, BSC: best supportive care

Cost-effectiveness results (onasemnogene v BSC)

EAG provide 2 scenario analyses to explore uncertainty

EAG scenario analysis: 2 *SMN2* copies

EAG scenarios	Incremental (OA v BSC)		ICER
	Cost	QALYs	£/QALY
A1: Company base case (deterministic)	[redacted]	[redacted]	[redacted]
Scenario 1: Milestone loss is equal to that of patients in the BSC arm	[redacted]	[redacted]	[redacted]
Scenario 2: Social care costs set to zero	[redacted]	[redacted]	[redacted]

EAG scenario analysis: 3 *SMN2* copies

EAG scenarios	Incremental (OA v BSC)		ICER
	Cost	QALYs	£/QALY
A1: Company base case (deterministic)	[redacted]	[redacted]	[redacted]
Scenario 1: Milestone loss is equal to that of patients in the BSC arm	[redacted]	[redacted]	[redacted]
Scenario 2: Social care costs set to zero	[redacted]	[redacted]	[redacted]

OA: onasemnogene abeparvovec, BSC: best supportive care

Cost-effectiveness results (onasemnogene v onasemnogene/BSC)

EAG provide 2 scenario analyses to explore uncertainty

EAG scenario analysis: 2 *SMN2* copies

EAG scenarios	Incremental (OA v OA/BSC)		ICER
	Cost	QALYs	£/QALY
A1: Company base case (deterministic)	[redacted]	[redacted]	Pre-symptomatic OA dominant
Scenario 1: Milestone loss = BSC arm	[redacted]	[redacted]	Pre-symptomatic OA dominant
Scenario 2: Social care costs set to zero	[redacted]	[redacted]	Pre-symptomatic OA dominant

EAG scenario analysis: 3 *SMN2* copies

EAG scenarios	Incremental (OA v OA/BSC)		ICER
	Cost	QALYs	£/QALY
A1: Company base case (deterministic)	[redacted]	[redacted]	Pre-symptomatic OA dominant
Scenario 1: Milestone loss = BSC arm	[redacted]	[redacted]	Pre-symptomatic OA dominant
Scenario 2: Social care costs set to zero	[redacted]	[redacted]	Pre-symptomatic OA dominant

OA: onasemnogene abeparvovec, BSC: best supportive care

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Cost-effectiveness results – NICE request

Company additional analysis (NICE request)

Company provide updated analysis based on age at treatment

Company additional Scenario 1: treated at age 6 months or older

Economic analysis results for full cohort of Population P* (weighted results) + *SMN2* subgroups

Incremental outcomes (Onasemnogene vs BSC)				
	Costs (£)	QALYs (Undisc)	QALYs	ICER
Onasemnogene abeparvovec vs BSC	[redacted]	[redacted]	[redacted]	[redacted]
2 *SMN2* copy subgroup				
Onasemnogene abeparvovec vs BSC	[redacted]	[redacted]	[redacted]	[redacted]
3 *SMN2* copy subgroup				
Onasemnogene abeparvovec vs BSC	[redacted]	[redacted]	[redacted]	[redacted]

Population P* = population used in company additional analysis (company define as those aged 6 months and older where SMA type 1 will not develop) – NICE technical team and lead team interpret this as analysis for those aged 6 months

Company additional analysis (NICE request) (2)

Company additional Scenario 1: treated at age 6 months or older assuming efficacy loss

Economic analysis results (efficacy loss scenario) for full cohort of Population P* + *SMN2* subgroups

Incremental outcomes (onasemnogene abeparvovec vs BSC)				
	Costs (£)	QALYs (Undisc)	QALYs	ICER
Onasemnogene abeparvovec vs BSC	[redacted]	[redacted]	[redacted]	[redacted]
2 *SMN2* copy subgroup				
Onasemnogene abeparvovec vs BSC	[redacted]	[redacted]	[redacted]	[redacted]
3 *SMN2* copy subgroup				
Onasemnogene abeparvovec vs BSC	[redacted]	[redacted]	[redacted]	[redacted]

(analysis assumes 20% efficacy reduction in 2-copy patients and 10% efficacy reduction in 3-copy patients)

NICE BSC: best supportive care

Company additional analysis (NICE request) (3)

Company additional Scenario 1: treated at age 6 months or older assuming equal split of SMA type 2 and 3 in comparator arm

Economic analysis results (equal split SMA type 2 and 3 in BSC arm) for Population P* + *SMN2* subgroups

Incremental outcomes (onasemnogene abeparvovec vs BSC)				
	Costs (£)	QALYs (Undisc)	QALYs	ICER
3 *SMN2* copy subgroup with equal split of SMA type 2 and type 3				
Onasemnogene abeparvovec vs BSC	[redacted]	[redacted]	[redacted]	[redacted]
Equal split of SMA type 2 and 3 and 10% reduction in efficacy (population P*)				
Onasemnogene abeparvovec vs BSC	[redacted]	[redacted]	[redacted]	[redacted]

The NICE lead team and NICE technical team consider this analysis to better reflect the NICE request (a child aged 12 months at treatment)

NICE BSC: best supportive care

Company additional analysis (NICE request) (4)

Company provide updated analysis based on age at treatment

Company additional scenario 2 (delays in treatment)

Economic analysis results (delays in treatment after 6 weeks)

Incremental outcomes (onasemnogene abeparvovec vs BSC)						
	Costs (£)	QALYs (Undisc)	QALYs	ICER	ICER: 2 *SMN2* copies	ICER: 3 *SMN2* copies
2 week treatment delay						
OA vs BSC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
4 week treatment delay						
OA vs BSC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
6 week treatment delay						
OA v BSC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

OA: onasemnogene abeparvovec, BSC: best supportive care

Key issues

The key issues as outlined in the EAG report

Issue	ICER impact
Generalisability of SPR1NT trial to NHS practice [NICE lead team identified issue]	High
What is the most relevant comparator?	High
Long-term clinical effectiveness of onasemnogene abeparvovec administered pre-symptomatically is not known	Unknown
Clinical effectiveness evidence of onasemnogene abeparvovec is only available from trials with small sample sizes	Unknown
Population should be considered by number of copies of the *SMN2* gene	Medium
EAG exploration of areas of uncertainty	Medium

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Thank you.