NICE National Institute for Health and Care Excellence

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Onasemnogene abeparvovec for treating spinal muscular atrophy

Lead team presentation

1st Evaluation meeting

Highly Specialised Technologies committee, 8th October 2020

Chair: Peter Jackson

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Company: Novartis Gene Therapies

ERG: BMJ TAG

Key abbreviations

AE	Adverse event	NIV	Non-invasive ventilation
BSC	Best supportive care	NR	Not reported
CI	Confidence interval	ONS	Office for National Statistics
EAMS	Early Access to Medicines Scheme	OS	Overall survival
EFS	Event-free survival	PAS	Patient Access Scheme
EMA	European Medicines Agency	PAV	Permanent assisted ventilation
EPAR	European Public Assessment Report	QALY	Quality-adjusted life year
EQ-5D	EuroQol 5 dimensions	RCT	Randomised controlled trial
EQ-5D-5L	EuroQol 5 dimensions 5 levels	SD	Standard deviation
HDU	High dependency unit	SMA	Spinal muscular atrophy
HRQoL	Health-related quality of life	SMN	Survival motor neurone
ICER	Incremental cost-effectiveness ratio	SmPC	Summary of product characteristics
ICU	Intensive care unit	SoC	Standard of care
LY	Life years	TEAE	Treatment-emergent adverse event
MAA	Managed access agreement		

History of the topic

- Following a submission in 2019 the company advised of an extension to its regulatory timings – **committee meeting delayed**
  - ERG report produced and shared with company January 2020
  - Supplementary appendix and updated economic model submitted by company in May 2020 incorporating updated trial data. ERG produced updated report.
- **Original anticipated indication:** for spinal muscular atrophy type 1
- **Final SmPC indication:** for the treatment of:

  - patients with 5q spinal muscular atrophy (SMA) with a bi-allelic mutation in the *SMN1* gene and a clinical diagnosis of SMA Type 1, or

  - patients with 5q SMA with a bi-allelic mutation in the *SMN1* gene and up to 3 copies of the *SMN2* gene.
- **SmPC treatment initiation and dosing rules:**
  - Before administration, baseline laboratory testing including **AAV9 antibody testing is required**
  - Recommended dosing given for people who **weigh 2.6 kg to 21.0 kg**
  - **Safety and efficacy in premature neonates** before reaching full-term gestational age **have not been established**. No data are available
  - 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**

Key Issues: clinical effectiveness

- Clinical Evidence
  - Are the onasemnogene clinical trials generalisable to the:
    - indicated population in the marketing authorisation and SmPC?
    - NHS clinical practice in England?
    - future NHS clinical practice in England?
  - Is the NeuroNext (natural history) study the most appropriate to reflect best supportive care outcomes?
  - Are there other populations likely to benefit from treatment beyond those included in the clinical trials?
- Does the committee conclude the clinical trials capture:
  - Benefits that are important to patients? All relevant aspects of the disease?
- Clinical effectiveness
  - How effective is onasemnogene?
  - How robust are the trial results?
  - How uncertain are long-term effects of treatment?
  - Are the interim results for the pre-symptomatic population robust enough for decision-making?

Nature of the condition: Spinal Muscular Atrophy (SMA)

- **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
  - Lack of SMN protein causes the motor neurones to malfunction, deteriorate and eventually die
- Causes muscle weakness and progressive loss of movement
- Motor neurones control walking, crawling, arm movement, head and neck movement, swallowing and breathing
- 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
  - Patient experts emphasised that there is a spectrum across these different types and that boundaries can be blurred
- Some people can be diagnosed pre-symptomatically if they have a sibling with SMA – pre-natal screening is not routinely done in clinical practice in England
- Substantial effects on families and carers, including impact of caring for the patient, need for specialist equipment and ongoing emotional, financial and social impacts

Nature of the condition: Spinal Muscular Atrophy (SMA) Type 1

- **SMA type 1 is the most severe form of SMA and the main genetic cause of infant mortality (if untreated)**: symptoms arise before age 6 months. Babies unable to sit independently and have low muscle tone (hypotonia)
- **Affects every aspect of infants life**: never gain developmental milestones after initial presentation, severe muscle weakness affecting movement, swallowing and breathing
- **Severity can be liked to age at which symptoms appear** - earlier onset associated with more severe disease. Time between onset and treatment administration is important
- Most people with SMA type 1 will die before 2 years of age when treated with best supportive care

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 – 40 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

SMN2 copy number

- *SMN2* gene also produces SMN protein
- Higher numbers of the *SMN2* gene copies, the more SMN protein is produced by the cells
- Disease severity is related to the *SMN2* gene copy number and age of symptom onset
- Clinical expert stated that *SMN2* copy number is the most important factor in prognosis for pre-symptomatic SMA

SMN2* copy number by SMA type							
SMA type	**Number of people**	**Proportion of people with each *SMN2* copy number**					
		1	**2**	**3**	**4**	**5**	**6**
1	1,256	7%	**73%**	20%	<1%	<1%	0%
2	1,160	<1%	16%	**78%**	5%	<1%	0%
3	1,043	0%	5%	**49%**	44%	2%	<1%
Abbreviations: SMA, spinal muscular atrophy; SMN2, survival motor neurone 2 gene							

NICE

*Based on Calucho et al 2018

Current treatment options

- No active treatments currently routinely commissioned in the NHS
- SMA is managed through multidisciplinary supportive care
- Supportive care does not affect disease progression but aims to minimise impact of disability, address complications and improve quality of life
- Supportive care may involve:
  - respiratory, gastroenterology and orthopaedic care
  - nutritional support
  - physiotherapy
  - assistive technologies
  - occupational therapy
  - social care
- Nusinersen (Spinraza) is the only active treatment available for treating SMA but is not routinely commissioned and recommended through a managed access agreement (MAA) for pre-symptomatic SMA and SMA types 1, 2 and 3

Clinical experts: current treatments

Aims of current treatment

- Aim of treatment and the outcome will depend on the timing of the treatment – early treatment associated with better outcomes
- Aims include improving all aspects of muscle function including mobility, respiratory function, truncal strength and swallowing

Current treatments

- Best supportive care (BSC)
- Nusinersen available via a managed access agreement (MAA)

Without treatment (Best supportive care)

- Those with untreated (BSC) SMA type 1 will never manage to sit independently
- Untreated patients need ventilation at some point (unless death occurs before)

Unmet need

- Untreated SMA type 1 is one of leading genetic causes of infant death
- Nusinersen associated with some challenges - repeated intrathecal administration and efficacy of medication: better treatments still needed

Clinical experts: onasemnogene

Innovation

- Novel change in treatment, requiring new pathways, re-emphasising early and rapid diagnosis
- Clearly a ‘step-change’ in treatment of newly diagnosed patients with SMA type 1

Benefits

- Increase in survival and health-related quality of life compared to standard care
- More benefits with earlier treatment

Subgroups

- People more severely affected and older less likely to see improvement of condition - aim will only be to prevent further progression
- People with only 1 *SMN2* copy would most likely not benefit from the treatment
- People with SMA type 2 and 3 not studied in clinical trials to date
- Treatment after 6 months of age may still result in significant and substantial impact on health-related benefits, but there is a lack of data to support this

Other considerations

- Clear guidance needed on eligibility criteria for the treatment
- Fast testing of for anti-AAV antibodies required (currently not routinely available)

NHS England comments

- Pathway for diagnosis well defined – standard genetic testing widely available
- Care delivered as set out in the international standards of care
- Onasemnogene's place in current treatment pathway not well defined – new treatment with a novel mode of administration
    - Including logistics of providing intervention and services required to provide treatment should it receive positive NICE guidance
- Onasemnogene expected to require new pathways for preparation of patients, transfer of medicine from manufacturer, clinical delivery of medicine and long-term monitoring after treatment
- Variation to the funding requirement may be needed
- Consideration should be given to role of onasemnogene in relation to nusinersen use
- Risdiplam also available via the EAMS for individuals with type 1 and type 2 SMA aged 2 months and older and who are not suitable for treatment with nusinersen
- Incident population is small (approximately 40) – challenges of providing centres across the country as clinical expertise will be concentrated
- Consideration should be given to prevalent population in terms of eligibility
- Staff at highly specialised centres will need to be trained – should be provided by the company

Professional group submission

British Society of Childrens Orthopaedic Surgeons

Current management

- Usually a multidisciplinary team led by a paediatric neurologist at tertiary paediatric centres

Use of orthopaedic surgery

- Rarely indicated in this patient group – short life expectancy and high potential for respiratory complications associated with major surgery such as scoliosis correction
- Almost never an indication to stabilise dislocated hips for pain or function – lack of response to treatment for muscle weakness which causes these problems
- Use may increase if new treatments improve survival or reverse muscle weakness

Implementation

- If surgery to spine and wider lower limb musculoskeletal system is required, this may necessitate resources to tertiary centres to match demand – surgical technology already available on NHS and well established

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 1014 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

NICE 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

Patient and carer group submissions

Patient and carer group submissions

Living with SMA – impact on infants with SMA type 1

Symptoms of SMA type 1

- Intelligence is not affected
- Unable to lift or support head or sit unsupported
- Difficultly with rolling over
- Ability to move hands and fingers but difficulty moving arms and legs
- Breathing muscle weakness
- Increased risk of chest infections which can be life threatening
- Difficulty swallowing salvia, feeding and gaining weight

- SMA type 1 is fatal if no active treatment is given.
- Most physical abilities lost on progression

Other considerations

- Positioning is very important – if infant sits too upright or lies on anything curved then chest may concertina (“hunch up”)
  - During the day, position needs to be changed every hour or so
- 60 to 90% of those with SMA types 1 and 2 develop scoliosis – may use spinal brace

Patient and carer group submissions

Current treatments

Standard care treatments

- Multidisciplinary care (includes physiotherapy, dietary care, speech and language therapy, palliative care)
- Respiratory care: Including suction machines to remove secretions in mouth, BiPAP and non-invasive ventilation – small number will have tracheostomy
- Nutritional care: *"safe swallowing one of the most important aspects of care"* – short-term options include feeding through a nasogastric (NG) or nasojejunal (NJ) tube. A Gastrostomy (PEG) tube is a longer-term option

- High number of specialities involved in the multidisciplinary team providing care and support, *"this can feel **overwhelming**"*
- Large amounts of medical equipment needed in the home
- Significant burden – manging different aspects of care including use of invasive treatment
- "*Palliative care is very much **lacking**, and a shortfall of proper physiotherapy support means that people with SMA have very poor prognosis*."
- Poor prognosis without active treatment, ***"no hope"** (verbal communication)*

Patient and carer group submissions

Impact of current treatment on carers

- Babies with SMA type 1 require very high levels of care which has extreme impact on caregivers
- Frequent hospital appointments, planned/unplanned emergency admissions and involvement of palliative and hospice care
- *"As SMA progresses most of physical abilities are lost and the person becomes **completely dependant on carers**"*
- *"The carer will have to become a medical expert and the life you have dreamed for you child and yourself becomes a permanent loss".* Caregiving is "***physically and mentally draining***"
- *"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 amount of medical equipment"*
- Diet has to be very carefully monitored and managed, mealtimes take longer due to risk of choking. Carers have to monitor temperature constantly
- High levels of anxiety among caregivers, *"Care is **24 hours - 7 days a week**"*

Patients' and carers' perspectives

Impact on families

- *"Impact of a diagnosis of early onset SMA Type 1 on families is **enormous**. It often comes as a shock….. feelings of **disbelief, confusion, anger** and **sadness**"*
- Carers report sleep deprivation. often one parent will give up or cut back their paid work which impacts financial situation, ***"social lives disappear"***
- *Parents experience "**chronic grief** and potential **looming loss** of their child"*
- Many families must adjust living arrangements, with adaptations to housing and vehicles – which also incurs financial costs
- Those also caring for other children can *"struggle to keep up"* – other children may feel like they get less attention. They are also impacted emotionally by the impact of SMA
- Impact extends to siblings, grandparents, other relatives and friends who help

Patient and carer group submissions

Potential benefits of onasemnogene

- SMA UK/ MDUK UK survey – 14 parents of children with SMA type 1
  - When asked for their view of onasemnogene as a treatment for an infant newly diagnosed with SMA Type 1: 13 (93%) said it was totally acceptable; 1 (7%) considered it acceptable
  - Strong advantages of onasemnogene treatment included the one-off nature of the treatment, possible effects on breathing/motor milestones and life expectancy, and how the treatment is delivered
  - No respondent stated any strong disadvantages to onasemnogene treatment. Potential risks and how they are managed was considered by 8 (57%) as neither an advantage nor disadvantage – this is not an unexpected result.
- SMA UK highlight that it was difficult to receive more responses to their survey, due to the complexity of the questions and the fact that parents caring for those with SMA type 1 have little time

Patients' and carers' perspectives

Potential benefits of onasemnogene

- Welcome option of a **one-off treatment**

*"the possibility of one-off treatment is **very appealing and exciting**."*

*"Access to this 'one-off' intravenous treatment leading to improvements in the outcomes listed in the NICE scoping document would be a **step-change in the treatment and management of the condition**."*

*"Patients or patient carers **do not see any disadvantages** of this technology"*

- Onasemnogene as a treatment option **brings hope**

"This is an exceptional chance for children with SMA to grow up without symptoms present and have a life without influence of this debilitating condition!"

- Potential benefits for **all children** with SMA with those treated when younger potentially showing faster results
  - Including pre-symptomatic patients is essential (verbal communication)
- Noted the associated costs, trips to the hospital and potential complications that may arise with other active treatment options

Patients' and carers' perspectives

Important issues not captured in submissions but expressed verbally to NICE technical team

- Encourage committee to consider the transferability of trial evidence beyond population in trial defined by SMA type
  - Consider a managed access agreement (MAA) option for groups without direct trial data. Lots of research being done currently
- Fine motor control is also important for improvements in quality of life
- Slowing down disease progression or stabilisation of disease is also highly valued
- While trial evidence is impressive, carers are aware that treatment with onasemnogene may not be a cure
- Any health improvements which reduce caregiver burden would be very welcome
  - Reduced feeding/ventilatory support and gaining ability to speak highly valued
- Still a high unmet need in this population. Concerns exist regarding regional SMA expertise, with some diagnosis being delayed
- Carers need to be well-informed when discussing treatment options

Clinical effectiveness evidence

Decision Problem (1)

- NICE reissued the final scope post-company submission to reflect the population in the indication given marketing authorisation
- Nusinersen was not included as a comparator in the reissued scope as it is recommended for use in a managed access agreement and not routinely commissioned

	Original NICE Scope	Company submission	Company rationale	Reissued NICE scope
Population	SMA type 1	SMA type 1 with 2 *SMN2* copies	Submission covers population in clinical trial	Indicated population in marketing authorisation*
Subgroups	If evidence allows, consideration may be given to a subgroup of people with pre-symptomatic disease	Interim evidence for a pre-symptomatic population given	SPR1NT trial ongoing	No change
Comparator	• Best supportive care • Nusinersen (subject to NICE appraisal)	Best supportive care	As agreed with NICE, nusinersen is not a comparator - not recommended for routine use by NHS	Best supportive care

* 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

Decision Problem (2)

	NICE Scope (original and reissued)	Company submission	Company rationale
Outcomes	• motor function (including, sitting, standing, walking) • frequency and duration of hospitalisation • speech and communication • respiratory function • complications of SMA (examples include scoliosis and muscle contractures) • need for non-invasive or invasive ventilation • mortality • adverse effects of treatment • health-related quality of life (for patients and carers)	As per scope. • Event-free survival (EFS) also assessed (defined as permanent ventilation*-free survival) • Health-related quality of life of caregivers explored in scenario analyses only	• EFS is a primary or secondary outcome in onasemnogene clinical trials • Lack of robust utilities for caregivers of SMA type 1

*Permanent ventilation defined by tracheostomy or by the requirement of ≥16 hours of respiratory assistance per day (via non-invasive ventilatory support) for ≥14 consecutive days in the absence of an acute reversible illness, excluding perioperative ventilation.

Marketing authorisation and clinical evidence

Onasemnogene is 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

Evidence presented by company

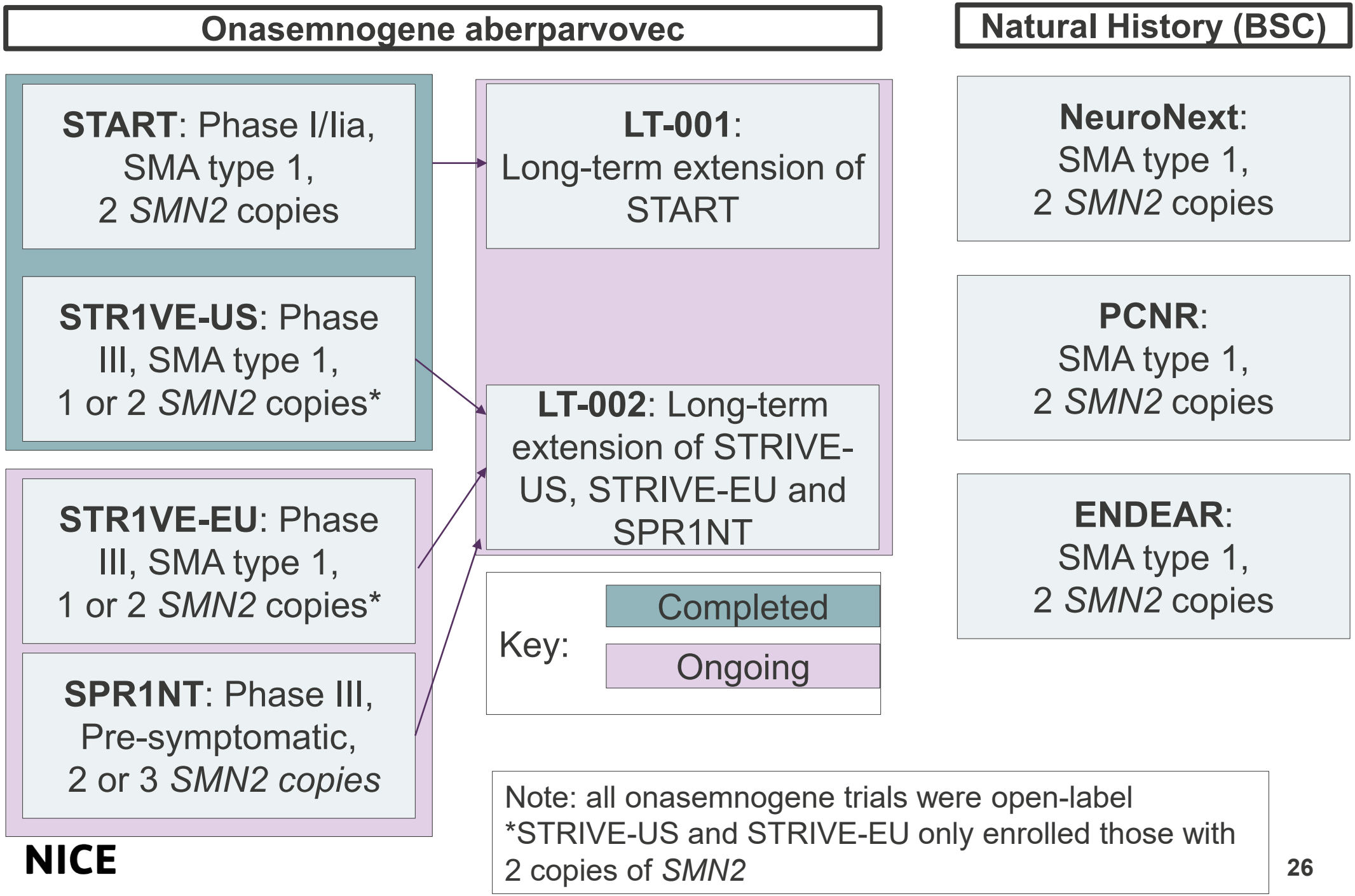
Clinical trial evidence:
START, STR1VE-US, STR1VE-EU:
SMA type 1 diagnosis, <6 months at treatment

Clinical trial evidence:
SPR1NT:
Pre-symptomatic,
<6 weeks old at treatment

Other considerations

Clinical and patient experts highlight that there are people with SMA who may benefit from treatment covered by MA wording (2nd bullet point) not included in clinical trial evidence

Clinical evidence summary



Summary: START and STRIVE-US

	START	STR1VE-US
Description	Phase I/IIa, open-label, one-time infusion, ascending-dose, single-centre study (US)	Phase III, open label, single-arm, one-time infusion, multi-centre (US)
Trial eligibility criteria	• SMA type 1 with bi-allelic *SMN1* gene mutations with 2 copies of *SMN2* • Patients 6 months of age and younger at date of treatment	• SMA type 1 with bi-allelic *SMN1* gene mutations with 1* or 2 copies of *SMN2* • Patients 6 months of age and younger at date of treatment
Duration of follow up	2 years post dose	18 months of age
Population size	15 (Cohort 1: 3 - low dose. **Cohort 2: 12 therapeutic dose****)	22

* no patients with 1 copy of *SMN2* enrolled

** Only those receiving therapeutic dose are included in economic analysis

Summary: START and STR1VE-US outcomes

START	STR1VE-US
Primary outcomes and objective	
Safety (primary objective)	Independent sitting for ≥30 seconds (efficacy endpoint)
Survival without permanent ventilation (efficacy endpoint)	Survival without permanent ventilation (efficacy endpoint)
Other outcomes	
Motor milestone achievements	Motor milestone achievements
Change from baseline in CHOP-INTEND* score**	Change from baseline in fine and gross motor components of Bayley Scales of Infant and Toddler Development
Ability to thrive	Ability to thrive
Nutritional status and swallowing function	Change from baseline in gross motor function as determined by improvement in CHOP-INTEND* score
Motor neurone function	% achieving CHOP-INTEND score of ≥40, ≥50 and ≥58
	Change in peroneal nerve CMAP amplitude
	Age independent sitting (30 seconds) is first achieved
	% independent of ventilatory support at 18 months

*Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders
**During the second year of the study, motor milestones of patients with CHOP-INTEND scores ≥62 was also assessed using the Bayley Scales

CHOP-INTEND and BAYLEY scale outcomes

CHOP-INTEND

The scale ranges from 0 to 64, with higher scores indicating better functioning status

The company submission highlights:

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

Bayley Scales

Company states the mean Bayley scale score is 10, with standard deviation of ±3 points; thus, a scaled score of ≤7 on the Bayley Scales would be considered to be low

START: gross and fine motor subtests (part of the motor domain) administered if a child reached or exceeded a CHOP-INTEND score of 60 out of 64

STR1VE-US: gross and fine motor subtests of the motor domain were administered at screening and each month. Cognitive and language domains administered every 6 months

Summary: STR1VE-EU and SPR1NT

	STR1VE-EU	SPR1NT (Pre-symptomatic)
Description	Phase III, open label, single-arm, single-dose trial	Phase III, open label, single-dose trial
Eligibility Criteria	• SMA type 1 with bi-allelic *SMN1* gene mutations with 1* or 2 copies of *SMN2* • ≤ 6 months of age at treatment	• Pre-symptomatic with bi-allelic deletion of *SMN1*, and 2 or 3 copies of *SMN2* • ≤6 weeks of age at treatment
Selected Outcomes	sitting without support ≥10 seconds	• those with 2 copies *SMN2*, independent sitting ≥ 30 seconds • those with 3 copies *SMN2*, the ability to stand without support for ≥3 seconds
Follow up	18 months	2 copies of *SMN2*: 18 months 3 copies of *SMN2*: 24 months
Population size	33	Currently 30
Completion (estimated)	Quarter 4 2020	Q4 2020 (2 *SMN2* copies) Q2 2021 (3 *SMN2* copies)

NICE

* no patients with 1 copy of *SMN2* enrolled

Ongoing trials

Summary: LT-001 & LT-002

	LT-001	LT-002
Description	Long term extension of START trial	Long term extension of all other onasemnogene trials
Selected Outcomes	Safety outcomes Efficacy assessments: assess developmental milestones (New milestones not documented during START must be supported by video evidence)	Safety outcomes Efficacy assessments: assess developmental milestones (New milestones not documented during onasemnogene trials must be supported by video evidence)
Completion (estimated)	Quarter 4 2033	Quarter 4 2034
Population size	13	Planned: approximately 308 • Cohort 1 (patients dosed intravenously): approximately 83 • Cohort 2 (patients dosed intrathecally): approximately 225

- Company also state they are sponsoring a prospective Global SMA Disease Registry (RESTORE, AVXS-101-RG-001) – aiming to enroll 500 SMA patients (20% of which on new SMA treatments such as onasemnogene)

Baseline characteristics – SMA type 1

Characteristics	START*	STR1VE-US	STR1VE-EU
SMN2 copy number	2	2	2
Age at symptom onset months (SD)	2.3 (1.47)	1.9 (1.24)	-
Age at diagnosis (range – min, max)	67.8 days (1, 137)	2.6 months (0, 5.4)	[redacted]
Age at treatment administration, months (SD) [range – min, max]	3.4 (2.06) [0.9, 7.9]	3.7 (1.61) [0.5,5.9]	[redacted]
Sex - % Female	58.3	54.5	[redacted]
Weight, kg (SD) [range - min, max]	5.7 (1.34) [-]	5.8 (-) [3.9, 7.5]	[redacted]
Mean CHOP-INTEND (SD) (range - min, max)	28.2 (12.3) [-]	32.0 (9.69) [-]	[redacted]
Swallowing thin liquid - % Yes	33.3	100	[redacted]
Non-oral feeding support -% Yes	41.7	0	[redacted]
Ventilatory support -% Yes	8.3**	0	[redacted]

*Cohort 2 (therapeutic dose), n=12

** Does not include one additional patient in Cohort 2 who was receiving BiPAP at baseline but for whom data was mis-entered at the clinical site

SD: standard deviation

SMA type 1: Clinical trial baseline characteristics

Theme	ERG comments

Onasemnogene SMA Type 1 clinical trials	• ERG clinical experts stated baseline characteristics broadly comparable to SMA type 1 population seen in NHS clinical practice
	  • START most closely matched % needing feeding/ventilatory support
	  • Baseline characteristics variations can arise due to small numbers
	• No patients in STR1VE-US needed feeding/ventilatory support: key difference from other studies – suggests less severe disease

Baseline characteristics – Pre-symptomatic

Characteristics – SPR1NT trial	Cohort 1 [n=14]	Cohort 2 [n=15]
SMN2 copy number	2	3
Age at diagnosis - months (range – min, max)	[redacted]	[redacted]
Age at treatment (range – min, max)	[redacted]	[redacted]
Sex - % Female	[redacted]	[redacted]
Weight kg (SD)	[redacted]	[redacted]
Mean CHOP-INTEND (range – min, max)	[redacted]	[redacted]
Swallowing thin liquid (%Yes)	[redacted]	[redacted]
Non-oral feeding support (%Yes)	[redacted]	[redacted]
Ventilatory support (%Yes)	[redacted]	[redacted]

NICE SD: standard deviation

Pre-symptomatic SMA: Clinical trial baseline characteristics

Theme	ERG comments
Pre-symptomatic clinical trial	• Baseline characteristics of Cohort 1 (2 *SMN2* copies) and Cohort 2 (3 *SMN2* copies) of SPR1NT are generally comparable, but those in Cohort 2 marginally older at time of treatment. All could swallow a thin liquid at baseline, as per inclusion criterion of SPR1NT • Challenging to predict type of SMA likely to develop based only on copy number • A large proportion with two copies of *SMN2* likely to develop SMA type 1 (73%). By contrast, those with three copies of *SMN2* more likely to develop SMA type 2 (78%), but a proportion will develop SMA type 1 (20%)

Natural history clinical evidence

- Company identified 3 natural history/placebo studies for the comparison between onasemnogene and BSC: NeuroNext, PCNR and ENDEAR

	NeuroNext [n=16]	PCNR [n=23]	ENDEAR [n=41]
Design	Longitudinal, multicentre, prospective, natural history study, U.S	Natural history study, U.S	Sham placebo arm of phase III RCT nusinersen trial
Population	SMA type 1 with 2 *SMN2* copies	SMA type 1 with 2 *SMN2* copies	SMA type 1 with 2 *SMN2* copies
Follow up	24 months	36 months	13 months

ERG's identified strengths and weaknesses of these studies in terms of their comparability with START and STRIVE-US			
Strengths	Prospective design, relatively mature data	Longest follow-up	Largest sample size
Weaknesses	Small sample size. Less stringent definition of PAV (leads to overestimation of EFS)	Small sample size. Partly retrospective: subject to potential selection bias	Short follow-up. Population slightly older

Natural history studies: Further ERG comments

Theme	ERG comments
Natural history studies	• All natural history studies had merits and limitations • Baseline age similar in START, STR1VE-US and NeuroNext Slightly older in ENDEAR. Much higher in PCNR, partly due to retrospective design (3 were 7, 9, 14 years old and on PAV and 4 people were between 2 and 4 years old) • More ventilatory support needed in NeuroNext and fewer needed nutritional support in ENDEAR compared to START. Large % not requiring ventilation in PCNR suggests better pulmonary function • CHOP-INTEND scores similar across studies
ERG preferred natural history study	**ERG prefers use of NeuroNext** to model BSC outcomes due to its prospective design and maturity of event-free and overall survival data compared to other studies (used in both company and ERG base case)

Clinical evidence: ERG comments

Theme	ERG comments
Small population size	• Differences in baseline characteristics or a single outcome event can have large impact on results • Only naive comparisons (no adjustment) can be made between onasemnogene and BSC
Natural history studies based primarily/exclusively in US	• Tracheostomy more commonly used (patients can be kept alive longer) • OS likely to be longer than in UK
Lack of data on long-term efficacy and safety	• Limited duration of interim LT-001 data up to 4.4 years follow up • Unknown if infants with SMA type 1 treated with onasemnogene maintain, gain or lose motor function as they grow older

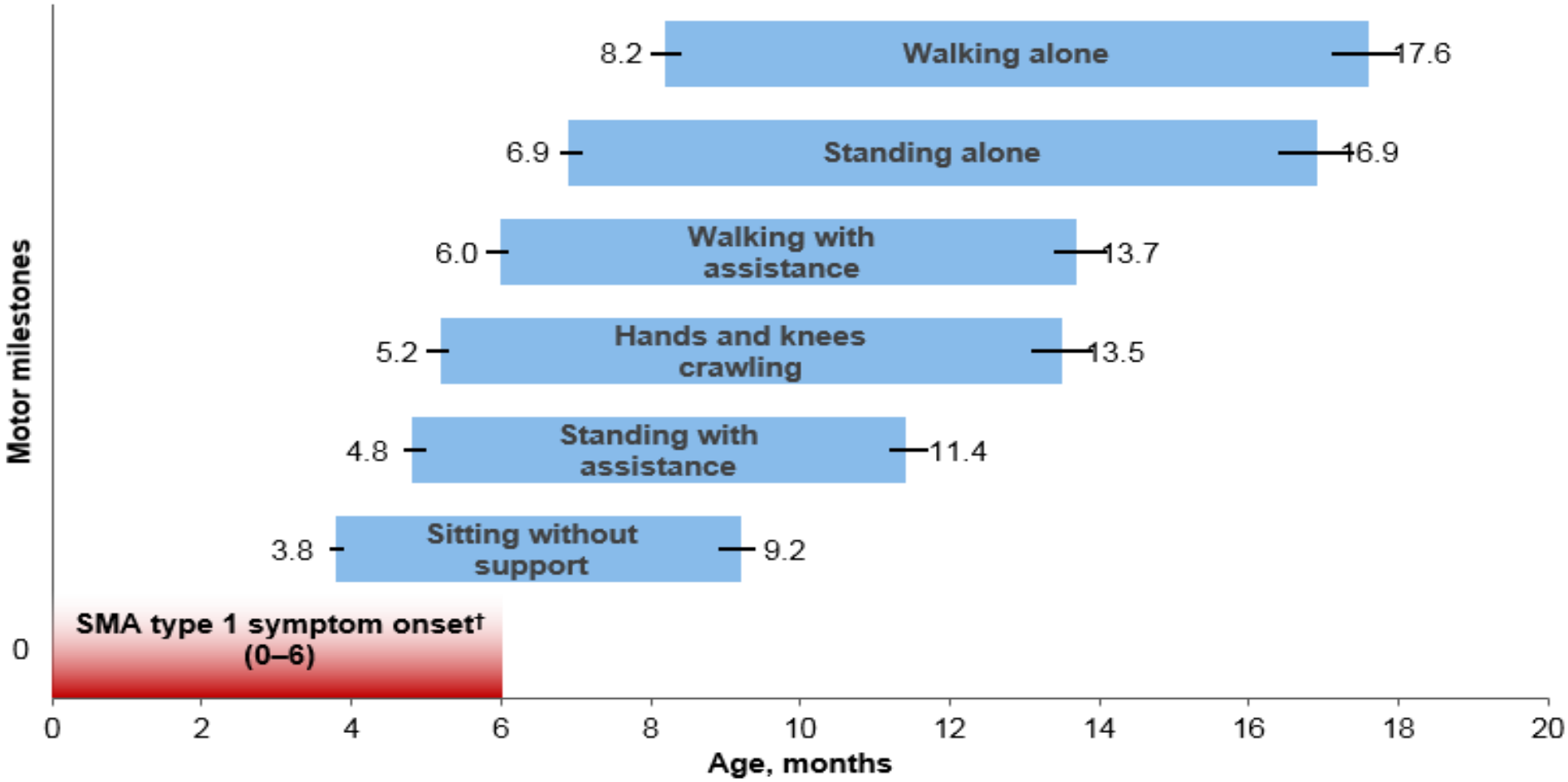
Summary of clinical effectiveness analyses

- Outcomes included in company submission were:
  - Event-free survival (avoidance of permanent ventilation or death)
  - Motor functioning:
    - Independent sitting
    - Independent walking
    - CHOP-INTEND Scores
    - Bayley scales
    - Ventilation/nutritional support

- Naïve comparison with natural history studies
  - NeuroNext used in company and ERG base case

Clinical effectiveness results

SMA type 1 onset and normal motor milestone achievements



- Red box highlights the age range of symptom onset in SMA type 1 – those with SMA type 1 never gain the outcomes listed. Short life expectancy (< 2 years)
- Numerical values on blue bars highlight 1st and 99th percentile range for outcomes with 95% confidence intervals shown

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Clinical effectiveness results:

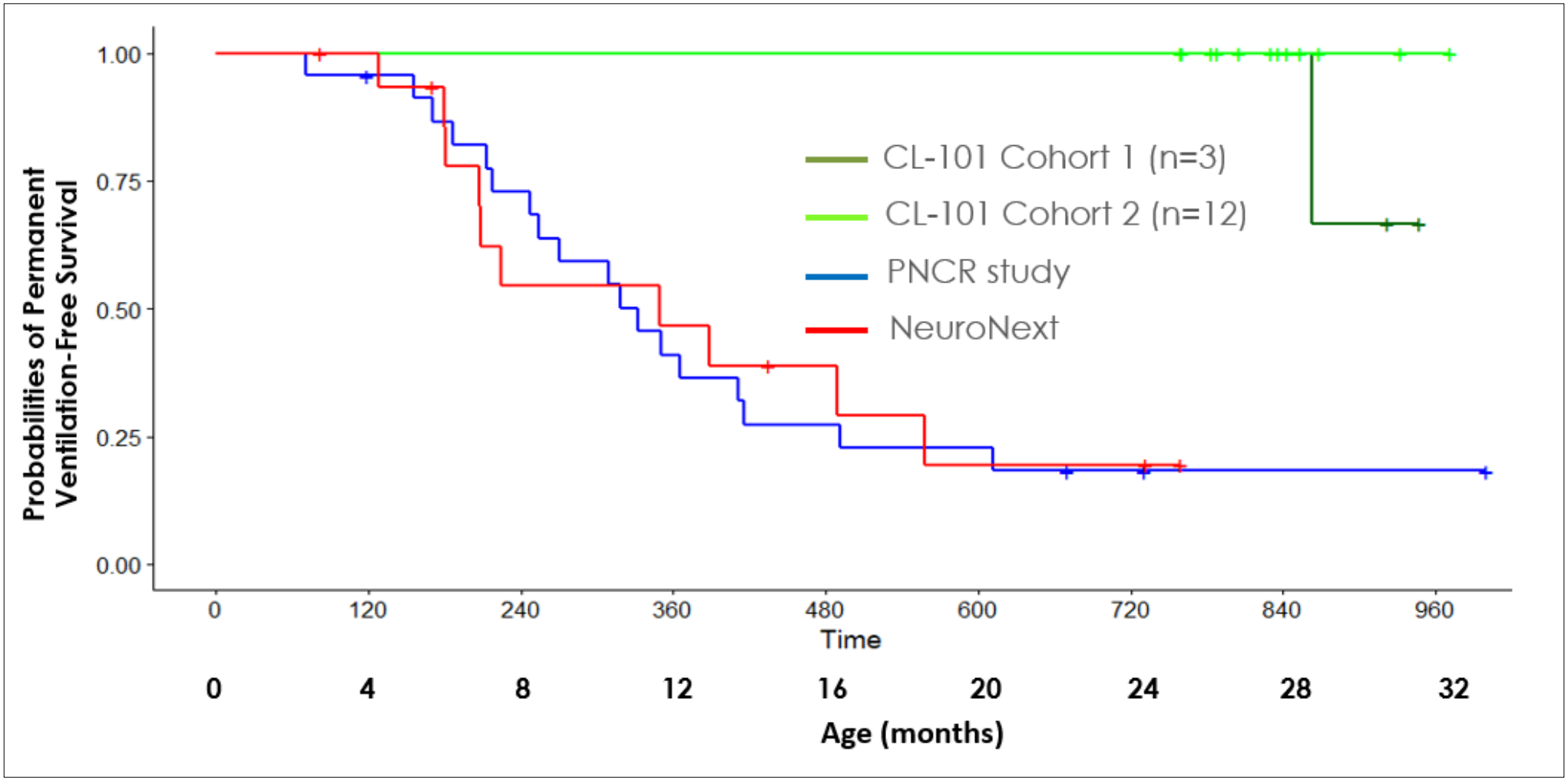
Event-free survival (Survival without permanent ventilation*)

Study	Time of follow-up	Survived without permanent ventilation
START (therapeutic dose cohort) [n=12]	13.6 months of age	12 **(100%)**
	24 months post dose	12 **(100%)**
STR1VE-US [n=22]	>10.5 months of age	21 **(95.5%)**
	≥13.6 months of age	20 **(90.9%)**
	18 months of age	20 **(90.9%)**
STR1VE-EU [n=33]	Median 11.9 months (range 1.8 to 15.4). Median age 15.4 months (range: 6.9 to 18.6)	********
LT-001 (follow-up of START) [n=10]	Median age 4.5 years (range 4.3 to 5.6 years)	10 **(100%)**

*Permanent ventilation defined by tracheostomy or by the requirement of ≥16 hours of respiratory assistance per day (via non-invasive ventilatory support) for ≥14 consecutive days in the absence of an acute reversible illness, excluding perioperative ventilation.

Event-free survival: START trial

Event-free survival in START compared to natural history controls (PCNR and NeuroNext)



CL-101 cohort 1: received low onasemnogene dose
CL-101 cohort 2: received therapeutic onasemnogene dose

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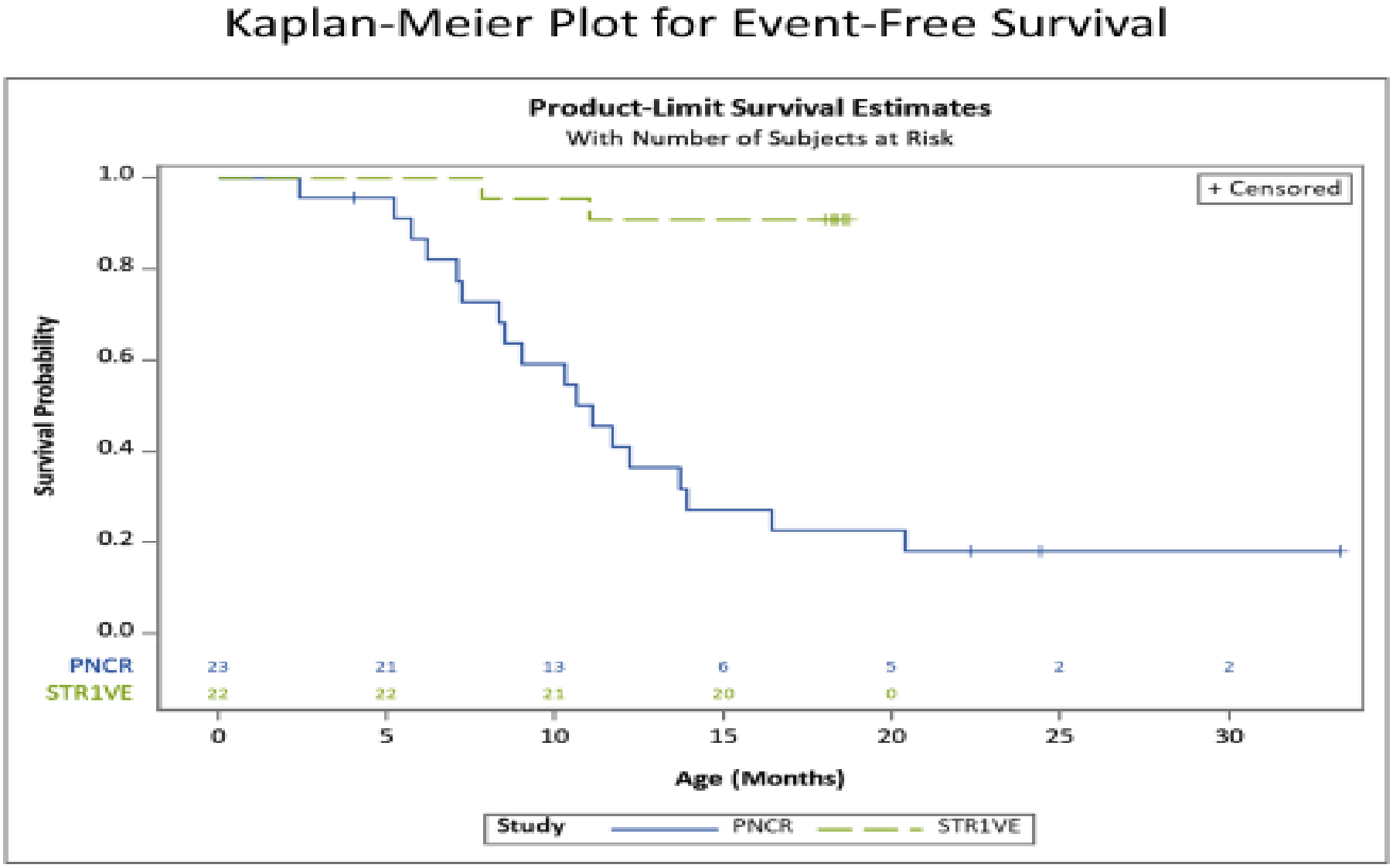
Event-free survival: STR1VE-US

Event-free survival in STR1VE-US compared to natural history control (PNCR)



Results: Natural history studies

Characteristic	NeuroNext control (N=16)	PNCR control (N=23)	ENDEAR sham arm (N=41)
Time of follow-up, months	14	14	13
• **Death, n (%)**	7 (43.8)	7 (30.4)	16 (39.0)
• **Death or PAV, n (%)**	8 (50.0)	16 (69.6)	28 (68.3)
End of follow-up, months	24	36	13
• **Death, n (%)**	8 (50.0)	11 (47.8)	16 (39.0)
• **Death or PAV, n (%)**	10 (62.5)	18 (78.3)	28 (68.3)
Abbreviations: PAV, permanent assisted ventilation			

- Motor milestones were not achieved by any patient included in the natural history studies

Clinical effectiveness results: Motor functioning

Pooled in economic model

Motor Milestone	START [n=12] (therapeutic dose cohort)	STR1VE-US [n=22]	STR1VE-EU [n=33] (Interim)
Age at follow-up (range)	~30 months	18 months	15.4 months (6.9 to 18.6)
Rolling (back to side from both sides)	9 (75%)	13 (59%)	[redacted]
Hold head erect ≥3 seconds, unsupported	11 (91.7%)	17/20* (85%)	[redacted]
Sits with support	11 (91.7%)	-	[redacted]
Sits alone ≥5 seconds	11 (91.7%)	-	[redacted]
Sits alone ≥10 seconds	10 (83.3%)	14 (63.6%)	[redacted]
Sits alone ≥15 seconds	9 (75%)	-	[redacted]
Sits alone ≥30 seconds	9 (75%)	14 (63.6%)	[redacted]
Stands with assistance	2 (16.7)	1 (4.5%)	[redacted]
Stands alone	2 (16.7)	1 (4.5%)	[redacted]
Walks with assistance	2 (16.7)	1 (4.5%)	[redacted]
Walks alone	2 (16.7)	1 (4.5%)	[redacted]

Milestones informing economic model

*Two infants who were able to hold head erect for ≥3 seconds without support at screening visit are not included.

Clinical effectiveness results: Other outcomes (1)

Motor Achievement	START [n=12]	STR1VE-US [n=22]	STR1VE-EU [n=33] (interim data)
CHOP-INTEND scores at baselines	28.2 (12.3)	32.0 (9.69)	[redacted]
CHOP-INTEND increase at study end	+30.7	NR	NR
CHOP-INTEND increase at 6 months	NR	+14.6 (7.04)	[redacted]
[redacted]			
Bayley Scale fine motor increase	[redacted]	[redacted]	[redacted]
Bayley Scale raw motor increase	[redacted]	[redacted]	[redacted]
[redacted]			
Maintained ability to thrive**	5/7 (71.4%)	9/22 (40.9)	NR

Abbreviations: NR, not reported; SD: standard deviation

*In START, only those with ≥62 CHOP-INTEND [n=4] score were assessed on Bayley Scales

**defined as: ability to tolerate thin liquids, not receiving nutrition through mechanical support and maintained weight (>3rd percentile for age and gender)

CHOP-INTEND and Bayley scale results (2)

- **CHOP-INTEND*: STR1VE-US [n=22]**
  - 21 infants (95.5%) maintained or achieved a score ≥40,
  - 14 of these infants (63.6%) maintained or achieved a score ≥50,
  - 5 of these infants (22.7%) achieved a maximum/near maximum score of ≥58
- **CHOP-INTEND*: START cohort 2 (therapeutic dose) [n=12]**
  - 11 infants (91.7%) maintained or achieved a score ≥40
  - 11 of these infants (91.7%) maintained or achieved a score ≥50
  - 4 of these infants (33.3%) achieved a maximum/near maximum score of ≥60
    - Company note:
      - SMA type 1 receiving BSC alone rarely achieve and never maintain a CHOP-INTEND score of ≥40 and show a rapid decline in CHOP-INTEND scores over time
- **Bayley scales**
  - Company note that low or zero raw scores are to be expected of infants with symptomatic SMA type 1 in the gross motor subset of the Bayley scales

*CHOP-INTEND scale ranges from 0 to 64 - higher scores indicating better functioning status. Company submission highlights: score ≥40 is beyond that reported in the literature for maximum transiently achieved function amongst symptomatic patients with SMA type 1 > 6 months of age. Achieving a score ≥50 would suggest the potential to gain milestones such as independent sitting

Clinical effectiveness results: Other outcomes (3)

	START	STR1VE-US	STR1VE-EU (interim data)
Respiratory			
NIV baseline	1 (8.3%)	0 (0%)	[redacted]
NIV during study	6 (50%)	7 (31.8%)	[redacted]
NIV free at end of study	6 (50%)	18 (81.8%)	NR
Required PAV	0 (0%)	1 (4.5%)	[redacted]
Nutritional status/ swallowing status			
Swallow thin liquids at baseline	4 (33.3%)	22 (100%)	[redacted]
Swallow thin liquids at end of study	10 (83.3%)	NR	NR
Non-oral feeding support during study	NR	7 (31.8%)	[redacted]
Non oral feeding support end of study	NR	3 (13.6%)	[redacted]
Safely swallow - oral feeding baseline	7 (58%)	NR	NR
Safely swallow – oral feeding end of study	11 (92%)	NR	NR
Exclusively feed by mouth baseline	7 (58%)	NR	NR
Exclusively feed by mouth end of study	6 (50%)	NR	NR

NICE NR = Not reported, PAV = permanent-assisted ventilation, NIV = non-invasive ventilation

Clinical effectiveness results:

LT-001 [n=10] (long term follow-up of START trial)

- At 31 December 2019 data cut, all enrolled patients (n=10) reported to have maintained their achieved motor milestones, with * patents gaining new milestones during follow-up, median age 4.5 years (range 4.3 to 5.6 years):
  - 2 gained the video-assessed milestone of 'stands with assistance';
  - **********.
  - **********)

- No patient from START cohort 2 received nusinersen in trial period. SMA targeted therapies are permitted in LT-001. At data cut ********** were receiving ongoing nusinersen (reasons not recorded)

- ERG notes the two patients who achieved video-confirmed milestone of 'stands with assistance' during LT-001 have not been treated with nusinersen at any point

Clinical effectiveness results:

SPR1NT – Pre-symptomatic population

Milestone achieved (31st December 2019 data cut – median age of 10.5 months (range 6 - 18.6)		Cohort 1 (two copies SMN2) (N=14)	Cohort 2 (three copies SMN2) (N=15)
Holds head erect for ≥3 seconds without support (%)		[redacted]	[redacted]
Turns from back to both right and left sides (%)		[redacted]	[redacted]
Sits alone without support for ≥30 seconds (%)		8 (57.1)	[redacted]
Sits alone without support for ≥10 seconds (%)		[redacted]	[redacted]
Crawls at least 5 feet (%)		[redacted]	[redacted]
Crawls at least 3 movements (%)		[redacted]	[redacted]
Stands with assistance	Supports own weight for ≥2 seconds (%)	[redacted]	[redacted]
	Stands holding a stable object (%)	[redacted]	[redacted]
Pulls to stand (%)		[redacted]	[redacted]
Stands alone	≥3 seconds (%)	[redacted]	4 (26.7)
	≥10 seconds (%)	[redacted]	[redacted]
Walks with assistance	Bayley Scales (%)	[redacted]	[redacted]
	WHO MGRS (%)	[redacted]	[redacted]
Walks alone	Bayley Scales (%)	[redacted]	[redacted]
	WHO MGRS (%)	4 (28.6)	3 (20.0)

Adverse events in onasemnogene trials

TEAEs	START Cohort 2 Therapeutic dose n (%) (N=12)	STR1VE-US n (%) (N=22)	STR1VE-EU n (%) (N=33)	SPR1NT n (%) (N=30†)	Therapeutic dose n (%) (N=97)*
Patients with ≥1 TEAE	12 (100)	22 (100)	32 (97.0)	30 (100)	96 (99.0)
TEAE ≥Grade 3 severity	10 (83.3)	10 (45.5)	13 (39.4)	6 (20.0)	39 (40.2)
TEAEs related to study treatment	3 (25.0)	12 (54.5)	24 (72.7)	17 (56.7)	56 (57.7)
Serious TEAEs	10 (83.3)	10 (45.5)	19 (57.6)	6 (20.0)	45 (46.4)
TEAE causing study discontinuation	0	2 (9.1)	1 (3.0)	0	3 (3.1)
TEAE resulting in death	0	1 (4.5)	1 (3.0)	0	2 (2.1)

**All patients except START cohort 1: low dose

Onasemnogene SmPC:

- To manage a possible increase in liver transaminases, all patients should receive oral prednisolone 24 hours prior to onasemnogene administration, with continued administration of prednisolone for 30 days following treatment
- Following administration of onasemnogene, patients will also require monitoring of liver function, platelet, and cardiac troponin I at regular intervals

NICE TEAE: treatment-emergent adverse event, SmPC: Summary of Product Characteristics

Key Issues: clinical effectiveness (recap)

- Clinical Evidence
  - Are the onasemnogene clinical trials generalisable to the:
    - indicated population in the marketing authorisation and SmPC?
    - NHS clinical practice in England?
    - future NHS clinical practice in England?
  - Is the NeuroNext (natural history) study the most appropriate to reflect best supportive care outcomes?
  - Are there other populations likely to benefit from treatment beyond those included in the clinical trials?
- Does the committee conclude the clinical trials capture:
  - Benefits that are important to patients? All relevant aspects of the disease?
- Clinical effectiveness
  - How effective is onasemnogene?
  - How robust are the trial results?
  - How uncertain are long-term effects of treatment?
  - Are the interim results for the pre-symptomatic population robust enough for decision-making?

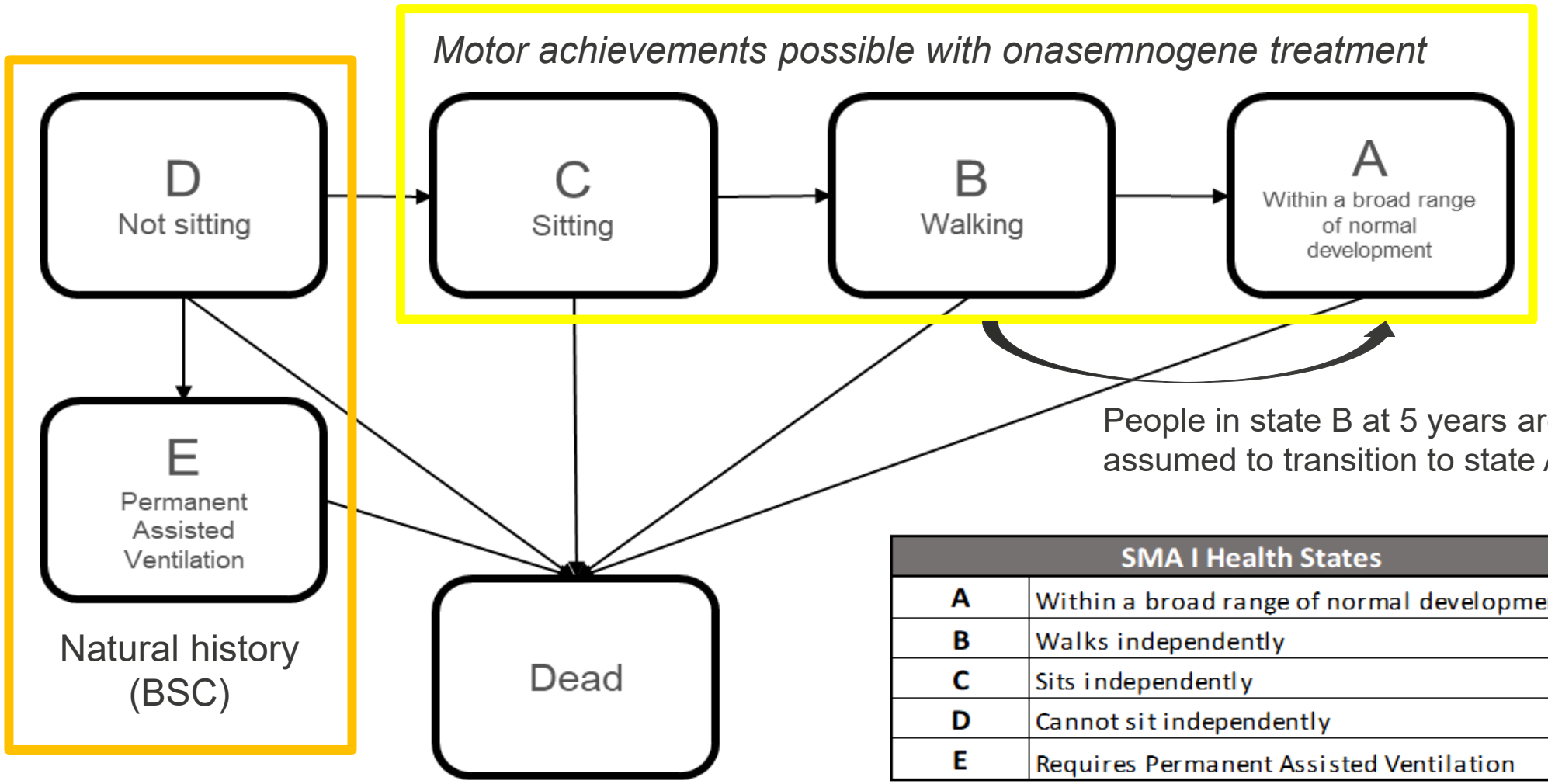
Cost effectiveness

Description of health states in the model

State	Motor features	Additional features
A	Within a broad range of normal development	
B*	Walks unassisted	• No breathing difficulties. Normal number and severity of chest infections • Does not require a feeding tube. Few difficulties swallowing, able to eat and swallow water. Normal talking ability
C	Sits unassisted	• May have breathing problems and sometimes require NIV • Chest infections more frequently than a typically developing child of same age • Some difficulties with eating and swallowing but able to swallow thin liquids and take some food by mouth. Risk of choking. Temporary placement of a gastric tube may be required • Requires help moving. Can talk, but ability to speak will deteriorate over time
D	Not sitting	• Experiences breathing problems and requires regular NIV for a number of hours every night or during the day. Development of chest infections more frequently • Difficulties feeding and swallowing. High risk of choking. Only able to swallow thick fluids. Fed by a feeding tube (gastrostomy) • Requires moving regularly. Unable to talk, but can make sounds and cry
E	Permanent assisted ventilation	• Require 24-hour NIV. May require a tracheostomy if NIV is not working well • Require gastrostomy to be surgically placed directly into the stomach due to difficulty feeding and swallowing. High risk of choking. Require moving regularly. • Develop chest infections more often than healthy children of the same age. Unable to talk, but can make sounds and cry
Abbreviations: NIV, non-invasive ventilation		

*People in state B at 5 years are assumed to transition to state A (within a broad range of normal development)

Company economic model structure



SMA I Health States	
A	Within a broad range of normal development
B	Walks independently
C	Sits independently
D	Cannot sit independently
E	Requires Permanent Assisted Ventilation

Economic model based on motor function and need for permanent assisted ventilation (PAV)

Modelling approach (1)

- All patients start in health state D (non sitting)
- Patients without onasemnogene (BSC) never sit (D) and have a probability of needing PAV (E) or dying (they cannot move to higher functioning states). This is assumed in the short term and long-term: based on natural history of SMA type 1
- With onasemnogene, patients may remain in non-sitting state (D), or move to PAV (E) state
  - or they may attain motor milestones and move to higher functioning states of unassisted siting (C), in which they may remain or move to walking state (B)
- Assumption that the children occupying state C after 3 years of age will remain there for the rest of their lives
  - Life expectancy and costs modelled on SMA type 2
- Those in state B at 3 years of age assumed to move to state A (broad range of normal development) at 5 years of age – based on World Health Organisation (WHO) reported windows of motor milestone achievement
  - Those in state A remain there for lifetime and normal life expectancy assumed for state A: based on life expectancy for SMA type 3. Costs are modelled on SMA type 3

Abbreviations: PAV: Permanent assisted ventilation

Modelling approach (2)

- Different parametric curves are fitted to each health state to model long term survival
- Costs and utilities are attached to time spent in each states over the lifetime of the model and discounted to provide cost-effectiveness estimates
- Structure of model is judged by the ERG to be appropriate and was used by the Institute for Clinical and Economic Review (ICER) in their appraisal of the treatment
- Cycle length of 6 months in first 3 years with yearly cycles after
- Estimates of treatment effectiveness in first 3 years of the model based on pooled motor milestone data from START and STR1VE-US trials (offset by 6 months - motor achievements assumed to occur in next cycle)
- START and STR1VE-US trials follow patients to different time points (START until ~30 months and STR1VE-US until 18 months of age) – assumptions on additional milestones achieved between 18 and 30 months in STR1VE-US are made by the company
- STR1VE-EU and LT-001 interim data used as supportive evidence (results not used in pooled dataset)

Key Issues: cost effectiveness

- What should the transitions in the 3-year model be?
  - What is committee's view on the company's assumption that there would be an extra sitter and an extra walker relative to the numbers seen in the pooled data?
  - What is the relevant threshold for independent sitting in the 3-year model?
- Is it reasonable to assume that patients persist in the state they are in after 3 years?
- Are the extrapolations of events from the 3-year data acceptable?
- What should the utilities attached to the states be?
  - What is committee's view on using different utilities depending on treatment?
- What costs should be attached to the states?
- What is Committee's view of the uncertainties in the model results?
- What discount rate should be applied? What threshold for cost effectiveness is relevant?
- What is the most plausible ICER range?
- What is committee's view on the pre-symptomatic population analysis
- What factors affecting the guidance need to be taken into account?
  - Equalities issues?
  - Additional factors?

Pooling of START and STR1VE-US data

Company combine data from START and STR1VE-US trials

- Follow-up period differs between the two trials:
  - 24 months post dose in START (approximately **30 months of age**) and
  - until **18 months of age** in STR1VE-US

- Company highlight that more milestones could be achieved in STR1VE-US between 18 and 30 months of age, although difficult to predict
- Company base case assumes **1 additional independent sitter and 1 additional independent walker,** added to last cycle of short-term model (aged 30 to 36 months)
- Company state this is a conservative assumption – *"minimum number of additional achievements"*

- Company justify assuming additional motor milestones beyond observed data as:
  - Clinical experts advised company it is unlikely no further milestones would be achieved beyond 18 months in STR1VE-US – longer-term data needed
  - 18 months is just past upper WHO range for walking independently
  - START data showed development of milestones after 18 months of age (5 sat unassisted and 2 walked unassisted after this point)
  - START and STR1VE-US data show milestones in trials are *"delayed"* compared to normal development

NICE

WHO: World Health Organisation

Pooling of START and STR1VE-US data (2)

Company uses different independent sitting thresholds for each data set

- Company define sitting unassisted (State C in model) for START data in pooled dataset as *"sitting unassisted for ≥5 seconds"* - matching the item 22 on Bayley-III assessment tool gross motor subtest. Rationale:
  - Attainment confirmed through video review by external reviewer
  - Threshold of *sitting alone for ≥30 seconds* is not used for START data as:
    - *2* patients would not be included in state C: considered overly pessimistic[redacted]

- Definition used for 'sitting unassisted' for STR1VE-US data in pooled dataset is "*sitting unassisted for ≥30 seconds"* - matching item 26 on Bayley-III assessment tool gross motor subtest. Rationale:
  - Outcome co-primary endpoint of STR1VE-US
  - Milestones confirmed through video review by an external reviewer

ERG comment: Transitions in short term model

Theme	ERG comments
Using pooled data on motor milestone achievement from START and STR1VE-US is appropriate	• Aligns with published economic models for SMA type 1 • "Offsetting" milestone achievements by 6 months is reasonable and conservative (offset by 6 months - motor achievements assumed to occur in next cycle)
Reasonable to assume additional motor milestones after 18 months of age but no robust data to confirm this	• One clinical expert suggested assumption of an additional walker between 18 and 30 months is strong • Based on clinical expert advice, ERG consider the two scenarios of relevance is one with one additional sitter (no additional walker) and one which used only observed trial data (ERG Base case) • Using only observed data could be seen as a conservative approach
Clinical validity of the < 5 second threshold used for sitting unassisted is uncertain	• <5 seconds too short to be clinically different from D state (not sitting) • ERG clinical experts stated that >30 seconds was more clinically relevant

Short-term model transitions

Summary of base case assumptions and impact on final cycle distributions:
Cycles 1-5 based on observed trial data from pooled from START and STR1VE-US
Cycle 6a = Company base case: observed data plus 1 additional sitter and 1 additional walker
Cycle 6b = ERG base case: observed data only
Cycle 6c = ERG base case with only 1 additional sitter (no additional walker)

Model cycle	Age at end of cycle (months)	Not sitting (D state)			Sitting (C state)			Walking (B state)	
		n	%	D to C	n	%	C to B	n	%
1	6	34	100%	0%	0	0%	0%	0	0%
2	12	32	100%	0%	0	0%	0%	0	0%
3	18	24	75.0%	25%	8	25.0%	0%	0	0%
4	24	13	40.6%	45.8%	18	56.3%	12.5%	1	3.1%
5	30	9	28.1%	30.8%	20	62.5%	11.1%	3	9.4%
6a	36	**6**	18.8%	33.3%	**22**	68.8%	5%	**4**	12.5%
6b	36	**7**	21.9%	22.2%	**22**	68.8%	0%	**3**	9.4%
6c	36	**6**	18.8%	33.3%	**23**	71.9%	0%	**3**	9.4%

Long-term extrapolation of event-free survival and overall survival (1)

Company use standard parametric survival distributions applied to KM data for both OS and EFS. Fit of the curves assessed using AIC, BIC and visual inspection

Health state D (non-sitting)

- Used EFS and OS data from NeuroNext (Natural history study)
- Weibull distribution for both OS and EFS - Distribution truncated to zero at 4 years

Health state E (permanent ventilation)

- % in this state = difference in state D EFS and OS based on NeuroNext KM data, extrapolated using a Weibull distribution
- Long term OS extrapolation = data from Gregoretti et al (retrospective chart review of SMA type 1 patients - Italy) and exponential distribution - applied to all data to avoid overfitting the model
- OS is assumed the same in health state E for both arms. Due to plateau – data truncated to zero at 16 years by the company

Abbreviations: OS, overall survival; EFS, event-free survival, KM, Kaplan-Meier

Long-term extrapolation of event-free survival and overall survival (2)

Health state C (Sitting)

- Company assumed OS will be the same as SMA type 2. Long term KM data for SMA type 2 taken from Zerres et al (52-year prospective and retrospective study)
- Generalised gamma distribution used with no truncation, based on statistical fit. Applied in long term model (no patients gaining ability to sit died in START or STR1VE-US)

Health state B/A (Walking and within a broad range of normal development)

- Assumed OS of SMA type 3 - not significantly different to that of the general population, based on a Zerres et al study. Long term OS calculated using UK life tables

ERG comments:

- Modelling of OS for all health states and EFS for D state in both short- and long-term models considered appropriate. Modelling of states C/B reflective of US ICER report
- ERG clinical experts: “not unreasonable” to assume those with SMA type 1 who gain ability to sit have a life expectancy similar to that of SMA type 2. Also reasonable to assume normal life expectancy for those with SMA type 1 who could walk, however - no long-term evidence to inform this and some health problems associated with SMA likely

Abbreviations: OS, overall survival; EFS, event-free survival, KM, Kaplan-Meier

Event free and overall survival: Summary

Health State	Onasemnogene		Best supportive care	
	Short-term	Long-term	Short-term	Long-term
E - OS	Extrapolation of PAV patient mortality (Gregoretti et al. 2013[76]) using exponential distribution.			
D - EFS	Kaplan-Meier data from START and STR1VE-US	Extrapolation of NeuroNext data using Weibull distribution	Kaplan-Meier data from NeuroNext	Extrapolation of NeuroNext data using Weibull distribution
D - OS	Kaplan-Meier data from START and STR1VE-US	Extrapolation of Kaplan-Meier data from NeuroNext, adjusted to censor patients on PAV, using Weibull distribution	Kaplan-Meier data from NeuroNext adjusted to censor patients on PAV	Extrapolation of NeuroNext adjusted data using Weibull distribution
C - OS	Kaplan-Meier data from START and STR1VE-US	SMA type 2 mortality (Zerres et al. 1997[77]) extrapolated using generalised gamma distribution	No patients were assumed to achieve this motor milestone	
B & A - OS	Kaplan-Meier data from START and STR1VE-US	General population mortality (ONS life tables 2014-2016[78])	No patients were assumed to achieve this motor milestone	

Abbreviations: EFS, event-free survival; ONS, Office of National Statistics; OS, overall survival; PAV, permanent assisted ventilation.

Health-related quality of life

- HRQoL data were not collected in any onasemnogene trial, nusinersen trial or in natural history studies
- Company base their choice of utility values for each state on the US ICER report and ERG assumption for state E
  - Company also assumed onasemnogene treatment resulted in additional utility gains of 0.1 in state D (not sitting) and 0.05 in state C (sitting) – based on ERG and ICER report assumptions

Utility values used in company (and ERG) base case

State	Description	Utility	Source
E	PAV	**0**	Assumption based on the ERG interim report
D	Not sitting – BSC Not sitting – onasemnogene	**0.19** **<u>0.29</u>**	Thompson et al. 2017 **and on treatment utility of 0.1**
C	Sits unassisted – BSC Sits unassisted - onasemnogene	**0.60** **<u>0.65</u>**	Tappenden et al. 2018 **and on treatment utility of 0.05**
B	Walks unassisted	**General population**	Ara and Brazier 2010
A	Broad range of normal development		

Health-related quality of life

Company rationales for base case

State E utility lower than state D in company elicitation study. ERG's clinical experts stated state E could have a utility worse than death – ERG preferred assumption of a utility of 0 for state E, accepted by company.

For health **state D** – company use Thompson et al, also used in US ICER report

For health **state C** – company use a utility value taken from ERG clinical expert opinion in TA588 (nusinersen) – not preference-based

To account for interim motor milestones, on treatment utility of 0.1 for **state D** and 0.05 for **state C** was added – US ICER report also included these values

For health **states B and A**, general population utility applied (Ara and Brazier 2010). Company justify this approach as walking unassisted by 2 years is reflective of normal development (WHO report)

In company (and ERG) base case, caregiver utilities are not included. Company highlight lack of robust caregiver utilities and that the ICER report did not include caregiver utilities (*"counter-intuitive"* results: ICER increases). Scenarios including caregiver utilities are provided by both company and ERG

Health-related quality of life

Company rationales for base case

Company state their base case utilities:

- Considered most acceptable by US ICER report and ERG
- Except for state C, all utilities measured using EQ-5D
- State D utilities use parent proxy utilities – NICE reference case permitted when patient utilities are not possible
- Health state utilities considered plausible by company clinical advisory broad

Scenario analysis using:

- Company UK utilities elicitation study
- Alternative values from the Systematic literature review:
  - Utility values from CHERISH: PedsQL mapped to EQ-5D-Y (Thompson et al)
  - Clinician-proxy Case Vignette EQ-5D-Y (Lloyd et al. 2017),
  - Parent-proxy EQ-5D-3L, UK reports only (Thompson et al. 2017).
- Caregiver disutilities

ERG comments:

- Difficult to obtain robust utilities for patients with SMA type 1
- Company's base case utilities are appropriate and have provided an extensive range of scenario analysis covering range of plausible scenarios

Adverse events

- Adverse events (AEs) not included in company's economic model - company state it is difficult to separate out AEs due to treatment from complications associated with SMA itself, which are accounted for in health state costs and utilities
  - ERG agreed with company rationale for not including adverse events in utility estimates
- AE related to onasemnogene experienced by 25% of people in cohort 2 of START (3/12) and 54.5% in STR1VE-US (12/22)
- Most common: Increased transaminases and increased aspartate aminotransferase (to manage possible increases in liver transaminases, reflective of liver inflammation, all patients receive prophylactic oral prednisolone 24 hours prior to onasemnogene)
- Company state all treatment related AEs resolved during study period for START and STR1VE-US
- ERG notes that 11 (11.3%) patients across the 4 onasemnogene studies experienced a scoliosis TEAE, with only 1 patient reported as having scoliosis at baseline

Costs in the model: Onasemnogene

- Onasemnogene is administered as a single, peripheral, intravenous (IV) infusion, over 60 minutes, at a dose of 1.1x1014 vg/kg
  - The list price is £1,795,000 per dose
- Infants will require a test for AAV9 antibody prior to treatment with onasemnogene - funded and coordinated by the company at a central European lab
- Treatment will also require one pre-infusion visit at a secondary/tertiary neuromuscular centre followed by a two-night, three-day elective stay at a highly specialised infusion centre
  - Company applied administration cost of £2,803 (*elective inpatient costs; nervous system disorders; NHS Reference Costs)* – in sensitivity analysis this cost is multiplied by 10
- Onasemnogene treatment is given in addition to best supportive care

Health state costs

- Company conducted a UK HCRU study with 16 UK health professionals - asked about the frequency and duration of treatments over previous 12 months
- Company used ventilatory dependent costs from Noyes et al
- States C and B had estimated costs for SMA types 2 and 3 as proxies
- Company assumed state A incurs the same SMA-related health care as state B
- Scoliosis surgery rates of 56.67%, 19.62%, and 3.75% were applied for the D, C, and B states – based on HCRU study

SMA costs by health stage (annual)

Cost category	Cost source	SMA type 1		SMA type 2 as proxy	SMA type 3 as proxy
Health state		**E (PAV)**	**D (non-sitting)**	**C (sitting)**	**B/ A (walking)**
Drugs	UK HCRU study	£680	£919	£743	£939
Medical tests	UK HCRU study	£645	£873	£651	£533
Medical visits	UK HCRU study	£3,153	£4,264	£2,509	£2,217
Hospitalisation	UK HCRU study and Noyes et al	£200,247	£63,516	£37,336	£452
GP and Emergency	UK HCRU study	£325	£439	£183	£73
Health material	UK HCRU study	£3,172	£4,027	£2,079	£592
Social services	Noyes et al	£49,994	£27,896	£18,598	£2,952
Total		**£258,216**	**£101,934**	**£62,099**	**£7,759**

Health state costs – Ventilation

- 3 types of ventilatory support in model: tracheostomy, NIV>16 hours/day and NIV<16 hours/day

Health state	Ventilation group		Setting		Weighted
	Type	Proportion	Type	Proportion	Proportion
E	NIV>16 hours/day	77.4%	Home	70.0%	54.2%
			ITU	15.0%	11.6%
			HDU	15.0%	11.6%
	Tracheostomy	22.6%	Home	60.0%	13.6%
			ITU	10.0%	2.3%
			HDU	30.0%	6.8%
D	NIV<16 hours/day	84.0%	Home	90.0%	75.6%
			ITU	5.0%	4.2%
			HDU	5.0%	4.2%
	Non-ventilated	16.0%	-	-	16.0%
C	NIV<16 hours/day	56.0%	Home	90.0%	50.4%
			ITU	5.0%	2.8%
			HDU	5.0%	2.8%
	Non-ventilated	44.0%	-	-	44.0%
B/A	NIV<16 hours/day	20.0%	Home	100%	20.0%
	Non-ventilated	80.0%	-	-	80.0%

Abbreviations: NIV: Non-invasive ventilation, ITU: Intensive care unit, HDU: High dependency unit

Costs in model: ERG comments (1)

- ERG considers company approach to be overly complex
- ERG clinical experts – unreasonable to assume costs constant across lifetime of model – SMA-related care would increase with age (also not captured in TA588 model)
- Any increase in costs in higher mobility states would cause ICER to increase
- Subsequent treatment: ERG clinical experts stated that without long-term evidence on nusinersen use after onasemnogene, they would not offer this treatment
- Despite this [redacted] patients started nusinersen in LT-001
- Therefore assumption of no motor milestone loss partially based on potential impact of nusinersen treatment (ERG note LT-001 based in US – may overestimate use of subsequent treatment compared to UK)
- ERG run scenario [redacted]
  - Treatment assumed to continue until death – may not be realistic in clinical practice

Costs in model: ERG comments (2)

- ERG also queried why SMA type 2 and 3 incur 50% and 20% of social services costs of SMA type 1 – company stated this was not externally validated. Company provide extreme scenario in which SMA type 2 and 3 are associated with 100% of SMA type 1 social services costs
- To address ERG concerns that nusinersen-specific resource use was included in HCRU study (nusinersen received by [redacted] with SMA type 1) in health states E and D, company provided scenarios where nusinersen-naïve patients incurred costs 48.6% greater than nusinersen treated patients, based on Droege et al

Cost effectiveness results

Summary of company and ERG base case assumptions

	Company base case	ERG base case
Short term model	Observed pooled data of START (~30 months of age) and STR1VE-US (18 months of age)	
	Apply an independent sitting threshold of >5 seconds (START) and >30 seconds (STR1VE-US) (state C)	Results for thresholds of >5 seconds and >30 seconds (state C)
	1 additional sitter and 1 additional walker in STR1VE-US assumed between 18 to 30 months (age)	Only observed milestones in base case (1 additional sitter assumed in scenario analysis)
	Motor milestones achieved in first 3 years assumed maintained long term. No milestones gained/lost	

Cost-effectiveness results overview

Company base case

START and STR1VE-US observed data:

- Offset by 6 months and
- 1 additional walker + 1 additional sitter assumed
- Independent sitting >5 seconds for START, >30 seconds for STR1VE-US
- Motor milestones achieved by 3 years are maintained (none gained/lost over time)
- Health state costs = UK HCRU study
- Utilities of 0, 0.19/0.29, 0.65 and general population used for health states E (PAV), D (non-sitting), C (sitting), B/A (walking/normal range of development)
- NeuroNext study informs BSC outcomes

ERG and alternative analysis

- Offset assumption removed*
- Various assumptions (from no additional to 4 additional sitters and 4 additional walkers)***
- Both independent sitting thresholds used in ERG analysis
- Scenario analysis assuming some motor milestone lost*
- US ICER** and TA588 costs* used
- Alternative utility sources used and one-way sensitivity around base case values*
- Alternative natural history studies*

*analysis provided by company, **analysis provided by ERG,
*** analysis provided by both company and ERG

Company base case results: SMA type 1

- Assumes 1 extra sitter and 1 extra walker in addition to the observed pooled data from START and STR1VE-US

	Total costs* (£)	Total LYs	Total QALYs*	Inc. costs (£)	Inc. LYs	Inc. QALYs	ICER (£/QALY)
Deterministic							
Onasemnogene + BSC	[redacted]	15.68	10.21	[redacted]	13.53	10.00	[redacted]
BSC	381,131	2.15	0.21	-	-	-	-
Probabilistic							
Onasemnogene + BSC	[redacted]	14.44	9.38	[redacted]	12.30	9.16	[redacted]
BSC	378,637	2.13	0.22	-	-	-	-

BSC, best supportive care; ICER, incremental cost-effectiveness ratio; Inc, incremental; LYs, life years; QALY, quality-adjusted life year

 *Costs and QALYs discounted at 3.5%

Where QALYs and costs accrue: Company base case

Total QALYs by health state (Discounted 3.5%)			
Health state	**QALYs onasemnogene**	**QALYs BSC**	**Increment**
E (PAV)	0.00	0.00	**0.00**
D (Not-sitting)	0.55	0.21	**0.34**
C (Sitting)	6.99	0.00	**6.99**
B (Walking)	0.30	0.00	**0.30**
A (Normal range)	2.37	0.00	**2.37**
Total	10.21	0.21	10.00

Total costs by health state from original company submission (Discounted 3.5%)		
Health state	**Cost burden (%) onasemnogene**	**Cost burden (%) BSC**
E (PAV)	2%	76%
D (Not-sitting)	15%	24%
C (Sitting)	68%	0%
B (Walking)	2%	0%
A (Normal range)	13%	0%
Abbreviations: BSC, best supportive care; QALYs, quality-adjusted life years; PAV: permanent assisted breathing		

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Highlighted rows show the health states where most costs and QALYs accrue

Company sensitivity analyses

- Company sensitivity analyses included varying individual cost, utility and survival parameters (one-way sensitivity analysis)
- One-way sensitivity analysis varying parameters by -/+ 20%
  - following 5 parameters had the largest impact on the ICER

	Parameter Description	ICER (Δ£/ΔQALY)*	
		-20% from base case	+20% from base case
1	Onasemnogene drug costs	*********	*********
2	C state (sitting) utility value	*********	*********
3	Cost of hospitalisations C state (sitting)	*********	*********
4	Cost of social services C state (Sitting)	*********	*********
5	Cost of hospitalisations E state (PAV)	*********	*********

Multi-way analysis – varying 3 variables with most impact

Results ranged from low of ********* (20% reduction in C state (sitting) hospitalisation costs, 20% reduction in C state social services costs and 20% increase in the C state utility value) to a high of ********* (20% increase in C state hospitalisation costs, 20% increase in C state social services costs and 20% reduction in the C state utility value)

ERG comments:

- Hospitalisation category influenced by many variables (% assumed for each ventilation care type and setting). Limiting analysis to -/+ 20% for parameters does not capture all uncertainty

*Costs and QALYs discounted at 3.5%

Company scenario analyses

Selected scenarios	ICER (£/QALY)*	% change from baseline
Company base case	[redacted]	-
Cost assumptions		
Doubled SMA type 1 costs (RWE – TA588)	[redacted]	+12%
100% social care costs for non-permanent ventilated	[redacted]	+12%
Utility values		
CHERISH PedsQL mapping	[redacted]	-13%
Lloyd et al (2017) clinician-proxy vignette	[redacted]	+223%
Company utilities elicitation study	[redacted]	+61%
Alternative natural history source		
PCNR database	[redacted]	-15%
ENDEAR study	[redacted]	-13%
De Sanctis et al (2016) study	[redacted]	-15%
Exploratory analysis		
4 additional sitters and 4 additional walkers	[redacted]	-16%
State C associated with normal life expectancy	[redacted]	-14%
Treatment in START and STR1VE-US at ≤3.5 months old	[redacted]	-13%
Milestones not offset by 6 months	[redacted]	-2%

NICE *Costs and QALYs discounted at 3.5%

Abbreviations: RWE, real world evidence

ERG base case result: SMA type 1

- ERG base case removes company's assumption of 1 additional independent sitter and 1 independent walker in the pooled dataset (i.e observed data only)
- ERG state model unable to provide probabilistic results for ERG base case – PSA ICER likely higher

Treatment	Total costs* (£)	Total QALYs*	Inc costs	Inc QALYs	ICER (£/QALY)
BSC	381,131	0.21	-	-	
Onasemnogene + BSC	[redacted]	9.56	[redacted]	9.35	[redacted]

ERG also provide an analysis that applies an independent sitting threshold of ≥30 seconds which results in 2 patients no longer transitioning to state C

Treatment	Total costs* (£)	Total LYs	Total QALYs*	Inc costs	Inc LYs	Inc QALYs	ICER (£/QALY)
BSC	381,131	2.15	0.21	-	-	-	-
Onasemnogene + BSC	[redacted]	14.08	8.96	[redacted]	11.94	8.75	[redacted]

*Costs and QALYs discounted at 3.5%

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

ERG scenario analyses applied separately to the company base case

		Total Costs* (£)	Total QALYs*	Inc. costs (£)	Inc. QALYs	ICER (£/QALY)
0	Company's base case					
	Onasemnogene	[redacted]	10.21	[redacted]	10.00	[redacted]
	BSC	£381,131	0.21	-	-	-
1	Threshold for sitting independently of ≥30 seconds for the pooled dataset (observed motor milestones only) and removing company's base case assumption of 1 additional sitter and 1 additional walker					
	Onasemnogene	[redacted]	8.96	[redacted]	8.75	[redacted]
	BSC	£381,131	0.21	-	-	-
2	Threshold for sitting independently of ≥30 seconds for the pooled dataset and not including 1 additional walker					
	Onasemnogene	[redacted]	9.26	[redacted]	9.05	[redacted]
	BSC	£381,131	0.21	-	-	-
3	Use of US ICER model costs for health states included in the model (most modelling approaches and assumptions are based on the US ICER model)					
	Onasemnogene	[redacted]	10.21	[redacted]	10.00	[redacted]
	BSC	£544,139	0.21	-	-	-
4	Including subsequent nusinersen treatment costs					
	Onasemnogene	[redacted]	10.21	[redacted]	10.00	[redacted]
	BSC	£381,131	0.21	-	-	-

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*Costs and QALYs discounted at 3.5%

Cost-effectiveness analysis: Pre-symptomatic population

- Company present two scenarios using the economic model to present cost-effectiveness estimates for the pre-symptomatic population predictive of SMA type 1
- Company state data from SPR1NT are not sufficiently mature to inform a full cost-effectiveness analysis but have based the assumptions used for the 2 scenarios on the interim results from SPR1NT
- Company state that while patient pathway would likely be different for pre-symptomatic population – costs in the current model are likely to be overestimated

For scenarios A and B – the only change to the modelling is changing the motor milestones achieved to match those from the interim trial results of SPR1NT

Scenario A	Scenario B
100% achieve sitting and 100% achieve ability to walk in short-term model	100% achieve sitting and 82% achieve ability to walk in short term model
No patients receive PAV in short term model	
EFS and OS is 100% in the short-term model for patients in the D state	
Comparator = BSC for SMA type 1	

Cost-effectiveness analysis: Pre-symptomatic population

Scenario A

Treatment	Total costs* (£)	Total LYs	Total QALYs*	Incremental costs (£)	Incremental LYs	Incremental QALYs	ICER (£/QALY)
BSC	381,131	2.15	0.21	-	-	-	-
Onasemnogene + BSC	[redacted]	26.79	23.80	[redacted]	24.65	23.59	[redacted]

Scenario B

Treatment	Total costs* (£)	Total LYs	Total QALYs*	Incremental costs (£)	Incremental LYs	Incremental QALYs	ICER (£/QALY)
BSC	381,131	2.15	0.21	-	-	-	-
Onasemnogene + BSC	[redacted]	25.29	21.41	[redacted]	23.14	21.20	[redacted]

ERG comments:

- Company model constructed to reflect only SMA type 1 – key company assumption is pre-symptomatic patient population (up to three copies of the *SMN2* gene) covers a genotype that is predictive of SMA type 1
- In reality, some may go on to develop other types of SMA
- ERG do not consider the pre-symptomatic modelling robust enough for decision-making

*Costs and QALYs discounted at 3.5%

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

Discount rate

- Interim HST methods guide section 47:
  - *"…in cases when treatment restores people who would otherwise die or have a very severely impaired life to **full or near full health**, and when this is **sustained over a very long period (normally at least 30 years)**, analyses that use a non-reference-case discount rate for costs and outcomes may be considered.*
  - ***A discount rate of 1.5%** for costs and benefits **may be considered** by the Evaluation Committee if it is highly likely that, on the basis of the evidence presented, the long-term health benefits are likely to be achieved. Further, the Evaluation Committee will need to be satisfied that the introduction of the technology does not commit the NHS to significant irrecoverable costs."*

ERG comments: Discount rate

Appropriateness of 1.5% discount rate:

- Onasemnogene doesn't restore the majority of treated symptomatic SMA type 1 population to full or near full health (majority of those treated can sit unassisted but ERG clinical experts state they will still require substantial care)
  - However, START and STR1VE-US demonstrates a substantial survival benefit for patients who would have otherwise died
- ERG provides analysis using 1.5% discount rate for consideration by committee

Results using 1.5% discount rate

Deterministic analyses			Inc costs	Inc QALYs	ICER (£/QALY)	*Change in ICER
Company base case			[redacted]	14.67	[redacted]	[redacted]
ERG base case (observed milestones only)			[redacted]	13.52	[redacted]	[redacted]
ERG scenarios	1	ERG base case with independent sitter threshold of ≥30s	[redacted]	12.68	[redacted]	[redacted]
	2	And with 1 additional independent sitter	[redacted]	13.10	[redacted]	[redacted]
	3	US ICER model report costs	[redacted]	14.67	[redacted]	[redacted]
	4	Subsequent nusinersen treatment costs	[redacted]	14.67	[redacted]	[redacted]

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*From ICER with 3.5% discount rate applied

QALY weighting

- For ICERs above £100,000 per QALY, recommendations must take into account the magnitude of the QALY gain and the additional QALY weight that would be needed to fall below £100,000 per QALY
- To apply the QALY weight, there must be compelling evidence that the treatment offers significant QALY gains

Life incremental QALY gained	
Less than or equal to zero	1
11 to 29	Between 1 to 3 (equal increments)
Greater than or equal to 30	3

QALY gain undiscounted

Deterministic analyses			Inc QALY gain undiscounted	Inc QALY gain discounted	ICER* (£/QALY)
Company base case			21.19	10.00	[redacted]
ERG base case (observed milestones only)			19.19	9.85	[redacted]
ERG scenarios	1	ERG base case with independent sitter threshold of >30s	18.07	8.75	[redacted]
	2	And 1 additional independent sitter	18.62	9.05	[redacted]
	3	US ICER model report costs	21.19	10.00	[redacted]
	4	Subsequent nusinersen treatment costs	21.19	10.00	[redacted]

*ICER with 3.5% discount rate applied

NICE *Abbreviations: Inc, incremental*

Impact of technology beyond health benefits

- Company state that in addition to health benefits in the model, there will be other benefits.
  - If mobility is achieved and maintained, then schooling, educational attainment and participation in the workforce is possible
  - Interaction with wider community also possible
  - If gains in independence are achieved, this may alleviate caregiver burden – potentially allowing them to return to work (increased income)

Speech

11 (92%) in START* developed ability to speak at 24 months post-dosing.

- Evaluation of 7 of these children undertaken, using Bayley scale for language. Authors report that scores were within a normal range of development and schooling and potential for good quality of life should be possible.

*Cohort 2 (therapeutic dose)

Service design and delivery

- Onasemnogene SMA gene therapy should be implemented in specialist centres
- The infrastructure to support the implementation of a safe treatment environment will need to be in place before access can be allowed, this may require a variation to the funding requirement (NHS England)
- Testing for anti-AAV antibodies is currently not routinely available (Clinical expert) – company indicated that funding and coordination of this testing will be done by the company
- Close monitoring needed after treatment (Clinical expert)
- Professional organisation (British Society of Childrens Orthopaedic Surgeons) highlighted that if surgery to spine and wider lower limb musculoskeletal system is required, this may necessitate resources to tertiary centres to match demand – surgical technology already available on NHS and well established

Equality

- The company, do not consider there to be any equality issues relating to onasemnogene treatment
- Patient experts highlighted that SMA expertise varies by region, with some borderline SMA type 1/2 being misdiagnosed. Further to this, SMA is a spectrum of severity. This treatment is indicated for a severely disabled population
- 1 clinical expert submission stated that if inclusion criteria is for a selected subgroup of SMA1 patients for medical reasons, the equality issues will have to be addressed
- NHS England state they anticipate no equality issues for the incident population. Consideration should be given to prevalent population and whether a phased introduction (varying the funding requirement) to manage the implementation of the treatment is required

Innovation

- The company considers onasemnogene to be an innovative treatment:
  - Not only a step-change in management of SMA type 1, but may revolutionise the treatment of infants with this disease
  - With best supportive care (BSC) treatment, infants would have died. But with onasemnogene they may gain physical independence from caregivers
  - Pre-symptomatic population health gains even more dramatic

Factors affecting the guidance

- In forming the guidance, committee will take account of the following factors:

Nature of the condition	Clinical effectiveness
• Extent of disease morbidity and patient clinical disability with current care • Impact of disease on carers' QoL • Extent and nature of current treatment options	• Magnitude of health benefits to patients and carers • Heterogeneity of health benefits • Robustness of the evidence and the how the guidance might strengthen it • Treatment continuation rules
Value for money	**Impact beyond direct health benefits**
• Cost effectiveness using incremental cost per QALY • Patient access schemes and other commercial agreements • The nature and extent of the resources needed to enable the new technology to be used	• Non-health benefits • Costs (savings) or benefits incurred outside of the NHS and personal and social services • Long-term benefits to the NHS of research and innovation • The impact of the technology on the delivery of the specialised service • Staffing and infrastructure requirements, including training and planning for expertise

Key Issues: clinical effectiveness (recap)

- Clinical Evidence
  - Are the onasemnogene clinical trials generalisable to the:
    - indicated population in the marketing authorisation and SmPC?
    - NHS clinical practice in England?
    - future NHS clinical practice in England?
  - Is the NeuroNext (natural history) study the most appropriate to reflect best supportive care outcomes?
  - Are there other populations likely to benefit from treatment beyond those included in the clinical trials?
- Does the committee conclude the clinical trials capture:
  - Benefits that are important to patients? All relevant aspects of the disease?
- Clinical effectiveness
  - How effective is onasemnogene?
  - How robust are the trial results?
  - How uncertain are long-term effects of treatment?
  - Are the interim results for the pre-symptomatic population robust enough for decision-making?

Key Issues: cost effectiveness (recap)

- What should the transitions in the 3-year model be?
  - What is committee's view on the company's assumption that there would be an extra sitter and an extra walker relative to the numbers seen in the pooled data?
  - What is the relevant threshold for independent sitting in the 3-year model?
- Is it reasonable to assume that patients persist in the state they are in after 3 years?
- Are the extrapolations of events from the 3-year data acceptable?
- What should the utilities attached to the states be?
  - What is committee's view on using different utilities depending on treatment?
- What costs should be attached to the states?
- What is Committee's view of the uncertainties in the model results?
- What discount rate should be applied? What threshold for cost effectiveness is relevant?
- What is the most plausible ICER range?
- What is committee's view on the pre-symptomatic population analysis
- What factors affecting the guidance need to be taken into account?
  - Equalities issues?
  - Additional factors?

NICE National Institute for Health and Care Excellence

Onasemnogene abeparvovec for treating spinal muscular atrophy

Chair's presentation

2nd Evaluation meeting

Highly Specialised Technologies committee, 10th February 2021

Chair: Peter Jackson

Lead team: Paul Arundel, Ron Akehurst, Jeremy Manuel

Technical team: Alan Moore, Nicole Elliott

Company: Novartis Gene Therapies

ERG: BMJ TAG

History of the topic

- Following a submission in 2019 the company advised of an extension to its regulatory timings – **committee meeting delayed**
- **Original anticipated indication:** for spinal muscular atrophy type 1
- **Final SmPC indication:** for the treatment of:

  - patients with 5q spinal muscular atrophy (SMA) with a bi-allelic mutation in the *SMN1* gene and a clinical diagnosis of SMA Type 1, or

  - patients with 5q SMA with a bi-allelic mutation in the *SMN1* gene and up to 3 copies of the *SMN2* gene.

- **Committee meeting – October 2020**
  - Resulted in negative recommendations for types 0, 1, 2 and 3
  - Proposed MAA for pre symptomatic population
- **October – December 2020**
  - Company updated their commercial offer
  - Committee discussion on the proposed wording of a positive recommendation for symptomatic type 1 population (with reference to the trial inclusion criteria relating to age)
  - NICE met with the company and experts

Committee conclusions from ECM1

Committee considered the following analysis most appropriate for decision-making for SMA type 1:

- using the independent sitting threshold of 30 seconds or more
- assuming 1 additional sitter to the observed data from STR1VE US
- applying a 1.5% discount rate for costs and utilities
- assuming that motor milestones gained in the first 3 years in the economic model are maintained in the long term
- QALY weighting [redacted]

For pre-symptomatic SMA, the committee noted that onasemnogene had the potential to be cost-effective but that the company analysis were based on assumptions (not trial evidence) and that the model assumed all pre-symptomatic babies with up to 3 SMN2 copies would develop SMA type 1 (a significant proportion could develop type 2 or 3 SMA) – the SPR1NT trial is ongoing

Questions for discussion today

What is the likely response in children older than 6 months of age?

What is the likely clinical condition of patients diagnosed after 6 months?

Is age an important characteristic to define babies in whom onasemnogene is clinically and cost-effective?

Is there an alternative patient characteristic (other than age) that could be more appropriate to include in the recommendation to reflect the trial population?

The definition of type 1 SMA is symptom onset before 6 months of age – what proportion of babies are diagnosed before 6 months of age but treated over 6 months?

What proportion have symptom onset before 6 months (so are defined as having type 1 SMA) but don't receive a formal diagnosis until they are older than 6 months?

What is the gap between diagnosis and treatment now?

Is the gap between diagnosis and treatment expected to get shorter?

When is new born screening going to be in place?

Should we consider a MAA?

Nature of the condition: Spinal Muscular Atrophy (SMA) Type 1

- **SMA type 1 is the most severe form of SMA and the main genetic cause of infant mortality (if untreated)**: symptoms arise before age 6 months. Babies unable to sit independently and have low muscle tone (hypotonia)
- **Affects every aspect of infants life**: never gain developmental milestones after initial presentation, severe muscle weakness affecting movement, swallowing and breathing
- **Severity can be linked to age at which symptoms appear** - earlier onset associated with more severe disease. Time between onset and treatment administration is important
- Most people with SMA type 1 will die before 2 years of age when treated with best supportive care

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 – 40 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

Clinical expert statements - Oct 2020 ECM

Innovation

- Novel change in treatment, requiring new pathways, re-emphasising early and rapid diagnosis
- Clearly a 'step-change' in treatment of newly diagnosed patients with SMA type 1

Benefits

- Increase in survival and health-related quality of life compared to standard care
- More benefits with earlier treatment

Subgroups

- People more severely affected and older less likely to see improvement of condition - aim will only be to prevent further progression
- People with only 1 *SMN2* copy would most likely not benefit from the treatment
- People with SMA type 2 and 3 not studied in clinical trials to date
- Treatment after 6 months of age may still result in significant and substantial impact on health-related benefits, but there is a lack of data to support this

Other considerations

- Clear guidance needed on eligibility criteria for the treatment
- Fast testing of for anti-AAV antibodies required (currently not routinely available)*

NICE *AAV9 antibody testing will be funded and coordinated by Novartis Gene Therapies at a central European lab (Viroclinics, The Netherlands) – company submission.

Patient and carer group submissions – Oct 2020 ECM

Potential benefits of onasemnogene

- SMA UK/ MNDA UK survey – 14 parents of children with SMA type 1
  - When asked for their view of onasemnogene as a treatment for an infant newly diagnosed with SMA Type 1: 13 (93%) said it was totally acceptable; 1 (7%) considered it acceptable
  - Strong advantages of onasemnogene treatment included the one-off nature of the treatment, possible effects on breathing/motor milestones and life expectancy, and how the treatment is delivered
  - No respondent stated any strong disadvantages to onasemnogene treatment. Potential risks and how they are managed was considered by 8 (57%) as neither an advantage nor disadvantage – this is not an unexpected result.
- SMA UK highlight that it was difficult to receive more responses to their survey, due to the complexity of the questions and the fact that parents caring for those with SMA type 1 have little time

Patients' and carers' perspectives – Oct 2020 ECM

Potential benefits of onasemnogene

- Welcome option of a **one-off treatment**

*"the possibility of one-off treatment is **very appealing and exciting**."*

*"Access to this 'one-off' intravenous treatment leading to improvements in the outcomes listed in the NICE scoping document would be a **step-change in the treatment and management of the condition**."*

*"Patients or patient carers **do not see any disadvantages** of this technology"*

- Onasemnogene as a treatment option **brings hope**

"This is an exceptional chance for children with SMA to grow up without symptoms present and have a life without influence of this debilitating condition!"

- Potential benefits for **all children** with SMA with those treated when younger potentially showing faster results
  - Including pre-symptomatic patients is essential (verbal communication)
- Noted the associated costs, trips to the hospital and potential complications that may arise with other active treatment options

Patients' and carers' perspectives – Oct 2020 ECM

Important issues not captured in submissions but expressed verbally to NICE technical team

- Encourage committee to consider the transferability of trial evidence beyond population in trial defined by SMA type
  - Consider a managed access agreement (MAA) option for groups without direct trial data. Lots of research being done currently
- Fine motor control is also important for improvements in quality of life
- Slowing down disease progression or stabilisation of disease is also highly valued
- While trial evidence is impressive, carers are aware that treatment with onasemnogene may not be a cure
- Any health improvements which reduce caregiver burden would be very welcome
  - Reduced feeding/ventilatory support and gaining ability to speak highly valued
- Still a high unmet need in this population. Concerns exist regarding regional SMA expertise, with some diagnosis being delayed
- Carers need to be well-informed when discussing treatment options

NHS England comments - Oct 2020 ECM

- Pathway for diagnosis well defined – standard genetic testing widely available
- Care delivered as set out in the international standards of care
- Onasemnogene's place in current treatment pathway not well defined – new treatment with a novel mode of administration
    - Including logistics of providing intervention and services required to provide treatment should it receive positive NICE guidance
- Onasemnogene expected to require new pathways for preparation of patients, transfer of medicine from manufacturer, clinical delivery of medicine and long-term monitoring after treatment
- Consideration should be given to role of onasemnogene in relation to nusinersen use
- Variation to the funding requirement may be needed
- Risdiplam also available via the EAMS for individuals with type 1 and type 2 SMA aged 2 months and older and who are not suitable for treatment with nusinersen
- Incident population is small (approximately 40) – challenges of providing centres across the country as clinical expertise will be concentrated
- Consideration should be given to prevalent population in terms of eligibility
- Staff at highly specialised centres will need to be trained – should be provided by the company

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 abeparvovec is £1,795,000 for one-off dose • Simple discount patient access scheme (PAS) approved

NICE 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

Decision Problem (1)

- NICE reissued the final scope post-company submission to reflect the population in the indication given marketing authorisation
- Nusinersen was not included as a comparator in the reissued scope as it is recommended for use in a managed access agreement and not routinely commissioned

	Original NICE Scope	Company submission	Company rationale	Reissued NICE scope
Population	SMA type 1	SMA type 1 with 2 *SMN2* copies	Submission covers population in clinical trial	Indicated population in marketing authorisation*
Subgroups	If evidence allows, consideration may be given to a subgroup of people with pre-symptomatic disease	Interim evidence for a pre-symptomatic population given	SPR1NT trial ongoing	No change
Comparator	• Best supportive care • Nusinersen (subject to NICE appraisal)	Best supportive care	As agreed with NICE, nusinersen is not a comparator - not recommended for routine use by NHS	Best supportive care

* 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

Decision Problem (2)

	NICE Scope (original and reissued)	Company submission	Company rationale
Outcomes	• motor function (including, sitting, standing, walking) • frequency and duration of hospitalisation • speech and communication • respiratory function • complications of SMA (examples include scoliosis and muscle contractures) • need for non-invasive or invasive ventilation • mortality • adverse effects of treatment • health-related quality of life (for patients and carers)	As per scope. • Event-free survival (EFS) also assessed (defined as permanent ventilation*-free survival) • Health-related quality of life of caregivers explored in scenario analyses only	• EFS is a primary or secondary outcome in onasemnogene clinical trials • Lack of robust utilities for caregivers of SMA type 1

*Permanent ventilation defined by tracheostomy or by the requirement of ≥16 hours of respiratory assistance per day (via non-invasive ventilatory support) for ≥14 consecutive days in the absence of an acute reversible illness, excluding perioperative ventilation.

Marketing authorisation and clinical evidence

Onasemnogene is 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

Evidence presented by company

Clinical trial evidence:
START, STR1VE-US, STR1VE-EU:
SMA type 1 diagnosis, <6 months at treatment

Clinical trial evidence:
SPR1NT:
Pre-symptomatic,
<6 weeks old at treatment

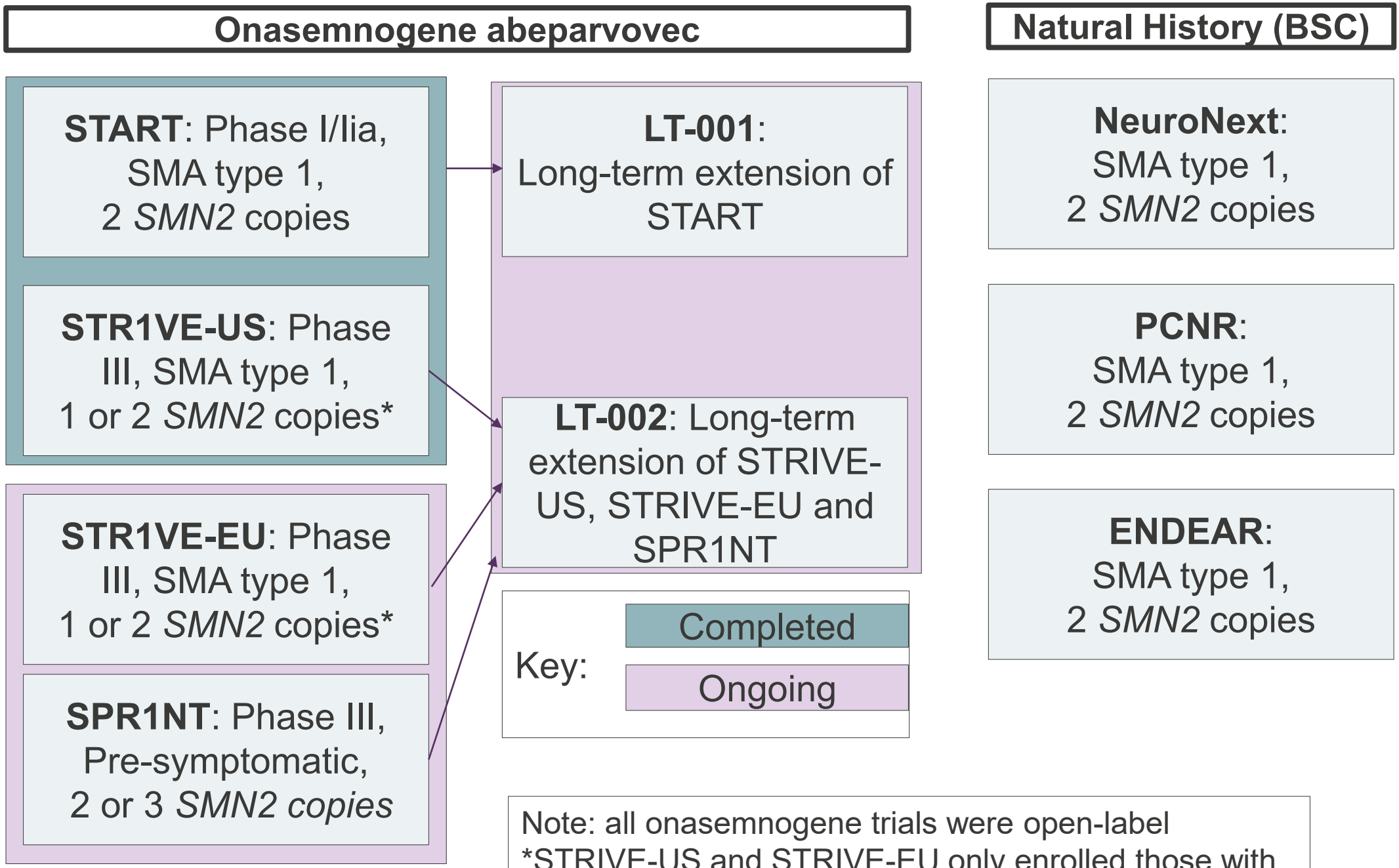
Other considerations

Clinical and patient experts highlight that there are people with SMA who may benefit from treatment covered by MA wording (2nd bullet point) not included in clinical trial evidence

SmPC

- **SmPC treatment initiation and dosing rules:**
  - Before administration, baseline laboratory testing including **AAV9 antibody testing is required**
  - Recommended dosing given for people who **weigh 2.6 kg to 21.0 kg**
  - **Safety and efficacy in premature neonates** before reaching full-term gestational age **have not been established**. No data are available
  - 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**

Clinical evidence summary



Note: all onasemnogene trials were open-label
*STRIVE-US and STRIVE-EU only enrolled those with 2 copies of *SMN2*

NICE

Summary: START and STRIVE-US

	START	STR1VE-US
Description	Phase I/IIa, open-label, one-time infusion, ascending-dose, single-centre study (US)	Phase III, open label, single-arm, one-time infusion, multi-centre (US)
Trial eligibility criteria	• SMA type 1 with bi-allelic *SMN1* gene mutations with 2 copies of *SMN2* • Patients 6 months of age and younger at date of treatment	• SMA type 1 with bi-allelic *SMN1* gene mutations with 1* or 2 copies of *SMN2* • Patients 6 months of age and younger at date of treatment
Duration of follow up	2 years post dose	18 months of age
Population size	15 (Cohort 1: 3 - low dose. **Cohort 2: 12 therapeutic dose****)	22

* no patients with 1 copy of *SMN2* enrolled

** Only those receiving therapeutic dose are included in economic analysis

Summary: START and STR1VE-US outcomes

START	STR1VE-US
Primary outcomes and objective	
Safety (primary objective)	Independent sitting for ≥30 seconds (efficacy endpoint)
Survival without permanent ventilation (efficacy endpoint)	Survival without permanent ventilation (efficacy endpoint)
Other outcomes	
Motor milestone achievements	Motor milestone achievements
Change from baseline in CHOP-INTEND* score**	Change from baseline in fine and gross motor components of Bayley Scales of Infant and Toddler Development
Ability to thrive	Ability to thrive
Nutritional status and swallowing function	Change from baseline in gross motor function as determined by improvement in CHOP-INTEND* score
Motor neurone function	% achieving CHOP-INTEND score of ≥40, ≥50 and ≥58
	Change in peroneal nerve CMAP amplitude
	Age independent sitting (30 seconds) is first achieved
	% independent of ventilatory support at 18 months

*Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders
**During the second year of the study, motor milestones of patients with CHOP-INTEND scores ≥62 was also assessed using the Bayley Scales

Summary: STR1VE-EU and SPR1NT

	STR1VE-EU	SPR1NT (Pre-symptomatic)
Description	Phase III, open label, single-arm, single-dose trial	Phase III, open label, single-dose trial
Eligibility Criteria	• SMA type 1 with bi-allelic *SMN1* gene mutations with 1* or 2 copies of *SMN2* • ≤ 6 months of age at treatment	• Pre-symptomatic with bi-allelic deletion of *SMN1*, and 2 or 3 copies of *SMN2* • ≤6 weeks of age at treatment
Selected Outcomes	sitting without support ≥10 seconds	• those with 2 copies *SMN2*, independent sitting ≥ 30 seconds • those with 3 copies *SMN2*, the ability to stand without support for ≥3 seconds
Follow up	18 months of age	2 copies of *SMN2*: 18 months of age 3 copies of *SMN2*: 24 months of age
Population size	33	Currently 30
Completion (estimated)	[redacted]	[redacted]

NICE

* no patients with 1 copy of *SMN2* enrolled

Summary: LT-001 & LT-002

	LT-001	LT-002
Description	Long term extension of START trial	Long term extension of all other onasemnogene trials
Selected Outcomes	Safety outcomes Efficacy assessments: assess developmental milestones (New milestones not documented during START must be supported by video evidence)	Safety outcomes Efficacy assessments: assess developmental milestones (New milestones not documented during onasemnogene trials must be supported by video evidence)
Completion (estimated)	Quarter 4 2033	Quarter 4 2034
Population size	13	Planned: approximately 308 • Cohort 1 (patients dosed intravenously): approximately 83 • Cohort 2 (patients dosed intrathecally): approximately 225*

- Company also state they are sponsoring a prospective Global SMA Disease Registry (RESTORE, AVXS-101-RG-001) – aiming to enroll 500 SMA patients (20% of which on new SMA treatments such as onasemnogene)

* Outside of scope

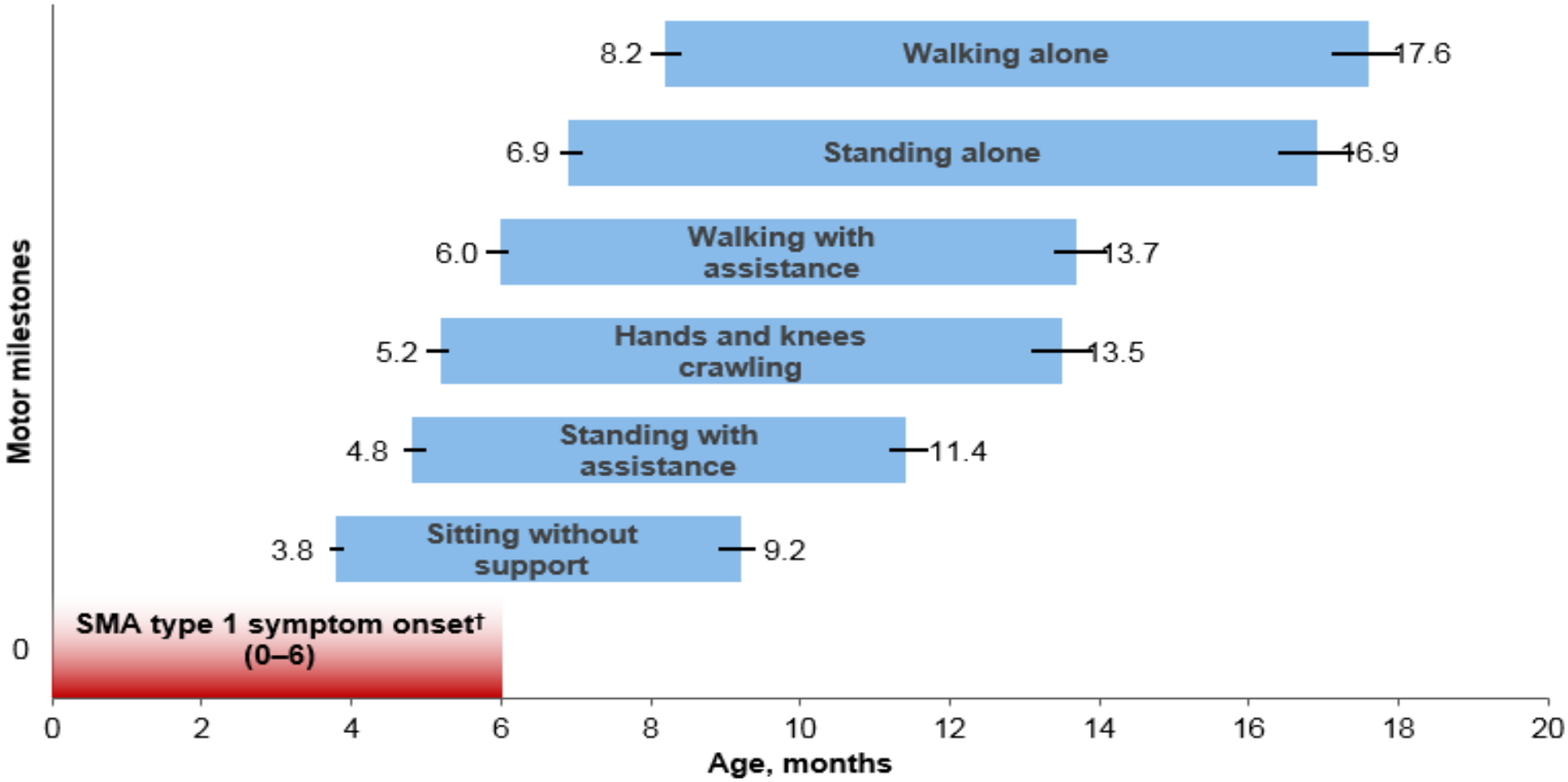
Baseline characteristics – SMA type 1

Characteristics	START*	STR1VE-US	STR1VE-EU
SMN2 copy number	2	2	2
Age at symptom onset months (SD)	2.3 (1.47)	1.9 (1.24)	-
Age at diagnosis (range – min, max)	67.8 days (1, 137)	2.6 months (0, 5.4)	XXXXXX
Age at treatment administration, months (SD) [range – min, max]	3.4 (2.06) [0.9, 7.9]	3.7 (1.61) [0.5,5.9]	XXXXXX
Sex - % Female	58.3	54.5	XXXXXX
Weight, kg (SD) [range - min, max]	5.7 (1.34) [-]	5.8 (-) [3.9, 7.5]	XXXXXX
Mean CHOP-INTEND (SD) (range - min, max)	28.2 (12.3) [-]	32.0 (9.69) [-]	XXXXXX XXXXXX
Swallowing thin liquid - % Yes	33.3	100	XXXXXX
Non-oral feeding support -% Yes	41.7	0	XXXXXX
Ventilatory support -% Yes	8.3**	0	XXXXXX

*Cohort 2 (therapeutic dose), n=12 SD: standard deviation

** Does not include one additional patient in Cohort 2 who was receiving BiPAP at baseline but for whom data was mis-entered at the clinical site

SMA type 1 onset and normal motor milestone achievements



- Red box highlights the age range of symptom onset in SMA type 1 – those with SMA type 1 never gain the outcomes listed. Short life expectancy (< 2 years)
- Numerical values on blue bars highlight 1st and 99th percentile range for outcomes with 95% confidence intervals shown

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Clinical effectiveness results:

Event-free survival (Survival without permanent ventilation*)

Study	Time of follow-up	Survived without permanent ventilation
START (therapeutic dose cohort) [n=12]	13.6 months of age	12 **(100%)**
	24 months post dose	12 **(100%)**
STR1VE-US [n=22]	>10.5 months of age	21 **(95.5%)**
	≥13.6 months of age	20 **(90.9%)**
	18 months of age	20 **(90.9%)**
STR1VE-EU [n=33]	Median 11.9 months (range 1.8 to 15.4). Median age 15.4 months (range: 6.9 to 18.6)	XXXXXX
LT-001 (follow-up of START) [n=10]	Median age 4.5 years (range 4.3 to 5.6 years)	10 **(100%)**

*Permanent ventilation defined by tracheostomy or by the requirement of ≥16 hours of respiratory assistance per day (via non-invasive ventilatory support) for ≥14 consecutive days in the absence of an acute reversible illness, excluding perioperative ventilation.

Clinical effectiveness results: Motor functioning

Motor Milestone	START [n=12] (therapeutic dose cohort)	STR1VE-US [n=22]	STR1VE-EU [n=33] (Interim)
Age at follow-up (range)	~30 months	18 months	15.4 months (6.9 to 18.6)
Rolling (back to side from both sides)	9 (75%)	13 (59%)	XXXXXX
Hold head erect ≥3 seconds, unsupported	11 (91.7%)	17/20* (85%)	XXXXXX
Sits with support	11 (91.7%)	-	XXXXXX
Sits alone ≥5 seconds	11 (91.7%)	-	XXXXXX
Sits alone ≥10 seconds	10 (83.3%)	14 (63.6%)	XXXXXX
Sits alone ≥15 seconds	9 (75%)	-	XXXXXX
Sits alone ≥30 seconds	9 (75%)	14 (63.6%)	XXXXXX
Stands with assistance	2 (16.7)	1 (4.5%)	XXXXXX
Stands alone	2 (16.7)	1 (4.5%)	-
Walks with assistance	2 (16.7)	1 (4.5%)	XXXXXX
Walks alone	2 (16.7)	1 (4.5%)	-

NICE Milestones informing economic model

*Two infants who were able to hold head erect for ≥3 seconds without support at screening visit are not included.

Post hoc analysis by age – ERG table 26

	START, Cohort 2 (N=12), STR1VE-US (N=22), POOLED (N=34)		POOLED START Cohort 2 & STR1VE-US (N=34)
	Dosing at ≤3.5 months of age (n=17)	Dosing at >3.5 months of age (n=17)	
Age at dosing, months, mean	[redacted]	[redacted]	[redacted]
Sits unassisted for ≥5 seconds[a], n	14/17 (82.4%)	[redacted]	[redacted]
Median age, months (range)	[redacted]	[redacted]	Not reported
Sits unassisted for ≥30 seconds[b], n	14/17 (82.4%)	[redacted]	[redacted]
Median age, months (range)[c]	[redacted]	[redacted]	Not reported
Walking unassisted[d]	3/17 (17.7%)	[redacted]	[redacted]
Median age, months (range)	[redacted]	[redacted]	Not reported

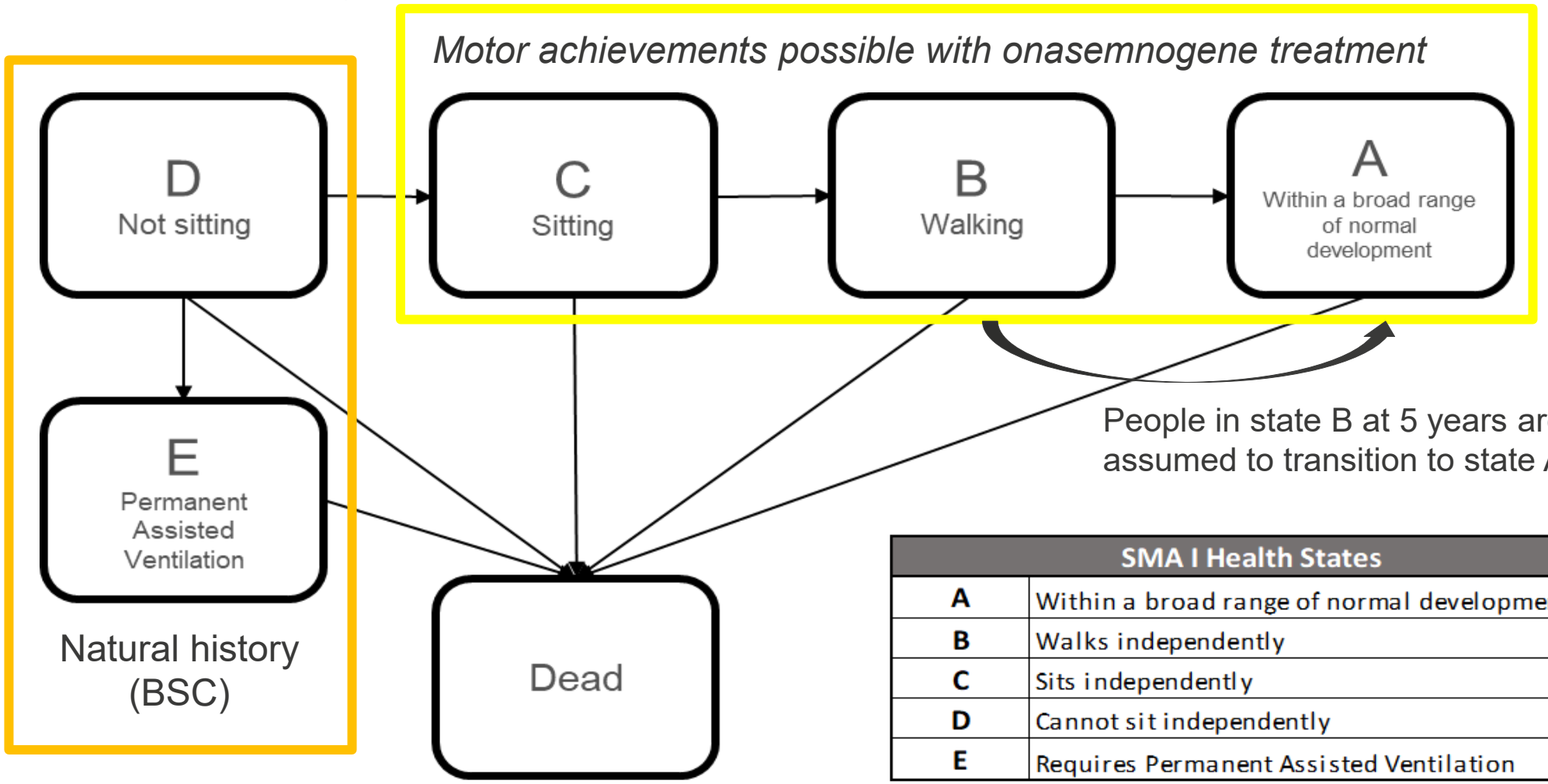
[a] Bayley Scales gross motor subtest item #22: "Child sits alone without support for at least 5 seconds" used for STR1VE-US (not centrally reviewed/confirmed). [redacted]. "Sits alone <10 seconds" for START (centrally reviewed/video-confirmed). All patients in the 'sitting < 10 seconds' category were able to sit for at least 5 seconds.

[b] Bayley Scales gross motor subtest item #26: "Child sits alone without support for at least 30 seconds" used for both STR1VE-US and START (centrally reviewed/confirmed for both).

[c] [redacted]

[d] Bayley Scales gross motor subtest item #43: "Child takes at least 5 steps independently, displaying coordination and balance" used for STR1VE-US. Gross Motor Checklist: "takes independent steps" and the Motor Milestone Development Survey 'walks independently' used for START (centrally reviewed/video-confirmed for both).

Company economic model structure



SMA I Health States	
A	Within a broad range of normal development
B	Walks independently
C	Sits independently
D	Cannot sit independently
E	Requires Permanent Assisted Ventilation

Economic model based on motor function and need for permanent assisted ventilation (PAV)

Modelling approach (1)

- Model based on patients included in clinical trials
- All patients start in health state D (non sitting)
- Patients without onasemnogene (BSC) never sit (D) and have a probability of needing PAV (E) or dying (they cannot move to higher functioning states). This is assumed in the short term and long-term: based on natural history of SMA type 1
- With onasemnogene, patients may remain in non-sitting state (D), or move to PAV (E) state
  - or they may attain motor milestones and move to higher functioning states of unassisted siting (C), in which they may remain or move to walking state (B)
- Assumption that the children occupying state C after 3 years of age will remain there for the rest of their lives
  - Life expectancy and costs modelled on SMA type 2
- Those in state B at 3 years of age assumed to move to state A (broad range of normal development) at 5 years of age – based on World Health Organisation (WHO) reported windows of motor milestone achievement
  - Those in state A remain there for lifetime and normal life expectancy assumed for state A: based on life expectancy for SMA type 3. Costs are modelled on SMA type 3

Abbreviations: PAV: Permanent assisted ventilation

Modelling approach (2)

- Different parametric curves are fitted to each health state to model long term survival
- Costs and utilities are attached to time spent in each states over the lifetime of the model and discounted to provide cost-effectiveness estimates
- Structure of model is judged by the ERG to be appropriate and was used by the Institute for Clinical and Economic Review (ICER) in their appraisal of the treatment
- Cycle length of 6 months in first 3 years with yearly cycles after
- Estimates of treatment effectiveness in first 3 years of the model based on pooled motor milestone data from START and STR1VE-US trials (offset by 6 months - motor achievements assumed to occur in next cycle)
- START and STR1VE-US trials follow patients to different time points (START until ~30 months and STR1VE-US until 18 months of age) – assumptions on additional milestones achieved between 18 and 30 months in STR1VE-US are made by the company
- STR1VE-EU and LT-001 interim data used as supportive evidence (results not used in pooled dataset)

Equality

- The company, do not consider there to be any equality issues relating to onasemnogene treatment
- Patient experts highlighted that SMA expertise varies by region, with some borderline SMA type 1/2 being misdiagnosed. Further to this, SMA is a spectrum of severity. This treatment is indicated for a severely disabled population
- 1 clinical expert submission stated that if inclusion criteria is for a selected subgroup of SMA1 patients for medical reasons, the equality issues will have to be addressed
- NHS England state they anticipate no equality issues for the incident population. Consideration should be given to prevalent population and whether a phased introduction (varying the funding requirement) to manage the implementation of the treatment is required

Summary of company and ERG base case assumptions

	Company base case	ERG base case
Short term model	Observed pooled data of START (~30 months of age) and STR1VE-US (18 months of age)	
	Apply an independent sitting threshold of >5 seconds (START) and >30 seconds (STR1VE-US) (state C)	Results for thresholds of >5 seconds and >30 seconds (state C)
	1 additional sitter and 1 additional walker in STR1VE-US assumed between 18 to 30 months (age)	Only observed milestones in base case (1 additional sitter assumed in scenario analysis)
	Motor milestones achieved in first 3 years assumed maintained long term. No milestones gained/lost	

SMA type 1

- Following ECM1 the XXXXXXX. The results using the committee's preferred analysis for SMA type 1 and the company's base case are shown below:

	Results per patient	Onasemnogene	Best supportive care	Incremental value
0	Company's Base case			
	Total Costs (£)	XXXXXXX	413,269	XXXXXXX
	QALYs	14.89	0.21	14.67
	Undiscounted QALYs	21.41	0.22	21.19
	ICER (£/QALY)			XXXXXXX
2	Threshold for sitting independently of ≥30 seconds for the pooled dataset (one additional sitter, no additional walker)			
	Total Costs (£)	XXXXXXX	413,269	XXXXXXX
	QALYs	13.31	0.21	13.10
	Undiscounted QALYs	18.84	0.22	18.62
	ICER (£/QALY)			XXXXXXX

Abbreviations: ICER, incremental cost effectiveness ratio; QALYs, quality adjusted life years

NICE Results using 1.5% discount rate

Scenario Analyses

We requested:

- A view from the ERG experts on age at diagnosis and clinical benefit
- A reduction in the numbers of patients achieving the milestones of sitting independently for ≥30 seconds and walking, based on pooled data from START and STR1VE-US regardless of age at treatment.
- Motor milestone achievement based on pooled data from START and STR1VE-US for babies treated older than 3.5 months of age.
- A scenario in which 25% of babies treated at age 3.5 months and older achieving the motor milestone of sitting independently for ≥30 seconds.
- **NB:** NICE and the committee requested that a scenario of 25% of babies treated at age 3.5 months and older achieving the motor milestone of walking, but the ERG notes that no babies treated older than 3.5 months of age in the pooled START and STR1VE-US trials achieved the milestone of walking. Refer to Table 26 of the ERG report for data on motor milestones by age at dosing in Cohort 2 in START, STR1VE-US, and the POOLED dataset.

ERG – experts (Feb 2020)

- 30-40% diagnosed older than 6 months
- Experts considered that children aged 6 months and over with SMA type 1 could potentially receive clinical benefit from treatment with Onasemnogene but this would depend on symptom severity at the start of treatment (which is influenced by the extent of loss of the units responsible for motor function)
- Experts considered that there is a critical threshold for loss of motor units, after which treatment with onasemnogene might not be as effective and, as a consequence, early treatment with onasemnogene is key.

ERG data range analysis

The ERG explored three assumptions for the data range analysis where a range of 1 to 3 patients do not achieve motor milestones, which are as follows:

- Reducing the number of sitters and transitioning these patients to the non-sitting health state from age 18 months onwards.
- Reducing the number of walkers and transitioning these patients to the sitting health state from age 24 months onwards.
- Simultaneously reducing the number of sitters and walkers and transitioning these patients to the non-sitting health state from age 24 months onwards

Observed motor milestone achievement

Motor milestone data preferred by the committee (including an additional sitter and a threshold of >30 seconds)

Age at end of cycle	Not sitting	Sitting but not walking	Walking	Dead or PAV
6	34	0	0	0
12	32	0	0	2
18	24	8	0	2
24	14	17	1	2
30	10	19	3	2
36	8	21	3	2
48	8	21	3	2

ERG data range analysis – impact on the ICER due to reduction in motor milestone achievement

Reduction in patients achieving motor milestones	Sitters → non-sitters	Walkers → sitters	Sitters and Walkers → non-sitters
Committee preferred base case			[redacted]
-1	[redacted]	[redacted]	[redacted]
-2	[redacted]	[redacted]	[redacted]
-3	[redacted]	[redacted]	[redacted]

Observed motor milestone achievement for babies treated with Onasemnogene aged 3.5 months and older

The ERG notes that the 3.5-month age threshold for the analysis is solely based on median age at treatment in START and STR1VE-US and there is no clinical rationale or evidence to support the use of 3.5 months as a threshold for treatment with onasemnogene.

Age at end of cycle	Not sitting	Sitting but not walking	Walking	Dead or PAV
6	[redacted]	[redacted]	[redacted]	[redacted]
12	[redacted]	[redacted]	[redacted]	[redacted]
18	[redacted]	[redacted]	[redacted]	[redacted]
24	[redacted]	[redacted]	[redacted]	[redacted]
30	[redacted]	[redacted]	[redacted]	[redacted]
36	[redacted]	[redacted]	[redacted]	[redacted]
48	[redacted]	[redacted]	[redacted]	[redacted]

Treatment age sensitivity analysis (discounted at 1.5%)

Results of the company's scenario using pooled motor milestone achievement data, as well as updated overall and event-free survival for babies treated with onasemnogene aged 3.5 months and older, as well as the company's original scenario for babies treated aged ≤3.5 months

Treatment	Total costs	Total LYs	Total QALYs	Incremental costs	Incremental LYs	Incremental QALYs	
Committee preferred base case							
BSC	413,269	2.28	0.21	-	-	-	
Onasemnogene + BSC	[redacted]	20.24	13.31	[redacted]	17.95	13.10	
Dosing at ≤3.5 months of age (n=17), sitting threshold of ≥30 seconds							
BSC	413,269	2.28	0.21	-	-	-	
Onasemnogene + BSC	[redacted]	24.55	17.24	[redacted]	22.27	17.03	
Dosing at >3.5 months of age (n=17), sitting threshold of ≥30 seconds							
BSC	413,269	2.28	0.21	-	-	-	
Onasemnogene + BSC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	

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

25% achievement of motor milestone of sitting independently - babies treated older than 3.5 months

- The ERG also performed a scenario, requested by NICE, where the number of babies treated with onasemnogene aged 3.5 months and older achieved the motor milestone of sitting independently for ≥30 seconds is reduced to 25% of the value obtained from the pooled trial data (rounded up to the closest whole number) in every cycle of the short-term model and the remainder stay in the non-sitting health state from age 18 months.

Treatment	Total costs	Total LYs	Total QALYs	Incremental costs	Incremental LYs	Incremental QALYs	
BSC	413,269	2.28	0.21	-	-	-	
Onasemnogene + BSC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	

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

Questions for discussion today

What is the likely response in children older than 6 months of age?

What is the likely clinical condition of patients diagnosed after 6 months?

Is age an important characteristic to define babies in whom onasemnogene is clinically and cost-effective?

Is there an alternative patient characteristic (other than age) that could be more appropriate to include in the recommendation to reflect the trial population?

The definition of type 1 SMA is symptom onset before 6 months of age – what proportion of babies are diagnosed before 6 months of age but treated over 6 months?

What proportion have symptom onset before 6 months (so are defined as having type 1 SMA) but don't receive a formal diagnosis until they are older than 6 months?

What is the gap between diagnosis and treatment now?

Is the gap between diagnosis and treatment expected to get shorter?

When is new born screening going to be in place?

Should we consider a MAA?