NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Nusinersen for treating spinal muscular atrophy [ID1069]

Committee Papers

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

SINGLE TECHNOLOGY APPRAISAL

Nusinersen for treating spinal muscular atrophy [ID1069]

Contents:

11. Company Supplementary Analysis (with PAS)

12. Evidence Review Group addendum (with PAS)

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

Pre-meeting briefing:
Nusinersen for treating spinal muscular atrophy – STA

This slide set is the pre-meeting briefing for this appraisal. It has been prepared by the technical team with input from the committee lead team and the committee chair. It is sent to the appraisal committee before the committee meeting as part of the committee papers. It summarises:

- The key evidence and views submitted by the company, the consultees and their nominated clinical experts and patient experts and
- The Evidence Review Group (ERG) report

It highlights key issues for discussion at the first appraisal committee meeting and should be read with the full supporting documents for this appraisal

Please note that this document includes information from the ERG before the company has checked the ERG report for factual inaccuracies

The lead team may use, or amend, some of these slides for their presentation at the Committee meeting

Key issues
Clinical effectiveness

Decision problem

- Is the population defined appropriately?
  - Can nusinersen be considered for types 0, 1, 2, 3 and 4 SMA?

Clinical evidence

- Are the clinical trials relevant to the use of nusinersen in clinical practice?
  - Generalisability to English population
  - Dosing regimen
- Does the evidence capture the most important outcomes for patients with SMA?
- How effective is nusinersen?
  - Early and later-onset SMA
  - Pre-symptomatic patients
  - Subgroups
  - Long-term benefits

Key issues
Cost effectiveness

- Is the economic model suitable for decision making?
  - Do the modelled health states based on motor milestones appropriately map the course of SMA and capture the key elements of disease?
- Are the assumptions for the change in motor milestones over time and movement of patients through the health states appropriate?
- Is the modelling and extrapolation of overall survival appropriate?
  - Survival advantage associated with improved motor function
- What are the most appropriate estimates of utilities? For patients and carers?
- Additional considerations
  - Population contains children: any additional considerations required?
  - Are the end-of-life criteria met?
  - Proposed managed access arrangement
- What are the most plausible ICERs?

Spinal muscular atrophy
Disease background

- SMA is a genetic, progressive neuromuscular disease most commonly caused by mutations in the *SMN1* on chromosome 5q.
  - *SMN1* gene encodes the “survival motor neurone” (SMN) protein
- SMA affects the motor neurones (nerves from the brain and spinal cord that control muscle movements). The lack of SMN protein causes the motor neurones to malfunction, deteriorate and eventually die, leading to muscle weakness and atrophy.
- It is a long term degenerative condition causing muscle weakness, and results in gradually worsening physical disabilities and mobility loss.
- SMA affects an estimated 1 in 6,000 to 1 in 10,000 births worldwide, and the incidence varies between different types of SMA.
  - It is estimated that about 100 people are born with SMA per year in the UK, and currently between 1,200 and 2,500 children and adults with SMA in the UK.

Classification and subtypes of SMA

SMA Type	Age of onset	Maximal motor milestone	Motor ability and additional features	Survival‡
Type 0	Before birth	None	Severe hypotonia; unable to sit and roll*	Respiratory insufficiency at birth: death within weeks
Type 1	2 weeks (Ia) 3 months (Ib) 6 months (Ic)	None	Severe hypotonia; unable to sit and roll†	Death/ventilation by 2 years
Type 2	6–18 months	Sitting	Proximal weakness: unable to walk independently	Survival into adulthood (typically >25 years)
Type 3	<3 years (IIIa) >3 years (IIIb) >12 years (IIIc)	Walking	May lose ability to walk	Normal life span
Type 4	>30 years or 10–30 years	Normal	Mild motor impairment	Normal life span

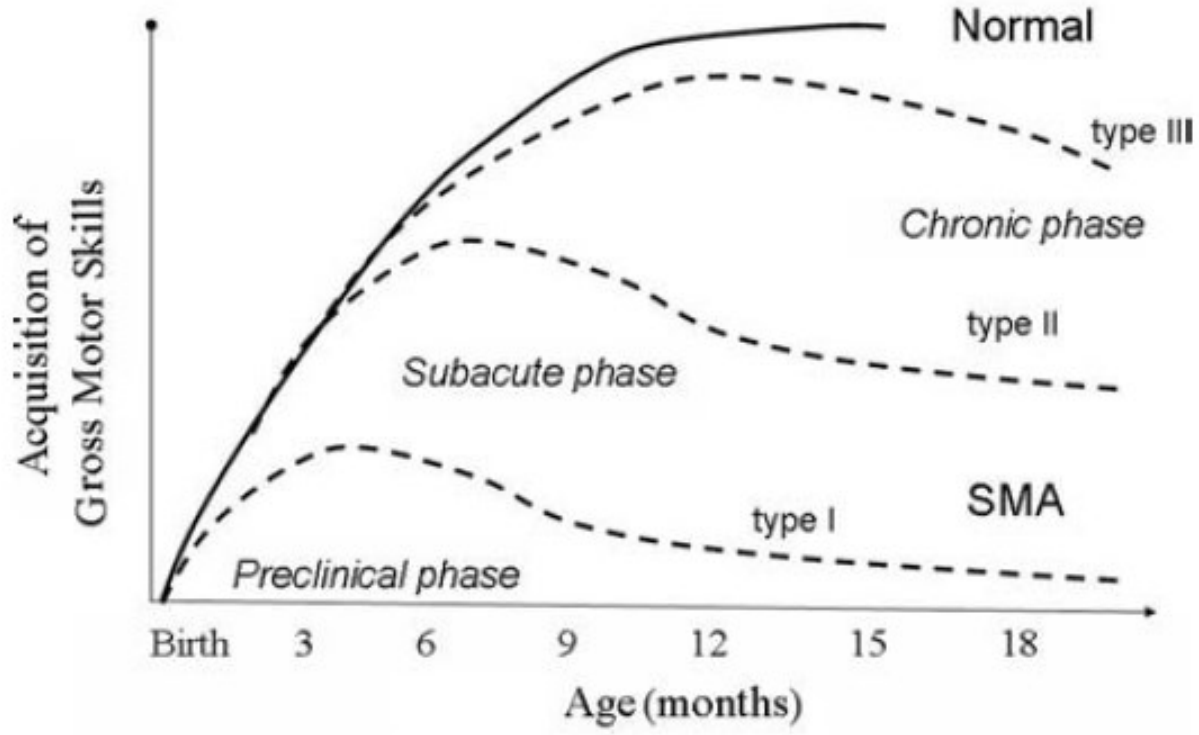
- Patient experts emphasised that there is a spectrum across these different types, and that the boundaries can be blurred.

Source: Company submission table 3, p15. * Need for respiratory support at birth; contractures at birth, reduced foetal movements †(Ia) joint contractures present at birth; (Ic) may achieve head control ‡ Prognosis varies with phenotype and supportive care interventions

Symptoms and complications

- With the exception of Type 0 SMA, the disease usually involves a pre-symptomatic period followed by rapidly progressive functional loss and a later relatively static phase with slow progression
- The severity of the symptoms is heterogeneous among people with SMA. Most symptoms relate to weakness and loss of movement, including:
  - progressive physical disability: patients may not reach motor milestones and often lose motor abilities over time
  - muscles closest to the trunk such as the neck, shoulder and pelvic girdle muscle are most affected.
  - chest infections due to muscle weakness in the upper chest.
  - nutritional and gastrointestinal complications: difficulties eating, swallowing, breathing and bowel movements.
  - orthopaedic problems: posture, contractures, scoliosis (occurs when the muscles supporting the bones of the spine become weaker), hip subluxation/dislocation.
    - progression of scoliosis may exacerbate respiratory dysfunction, gastrointestinal reflux, and increase postural discomfort
  - fatigue
- Despite these symptoms, cognitive ability is normal.

Symptoms and complications (1)



Broad relationship between age and gross motor skills acquisition, depending on the different phenotype of SMA

Patients' and carers' perspectives – *Living with SMA*

- Patients and carers highlighted the **impact of symptoms** on patients
  - Particularly physical abilities/mobility, respiratory problems/infections
  - Impact on ability to complete day-to-day activities
- Emphasised concerns about **losing abilities**
- Highlighted that patients may be reliant **on carers**; importance of independence
- **Psychosocial effects** – e.g. anxiety, depression, frustration

Dealing with the prognosis:	Social interactions:	Living with symptoms:
• Confronting premature death • Difficult treatment choices • Financial pressure • Lost expectations	• Social discomfort and stigma • Limitations on social activities • Struggle to achieve independence	• Loss of sleep, stress • Uncertainty, helplessness • Fear at loss of abilities

- Submissions highlighted that the symptoms and impact of SMA **vary between patients**, across the types of disease

"*I'm keen to participate in work and with friends but staying healthy is like running the wrong way on an escalator*"

"I now need help with personal care, which I find embarrassing and upsetting. I am fearful of the future and depressed about my situation most of the time"

Patients' and carers' perspectives – *Impact on families and carers*

- Submissions emphasised significant **physical burden**
  - Lifting and carrying
  - Deterioration of quality of life due to lack of sleep.

"'*The biggest challenges are: lack of sleep – I wake up 8-10 times a night, every night, to turn my son*"

- The condition causes **emotional suffering**
  - Stress
  - Need for constant vigilance
  - Effects on wider family, particularly siblings and grandparents

"The biggest challenges are…emotional distress at seeing my son's strength deteriorate in front of my eyes, despite everything we do to keep him as strong and as well as possible"

- **Financial pressure**
  - Need for equipment and adaptations
  - Reduced income

"*SMA has had a huge negative impact on the whole family in every area of our lives - financial, emotional, marital, personal, self-fulfilment and physical health*"

Current treatment options

- No disease-modifying therapies available for SMA
- The aim of the current treatments are predominantly to manage symptoms
- Treatment requires a multidisciplinary care approach:
  - **Respiratory**: such as airway clearance, antibiotic treatment of infections, non-invasive and invasive ventilation
  - **Nutritional**: changing food consistency, gastrostomy tube feeding, dietician assessment.
  - **Neuromuscular**: strength and range of joint motion, equipment for mobility, self-care and function, physiotherapy, spinal surgery
  - **Orthopaedic**: posture and pain management, regular exercise, scoliosis surgery
- Type and extent of supportive care can affect survival in infant-onset disease – e.g. gastrostomy feeding and non-invasive/invasive ventilation
- Unmet need for an effective treatment

Patients' and carers' perspectives – *Impact of current treatment*

- **Significant burden** – managing daily care and exercises, the use of invasive treatment and need for hospitalisation

"*frequent emergency admissions for up to 5 weeks at a time - the stress placed both on the child and probably more so on the parents…is immeasurable."*

- Submissions stressed the **lack of effect on disease progression**

"…works incredibly hard to maintain as much of his strength as possible…[but] will slowly lose strength, skill and ability"

- Submissions highlighted an **unmet need for SMA treatments**

"Current treatments focus on the management of symptoms, rather than addressing their underlying genetic cause. There are no other medicines currently available to help patients with SMA"

Patients' and carers' perspectives – *Potential benefits of nusinersen*

- Emphasised crucial benefit of treatment: **stopping progression and disease stabilisation**
  - Also potential for gains in quality of life and functioning – muscle function, respiratory strength and reaching new milestones
- **Even a small gain** in strength would make a huge difference to patients
- Treatment may allow greater abilities to complete **everyday activities**
- Potential benefits for **all types of SMA**
  - Highlighted that earlier treatment intervention may give better outcomes
- Recognise impacts of **intrathecal injection**, although manageable and outweighed by potential benefits

"I'm simply filled with hope for my child's future. This has had such a positive turnaround for our family, myself, my husband, siblings, grandparents"

Nusinersen (Spinraza, Biogen)

Marketing authorisation	"Nusinersen is indicated for the treatment of 5q SMA"
Mechanism of action	An antisense oligonucleotide, which stimulates the survival motor neurone (SMN)-2 gene to increase functional SMN protein levels.
Administration & dose	Intrathecal injection by lumbar puncture, 12 mg per administration 4 loading doses on days 0, 14, 28 and 63; maintenance dose once every 4 months.
List price	£75,000 per 12-mg vial PAS proposed (not formally approved; see appendix)
Availability	Under the Expanded Access Programme, eligible children with type 1 SMA can receive nusinersen under commercially confidential arrangements

Source: Company submission. **Abbreviations:** PAS, patient access scheme; SMA, spinal muscular atrophy; SMN, survival of motor neurone.

Decision problem (1)

	NICE scope	Company submission	Company rationale
Population	People with 5q SMA	Paediatric patients with 5q SMA with infantile onset (type I) or later onset (types II and III) SMA.	Narrower than the marketing authorisation (all patients with 5q SMA). Evidence base focuses on paediatric patients with types I-III SMA (the vast majority of cases), but not types 0 or 4.
Comparator	Best supportive care (BSC)	Sham procedure and standard care treatment	As per scope

ERG comments

Population: No data on patients with type 0 or type 4 SMA

Comparator:

- Comparator in clinical trials was sham procedure, economic analyses use “real-world care”
- Use of life-extending symptom care in trials, e.g. permanent respiratory support – observed survival may not be representative of the real world
    - Families entering trials may be more motivated to seek proactive support than some people in routine clinical practice

Decision problem (2)

	NICE scope/company submission	Company rationale
Outcomes	Included in scope and submission: • Motor function (including, where applicable, age appropriate motor milestones) • Respiratory function • Need for non-invasive or invasive ventilation • Mortality • Adverse effects of treatment • HRQL Additional outcomes presented by company: • Event-free survival (time to death or permanent assisted ventilation) and overall survival Not presented in company submission: • Complications of SMA (including, for example, scoliosis and muscle contractures) • Stamina and fatigue	Complications of SMA and stamina and fatigue are not were not collected in the pivotal clinical trials

Decision problem (3)

	NICE scope/company submission	Company rationale
Sub-groups	Consideration will be given to subgroups based on: • severity of disease (including considerations such as age of SMA onset, SMA type and genotype). Additional subgroups considered by company: • Disease duration. ENDEAR (early onset): ≤12 weeks, >12 weeks CHERISH (later onset): <25 months, ≥25 months	The pivotal trials had pre-specified subgroups based on disease duration and age at symptom onset.

ERG comments:
Subgroup data are limited.

Clinical effectiveness evidence

Clinical evidence: overview

Pre-symptomatic patients	Infantile onset (Type 1)	Both infantile and later onset (Type 1–3)	Later onset (Type 2 and 3)
CS5 **NURTURE**: Phase II, open-label target n=25	CS3B **ENDEAR**: Phase III, RCT n=122	CS7 **EMBRACE** Phase II, open-label n=21	CS4 **CHERISH**: Phase III RCT n=126
	CS3A: Phase II, open-label n=21	CS11 **SHINE**: Phase III, open-label extension for CS3B, CS4, CS12 target n=274	**CS1**: Open-label, dose escalation n=28
			CS10: open-label extension for CS1, n=18
			CS2: open-label, dose-escalation, n=34
			CS12: extension for CS2 and CS10, n=47

RCT - randomised controlled trial

Clinical evidence: ENDEAR and CHERISH (1)

	ENDEAR (early onset)	CHERISH (later onset)
Description	• Randomised, double blind, multicentre (including UK), phase III, sham-procedure controlled (n=122)	• Randomised, double-blind, multicentre, phase III, sham-procedure controlled (n=126)
Eligibility criteria	• Symptomatic people with SMA1 • Two copies of the *SMN2* gene • Younger than 6 months of age (180 days) at SMA symptom onset • Younger than 7 months of age (210 days) at screening	• Symptomatic people with SMA2-3 • Onset of clinical signs and symptoms consistent with SMA at more than 6 months of age • Age 2 to 12 years inclusive • Able to sit independently but never had the ability to walk independently • HFMSE score of 10 to 54 at screening

Clinical evidence: ENDEAR and CHERISH (2)

	ENDEAR (early onset)	CHERISH (later onset)
Outcomes	Primary • Motor function/milestones (HINE-2) • Event-free survival (EFS) Secondary • Motor function (CHOP INTEND, CMAP)	Primary • Motor function (HFMSE) Secondary • Motor milestones (WHO milestone, standing alone, walking with assistance) • Upper limb function (RULM)
Dosing	12 mg on days 1, 15, 29, and 64, followed by maintenance dose every 4 months	12 mg on days 1, 29, 85, followed by a maintenance dose 6 months later (day 274)

HINE-2 - Module 2 of the Hammersmith Infant Neurological Examination; CHOP INTEND, Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders; CMAP, compound muscle action potential; RULM - Revised Upper Limb Module; WHO - World Health Organization

Clinical evidence: motor function outcomes

HINE-2
(Hammersmith Infant Neurological Examination–2)
- 8 functions (grasp*, kicking, head control, rolling, sitting, crawling, standing, walking)
- Graded 0–2 or 0–4; max score 26 *(health child would score 22 at 1 year)*

CHOP INTEND
(Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders)
- 16 items, graded 0–4

HFSME
(Hammersmith Functional Motor Scale-Expanded)
- 33 items in 7 domains (sitting, rolling, crawling, standing, kneeling, jumping, stairs)
- Graded 0–2; max score 66

Higher score indicates better function

- Primary outcome of ENDEAR based on 'HINE-2 responders', defined as: ≥2-point increase (or maximal score) in kicking, OR ≥1-point increase in other functions, AND improvement in more categories than worsening
  - Introduced as a protocol change; original primary outcome was EFS
  - This is a novel outcome – not previously used, unclear whether there is evidence of an associated with functionally important outcomes

Clinical evidence – supportive studies

Study	CS3A (NCT01839656)	CS2 (NCT01703988)	CS12 (NCT02052791)	CS1 (NCT01494701)	CS10 (NCT01780246)
Study design	Phase II, open-label, multiple dose, single-arm, multi-centre study (N=21)	Phase I/IIa, open-label, multicentre, multiple-dose, dose-escalation study (N=34)	Phase I, multicentre, open-label, multiple-dose extension study (N=47)	Phase I, open-label, single-arm, ascending dose study (N=28)	Phase I, open-label, extension to CS1 (N=18)
Population	Infantile onset	Later onset	Later onset: patients who previously participated in CS2 and CS10	Later onset	Later onset: patients who previously participated in CS1
Doses	6-12 mg	3,6,9,12 mg	12 mg	1,3,6,9 mg	6,9 mg
Outcomes	Motor function (HINE-2 and CHOP INTEND), Event-free survival; overall survival, CMAP, AEs	Motor function (HFMSE, MUNE, ULM, 6MWT); HRQL (PedsQL, ACEND);CMAP; AEs.		Motor function (HFMSE; MUNE) HRQL (PedsQL) CMAP AEs	

Clinical evidence – ongoing studies

Study	Nurture (NCT02386553)	SHINE (NCT02594124)	EMBRACE (NCT02462759)
Study design	Phase II, open-label, multiple-dose, multicentre, single-arm (on-going)	Open-label extension study	Phase II, randomised, double-blind, sham-procedure controlled study
Population	Pre-symptomatic infants genetically diagnosed with SMA	Infantile and later onset SMA patients from ENDEAR and CHERISH, CS12 and CS3A	Patients with SMA who are not eligible to participate in the clinical studies ENDEAR and CHERISH
Intervention/ comparator	Nusinersen (N=20)	Nusinersen (N=274)	Nusinersen (N=21)
Doses	Multiple dose 12 mg Loading doses on day 1, 15, 29, 64; maintenance dose on day 183, 302, 421, 540, 659 and 778	Multiple dose 12 mg	Multiple dose 12 mg

Baseline characteristics – **ENDEAR** *(early onset) (1)*

	Nusinersen (N=80)	Control (N=41)
Female, n (%)	43 (54)	24 (59)
[redacted]	[redacted]	[redacted]
Age at symptom onset - mean (range), week	7.9 *(2–18)*	9.6 *(1–20)*
Age at SMA diagnosis mean (range), week	12.6 *(0–29)*	17.5 *(2–30)*
Disease duration at screening - mean (range), week	13.2 *(0–25.9)*	13.9 *(0–23.1)*
Age at first dose - mean (range), week	32.6 *(10.4–48.4)*	36.2 *(6–52.4)*
[redacted]	[redacted]	[redacted]
SMA symptoms, n (%)		
Hypotonia	80 (100)	41 (100)
Developmental motor delay	71 (89)	39 (95)
Paradoxical breathing	71 (89)	27 (66)
Pneumonia or respiratory symptoms	28 (35)	9 (22)
Limb weakness	79 (99)	41 (100)
Swallowing or feeding difficulties	41 (51)	12 (29)
Other	20 (25)	14 (34)

- Source: table 11 company submission. Abbreviations: SMN2, survival motor neurone 2

Baseline characteristics – **ENDEAR** (*early onset) (2)*

	Nusinersen (N=80)	Control (N=41)
Use of a ventilation support, n (%)	21 (26)	6 (15)
Use of a gastrointestinal tube, n (%)	7 (9)	5 (12)
Total HINE-2 score, mean (SD)	1.29±1.07	1.54±1.29
CHOP INTEND score, mean (SD)	26.63 (8.13)	28.43 (7.56)
CMAP amplitude, mV, mean (SD) Ulnar nerve Peroneal nerve	 0.226 (0.19) 0.371 (0.31)	 0.225 (0.12) 0.317 (0.29)

Source: company submission. Abbreviations: HINE-2 - Module 2 of the Hammersmith Infant Neurological Examination; CHOP INTEND, Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders; CMAP, compound muscle action potential; SD, standard deviation.

Baseline characteristics – **CHERISH** *(later onset) (1)*

	Nusinersen (N=84)	Control (N=42)
Female, n (%)	46 (55)	21 (50)
White, n (%)	64 (76)	30 (71)
Age at symptom onset - median (range), months	10.0 (6–20)	11.0 (6–20)
Age at SMA diagnosis - median (range), months	18.0 (0–48)	18.0 (0–46)
Age at screening - median (range), months	48 (24 – 108)	36 (24 – 84)
Time from diagnosis to enrolment - median (range), months	27.8 (2–86)	26.0 (2-72)
Time from disease onset to enrolment - median (range), months	39.3 (8–94)	30.2 (10–80)
Disease duration - median (range), months	39.3 (8–94)	30.2 (10–80)
SMN2 copy number, 2/3/4/unknown, %	7/88/2/2	10/88/2/0

Baseline characteristics – **CHERISH** *(later onset) (2)*

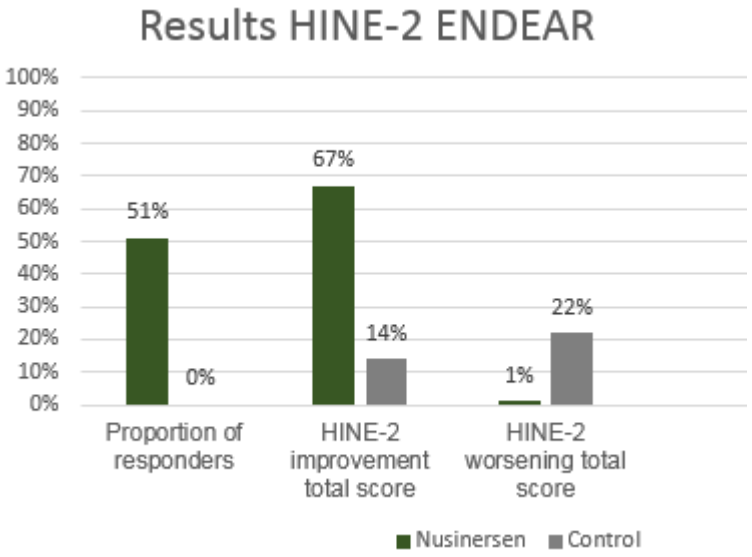
	Nusinersen (N=84)	Control (N=42)
Children who have ever achieved motor milestone, n (%)		
Sat without support	84 (100)	42 (100)
Walked with support	20 (24)	14 (33)
Stood without support	11 (13)	12 (29)
Walked ≥15 feet independently	0	0
Children using a wheelchair, n (%)	64 (76)	29 (69)
Mean (SD) HFMSE total score	22.4 (8.3)	19.9 (7.2)
Mean (SD) WHO total score	1.4 (1.0)	1.5 (1.0)
Mean (SD) RULM total score	19.5 (6.2)	18.4 (5.7)

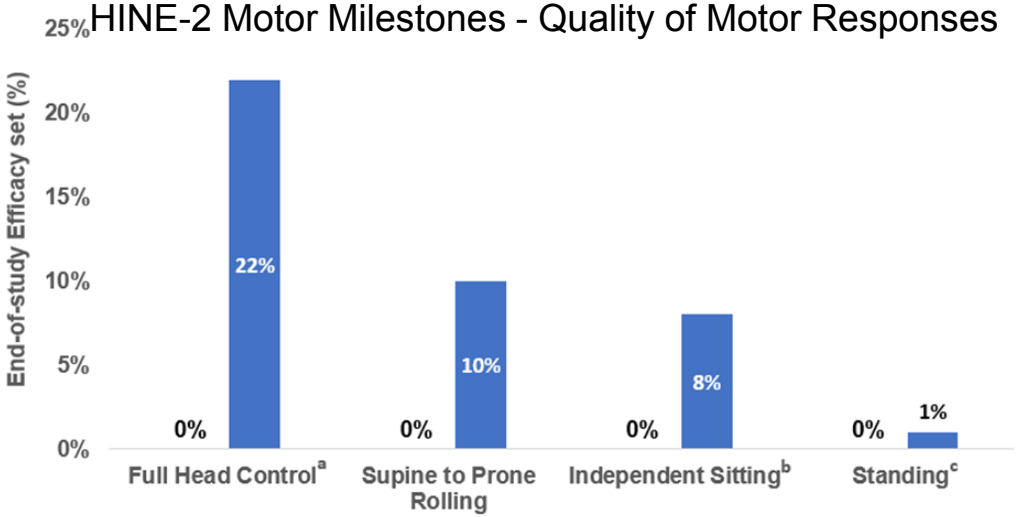
Source: company submission. Abbreviations: HFMSE, Hammersmith Functional Motor Scale-Expanded; RULM, Revised Upper Limb Module; SD, standard deviation; SMA, spinal muscular atrophy; SMN, survival motor neurone; WHO, World Health Organization

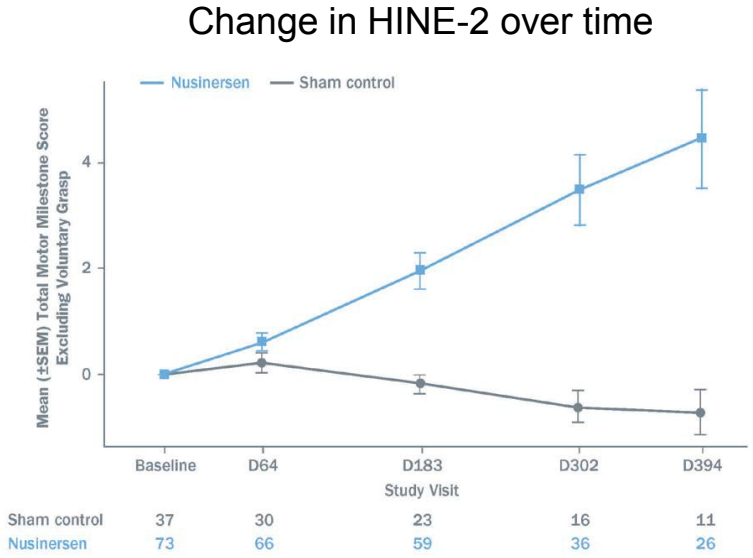
Results – **ENDEAR** *(early onset)* Motor function

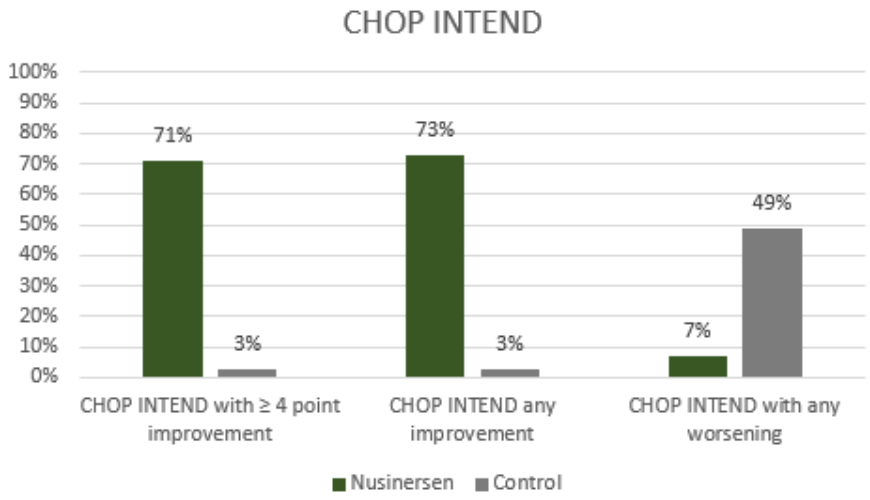
Outcome	Nusinersen	Control	Difference (95% CI)
Proportion of motor milestone responders (HINE-2) n (%) • improvement in total score • worsening in total score	37 (51) 49 (67) 1 (1)	0 (0) 5 (14) 8 (22)	[redacted] [redacted]; p<0.0001
CHOP INTEND with ≥4 point improvement n (%)	5 (71)	1 (3)	[redacted] [redacted]p<0.001
CHOP INTEND with any improvement	53 (73)	1 (3)	
CHOP INTEND with any worsening	5 (7)	18 (49)	
CMAP amplitude responders	26 (36)	2 (5)	p=0.001

Results – **ENDEAR** *(early onset)*
Motor function

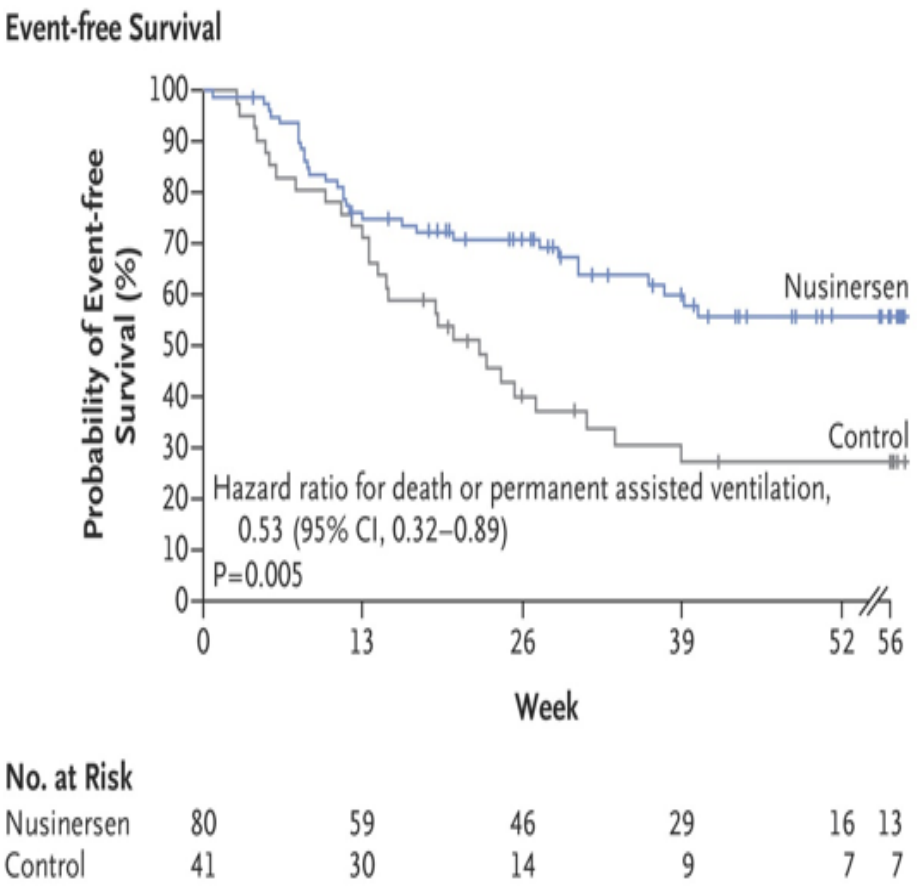


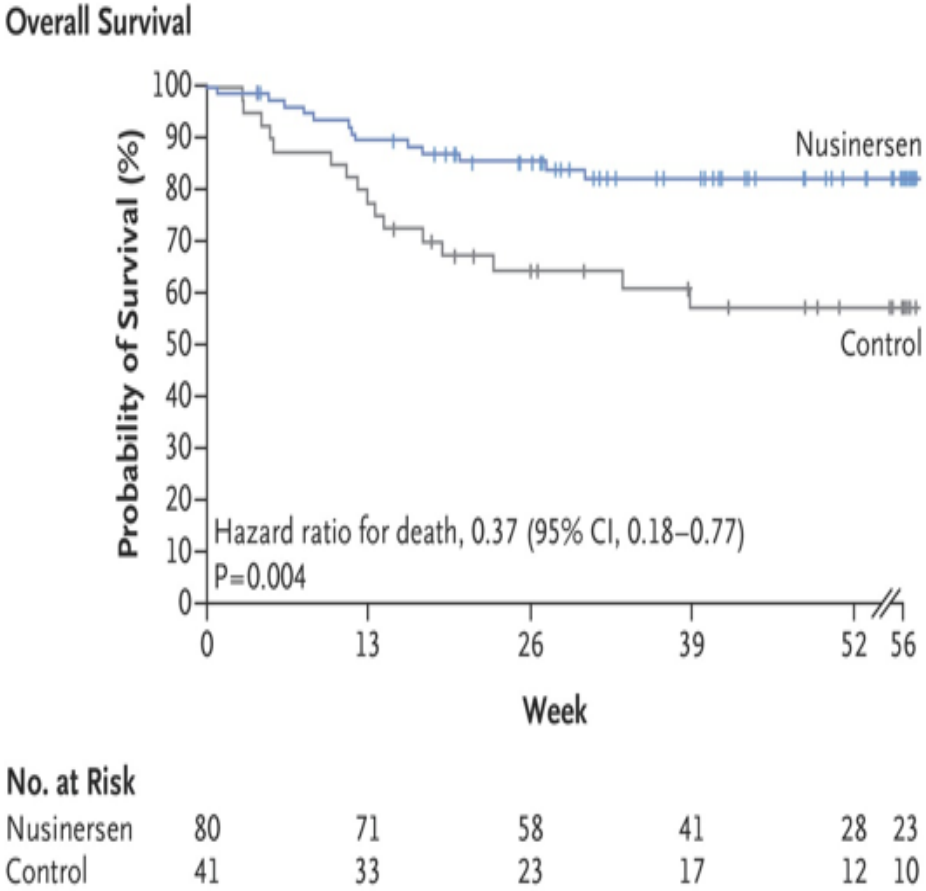






Results – **ENDEAR** (early onset) Event-free survival and overall survival





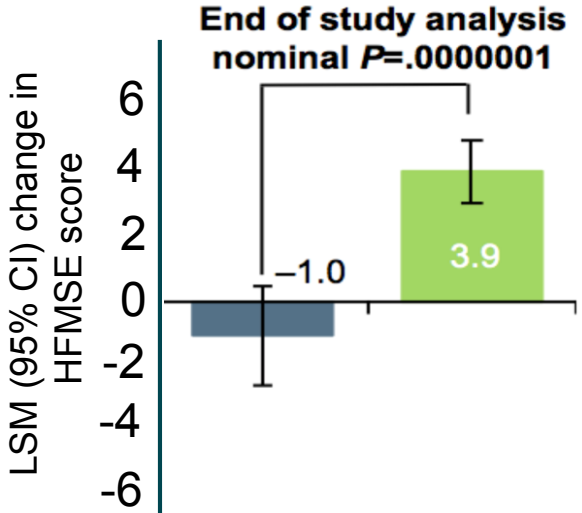
Statistically significant increases in both EFS (p=0.005) and OS (p=0.004) were observed for the nusinersen group

Results – **ENDEAR** *(early onset)* Respiratory function and hospitalisation

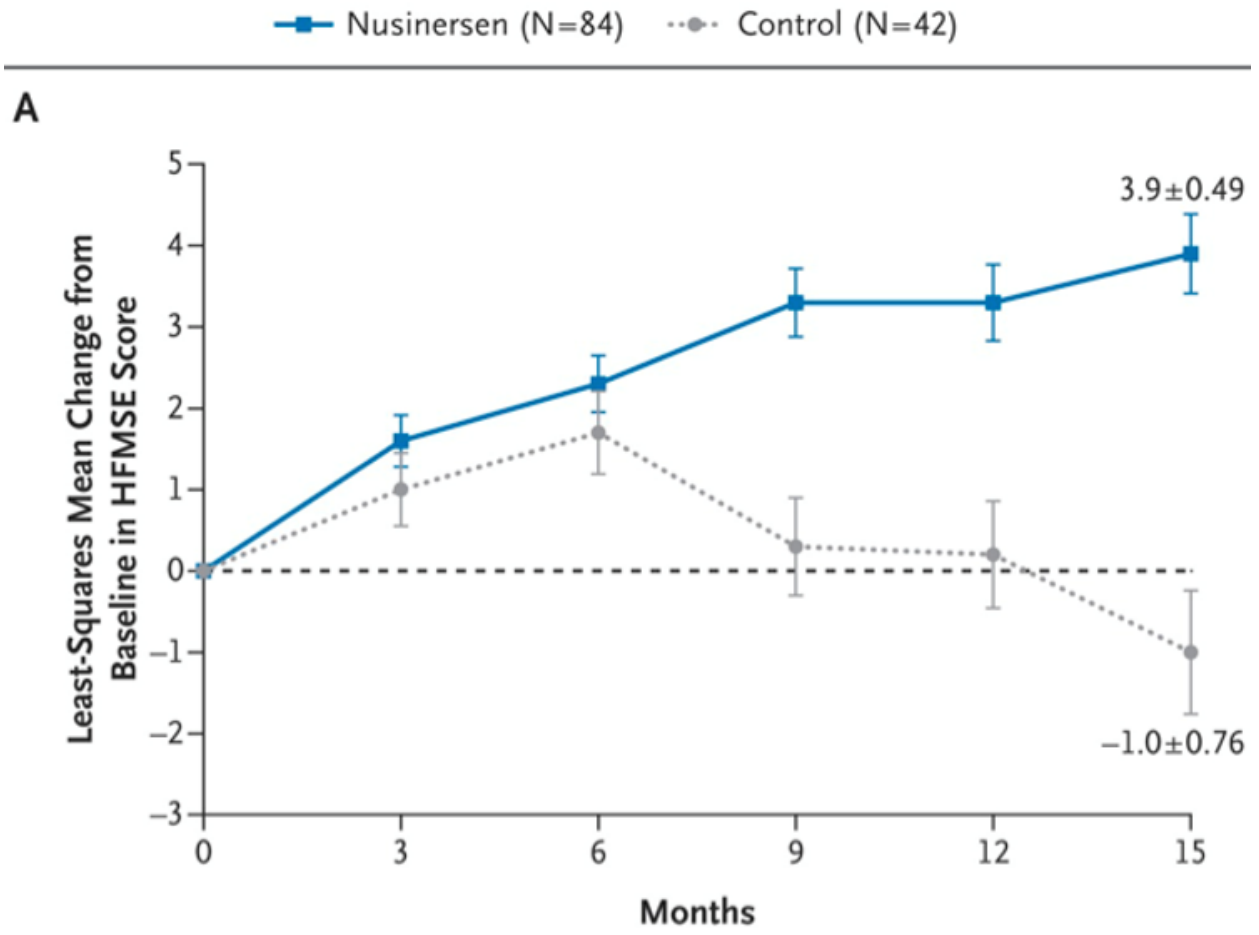
	Nusinersen	Control	
Respiratory function: annualised rate of serious respiratory events	[redacted]	[redacted]	[redacted]
Ventilation: % time on ventilator (LSM adjusted for baseline age and disease duration)	[redacted]	[redacted]	[redacted]
Hospitalisations: Adjusted annualised rate (per yr) Overall time hospitalised	[redacted]	[redacted]	[redacted]

Results – **CHERISH** (later onset) Motor function

	Nusinersen	Control	Difference (95% CI) and p-value
HFMSE score: change from baseline to month	3.9 (3.0, 4.9)	-1.0 (-2.5,0.5)	4.9 (3.1, 6.7) p=0.0000001
Children with change in HFMSE score of ≥3 points (%)	57 (46, 68)	26 (12, 40)	6 (2, 15); p<0.001
Motor milestones at 15 months: % who achieved ≥1 new motor milestone	20 (11,31)	6 (1, 20)	14 (-7, 34); p=0.08
RULM	4.2 (3.4, 5.0)	0.5 (-0.6, 1.6)	3.7 (2.3, 5.0) p=0.0000001



Results – **CHERISH** *(later onset)* Motor function



Results – **CHERISH** *(later onset)*
HRQoL

Clinical Global Impression of Improvement (CGI-I)

[redacted]

Paediatric quality of life inventory (PedsQL)

- [redacted]
- [redacted]
  - [redacted]

Caregiver burden (ACEND)

- [redacted]
- [redacted]
  - [redacted]

NURTURE – presymptomatic patients

- Population: 20 patients with presymptomatic SMA
  - 80% aged <1 month, 55% male; 65% had 2 SMN2 copies (expected to develop a more severe SMA phenotype than those with 3 copies*)
- Those infants assessed in the interim analysis had been in the study for a median of 317.5 days (range 2-524 days).
- Results: Motor function:

Motor milestone	Full head control	Independent sitting	Stands with support/unaided	Cruising /walking
Total achieving, n	15	12	9	6
Achieved at expected age, n/N (%)	15/16 (94%)	10/12 (83%)	7/11 (64%)	5/9 (56%)

  - From baseline, 16 of 18 subjects (89%) achieved and maintained improvements in the CHOP INTEND total score; 61% were 'responders'
- Results: Mortality and ventilation
  - All patients were alive and none required invasive ventilation.
  - 13% with 2 SMN2 copies required respiratory intervention for ≥6 hours/day continuously for ≥7 days.

Subgroup analyses: age and disease duration

- For all outcomes, greater treatment benefits were observed for younger children and those treated earlier in their disease course
- ENDEAR (below):
  - More pronounced treatment effects observed for infants with disease duration ≤12 weeks at screening
  - Age of onset (≤12 weeks vs >12 weeks) had a statistically significant effect on OS treatment effect
- CHERISH
  - Younger age and shorter disease duration associated with greater improvements in HFMSE and RULM

	Control vs nusinersen	Control vs nusinersen
Disease duration	≤12 weeks	>12 weeks
HINE-2: responders	0% vs 75%	0% vs 32%
CHOP-INTEND ≥4 pt improvement ≥4 pt worsening	 0% vs 88% 50% vs 0%	 5% vs 59% 43% vs 5%
OS	HR: 0.219	HR: 0.455
Age at symptom onset	≤12 weeks	>12 weeks
OS	[redacted]	[redacted]

Adverse events

- The most commonly reported adverse events in all (n=260) nusinersen-treated patients were:
  - Pyrexia 43%, upper respiratory tract infection 36%, nasopharyngitis 22%, vomiting 21%, headache 20%, constipation 19%, back pain 17%, cough 17%, pneumonia 16%, respiratory distress 12% and scoliosis 11%.
  - Diarrhoea, respiratory failure, post-lumbar puncture syndrome were all recorded in 10% of the population.
- EPAR notes that common adverse events were consistent with SMA, common conditions in the general population, age-appropriate events and lumbar puncture
- EPAR also notes there is no evidence that nusinersen is associated with toxicities reported with other antisense oligonucleotides (e.g. thrombocytopenia, renal disorders*)

Real-world evidence

- Experience with using nusinersen through the Expanded Access Programme at 16 specialised centres in UK and Ireland, Mar to Oct 2017
- 63 patients (25 males, 38 females) treated with nusinersen
- **CHOP INTEND**: mean total score increased from 25 (range 5–52) at baseline to 36 (range 9–51) at 5th injection
  - Most patients improved the CHOP INTEND total score (1–17 points); few remained stable
  - Only 1 decreased from baseline to 5th injection (limited mobility following bone fracture; increase from baseline after the 4th injection)
- **HINE-2** (16 patients): improvement of ≥2 points was observed in 8 patients, no cases of motor regression
- **Ventilation**:
  - At baseline, 33/63 patients were receiving non-invasive ventilation (NIV), 14 of them for >16 hours/day; none had tracheostomy
  - In 5 patients a reduction of the hours on NIV was noted; four additional patients needed to start NIV while on treatment

ERG comments on clinical evidence (1)

- A systematic review of clinical effectiveness evidence was not performed
- ENDEAR and CHERISH considered to be moderate risk of bias – concerns about blinding, outcome reporting and imbalance in dropouts (ENDEAR only)
- ENDEAR study population:
  - Imbalance in SMA symptoms between nusinersen and control groups
    - More paradoxical breathing, respiratory symptoms, ventilation and swallowing/feeding difficulties in nusinersen group
    - Suggests a worse prognosis for the nusinersen population
  - Clinical advisors suggested that patients in ENDEAR had a lower use of ventilation and tubes than would be expected in clinical practice
- CHERISH study population:
  - Due to strict entry criteria, population was more homogeneous and younger than population in clinical practice

ERG comments on clinical evidence (2)

- Dosing regimen for nusinersen in CHERISH was not consistent with marketing authorisation
- Use of different analysis sets makes it difficult to interpret findings
- Follow-up period is relatively short – long-term effect and need for dose adjustment is unknown
- No information on treatment taking into account disease severity, duration and progression
  - No data on patients with type 0 or type 4 SMA
  - Subgroup data are limited
  - Pre-symptomatic treatment (NURTURE) is challenging – unknown when patients with genetic diagnosis would develop symptoms, or how severe

Key issues
Clinical effectiveness

Decision problem

- Is the population defined appropriately?
  - Can nusinersen be considered for types 0, 1, 2, 3 and 4 SMA?

Clinical evidence

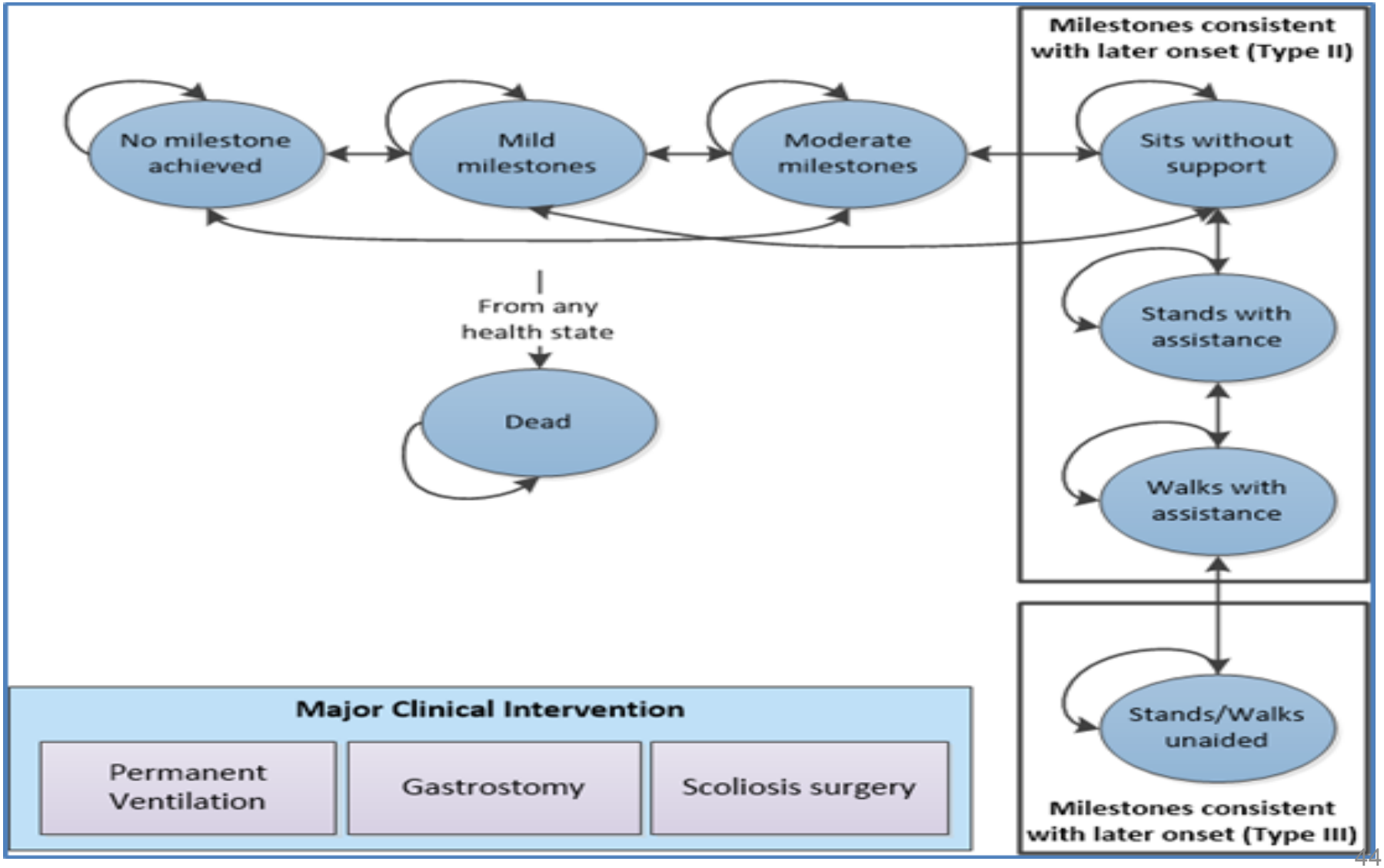
- Are the clinical trials relevant to the use of nusinersen in clinical practice?
  - Generalisability to English population
  - Dosing regimen
- Does the evidence capture the most important outcomes for patients with SMA?
- How effective is nusinersen?
  - Early and later-onset SMA
  - Pre-symptomatic patients
  - Subgroups
  - Long-term benefits

Cost effectiveness evidence

Economic model – approach

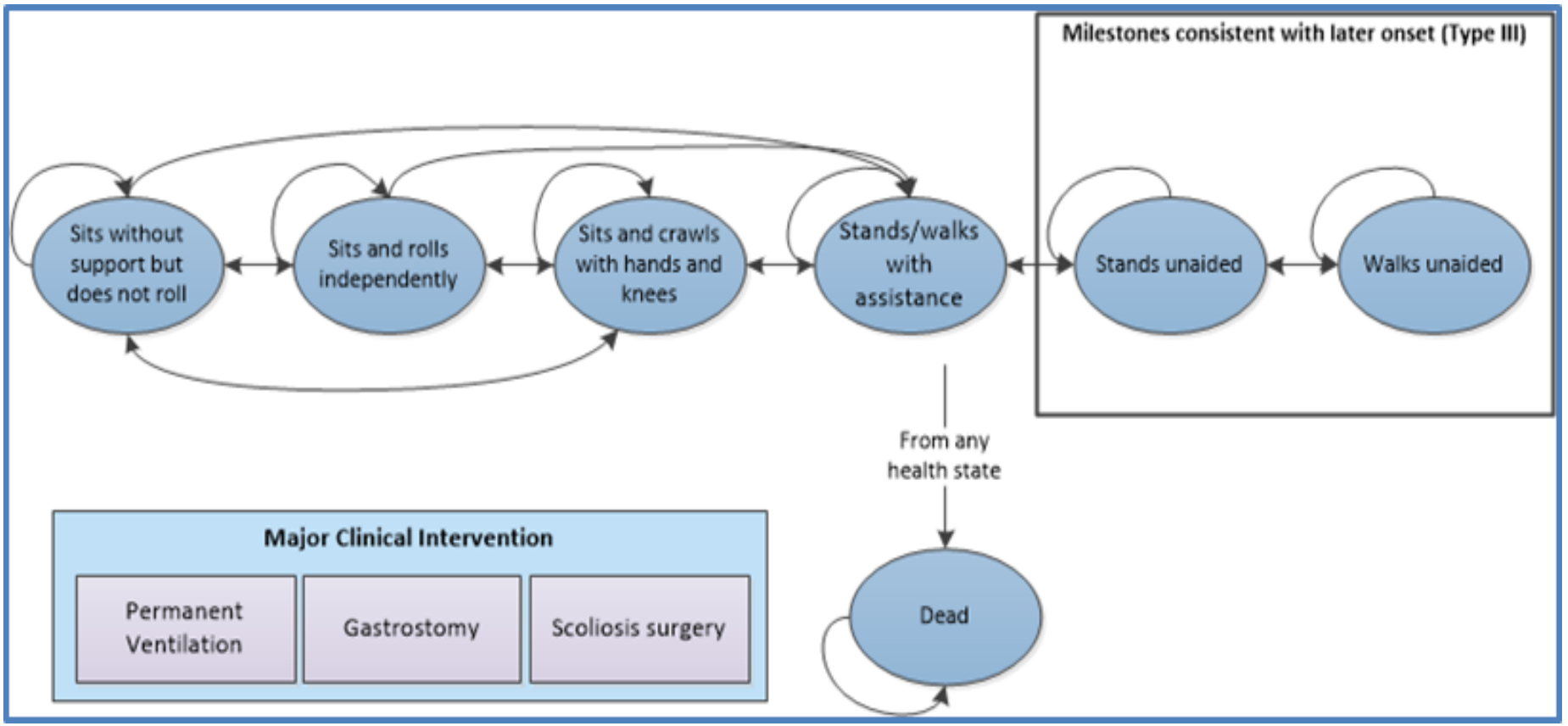
- Company presented 2 separate models:
  - **Early-onset**: SMA type 1
    - Initial age: 5.58 months
  - **Later-onset**: SMA type 2/3
    - Initial age: 43.71 months
- State transition approach, based on motor function milestones
  - Early-onset: HINE-2
  - Later-onset: HFMSE and WHO criteria
- Nusinersen vs usual care*
- NHS and PSS perspective
- Lifetime time horizon (60** and 80 years)
- Discounting at 3.5% for costs and health effects

Economic model structure – **early onset**



Source: Company submission, p116

Economic model structure – **later onset**



Source: Company submission, p166

Modelling approach – ERG comments

Complexity of modelling

- Model was exceptionally complex and impenetrable
- ERG replicated a simplified version of the model – showed the model had been implemented without significant error

Model structures focus only on motor milestones

- Models are consistent with key outcomes measured in the ENDEAR and CHERISH trials
- Motor milestones are important, and the instruments are appropriate
- However, motor function is not the sole determinant of HRQoL
  - Other symptoms (e.g. respiratory function, pain) and ability to participate in activities are also important

Sources of clinical data

	Early onset	Later onset
Starting state distribution	Baseline HINE-2 from ENDEAR	Baseline HFMSE from CHERISH
Transition probabilities	Month 0–13: HINE-2 data from ENDEAR Month 14+: mean and mean change in CHOP-INTEND from ENDEAR and CS3A	Month 0–15: HFMSE data from CHERISH Month 16+: mean and mean change in HFMSE from CHERISH, CS2 and CS12
Overall survival	ENDEAR Gregoretti et al, Zerres et al Adjusted general population	CHERISH Zerres et al General population
Probability and timing of scoliosis surgery	Assumption, Haaker and Fajuk	Bladen et al, Haaker and Fajuk

Transition probabilities

- Health state transitions were based on observed data in phase III trials (ENDEAR and CHERISH), supplemented by phase II trials for less-severe health states
  - For the period of study follow-up, transitions were based directly on observed data
  - After study follow-up, single transition matrix applied to each arm of each model, for all 4-monthly cycles*

	Early onset	Later onset
Trial period	HINE-2 data for 4 cycles, up to month 13	HFMSE data for 5 cycles, up to month 15
Post-trial	Mean CHOP-INTEND per health state + rate of change in CHOP-INTEND	Mean HFMSE per state + rate of change in HFMSE

After study follow-up, patients treated with nusinersen could not deteriorate, patients treated with usual care could not improve

*In early-onset model, an additional matrix was applied for month 13–14

Transition probabilities – ERG comments (1)

Assumptions of no deterioration for nusinersen and no improvement for usual care are highly optimistic and do not reflect the observed trial data

Clinical advice

- Long-term benefits of nusinersen on motor function are highly uncertain
- More likely that there would be a distribution, with some patients improving and some deteriorating

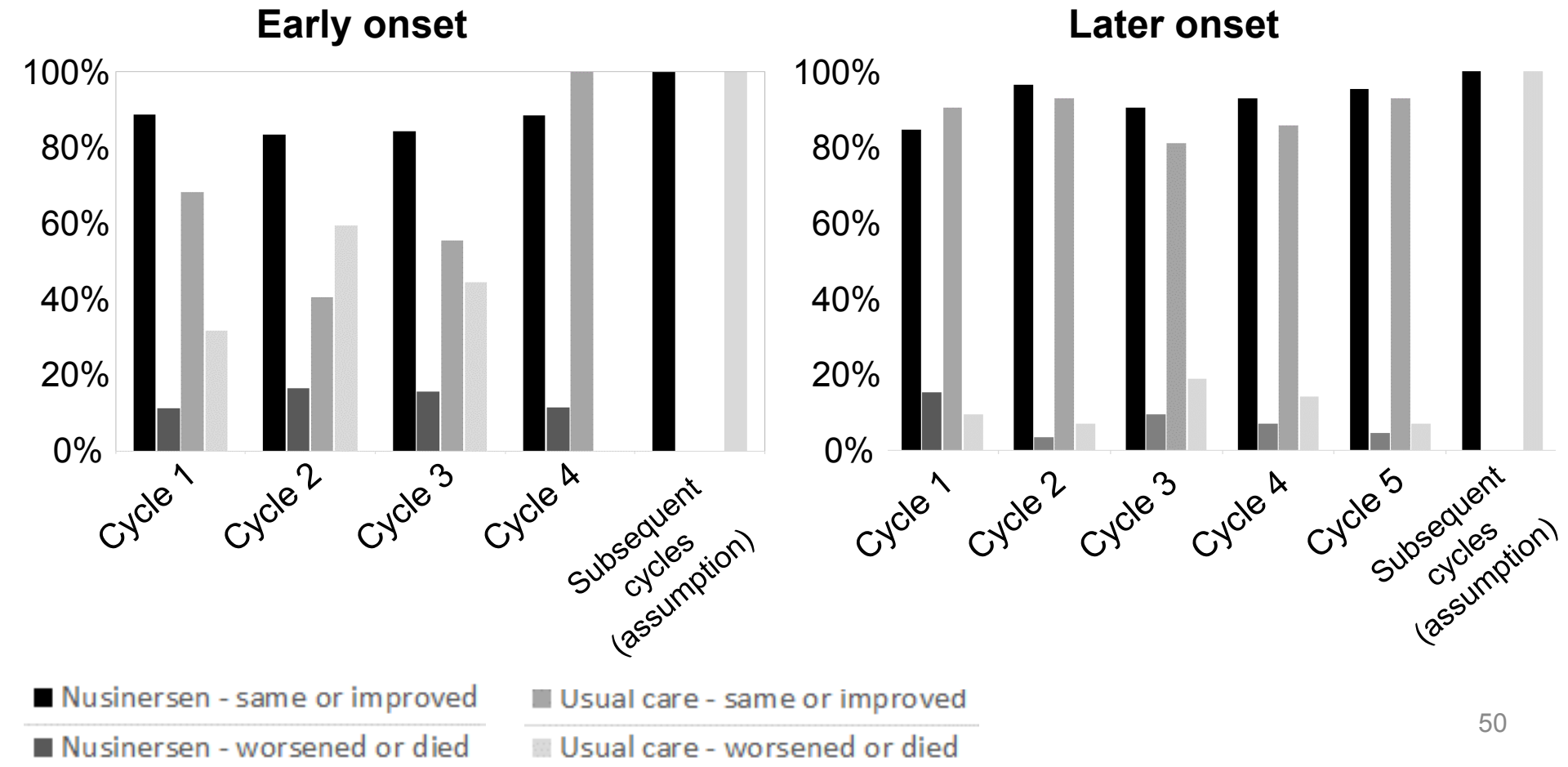
Calculation of transition probabilities

- Company's approach assumes perfect correlation between CHOP INTEND score and HINE-2 health state
- CHOP INTEND 'thresholds' between health states differ between nusinersen and usual care groups
- Rates of change of CHOP INTEND and HFMSE are assumed to be constant
- Calculation requires a constraint to avoid transition probabilities >1

Transition probabilities – ERG comments (2)

Consistency between observed and modelled data

- In trial, a proportion of patients receiving nusinersen moved to a worse health state, and a proportion receiving usual care moved to better states

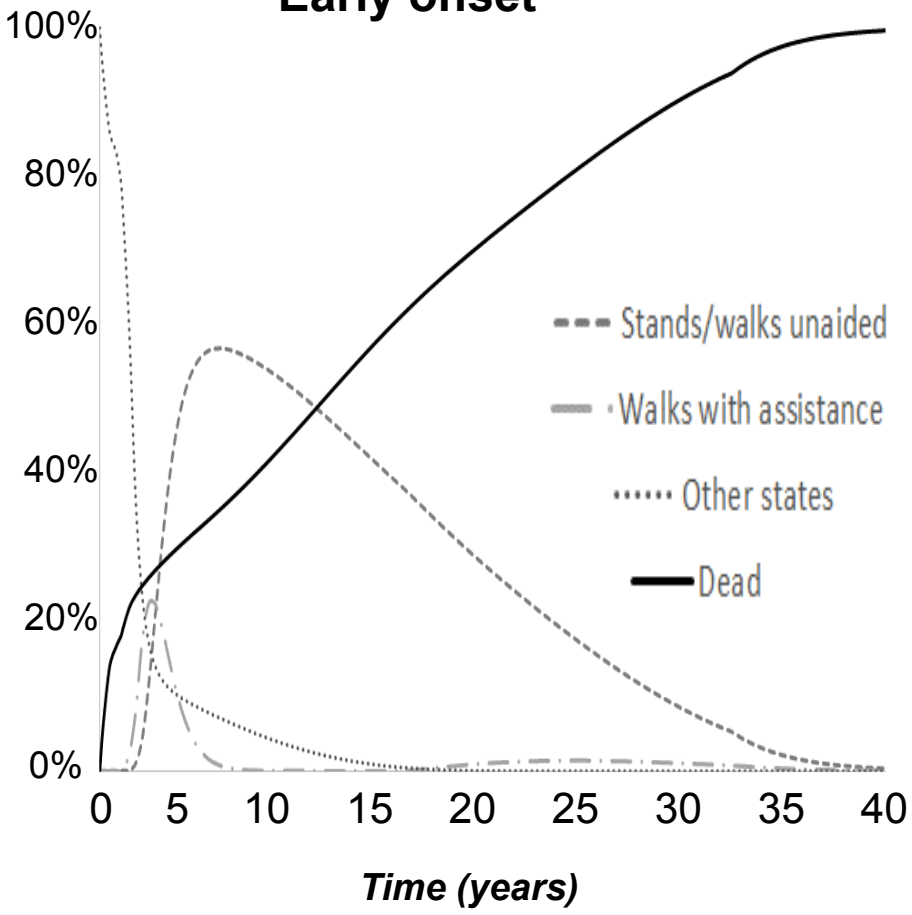


Transition probabilities – ERG comments (3)

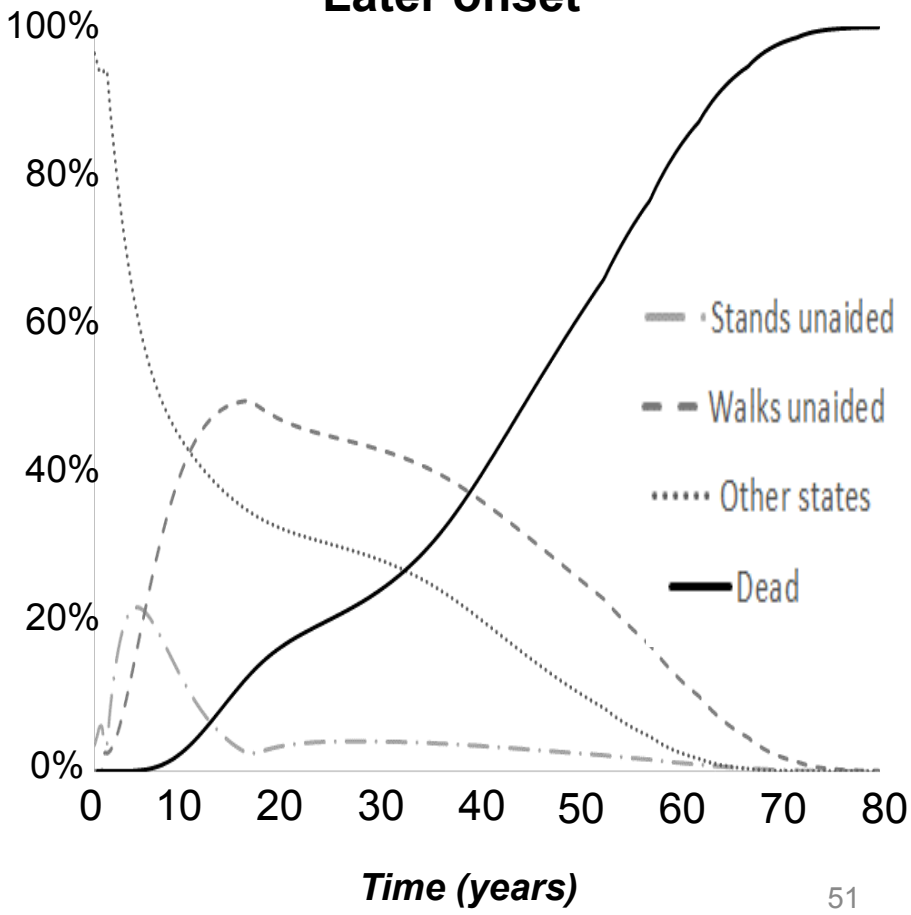
Consistency between observed and modelled data(cont)

- Company's assumptions predict that most surviving patients reach best health states within 5–15 years – not seen in trials

Early onset



Later onset



Overall survival (1)

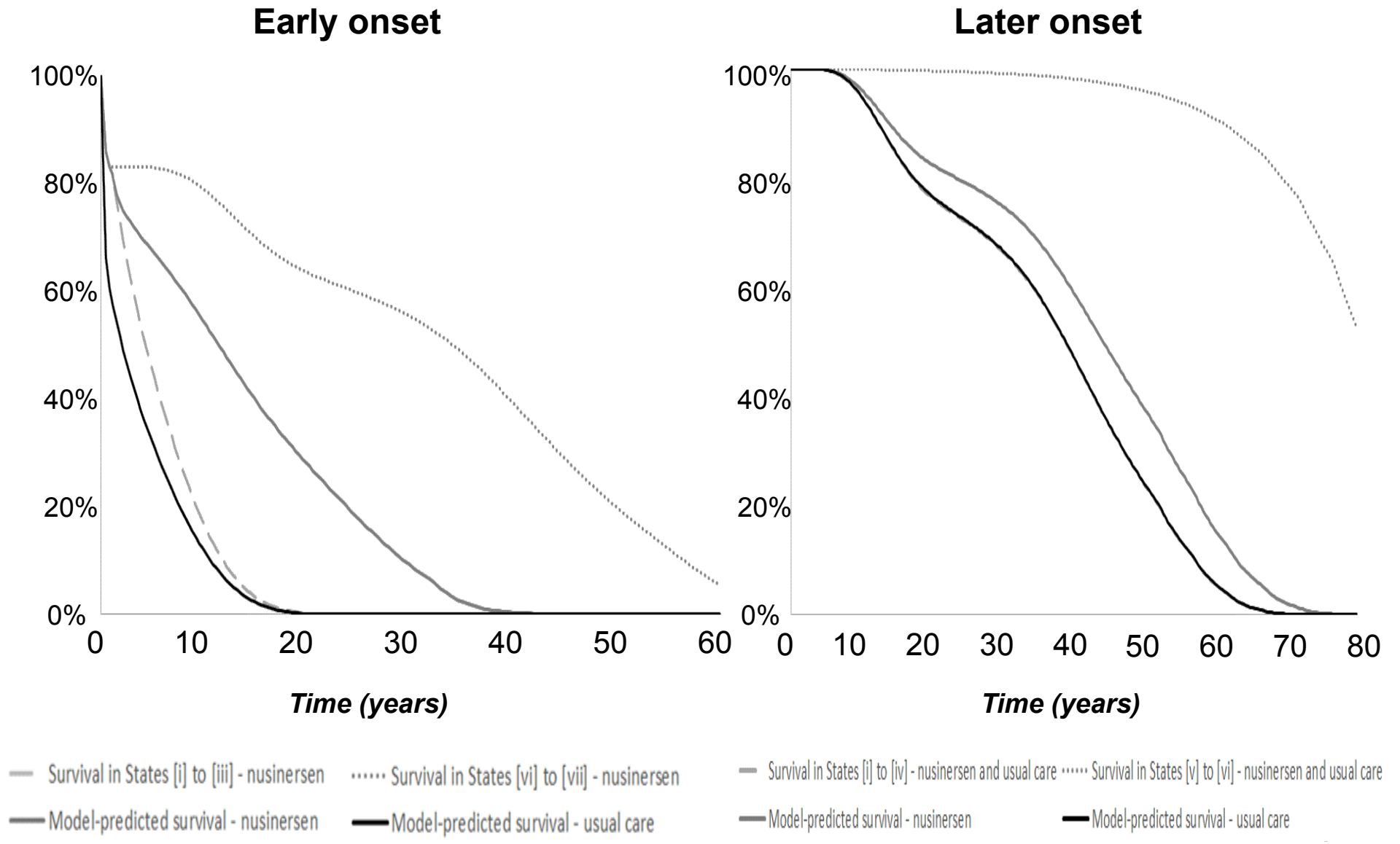
- In both models, after trial follow-up the company applied a mortality adjustment to the best health states, such that patients had a similar mortality risk to people with less-severe forms of SMA
  - **Early onset**: states 4–7: survival based on 10% of SMA type 1 mortality risk and *90% of SMA type 2 mortality risk*
  - **Later onset:** states 5 and 6: survival based on 50% of SMA type 2 mortality risk and *50% of general population mortality risk*

Overall survival (2)

- The company modelled overall survival using a combination of trial data, external study data and adjusted general population mortality

<table>
<tr><th></th><th colspan="3">Early onset</th><th colspan="3">Later onset</th></tr>
<tr><th></th><th>States 1–3</th><th colspan="2">States 4–7</th><th>States 1–4</th><th colspan="2">States 5–6</th></tr>
<tr><td>Trial period</td><td colspan="3">ENDEAR</td><td colspan="3">CHERISH - No deaths</td></tr>
<tr><td rowspan="3">Post-trial</td><td rowspan="2">Gregoretti et al</td><td>10%</td><td>90%</td><td rowspan="2">Zerres et al</td><td>50%</td><td>50%</td></tr>
<tr><td>Gregoretti et al</td><td rowspan="2">Zerres et al</td><td>Zerres et al</td><td rowspan="2">UK general population unadjusted</td></tr>
<tr><td>UK general population HR-adj (HR=5185)</td><td>UK general population HR-adj (HR=5185)</td><td>UK general population HR-adj (HR=26.4)</td><td>UK general population HR-adj (HR=26.4)</td><td>UK general population HR-adj (HR=26.4)</td></tr>
</table>

Overall survival (3)



Overall survival – ERG comments

ERG expressed concerns that the modelled overall survival was optimistic

- Complexity of approach
  - Company's complex approach carried important assumptions that were insufficiently justified
  - Simpler parametric extrapolation may be more plausible and transparent
- Use of external data
  - Gregoretti et al: unclear if the results are applicable to clinical practice, and did not align to ENDEAR survival (even after age adjustment)
  - Zerres et al: insufficient information to establish if the study population was similar to CHERISH
  - General population: constant hazard ratio applied, but proportional hazards assumption unlikely to hold
- Treatment effect – ***key concern***
  - OS benefit of nusinersen primarily driven by lower mortality in better health states (adjustment to type 2 SMA mortality)
    - "Conservative" hazard ratio (1.0) applied after trial follow-up is misleading
    - ***Weight applied to type 2 SMA mortality (90%) is insufficiently justified – clinical advisers considered this a large and optimistic assumption***

Health-related quality of life

- PedsQL data collected in CHERISH study in later onset SMA patients
- Mapped to EQ-5D using an algorithm published by Khan et al.
- Resulting utility values were applied directly to health states in later onset model
- Adapted for the early onset model based on an assumed correspondence of health states

Early onset model	Later onset model	Utility value
No milestones	Sits without support but does not roll	[redacted]
Mild milestones	Sits and rolls independently	[redacted]
Moderate milestones	Sits and rolls independently	[redacted]
Sits without support	Sits and crawls on hands and knees	[redacted]
Stands with assistance	Stands or walks with assistance	[redacted]
Walks with assistance	Stands without assistance	[redacted]
Stand or walks without assistance	Walks without assistance	[redacted]

Because of the transition probability assumptions, the utilities in the best and worst states have most influence on the results

Health-related quality of life: Carers

- Impact of SMA on carers captured by applying carer dis-utilities to each health state
  - Carer utility based on cross-sectional study of SMA patients (Bastida et al: [redacted]), adjusted for each health state
  - Compared with average general population utility (30.88 years, 80% female: 0.92) to give disutility
- Disutility due to bereavement of -0.04 also applied

Early onset model	Later onset model	Carer disutility
No milestones	Sits without support but does not roll	[redacted]
Mild milestones	Sits and rolls independently	[redacted]
Moderate milestones		[redacted]
Sits without support	Sits and crawls on hands and knees	[redacted]
Stands with assistance	Stands or walks with assistance	[redacted]
Walks with assistance	Stands without assistance	[redacted]
Stand or walks without assistance	Walks without assistance	[redacted]

Source: company's economic model.

Utilities in children

- PedsQL is a tool for measuring health-related quality of life in children
  - Child self report: ages 5–7, 8–12, 13–18
  - Parent proxy report: ages 2–4, 5–7, 8–12, 13–18
  - In order to generate utility scores, PedsQL must be mapped to another measure – e.g. EQ-5D-Y
    - Valued using the adult EQ-5D valuation set
- EQ-5D-Y is a child-friendly version of EQ-5D
  - Child self report: ages 8–18
  - Parent proxy report: ages 4–7, 8–18
  - Validated child and adolescent value set not yet available – valued using the adult EQ-5D valuation set
- Other alternative approaches may include:
  - Other preference-based measures – e.g. CHU-9D, HUI2
  - Other proxy reporting approaches – e.g. clinician valuation, expert elicitation

Health-related quality of life – ERG comments (1)

- ERG considered that the company's utility values had poor face validity
  - E.g. a patient surviving with SMA who achieves no milestones would accrue [redacted] QALYs over 10 years
  - High valuations in very poor health states, and limited range
- Mapping algorithm for PedsQL is limited – based on healthy schoolchildren aged 11–15, and included very few responses for poor health states
- Alternative utilities available from Bastida et al and Lloyd et al (vignette study based on EQ-5D assessments by clinicians)
  - Do not have the same methodological limitations, but still have limited face validity – very low valuations in worst health states
  - Although none of the datasets were ideal, of the 3 available utility sources the ERG preferred the vignette study

Early onset	Base case	Vignette study
No milestones	[redacted]	-0.24
Mild milestones	[redacted]	-0.12
Moderate milestones	[redacted]	-0.17
Sits wo support	[redacted]	-0.04
Stands w assistance	[redacted]	0.04
Walks w assistance	[redacted]	0.52
Stand/walks wo assistance	[redacted]	0.71

Later onset	Base case	Vignette study
Sits wo support	[redacted]	0.04
Sits and rolls	[redacted]	0.04
Sits and crawls	[redacted]	0.10
Stands/walks w assistance	[redacted]	0.39
Stands wo assistance	[redacted]	0.72
Walks wo assistance	[redacted]	0.72

Health-related quality of life – ERG comments (2)

- ERG considered that the company's approach to generate carer disutilities was not sufficiently justified
  - Unclear if the impact of each health state on a patient would be equal to that for the carer
  - Lack of face validity of patient utilities affects calculation of carer utilities
  - Calculations are arbitrary and based on other health states to the one being valued
- Alternative carer utilities (by SMA type) are available from Bastida et al

Early onset	Base case	Bastida et al	Later onset	Base case	Vignette study
No milestones	[redacted]	[redacted]	Sits wo support	[redacted]	[redacted]
Mild milestones	[redacted]	[redacted]	Sits and rolls	[redacted]	[redacted]
Moderate milestones	[redacted]	[redacted]	Sits and crawls	[redacted]	[redacted]
Sits wo support	[redacted]	[redacted]	Stands/walks w assistance	[redacted]	[redacted]
Stands w assistance	[redacted]	[redacted]	Stands wo assistance	[redacted]	[redacted]
Walks w assistance	[redacted]	[redacted]	Walks wo assistance	[redacted]	[redacted]
Stand/walks wo assistance	[redacted]	[redacted]			

Treatment cost

- Nusinersen acquisition cost: list price £75,000 per 12-mg vial
  - PAS proposed (not formally approved; see appendix)

- Administered via lumbar puncture
  - 40% inpatient, 30% outpatient, 30% day case

Nusinersen administration cost – weighted mean cost	
Age ≤5 years	£1,359
Age 6–18 years	£1,295
Age ≥18 years	£606

- Nusinersen regimen:
  - Early onset: days 0, 14, 28, 63 then every 4 months
  - Later onset: days 1, 30, 60, 90 then every 4 months
    - *NB: early onset regimen is consistent with ENDEAR study and MA; later onset differs from both CHERISH and MA*

Treatment duration: stopping rule

- Nusinersen is discontinued if it does not provide benefit or cannot be administered after scoliosis surgery
  - Lack of benefit: patient achieves no milestones or previous milestones are lost at the end of study follow-up (month 13 or 15)
  - Scoliosis surgery:

	Early onset	Later onset
% scoliosis surgery	1%	43%
% discontinuing nusinersen after surgery	20%	
Time of surgery since model start: Non-ambulant, ambulant	10 or 12 years*, 15 years	

**Usual care and nusinersen respectively*

Health state costs

- Health state costs were sourced from cross-sectional SMA study (Bastida et al)
  - Caregivers and people with SMA provided information about sociodemographic, costs of professional private care, the need for informal care, expenditure and resource utilisation related to the disease
  - Covered costs relating to respiratory, gastrointestinal, nutritional and orthopaedic care

	SMA type 1	SMA type 2	SMA type 3
Early onset model states	1–3	4–6	7
Later onset model states	–	1–4	5, 6
Drugs	[redacted]	[redacted]	[redacted]
Medical tests	[redacted]	[redacted]	[redacted]
Medical visits	[redacted]	[redacted]	[redacted]
Hospitalisations	[redacted]	[redacted]	[redacted]
GP & emergency	[redacted]	[redacted]	[redacted]
Health material	[redacted]	[redacted]	[redacted]
Social services	[redacted]	[redacted]	[redacted]
Total	[redacted]	[redacted]	[redacted]

- End-of-life costs: once-only end-of-life cost of £11,839 applied in early-onset model (not applied in later onset)

Company base case results – **early onset** (list price)

Base case results – early onset SMA, patient QALYs					
Technology	**Total costs (£)**	**Total QALYs**	**Inc. costs (£)**	**Inc. QALYs**	**ICER (£ per QALY)**
Nusinersen	2,258,852	7.86	2,187,311	5.37	**407,605**
Usual care	71,540	2.49			

Base case results – early onset SMA, patient and carer QALYs					
Technology	**Total costs (£)**	**Total QALYs**	**Inc. costs (£)**	**Inc. QALYs**	**ICER (£ per QALY)**
Nusinersen	2,258,852	7.61	2,187,311	5.44	**402,361**
Usual care	71,540	2.17			

Probabilistic results were similar to the deterministic (list price ICERs £408,712 and £404,270 per QALY gained respectively)*

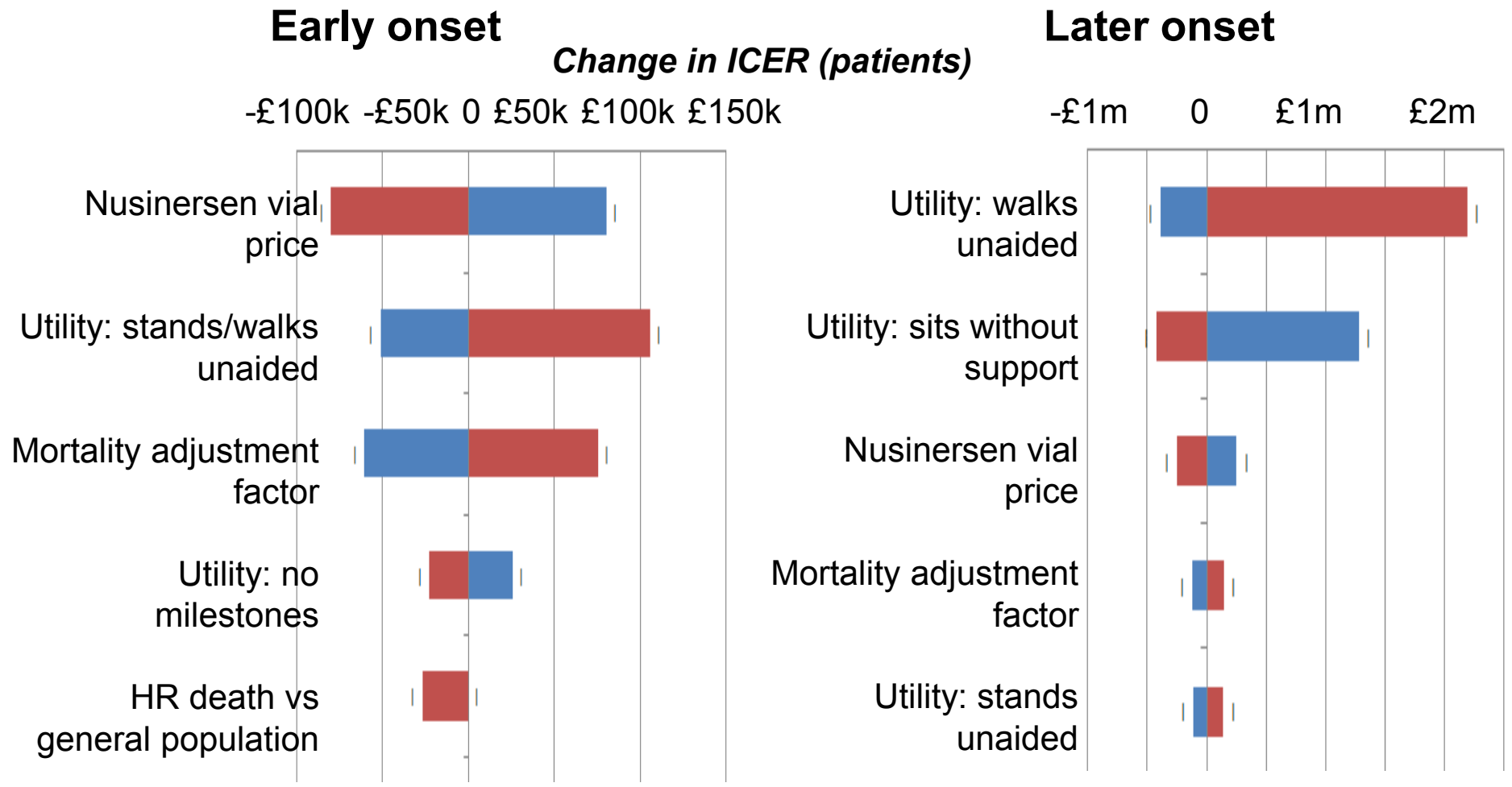
Company base case results – **later onset** (list price)

Base case results – later onset SMA, patient QALYs					
Technology	**Total costs (£)**	**Total QALYs**	**Inc. costs (£)**	**Inc. QALYs**	**ICER (£ per QALY)**
Nusinersen	3,148,754	16.88	2,964,442	2.37	**1,252,991**
Usual care	184,312	14.52			

Base case results – later onset SMA, patient and carer QALYs					
Technology	**Total costs (£)**	**Total QALYs**	**Inc. costs (£)**	**Inc. QALYs**	**ICER (£ per QALY)**
Nusinersen	3,148,754	15.66	2,964,442	3.30	**898,164**
Usual care	184,312	12.36			

Probabilistic results were similar to the deterministic (list price ICERs £1,286,149 and £933,088 per QALY gained respectively)*

Deterministic sensitivity analysis (list price)



The ICERs were most sensitive to cost of nusinersen, utility in the best and worst health and mortality adjustment factor applied to better health states

Company scenario analyses

Early onset	List price ICER*
Company base case	£407,605
Efficacy	
Mortality risk factor=1.00	£347,082
Mortality risk factor=0.00	£872,257
Proportion of nusinersen patients plateau	£417,355
Proportion of nusinersen patients plateau, then 10% progress per usual care	£421,445
Health state cost	
Health state costs include costs of major clinical events only	£442,838
Cost source – Klug et al	£405,194
Utility	
Patient utility based on vignettes	£421,703
Patient utility based on PedsQL type 2 (<25 months disease duration)	£387,628
Later onset	
Company base case	£1,252,991
Efficacy	
Mortality risk factor=1.00	£734,749
Mortality risk factor=0.00	£2,324,278
Proportion of nusinersen patients plateau	£1,371,100
Proportion of nusinersen patients plateau, then 10% progress per usual care	£1,393,262
Health state cost	
Health state costs include costs of major clinical events only	£1,276,308
Cost source – Klug et al	£1,258,136

Subgroup analysis: disease duration

- Company presented subgroup analyses based on disease duration at baseline (≤12 vs >12 weeks and <25 vs ≥25 months).

Early onset

Subgroup	ICER
Base case	£407,605
≤12 weeks disease duration	£ 398,912
>12 weeks disease duration	£422,874

Later onset

Subgroup	ICER
Base case	£1,252,991
<25 months disease duration	£1,263,457
≥25 months disease duration	£1,712,437

ERG comments – overview of main concerns

(1) Absence of economic evidence relating to Type 0 and Type IV SMA

(2) Model verification, errors and complexity of programming approach

(3) Concerns regarding model structures which focus only on motor milestones

(4) Highly favourable assumptions regarding the expected trajectory of nusinersen-treated patients through modelled motor milestone health states

(5) Highly favourable assumptions regarding the expected survival of nusinersen-treated patients

(6) Issues relating to estimated patient utilities

(7) Arbitrary calculations underpinning caregiver disutilities

(8) Issues relating to health state costs

(9) Representation of uncertainty

The ERG's key concerns relate to (1) the modelled motor function trajectories; (2) the modelled survival advantage for nusinersen and (3) the health utilities

ERG exploratory analyses

- ERG presented a preferred exploratory analysis:
  - Common starting state distribution for both treatment groups
  - Inclusion of end-of-life costs for the later onset population
  - Patient utilities from the vignette study (Lloyd *et al*)
  - Caregiver utilities from Bastida *et al*

ERG emphasised that the preferred analysis does not address its concerns that the modelled transition probabilities and survival were based on highly optimistic assumptions

- ERG also presented scenario analyses exploring patient utilities, mortality and disease progression

ERG's preferred analysis – **early onset** (list price)

ERG preferred results – early onset SMA, patient QALYs					
Technology	**Total costs (£)**	**Total QALYs**	**Inc. costs (£)**	**Inc. QALYs**	**ICER (£ per QALY)**
Nusinersen	2,264,226	4.42	2,192,722	5.20	421,303
Usual care	71,504	-0.78			

ERG preferred results – early onset SMA, patient and carer QALYs					
Technology	**Total costs (£)**	**Total QALYs**	**Inc. costs (£)**	**Inc. QALYs**	**ICER (£ per QALY)**
Nusinersen	2,264,226	2.43	2,192,722	3.47	631,583
Usual care	71,504	-1.04			

ERG's preferred analysis – **later onset** (list price)

ERG preferred results – later onset SMA, patient QALYs					
Technology	**Total costs (£)**	**Total QALYs**	**Inc. costs (£)**	**Inc. QALYs**	**ICER (£ per QALY)**
Nusinersen	£3,203,766	8.53	£3,014,078	7.37	£408,769
Usual care	£189,688	1.15			

ERG preferred results – later onset SMA, patient and carer QALYs					
Technology	**Total costs (£)**	**Total QALYs**	**Inc. costs (£)**	**Inc. QALYs**	**ICER (£ per QALY)**
Nusinersen	£3,203,766	5.12	£3,014,078	4.76	£632,850
Usual care	£189,688	0.36			

ERG's preferred analysis – **early and later onset** (list price)

Early onset		ICER*	ICER**
	Company's base case	£407,605	£402,361
1§	Average initial distribution for both treatment groups	£407,417	£402,159
2	Inclusion of end-of-life costs for the later onset model	£407,417	£402,159
3	Use of patient utilities from the vignette study	£421,303	£394,023
4	Caregiver utilities from Bastida et al	£407,417	£600,882
5	**ERG-preferred analysis: 1 + 2 + 3 + 4**	**£421,303**	**£631,583**

Later onset		ICER*	ICER**
	Company's base case	£1,252,991	£898,164
1§	Average initial distribution for both treatment groups	£1,221,051	£869,639
2	Inclusion of end-of-life costs for the later onset model	£1,220,817	£869,472
3	Use of patient utilities from the vignette study	£408,847	£360,122
4	Caregiver utilities from Bastida et al	£1,221,051	Dominated
5	**ERG-preferred analysis: 1 + 2 + 3 + 4**	**£408,769**	**£632,850**

*patient health gains only, ** patient health gains and caregiver QALY losses

ERG sensitivity analysis – **early and later onset**, patient impacts (list price)

Scenario info			ICER early onset*	ICER later onset*
ERG preferred analysis			**421,303**	**408,769**
Utilities				
6a	Patient utilities based Bastida et al		679,469	627,612
6b	Patient utilities based on clinical judgement		366,289	850,597
Mortality adjustment				
7	Exclusion of mortality adjustment for better health states		573,922	432,191
Long-term disease progression				
8a	Nusinersen patients lose milestones each cycle:	5%	450,926	455,934
8b		10%	496,787	552,283
8c		20%	674,945	1,011,268
8d	All patients stay in final state indefinitely after end of study		16,788,055	3,465,629
8e	All patients lose all milestones after end of study		Dominated	14,994,339

ERG sensitivity analysis – **early and later onset**, patient + caregiver impacts (list price)

Scenario info			ICER early onset**	ICER later onset**
ERG preferred analysis			**631,583**	**632,850**
Utilities				
6a	Patient utilities based Bastida et al		1,467,413	1,375,278
6b	Patient utilities based on clinical judgement		515,511	3,231,764
Mortality adjustment				
7	Exclusion of mortality adjustment for better health states		750,195	673,128
Long-term disease progression				
8a	Nusinersen patients lose milestones each cycle:	5%	652,213	699,062
8b		10%	696,405	834,754
8c		20%	904,003	1,459,562
8d	All patients stay in final state indefinitely after end of study		Dominated	3,831,118
8e	All patients lose all milestones after end of study		Dominated	18,436,952

End-of-life

- Company considers that NICE's criteria for life-extending treatments at the end of life apply to the early onset population
  - Company states that 'survival free of permanent ventilation' is more relevant than overall survival, as permanent ventilation may not be used in England

Short life expectancy *Normally less than 24 months*	***Company submission:*** Median age of death/permanent ventilation in natural history studies: 9–13 months [redacted] ENDEAR: Median EFS (sham group): 22.6 weeks
	ERG comments: Low survival rates may not reflect current practice; some patients with less-severe early onset disease may survive to school age Mean survival predicted by the model in the usual care group: 3.87 years
Life extension *Normally a mean of at least an 3 months vs current treatment*	***Company submission:*** ENDEAR: nusinersen associated with a significantly improved EFS and OS (HR 0.53 and 0.37 respectively); median not reached in nusinersen arm (week 56) NURTURE: at latest data cut-off, all pre-symptomatic children were still alive
	ERG comments: Mean survival extension predicted by the model: 9.12 years Considerable uncertainty in the survival benefit of nusinersen, and model may be optimistic, but plausible that nusinersen may extend survival by ≥3 months

Managed access arrangement

- Company propose that nusinersen be considered for an MAA, to address potential uncertainties
- Draft proposal developed following discussions with NHS England and NICE, for discussion by committee:
  - 5-year term
  - Eligibility criteria: within marketing authorisation, <18 years, SMN2 copy number ≥2
  - Stopping criteria: invasive ventilation, 2 consecutive measures of decline in motor function (>MCID), non-compliance
  - Data collection:
    - At 14 months then 12-monthly
    - Outcomes: survival, ventilation/respiratory events, motor function, quality of life (patient and carer)
    - Collection through SMART NET registry
    - Includes patients who discontinue nusinersen

Innovation and equalities

Innovation

- Company states that nusinersen represents a breakthrough and innovation that has been recognised in several countries
- Significant unmet need for patients with SMA
- First treatment that addresses the cause and natural history of motor neurone degeneration in SMA

Equalities

- No potential equality issues were identified during the scoping process
- Patients with SMA have a range of disabilities
- Company and patient groups consider that nusinersen should be considered for all ages and disabilities
- The population for which nusinersen is indicated includes children and adolescents

Key issues
Cost effectiveness

- Is the economic model suitable for decision making?
  - Do the modelled health states based on motor milestones appropriately map the course of SMA and capture the key elements of disease?
- Are the assumptions for the change in motor milestones over time and movement of patients through the health states appropriate?
- Is the modelling and extrapolation of overall survival appropriate?
  - Survival advantage associated with improved motor function
- What are the most appropriate estimates of utilities? For patients and carers?
- Additional considerations
  - Population contains children: any additional considerations required?
  - Are the end-of-life criteria met?
  - Proposed managed access arrangement
- What are the most plausible ICERs?

Authors

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- With input from the Lead Team (Steve O'Brien – Chair, Andrea Manca – Cost Lead, Kamal Balakrishnan – Clinical Lead, David Chandler – Lay Lead)

Appendix: Results including proposed Patient Access Scheme

Company base case results – **early onset** (PAS)

Base case results – early onset SMA, patient QALYs					
Technology	**Total costs (£)**	**Total QALYs**	**Inc. costs (£)**	**Inc. QALYs**	**ICER (£ per QALY)**
Nusinersen	[redacted]	7.86	[redacted]	5.37	[redacted]
Usual care	71,540	2.49			

Base case results – early onset SMA, patient and carer QALYs					
Technology	**Total costs (£)**	**Total QALYs**	**Inc. costs (£)**	**Inc. QALYs**	**ICER (£ per QALY)**
Nusinersen	[redacted]	7.61	[redacted]	5.44	[redacted]
Usual care	71,540	2.17			

Company base case results – **later onset** (PAS)

Base case results – later onset SMA, patient QALYs					
Technology	**Total costs (£)**	**Total QALYs**	**Inc. costs (£)**	**Inc. QALYs**	**ICER (£ per QALY)**
Nusinersen	[redacted]	16.88	[redacted]	2.37	[redacted]
Usual care	184,312	14.52			

Base case results – later onset SMA, patient and carer QALYs					
Technology	**Total costs (£)**	**Total QALYs**	**Inc. costs (£)**	**Inc. QALYs**	**ICER (£ per QALY)**
Nusinersen	[redacted]	15.66	[redacted]	3.30	[redacted]
Usual care	184,312	12.36			

Company scenario analyses

Early onset	PAS ICER*
Company base case	[redacted]
Efficacy	
Mortality risk factor=1.00	[redacted]
Mortality risk factor=0.00	[redacted]
Proportion of nusinersen patients plateau	[redacted]
Proportion of nusinersen patients plateau, then 10% progress per usual care	[redacted]
Health state cost	
Health state costs include costs of major clinical events only	[redacted]
Cost source – Klug et al	[redacted]
Utility	
Patient utility based on vignettes	[redacted]
Patient utility based on PedsQL type 2 (<25 months disease duration)	[redacted]
Later onset	
Company base case	[redacted]
Efficacy	
Mortality risk factor=1.00	[redacted]
Mortality risk factor=0.00	[redacted]
Proportion of nusinersen patients plateau	[redacted]
Proportion of nusinersen patients plateau, then 10% progress per usual care	[redacted]
Health state cost	
Health state costs include costs of major clinical events only	[redacted]
Cost source – Klug et al	[redacted]

Subgroup analysis: disease duration

- Company presented subgroup analyses based on disease duration at baseline (≤12 vs >12 weeks and <25 vs ≥25 months).

Early onset

Subgroup	PAS ICER
Base case	[redacted]
≤12 weeks disease duration	[redacted]
>12 weeks disease duration	[redacted]

Later onset

Subgroup	PAS ICER
Base case	[redacted]
<25 months disease duration	[redacted]
≥25 months disease duration	[redacted]

ERG's preferred analysis – **early onset** (PAS)

ERG preferred results – early onset SMA, patient QALYs					
Technology	**Total costs (£)**	**Total QALYs**	**Inc. costs (£)**	**Inc. QALYs**	**ICER (£ per QALY)**
Nusinersen	[redacted]	4.42	[redacted]	5.20	[redacted]
Usual care	71,504	-0.78			

ERG preferred results – early onset SMA, patient and carer QALYs					
Technology	**Total costs (£)**	**Total QALYs**	**Inc. costs (£)**	**Inc. QALYs**	**ICER (£ per QALY)**
Nusinersen	[redacted]	2.43	[redacted]	3.47	[redacted]
Usual care	71,504	-1.04			

ERG's preferred analysis – **later onset** (PAS)

ERG preferred results – later onset SMA, patient QALYs					
Technology	**Total costs (£)**	**Total QALYs**	**Inc. costs (£)**	**Inc. QALYs**	**ICER (£ per QALY)**
Nusinersen	[redacted]	8.53	[redacted]	7.37	[redacted]
Usual care	£189,688	1.15			

ERG preferred results – later onset SMA, patient and carer QALYs					
Technology	**Total costs (£)**	**Total QALYs**	**Inc. costs (£)**	**Inc. QALYs**	**ICER (£ per QALY)**
Nusinersen	[redacted]	5.12	[redacted]	4.76	[redacted]
Usual care	£189,688	0.36			

ERG's preferred analysis – **early and later onset** (PAS)

Early onset		ICER*	ICER**
	Company's base case	[redacted]	[redacted]
1§	Average initial distribution for both treatment groups	[redacted]	[redacted]
2	Inclusion of end-of-life costs for the later onset model	[redacted]	[redacted]
3	Use of patient utilities from the vignette study	[redacted]	[redacted]
4	Caregiver utilities from Bastida et al	[redacted]	[redacted]
5	**ERG-preferred analysis: 1 + 2 + 3 + 4**	[redacted]	[redacted]

Later onset		ICER*	ICER**
	Company's base case	[redacted]	[redacted]
1§	Average initial distribution for both treatment groups	[redacted]	[redacted]
2	Inclusion of end-of-life costs for the later onset model	[redacted]	[redacted]
3	Use of patient utilities from the vignette study	[redacted]	[redacted]
4	Caregiver utilities from Bastida et al	[redacted]	[redacted]
5	**ERG-preferred analysis: 1 + 2 + 3 + 4**	[redacted]	[redacted]

*patient health gains only, ** patient health gains and caregiver QALY losses

ERG sensitivity analysis – **early and later onset**, patient impacts (PAS)

Scenario info			ICER early onset	ICER later onset
ERG preferred analysis			[redacted]	[redacted]
Utilities				
6a	Patient utilities based Bastida et al		[redacted]	[redacted]
6b	Patient utilities based on clinical judgement		[redacted]	[redacted]
Mortality adjustment				
7	Exclusion of mortality adjustment for better health states		[redacted]	[redacted]
Long-term disease progression				
8a	Nusinersen patients lose milestones each cycle:	5%	[redacted]	[redacted]
8b		10%	[redacted]	[redacted]
8c		20%	[redacted]	[redacted]
8d	All patients stay in final state indefinitely after end of study		[redacted]	[redacted]
8e	All patients lose all milestones after end of study		[redacted]	[redacted]

ERG sensitivity analysis – **early and later onset**, patient + caregiver impacts (PAS)

Scenario info			ICER early onset	ICER later onset
ERG preferred analysis			[redacted]	[redacted]
Utilities				
6a	Patient utilities based Bastida et al		[redacted]	[redacted]
6b	Patient utilities based on clinical judgement		[redacted]	[redacted]
Mortality adjustment				
7	Exclusion of mortality adjustment for better health states		[redacted]	[redacted]
Long-term disease progression				
8a	Nusinersen patients lose milestones each cycle:	5%	[redacted]	[redacted]
8b		10%	[redacted]	[redacted]
8c		20%	[redacted]	[redacted]
8d	All patients stay in final state indefinitely after end of study		[redacted]	[redacted]
8e	All patients lose all milestones after end of study		[redacted]	[redacted]

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal

Nusinersen for treating spinal muscular atrophy [ID1069]

Document B

Company evidence submission

March 2018

File name	Version	Contains confidential information	Date
20180315_Nusinersen (Spinraza)_NICE_Main Submission Document B_[redacted]	1.0	no	15th March 2018

Contents

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Table of Abbreviations

Abbreviation	Definition
ACEND	Assessment of Caregiver Experience with Neuromuscular Disease
ADA	Anti-drug antibody
ADL	Activities of daily living
AE	Adverse event
AIC	Akaike information criterion
ANCOVA	Analysis of covariance
ASO	Antisense oligonucleotide
BIC	Bayesian information criterion
BiPAP	Bi-level airway positive pressure
CE	Conformité Européenne
CGI	Clinical Global Impression
CGI-I	Clinical Global Impression – Improvement
CHI	Mean CHOP INTEND score
CHMP	Committee for Medicinal Products for Human Use
CHOP INTEND	Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders
CI	Confidence interval
CMAP	Compound muscle action potential
CNS	Central nervous system
CPAP	Continuous positive airway pressure
CSF	Cerebrospinal fluid
CSR	Clinical study report
CT	Computed tomography
EAP	Expanded Access Programme
EPAR	European public assessment report
EMA	European Medicines Agency
EQ-5D	European Quality of Life-5 Dimensions
EQ-5D-Y	European Quality of Life-5 Dimensions Youth version
EQ-5D-3L	European Quality of Life-5 Dimensions 3-level scale
FDA	Food and Drug Administration
GP	General practitioner
GT	Gastrostomy tube
HFMSE	Hammersmith Functional Motor Scale-Expanded
HINE	Hammersmith Infant Neurological Examination
HINE-2	Module 2 of the Hammersmith Infant Neurological Examination
HR	Hazard ratio
HRQL	Health-related quality of life
IBS	Integrated Brier score
ICER	Incremental cost-effectiveness ratio
IES	Interim efficacy set
Inc.	Incremental
ITT	Intention to treat
IQR	Interquartile range
IXRS	Interactive Voice/Web-Response System
K-M	Kaplan-Meier
LP	Lumbar puncture
LS	Least squares
LYG	Life years gained
MI-E	Mechanical insufflation/exsufflation
MCID	Minimal clinically important difference
mRNA	Messenger ribonucleic acid
MUNE	Motor Unit Number Estimation

NG	Nasogastric
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
NIV	Non-invasive ventilation
NJ	Nasojejunal
NMD	Neuromuscular disease
NMM	Neuromuscular Module
NRA	Non-invasive respiratory aid
NT	No treatment
OT	Occupational Therapy
OWSA	One-way sensitivity analysis
PAS	Patient Access Scheme
PAES	Post-authorisation efficacy study
PEDI	Pediatric Evaluation of Disability Inventory
PbR	Payment by Results
PedsQL	Paediatric Quality of Life Inventory
PedsQL GCS	PedsQL Measurement 4.0 General Core Scales
PROM	Patient-reported outcomes measures
PSA	Probabilistic sensitivity analysis
PT	Physiotherapy
QALY	Quality-adjusted life year
RULM	Revised Upper Limb Module
RCT	Randomised controlled trial
SAEs	Serious adverse events
SCC	International Standard of Care Committee
SD	Standard deviation
SE	Standard error
SF-36	36-Item Short Form Survey
SLR	Systematic literature review
SMA	Spinal muscular atrophy
SMA-HI	Spinal Muscular Atrophy Health Index
SMN	Survival of motor neuron
SmPC	Summary of product characteristics
STA	Single technology appraisal
TV	Tracheostomy with ventilator
ULM	Upper Limb Module
UK	United Kingdom
VAS	Visual analogue scale
VT	Elective tracheostomy and invasive mechanical ventilation
WHO	World Health Organization

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

1.1 Decision problem

The technology's full marketing authorisation includes the treatment of all patients with 5q spinal muscular atrophy (SMA), which accounts for approximately 90% of all SMA forms.

The submission focuses on part of the technology's marketing authorisation, specifically patients with pre-symptomatic SMA, infantile onset (those who have or are most likely to develop type I) or later onset (those who have or are most likely to develop types II and III) SMA. The proposed population is narrower than the marketing authorisation (which includes all patients with 5q SMA) because the evidence base on nusinersen is confined to patients with pre-symptomatic, symptomatic infantile onset and later onset SMA.(1) Patients with type 0 and type IV (adult onset) SMA are omitted from the submission, despite market authorisation,(1) as there is no clinical evidence for nusinersen in type 0 and type IV that meets the requirements for technology appraisal at the current time.

Table 1.The decision problem

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
Population	People with 5q SMA	Pre-symptomatic and symptomatic people with 5q SMA who have infantile onset (those who have or are most likely to develop type I) or later onset (those who have or are most likely to develop types II and III) SMA	The proposed population is narrower than the marketing authorisation (which includes all patients with 5q SMA) because the evidence base on nusinersen is limited to patients with pre-symptomatic and symptomatic infantile onset and later onset SMA
Intervention	Nusinersen	Nusinersen	N/A
Comparator(s)	Best supportive care	Sham procedure and standard of care treatment	Biogen consider that the most appropriate comparator is sham procedure (administered by lumbar puncture prick), as no disease-modifying therapies (other than nusinersen) are approved or routinely used in SMA
Outcomes	The outcome measures to be considered include: • Motor function (including, where applicable, age appropriate motor milestones) • Respiratory function • Complications of SMA (including, for example, scoliosis and muscle contractures) • Need for non-invasive or invasive ventilation • Stamina and fatigue	The outcome measures to be considered include: • Motor function (including, where applicable, age appropriate motor milestones) • Event-free survival (time to death or permanent assisted ventilation) and overall survival • Respiratory function • Need for non-invasive or invasive ventilation • Mortality	Complications of SMA (including, for example, scoliosis and muscle contractures), and stamina and fatigue, are not included as these outcomes were not collected in the pivotal clinical trials

	• Mortality • Adverse effects of treatment • HRQL	• Adverse effects of treatment • HRQL	
Economic analysis	The reference case stipulates that the cost effectiveness of treatments should be expressed in terms of incremental cost per QALY. The reference case stipulates that the time horizon for estimating clinical and cost effectiveness should be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared. Costs will be considered from an NHS and personal social services perspective.	The economic analysis considers 2 de novo models to assess the cost-effectiveness of nusinersen using motor milestones health states – 1 relating to infantile onset SMA and the other to later onset SMA. The pre-symptomatic health state is being developed but could not be modelled in time for submission.	N/A
Subgroups to be considered	Consideration will be given to subgroups based on severity of disease (including considerations such as age of SMA onset, SMA type and genotype [including *SMN2* copy number]). Guidance will only be issued in accordance with the marketing authorisation. Where the wording of the therapeutic indication does not include specific treatment combinations, guidance will be issued only in the context of the evidence that has underpinned the marketing authorisation granted by the regulator.	The pivotal trials in infantile onset (ENDEAR) and later onset SMA (CHERISH) included pre-specified subgroups based on disease duration and age at symptom onset. For infantile onset SMA patients the economic analysis has evaluated the subgroups based on age at onset of SMA symptoms and disease duration (>12 weeks and ≤12 weeks) from the ENDEAR trial For later onset SMA patients, subgroup analysis has not been conducted in the economic analysis due to the small subgroup sample sizes within	N/A

Special considerations including issues related to equity or equality	NR	N/A	N/A

Abbreviations: N/A, non-applicable; NR, not reported; HRQL, health-related quality of life; NHS, national health service; QALY, Quality-adjusted life year; SMA, spinal muscular atrophy;

1.2 Description of the technology being appraised

Appendix C includes the Summary of Product Characteristics (SmPC) and the European Public Assessment Report (EPAR).

Table 2.Technology being appraised

UK approved name and brand name	Nusinersen (Spinraza®)
Mechanism of action	Nusinersen is an ASO that increases the level of functional SMN protein, binding to a splice silencing site on intron 7 of the *SMN2* pre-messenger ribonucleic acid (mRNA), displacing factors that normally suppress splicing. Displacement of these factors leads to increased retention of exon 7 in the *SMN2* mRNA transcripts and hence, increased translation to functional full-length SMN protein.(2) Healthy individuals have 2 SMN genes, *SMN1* and *SMN2*, located on chromosome 5q. *SMN1* in healthy, unaffected individuals predominantly produces the functional full-length SMN protein. *SMN2* predominantly produces a shortened, unstable, non-functioning and rapidly degraded isoform. All patients with SMA have a loss or mutation of *SMN1*, but retain at least 1 copy of *SMN2*, which is able to produce a small quantity of functional SMN protein. However, the small amount of SMN protein produced does not fully compensate for the loss of *SMN1*.(3,4)
Marketing authorisation/CE mark status	Nusinersen has marketing authorisation from the EMA (granted on 30 May 2017(5)), for the treatment of 5q SMA.(2)
Indications and any restriction(s) as described in the SmPC	The indication in the UK is for the treatment of 5q SMA, as per the marketing authorisation from the EMA.(2) Further details are available in Appendix C.
Method of administration and dosage	Treatment with nusinersen should be initiated as early as possible after diagnosis with 4 loading doses on days 0, 14, 28 and 63. A maintenance dose should be administered once every 4 months thereafter. The recommended, licensed dose is 12 mg (5 ml) per administration for the loading dose and the maintenance dose.(2) Nusinersen is administered as an intrathecal bolus injection over 1–3 minutes, via lumbar puncture, directly into the CSF.(2)
Additional tests or investigations	No additional tests or investigations are required to identify infantile onset or later onset patients; a diagnosis is confirmed through genetic tests and physical examinations, regardless of treatment choice. *Lumbar puncture procedure* The use of ultrasound or other imaging techniques to assist with intrathecal administration of nusinersen can be considered at the physician's discretion, although this may only be relevant for very young patients and those with scoliosis.(2) *Thrombocytopaenia and coagulation abnormalities*

	Thrombocytopaenia and coagulation abnormalities, including acute severe thrombocytopaenia, have been observed after administration of other subcutaneously or intravenously administered ASOs. While none have been observed with nusinersen to date, if clinically indicated, platelet and coagulation laboratory testing is recommended prior to administration of nusinersen.(2) *Renal toxicity* Renal toxicity has been observed after administration of other subcutaneously and intravenously administered ASOs, although not with nusinersen to date. If clinically indicated, urine protein testing (preferably using a first morning urine specimen) is recommended. For persistent elevated urinary protein, further evaluation should be considered.(2)
List price and average cost of a course of treatment	Nusinersen is priced at £75,000 per vial and the total budget impact is expected to be predictable due to the small and identifiable population for SMA. In year 1, patients receive 4 loading doses (days 0, 14, 28 and 63) followed by maintenance dosing once every 4 months (on days 183 and 302). In subsequent years, patients receive 3 maintenance doses per year (in 4-month intervals). [redacted] [redacted]
Patient access scheme (if applicable)	Not applicable, but ongoing discussions on a commercial agreement are taking place with NHS England.

Abbreviations: ASO, antisense oligonucleotide; CSF, cerebrospinal fluid; EMA, European Medicines Agency; SMA, spinal muscular atrophy; SMN, survival of motor neuron; SmPC, summary of product characteristics; CE, Conformité Européenne.

1.3 Health condition and position of the technology in the treatment pathway

1.3.1 Infantile onset and later onset spinal muscular atrophy

SMA is a rare, genetic, neuromuscular disease, which is debilitating for all patients and fatal for the worst affected.(5) The disease not only affects patients' musculoskeletal system, but also their respiratory and gastrointestinal system.(6) SMA is recognised by the European Medicines Agency (EMA) as an orphan disease, but is the leading genetic cause of infant mortality.(7) Individuals with SMA have an insufficient level of functional survival of motor neuron (SMN) protein caused by the absence of the *SMN1* gene; over time, this leads to progressive loss of motor function and respiratory failure.(1,3) When an infant or child presents with a history of motor difficulties and the symptoms and physical examination support a diagnosis of SMA, a diagnosis can be confirmed through genetic analysis.(3,8)

The disease presents across a spectrum of subtypes (0-IV, of which types I-III are relevant to the decision problem; section 1.1), with greater disease severity linked to younger age of onset, as shown in Table 3.(9) Type I, and types II-III can be grouped into infantile onset SMA and later onset SMA, respectively based on age of onset and motor function achieved.

Table 3. Classification and subtypes of spinal muscular atrophy

Type	Age of onset	Maximal motor milestone	Motor ability and additional features	Prognosis [c]
SMA 0	Before birth	None	Severe hypotonia; unable to sit and roll [a]	Respiratory insufficiency at birth: death within weeks
SMA I	2 weeks (Ia) 3 months (Ib) 6 months (Ic)	None	Severe hypotonia; unable to sit and roll [b]	Death/ventilation by 2 years
SMA II	6–18 months	Sitting	Proximal weakness: unable to walk independently	Survival into adulthood
SMA III	<3 years (IIIa) >3 years (IIIb) >12 years (IIIc)	Walking	May lose ability to walk	Normal life span
SMA IV	>30 years or 10–30 years	Normal	Mild motor Impairment	Normal life span

Abbreviations: SMA, spinal muscular atrophy
[a] Need for respiratory support at birth; contractures at birth, reduced foetal movements
[b] Ia joint contractures present at birth; Ic may achieve head control
[c] Prognosis varies with phenotype and supportive care interventions
Source: Farrah et al. 2017(9)

Infantile onset SMA (type I) is a severe form of the disease estimated to account for 5.83 per 100,000 live births.(10,11) Prevalence is estimated at around 0.1 per 100,000

population due to high mortality rates as patients rarely survive to their second birthday.(7) Symptoms appear before 6 months and include muscle weakness of varying severity mainly evident as hypotonia, inability to lift head/poor head control, and poor feeding.(12–14)

Patients with infantile onset SMA have limited motor development and fail to develop motor milestones, never achieving sitting without support.(15) Patients continue to deteriorate – losing any motor function gained prior to the onset of symptoms, and increasing the need for respiratory intervention.(6,16) They often experience pulmonary complications, which contribute to respiratory failure due to impaired secretion clearance, insufficient ventilation and oxygenation. Other complications may include nutritional deficiencies, the need for feeding support and risk of aspiration pneumonia, as a result of gastrointestinal complications.(17) Therefore, patients with infantile onset SMA have severe physical disability and patients experience early morbidity due to respiratory insufficiency and aspiration pneumonia. The median age for death or permanent respiratory support (a composite endpoint used in clinical trials in this population) is approximately 9–13 months.(18) The differential use of life-extending symptomatic care, including permanent respiratory support, means that real world survival may not reflect clinical trials. [redacted]

Later onset patients are most likely to develop type II or III SMA, with an estimated incidence rate of 2.66 and 1.20 per 100,000 live births, respectively.(10) Later onset SMA is associated with a loss of motor function over time and numerous secondary complications. The disease presents from 6 months of age with patients exhibiting a wide spectrum of clinical phenotypes. The severity of impairment in motor function is highly variable from those able to sit unaided to those with the ability to walk without support. Even if achieved, higher function motor milestones (such as the ability to walk unaided) may be delayed and progressive loss of muscle strength causes diminishing upper limb and general motor function over time.(15) As a result, the majority of patients who can walk unaided gradually lose this ability over time.(20) Scoliosis also emerges in many non-ambulatory patients,(21) leading to increased risk for respiratory disease and, subsequently, a shortened life expectancy.(6,22) Children with the condition have weak muscles in the upper chest making breathing and coughing more difficult, increasing the risk of chest infections.(18) Frequent pain is also a common occurrence, as reported in a Swedish survey of 17 adolescents (12-18 years of age) with SMA. Thirteen patients (77%) experienced pain during the last 3 months, with 12 (71%) reporting persistent or recurrent chronic pain.(23)

[redacted]

[redacted]

Although patients with later onset SMA usually survive into adulthood, the considerable morbidity of the disease is associated with lifelong impacts on health-related quality of life (HRQL), ability to live independently and requirements for care because of contractures to the lower extremities, hypermobile joints in the upper extremities and recurrent fractures.(21,24) Pain caused by severe contractures, osteoporosis, vertebral fractures, orthopaedic procedures or muscular overuse, is also a frequent occurrence and major feature of SMA.(23) Furthermore, later onset (type II and type III) SMA imposes a major physical and psychological burden due to the progressive decline in health, including fear of losing independence, struggle with feeding and impaired breathing.(23,25)

Despite the rare nature of the disease, both infantile onset and later onset SMA pose a substantial economic burden to the healthcare system, SMA families (a high proportion of working parents with SMA have to reduce or even leave their jobs, leading to financial strain and further impacting on their HRQL(26)) and wider society. As a proxy for this in England and Wales, a survey of SMA families in Scotland found that 79% (n=15/19) of the main unpaid carers had to give up work completely or drop to part time.(27) This is driven by increased utilisation of healthcare resources, such as inpatient and intensive care stays, outpatient visits, non-medical costs, professional caregiving and durable medical equipment.(26,28,29) Parents of children with SMA (types I-III) in Scotland reported that they attend 2–6 appointments per month in connection with their child's SMA, and spend up to 80 hours per month on non-caring, SMA-related tasks.(27) As the disease progresses, patients require more intensive treatments.

1.3.2 Clinical pathway of care for spinal muscular atrophy

The international treatment guidelines for patients with type I-IV SMA include a two-part updated consensus statement by the International Standard of Care Committee (SCC) of the topics covered in the previous recommendations. Part 1 provides an update on diagnosis, rehabilitation, orthopaedic and spinal management in SMA, whereas part 2 discusses the pulmonary management, acute care, other organ involvement, ethical issues, medications, and the impact of new treatments for SMA.(30,31)

The updated SCC for SMA consensus statement addresses 3 functional levels of the patients: non-sitter, sitter, and walker (rather than SMA types I-IV). The non-sitters include patients who currently are not able to sit independently (i.e. the infantile (type I) onset population); the sitters include those who can sit independently but cannot walk independently; the walkers can walk independently.(31) The recommendations from the SCC consensus statement are summarised in Table 4.(8)

Table 4. Clinical management recommendations from the consensus statement by the SCC for SMA

<table>
<tr><th>Type of care</th><th>Non-sitters</th><th>Sitters</th><th>Walkers</th></tr>
<tr><td colspan="4">Pulmonary care</td></tr>
<tr><td>Anticipatory respiratory care</td><td colspan="3">• Understanding the child's baseline, deviations from his/her baseline, hypoventilation and intervention
• Acute illness management including rapid access to specialty medical care providers
• Nutrition and hydration
• A low threshold to start antibiotics
• Routine immunisations</td></tr>
<tr><td rowspan="3">Chronic respiratory management</td><td colspan="3">Airway clearance:
• Assisted cough (MI-E or manual)
• Secretion mobilisation techniques (chest physiotherapy, postural drainage)
• Oximetry to guide therapy
Respiratory support:
• NIV
CPAP (goal to transition to BiPAP)</td></tr>
<tr><td>• Option: Care without ventilation support
• Palliative care
• Tracheotomy</td><td>Airway clearance/ respiratory support, as needed</td><td rowspan="2">Airway clearance/ respiratory support not likely to be required until late into the disease course</td></tr>
<tr><td colspan="2">NIV with high span BiPAP, even for short daytime periods</td></tr>
<tr><td rowspan="2">Acute care management</td><td colspan="3">Airway clearance:
• Assisted cough (MI-E or manual), oral or airway suctioning
• Oximetry
• Chest physiotherapy
• Postural drainage
Respiratory support:
• Acute use of NIV
• Oxygen therapy</td></tr>
<tr><td colspan="2">Respiratory support:
• Daytime NIV with airway clearance
• Intubation and mechanical ventilation
• Palliative care</td><td>Respiratory support:
• NIV for home use</td></tr>
<tr><td colspan="4">Gastrointestinal and nutritional care</td></tr>
<tr><td>Feeding and swallowing difficulties</td><td colspan="3">• Changing food consistency
• Positioning and seating alterations and orthotic devices
• Nutritional supplementation through NG or NJ feeding
• Gastrostomy tube feeding</td></tr>
<tr><td>Gastrointestinal dysfunction</td><td colspan="3">Management of gastroesophageal reflux:
• Short term use of acid neutralisers and/or inhibitors of acid secretion
• Prokinetic agents
• Probiotics
• Laparoscopic anti-reflux Nissen fundoplication</td></tr>
</table>

Type of care	Non-sitters	Sitters	Walkers
Growth and under or over nutrition problems	• Monitoring of growth velocity (growth charts) • Dietician assessment of nutritional intake • Appropriate intake of calcium and vitamin D • Monitor pre-albumin levels		
Management of nutrition in acutely sick SMA patients	• Avoid prolonged fasting due to high risk of hypoglycaemia • Enteral and/or parenteral feeding to meet caloric needs within 4-6 hours of acute illness admission • Post-operative caloric supplementation		
Neuromuscular and musculoskeletal evaluation			
Managing musculoskeletal system problems and related functional impairments	• Assessments of strength and range of joint motion, relevant motor functional scales and timed tests to monitor those aspect of function that reflect activities of daily living		
Orthopaedic care and rehabilitation			
Managing problems caused by muscle weakness	• Wheelchair mobility • Environmental controls and home modifications		
	• Nutritional support • Posture management with supportive seating • Contracture management by splinting • Pain management • Therapy for ADL and assistive equipment • Limb orthotics	• Contracture management by stretching, bracing, serial casting, orthotics and supports/ slings • Regular exercise and standing with appropriate assistive devices and orthotics • Spine orthotics and surgery	• Contracture management and education • PT and OT • Regular exercise and walking with appropriate assistive devices and orthotics • Spine/limb orthotics and surgery
Orthopaedic surgery	Nonsitters do not benefit from surgery	• Hip subluxation and contractures • Scoliosis surgery	
Other care			
Perioperative care	Due to high risk for post-anaesthesia complications, respiratory status needs to be optimised and orthotic interventions need to be adjusted before surgery. After surgery, close monitoring, aggressive respiratory management, and rapid mobilisation, may be required.		

Abbreviations: ADL, activities of daily living; BiPAP, bi-level positive airway pressure; CPAP, continuous positive airway pressure; NIV, non-invasive ventilation; NG, nasogastric; NJ, nasojejunal; MI-E, mechanical insufflation/exsufflation; PT, physiotherapy; OT, occupational therapy; SCC, International Standard of Care Committee; SMA, spinal muscular atrophy
Source: Treat-NMD(8); Mercuri 2017(30)

For both infantile onset and later onset patients, there is currently no effective disease-modifying therapy for SMA.(5) As described in Table 4, current medical care is supportive and is focused on respiratory and nutritional support. Chronic respiratory management includes providing methods for airway clearance, including mechanical insufflation / exsufflation or manual cough assist and non-invasive ventilator support

such as bi-level positive airway pressure (BiPAP). Acute respiratory infections are often life-threatening and require the same methods of increased airway clearance and increased ventilation support. Nonetheless, despite best supportive efforts, the progression of respiratory deficits, continuous progression of weakness, and consequent premature death are unavoidable.

Patients with infantile onset SMA cannot sit independently. Their care involves intensive and invasive therapies which may encompass ventilation for respiratory care, gastrostomy tube placement for nutritional support, and the use of assistive equipment.(6,32,33)

Studies have shown that the type and extent of supportive care provided can prolong survival of infantile onset patients, but often due to dependence upon gastrostomy tube and non-invasive ventilation or tracheotomy/ventilator support.(11,13,14,34–39) [redacted] The median age for death or permanent respiratory support for infantile onset SMA is approximately 9–13 months.(18) This composite endpoint takes into account that without dependence upon ventilation support the infant would have died. This endpoint may be more relevant to the situation in England, where permanent ventilation may not be provided to patients; [redacted]

Overall, despite highly invasive symptomatic care helping to prolong survival of infantile onset patients, it does not slow or prevent the decline of motor and respiratory function. In particular, tracheotomy and permanent ventilation are deemed controversial therapies.(8) Furthermore, laparoscopic anti-reflux Nissen fundoplication during gastrostomy tube placement is associated with high surgical and anaesthetic risks.(8) Therefore, the burden associated with ventilation and gastrostomy tube treatment is likely to outweigh the benefit of extending overall survival by only a few months.

The care of later onset SMA patients is based on ongoing evaluations and varies according to symptoms and the current functional status of the patient. Later onset SMA patients may have less need for intensive nutritional support and may have preserved pulmonary function until later into their disease course,(8) however they are highly likely to require surgery, bracing and physical therapy for scoliosis.(6)

Pain management and palliative care for patients with infantile onset or later onset SMA is provided based on clinical need.(40)

[redacted] Therefore, it is difficult to define a UK standard of care for SMA. Because the mechanism of disease is not being altered by the current standard of care, the neuronal loss will continue and symptoms will inevitably progress. Therefore, patients with SMA have an urgent unmet need as no therapy has been approved to date that can reverse, delay, or halt the progressive decline in motor function and disability associated with all types of SMA.

Of note, the recent update to the standard of care recommendations for SMA acknowledges that nusinersen has received recent approval both by the Food and Drug Administration (FDA) and the EMA and has become commercially available in many countries, with the caveat that at the time the consensus process was completed, nusinersen had not completed the regulatory process and was not commercially available.(31) Recommendations on the use of nusinersen are therefore limited in the updated guideline.

The update reinforces that a multidisciplinary treatment approach is the key element in the management of SMA patients.(30)

1.3.3 Proposed place of nusinersen within the clinical pathway

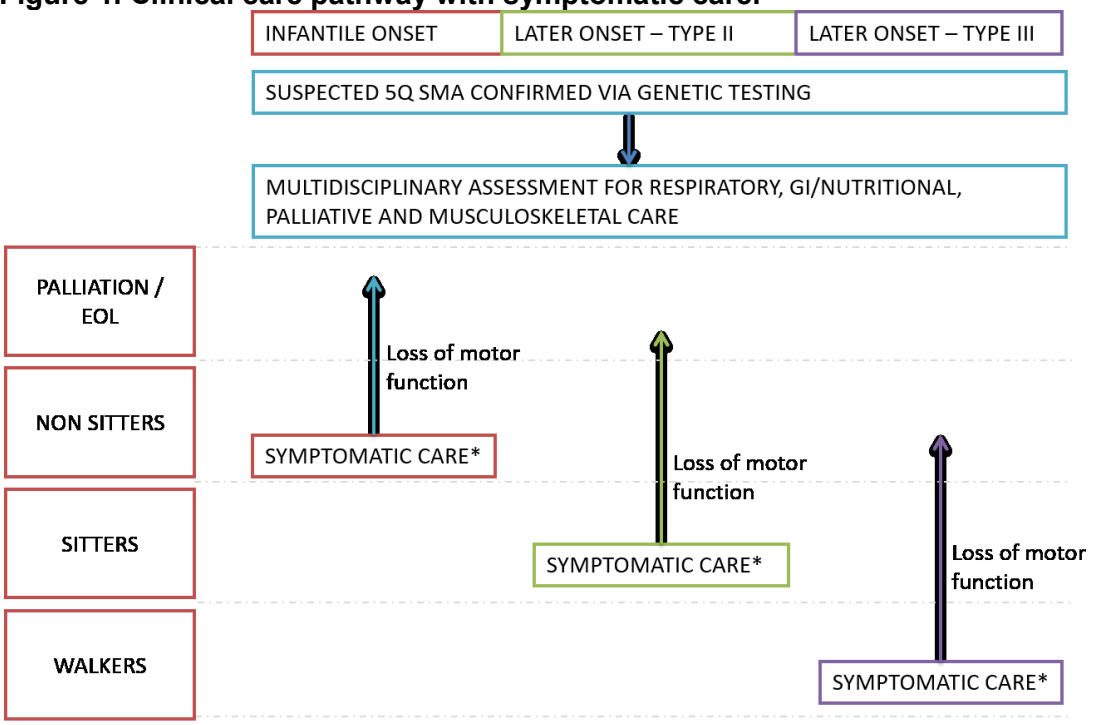
The anticipated place of nusinersen in therapy is as a first-line treatment for all SMA patients as soon as possible after diagnosis, in addition to existing symptomatic care. Nusinersen, an antisense oligonucleotide (ASO), is the first and only approved disease-modifying treatment for SMA since the disease was first described.(5)

Following the achievement of motor milestones and significant reduction in mortality in a pre-planned analysis, the phase III studies were stopped early and all patients in the sham-control arm were transitioned onto nusinersen in an extension study.(1) In light of these findings and the high unmet need in SMA, nusinersen received a positive benefit-risk assessment by the Committee for Medicinal Products for Human Use (CHMP) under accelerated assessment; it was subsequently approved by the EMA for the treatment of all patients with SMA.(1) Figure 1 shows the care pathway for patients with infantile onset and later onset SMA, who receive symptomatic treatment, while Figure 2 demonstrates the change in the care pathway with nusinersen as a first-line

treatment immediately after diagnosis. The anticipated short and long-term changes in patient outcomes with nusinersen are driven by the addition of a disease-modifying treatment to symptomatic care.

The suggested place in therapy and outcomes of the amended care pathway shown in Figure 2 is based on consultation with specialist clinicians at an expert panel meeting,(33) evidence from the pivotal phase III studies in patients with infantile onset SMA (ENDEAR) and later onset SMA (CHERISH), and an ongoing study in pre-symptomatic patients (NURTURE).The majority of children on nusinersen in these studies demonstrate motor milestones maintenance and achievement which are a deviation from the natural history. Some children derive substantial benefit from nusinersen, such as motor milestone development that is more consistent with normal development. Because SMA is a progressive degenerative disease, it should also be noted that stabilisation of a patient's current clinical state has been reported to represent a therapeutic progress that is substantially valued by patients and carers.(43,44)

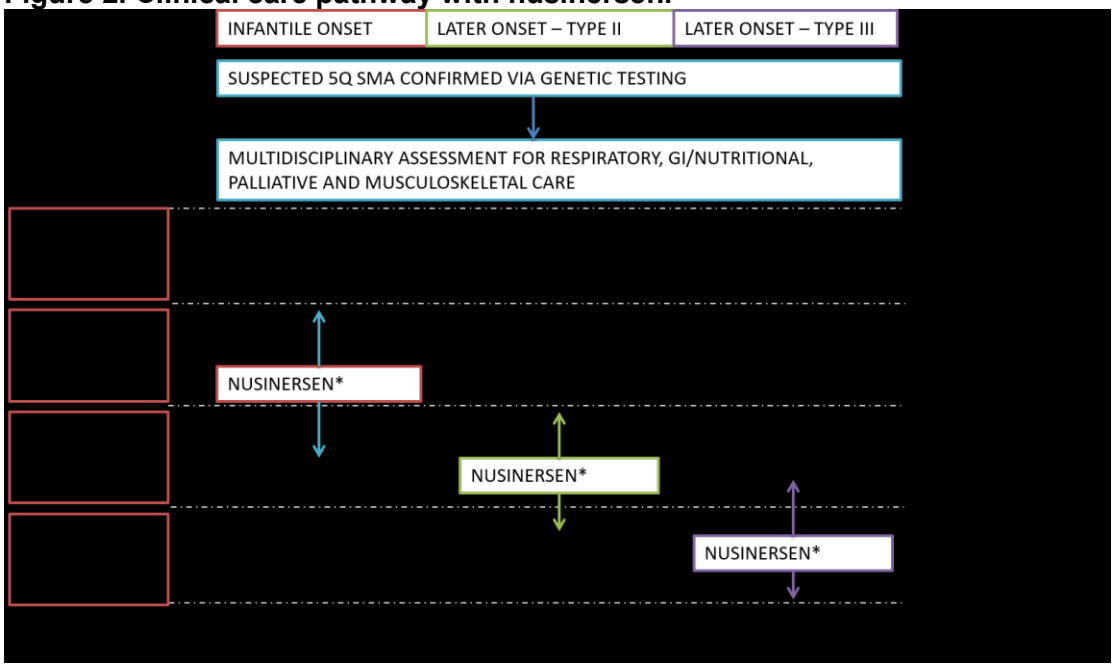
Figure 1. Clinical care pathway with symptomatic care.



**According to clinical need*

Abbreviations: EOL, end-of-life; SMA, spinal muscular atrophy

Figure 2. Clinical care pathway with nusinersen.



Abbreviations: EOL, end-of-life; SMA, spinal muscular atrophy

Subgroup analyses of outcomes by age at screening conducted in ENDEAR and CHERISH, and the clinical outcomes for the pre-symptomatic population from NURTURE,(45) indicate that earlier treatment with nusinersen prior to or following symptom onset leads greater clinically meaningful improvements in young children with varying degrees of disease severity.(1) Therefore nusinersen will be of the greatest benefit to patients the earlier it is initiated following symptom onset of SMA.

To meet the immediate treatment need nusinersen is available via an agreed Expanded Access Programme (EAP). Based on the evidence reviewed by the EMA, and due to the significant clinical importance of patients with genetically confirmed type I SMA, NHS England have issued an urgent clinical commissioning policy statement supporting the routine commissioning of nusinersen while the treatment is appraised through the single technology appraisal (STA) process.(42)

The EAP was set up by Biogen and is designed to provide access to nusinersen for eligible children with infantile onset SMA (type I). It is only available to children with SMA type I where both the child's medical team and the child's parents/guardians have agreed that it could be of potential benefit and that the child is eligible for the treatment. The EAP is a world-wide initiative, of which the UK is a participant, including 12 centres in England, 1 in Wales, 2 in Scotland, and 1 in Northern Ireland. [redacted] Under the terms of the EAP, Biogen funds the drug free to eligible children accepted on the EAP for the child's lifetime or until it is commissioned by the NHS.(42,46)

1.4 Equality considerations

The licensed indication for nusinersen includes all patients with SMA but the economic evaluation only includes infants and children due to the inclusion criteria of the available clinical evidence. Older patients will also have a range of disabilities and may be wheelchair-bound. Given the lack of other disease-modifying treatments and the assumption that all patients will benefit from treatment,(1) it is important that all age groups and patient disabilities are considered regarding access to treatment. Biogen accepts that the current collection of efficacy evidence is only measured in the paediatric population.

B.2 Clinical effectiveness

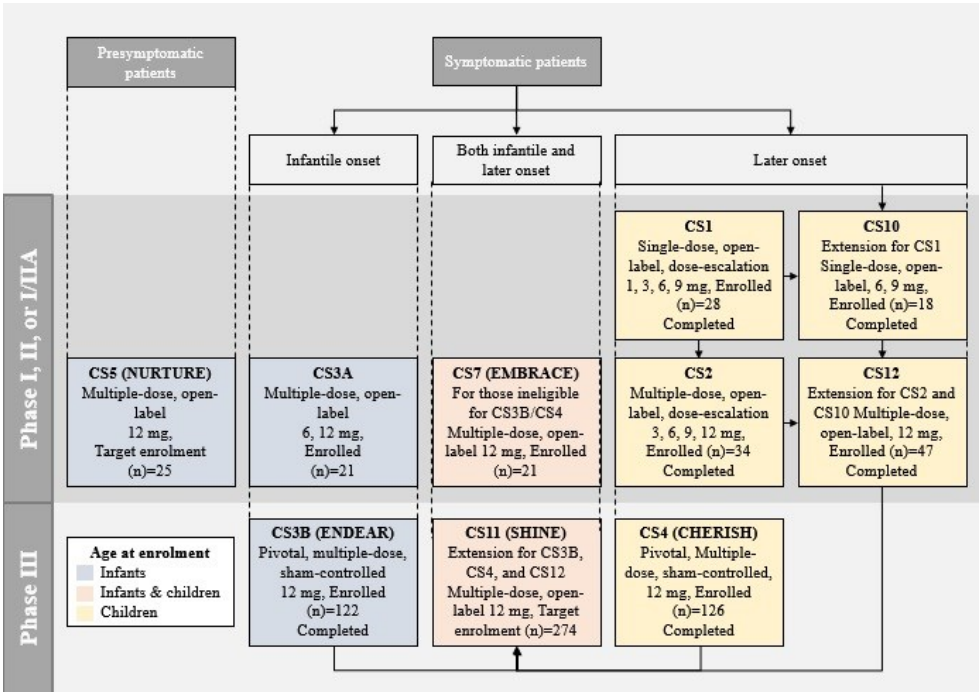
2.1 Identification and selection of relevant studies

A systematic literature review (SLR) to identify relevant studies reporting the clinical efficacy and safety of nusinersen was not conducted because no relevant studies have been conducted outside of Biogen's clinical development programme. More details are included as part of Appendix D.

2.2 List of relevant clinical effectiveness evidence

The nusinersen clinical development programme was designed to evaluate nusinersen across a range of SMA phenotypes to address the unmet medical need in patients with SMA. The extensive programme includes 3 completed and 7 ongoing clinical studies: 2 studies in symptomatic infantile onset SMA, 5 studies in symptomatic later onset (type II and type III) SMA, 1 study in patients with genetically diagnosed, pre-symptomatic SMA, and 2 studies in patients with symptomatic infantile- and later onset SMA, covering a large number of patients in the context of an orphan disease (Figure 3).

Figure 3. Overview of the nusinersen clinical development programme



Note: Spinal muscular atrophy type refers to enrolment ages.

Infantile onset = symptom onset prior to or equal to 6 months. Later onset = symptom onset after to or equal to 7 months. Pre-symptomatic patients are those genetically destined to develop SMA but don't currently have symptoms.

Source: Nusinersen EPAR (1)

A summary of the trials of relevance to the submission are shown in Table 5 (main evidence) and Table 6 (supportive evidence).

The 2-pivotal double-blind phase III RCTs of relevance to this submission (clinical efficacy and the economic model) are:

- Infantile onset patients (ENDEAR [CS3B]): A pivotal phase III, randomised, sham-controlled clinical trial to assess the efficacy and safety of nusinersen administered intrathecally in symptomatic, infantile onset infants (i.e. those who have or are most likely to develop SMA type I)

- Later onset patients (CHERISH [CS4]): A pivotal phase III, randomised, sham-controlled clinical trial to assess the efficacy and safety of nusinersen administered intrathecally in symptomatic, later onset patients (i.e. those who have or are most likely to develop SMA type II or III)

The control for the phase III studies was a sham procedure (administered as a small needle prick on the lower back at the location where the nusinersen intrathecal injection is normally made, on the same study days), as no disease-modifying therapies (other than nusinersen) are approved or routinely used in SMA.

The results of the interim analysis for each of the phase III studies (ENDEAR and CHERISH) were reviewed by an Independent Data and Safety Monitoring Board and a Joint Unblinded Senior Management Team from Ionis Pharmaceuticals and Biogen. As a result of meeting their pre-specified primary endpoints and demonstrating sustained and clinically meaningful benefits compared with the control group, both studies were terminated early. Patients were transitioned onto active treatment (nusinersen) in an ongoing extension study (SHINE).(47)

NURTURE (SM201/CS5; an ongoing, phase II, open-label study in pre-symptomatic infants likely to develop SMA type I or II) was not used to populate the economic model but is included in sections 2.2–2.6. The results of this study support the idea that early initiation with nusinersen is likely to achieve the greatest benefit: most of the pre-symptomatic patients in NURTURE treated with nusinersen are achieving motor milestones not regularly acquired by SMA patients and generally more consistent with normal development. This study was not included in the economic model because it was not possible to estimate how many patients would be SMA type I or SMA type II and therefore calculations on the economic impact would be speculative in nature.

Other trials with supportive evidence include a phase II clinical trial in infantile onset infants (CS3A)(74) and 4 phase I clinical trials in later onset patients (CS1, CS2, CS10, CS12) (83,84) (Table 6). The results of CS1, CS2, CS10 and CS12 support the safety findings for nusinersen; an integrated analysis of the safety of nusinersen across all 8 trials has been conducted, as reported in Section 2.10.1. In addition, long-term data from CS3A, CS2 and CS12 have been used in the economic model (Table 6). The

study design and efficacy results of these supportive studies are briefly summarised in Appendix L.

A further 2 on-going clinical trials (SHINE and EMBRACE) were not included in this submission as data are not available. SHINE (NCT02594124) is an ongoing extension study for patients who previously participated in ENDEAR, CHERISH, CS12 and CS3A.(47) EMBRACE is an ongoing phase II study to assess the safety and tolerability of nusinersen in participants with SMA who are not eligible to participate in the clinical studies ENDEAR or CHERISH,(48) and is therefore not considered relevant to the scope of this submission.

Table 5. Clinical effectiveness evidence: ENDEAR, CHERISH and NURTURE (main evidence)

Study	ENDEAR (CS3B) (NCT02193074)	CHERISH (CS4) (NCT02292537)	NURTURE (CS5/SM201) (NCT02386553)
Study design	Pivotal phase III, randomised, double blind, multicentre, sham-procedure controlled (completed)	Pivotal phase III, randomised, double-blind, multicentre, sham-controlled (completed)	Phase II, open-label, multiple-dose, multicentre, single-arm (on-going)
Population	Symptomatic infantile onset SMA (N=122)	Symptomatic later onset SMA (N=126)	Pre-symptomatic infants genetically diagnosed with SMA (likely to develop infantile or later onset) (target enrolment: N=25)
Intervention/comparator	Nusinersen (N=80) vs. sham-procedure control (N=41)	Nusinersen (N=84) vs Sham procedure control (N=42)	Nusinersen (N=20)
Supports marketing authorisation	Yes: main	Yes: main	Yes: supportive
Used in economic model	Yes	Yes	No
Rationale for use/non-use in the model	This trial supports the economic analysis because it is the pivotal phase III study in patients with symptomatic infantile onset SMA	This trial supports the economic analysis because it is the pivotal phase III study in patients with symptomatic later onset SMA	This study was not included in the economic model because it was not possible to estimate how many patients would be SMA type I or SMA type II and therefore calculations on the economic impact would be speculative in nature.
Reported outcomes specified in the decision problem [a, b] (**bold=outcomes incorporated in the economic model**)	• **Motor function (proportion of motor milestone responders assessed using the HINE-2 and CHOP-INTEND responders)** • **Event-free survival [b]; overall survival** • **Participants (%) not requiring permanent ventilation** • **Number of hours of ventilation support** • Number of serious respiratory events • CMAP [c]	• **Motor function (HFMSE score and WHO motor milestones;** RULM score) • **HRQL (PedsQL score;** CGI-I; ACEND score) • AEs	• Event-free survival [d]; overall survival • Proportion of patients developing clinically manifested SMA [e] • Motor function (HINE-2, WHO motor milestones; CHOP INTEND) • AEs

	• AEs *Subgroup analysis* • **Pre-specified subgroup analysis based on age at onset of SMA symptoms and disease duration (≤12 weeks and >12 weeks): Motor milestone response and overall survival**		
All other reported outcomes	• **Number and length of hospitalisations**	• Disease-related hospitalisations	• Change in baseline in growth parameters

Abbreviations: ACEND, Assessment of Caregiver Experience with Neuromuscular Disease; AE, adverse event; CGI-I, Global Impression of Change – Improvement; CHOP INTEND, Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders; CMAP, compound muscle action potential; HFMSE, Hammersmith Functional Motor Scale Expanded; HINE-2, Module 2 of the Hammersmith Infant Neurological Examination; HRQL, health-related quality of life; PedsQL, Paediatric Quality of Life Inventory; RULM, Revised Upper Limb Module; SMA, spinal muscular atrophy; WHO, World Health Organization

[a] The outcomes in the NICE scope are: motor function (including, where applicable, age appropriate motor milestones); respiratory function; complications of spinal muscular atrophy (including, for example, scoliosis and muscle contractures); need for invasive ventilation; mortality; adverse effects of treatment; HRQL

[b] Defined as time to death or permanent ventilation (tracheostomy or ≥16 hours ventilatory support per day for >21 days)

[c] CMAP is an electrophysiological technique that can be used to determine the approximate number of motor neurons in a muscle or group of muscles; it is a well validated method for tracking disease progression in neuromuscular disorders

[d] Defined as time to death or respiratory intervention (invasive or non-invasive ventilation for ≥6 hours per day continuously for ≥7 days or tracheostomy)

[e] Defined by: age-adjusted weight <5th percentile or decrease of ≥2 major weight growth curve percentiles (3rd, 5th, 10th, 25th, or 50th) or a percutaneous gastric tube placement for nutritional support; failure to achieve age-appropriate attainment of the 6 WHO motor milestones

Table 6. Clinical effectiveness evidence: CS3A, CS2, CS12, CS1, CS10 (supporting evidence)

Study	CS3A (NCT01839656)	CS2 (NCT01703988)	CS12 (NCT02052791)	CS1 (NCT01494701)	CS10 (NCT01780246)
Study design	Phase II, open-label, multiple dose, single-arm, multi-centre study	Phase I/IIa, open-label, multicentre, multiple-dose, dose-escalation study	Phase I, multicentre, open-label, multiple-dose extension study	Phase I, open-label, single-arm, ascending dose study	Phase I, open-label, extension to CS1
Population	Symptomatic infantile onset SMA	Symptomatic later onset SMA	Symptomatic later onset SMA: subjects from CS2 and CS10	Symptomatic later onset SMA	Symptomatic later onset SMA: patients who previously participated in CS1
Intervention/comparator	Nusinersen (N=21)	Nusinersen (N=34)	Nusinersen (N=47)	Nusinersen (N=28)	Nusinersen (N=18)
Supports marketing authorisation	Yes: supportive	Yes: supportive	Yes: supportive	Yes: supportive	Yes: supportive
Used in economic model	Yes	Yes	Yes	No	No
Rationale for use/non-use in the model	The uncontrolled nature of the study meant that ENDEAR was mainly used to represent the infantile onset population. However, beyond trial follow-up, the model used long-term CHOP INTEND scores from this study	The uncontrolled nature of these studies meant that CHERISH was mainly used to represent the later onset population. However, beyond trial follow-up, the model used long-term HFMSE data from the CS2 and CS12 in symptomatic patients with later onset SMA.		The uncontrolled nature of these studies meant that CHERISH was mainly used to represent the later onset population.	
Reported outcomes specified in the decision problem [a] **(bold=outcomes incorporated in the economic model)**	• Motor function (HINE-2 and **CHOP INTEND)** • Event-free survival; overall survival • CMAP [b] • AEs	• Motor function (**HFMSE**; Motor Unit Number Estimation (MUNE), ULM, 6MWT) • HRQL (PedsQL, ACEND) • CMAP [b] • AEs	• Motor function (**HFMSE**; MUNE, ULM, 6MWT) • HRQL (PedsQL, ACEND) • CMAP [b] • AEs	• Motor function (HFMSE; MUNE) • HRQL (PedsQL) • CMAP • AEs	• Motor function (HFMSE; MUNE) • HRQL (PedsQL) • CMAP • AEs

Abbreviations: 6MWT, 6 Minute Walk Test; ACEND, Assessment of Caregiver Experience with Neuromuscular Disease; AE, adverse event; CHOP INTEND, Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders; CMAP, compound muscle action potential; HFMSE, Hammersmith Functional Motor Scale Expanded; HINE-2, Module

2 of the Hammersmith Infant Neurological Examination; HRQL, health-related quality of life; MUNE, Motor Unit Number Estimation; PedsQL, Paediatric Quality of Life Inventory; SMA, spinal muscular atrophy; ULM, Upper Limb Module; WHO, World Health Organization

[a] The outcomes in the NICE scope are: motor function (including, where applicable, age appropriate motor milestones); respiratory function; complications of spinal muscular atrophy (including, for example, scoliosis and muscle contractures); need for invasive ventilation; mortality; adverse effects of treatment; HRQL

[b] CMAP is an electrophysiological technique that can be used to determine the approximate number of motor neurons in a muscle or group of muscles; it is a well validated method for tracking disease progression in neuromuscular disorders

2.3 Summary of methodology of the relevant clinical effectiveness evidence

2.3.1 Comparative summary of the methodology

A summary of the methodology for ENDEAR, CHERISH and NURTURE is shown in Table 7. The eligibility criteria for are shown in Table 8.

Table 7. Comparative summary of trial methodology for ENDEAR, CHERISH and NURTURE

Trial name	ENDEAR	CHERISH	NURTURE (supportive study)
Location	31 centres in Australia, Belgium, Canada, France, Germany, Italy, Japan, Korea, Spain, Sweden, Turkey, UK, US	24 centres in 10 countries: Canada, China, France, Germany, Italy, Japan, Korea, Spain, Sweden, US	Centres across 10 countries in Argentina, Australia, Germany, Israel, Italy, Qatar, Taiwan, Turkey, UK, US
Trial design	Phase III, randomised, double blind, multicentre, sham-procedure controlled (completed) Using an IXRS, eligible patients were randomised 2:1 to receive nusinersen or sham procedure control, respectively.	Phase III, randomised, double-blind, multicentre, sham-controlled (completed) Randomisation: 2:1 ratio using an IXRS.	Phase II, open-label, multiple-dose, multicentre, single-arm (on-going)
Patient population	Symptomatic infantile onset SMA	Symptomatic later onset SMA	Pre-symptomatic infants genetically diagnosed with SMA
Settings and locations where the data were collected	Secondary care	Secondary care	Secondary care
Trial drugs (the interventions for each group with sufficient details to allow replication, including	Nusinersen (N=80): administered as a single intrathecal lumbar puncture injection with a scaled 12 mg loading dose on study days 1, 15, 29, and 64, followed by maintenance dosing once every 4 months (on days 183 and 302).	Nusinersen (N=84): administered as a single intrathecal lumbar puncture injection. A single dose level of nusinersen 12 mg was delivered as 4 doses administered over 9 months using a loading regimen (days 1, 29, 85),	Nusinersen (N=20): administered as a 12-mg scaled equivalent dose of intrathecal nusinersen. The dosing schedule is: loading doses on day 1, 15, 29, 64; Maintenance dose on day 183, 302, 421, 540, 659 and 778

Trial name	ENDEAR	CHERISH	NURTURE (supportive study)
how and when they were administered) Intervention(s) (N=[x]) and comparator(s) (N=[x])	Sham-control (N=41): administered as small needle prick to the skin over the lumbar spine on the same study days	followed by a maintenance dose given 6 months later (day 274) Sham-control (N=42): administered as a small needle prick on the lower back at the location where the intrathecal injection is normally made, on the same study days	
Permitted and disallowed concomitant medication	Permitted concomitant medications included any prescribed treatments deemed necessary for AEs or to provide adequate supportive care. Study patients were prohibited from receiving other experimental agents during the study. This included marketed agents at experimental doses that were being tested for the treatment of SMA (e.g., valproate, riluzole, creatine, sodium phenylbutyrate, hydroxyurea, and salbutamol)	Permitted concomitant medications included any prescribed treatments deemed necessary for AEs or to provide adequate supportive care. Study patients were prohibited from receiving other experimental agents during the study. This included marketed agents at experimental doses that were being tested for the treatment of SMA (e.g., oral albuterol/salbutamol, riluzole, carnitine, creatine, sodium phenylbutyrate, valproate, and hydroxyurea).	Permitted concomitant medications included any prescribed treatments deemed necessary for AEs or to provide adequate supportive care Study participants were prohibited from receiving other experimental agents during the study. This included marketed agents at experimental doses that were being tested for the treatment of SMA (e.g., e.g., valproate, riluzole, carnitine, sodium phenylbutyrate, hydroxyurea, and salbutamol)
Primary outcomes (including scoring methods and timings of assessments) (**bold=outcomes incorporated in the economic model**)	• **Proportion of motor milestone responders assessed using the HINE-2: assessed at screening, and prior to dosing on days 64, 183, 302 and 394** • **Event-free survival, i.e., time to death or permanent ventilation (tracheostomy or ≥16 hours ventilatory support per day for >21 days)**	• **Change from baseline in HFMSE score at 15 months: assessed at screening and on days 92 (3 months), 169 (6 months), 274 (9 months), 365 (12 months) and 456 (15 months)**	Event-free survival as time to death or respiratory intervention (defined as invasive or non-invasive ventilation for ≥6 hours per day continuously for ≥7 days or tracheostomy)
Other outcomes used in the economic model/specified in the scope (**bold=outcomes incorporated in the economic model**)	*Secondary* • **CHOP INTEND responders (≥4-point improvement from baseline at the later of day 183, 302, or 394)** • **Survival rate** • **Participants (%) not requiring permanent ventilation**	*Secondary* • **Proportion of children achieving a ≥3-point increase from baseline in HFMSE score at 15 months**	*Secondary* • Proportion of patients developing clinically manifested SMA as defined by: ○ Age-adjusted weight <5th percentile or decrease of ≥2 major weight growth curve

Trial name	ENDEAR	CHERISH	NURTURE (supportive study)
	• Proportion of CMAP responders (peroneal CMAP amplitude increasing to or maintained at ≥1 mV vs. baseline at the later of day 183, 302, or 394 assessments) • Time to death or permanent ventilation in the 2 subgroups of participants above and below the study median disease duration *Key tertiary* • **Number of hours of ventilation support** • **Number and length of hospitalisations** • Number of serious respiratory events	• **Proportion of children achieving any new WHO motor milestone at 15 months** • **Number of WHO motor milestones achieved per child at 15 months** • **Proportion of children achieving standing alone at 15 months** • **Proportion of children achieving walking with assistance at 15 months** • Change from baseline in RULM score at 15 months *Key tertiary* • **Change from baseline in PedsQL score** • CGI-I (investigator and caregiver assessment) • Change from baseline in ACEND score • Disease-related hospitalisations	percentiles (3rd, 5th, 10th, 25th, or 50th) or a percutaneous gastric tube placement for nutritional support ○ Failure to achieve age-appropriate attainment of the 6 WHO motor milestones • Overall survival i.e. proportion of patients alive • Percentage of participants who attained motor milestones assessed as part of HINE-2 • Attainment of motor milestones as assessed by WHO criteria • Change from baseline in the CHOP INTEND motor function scale • Change in baseline in growth parameters
Pre-planned subgroups (**bold=outcomes incorporated in the economic model**)	• **Pre-specified subgroup analysis based on age at onset of SMA symptoms and disease duration (≤12 weeks and >12 weeks): Motor milestone response and overall survival**	• Pre-specified subgroup analysis based on disease duration (<25 months; ≥25 months <44 months and ≥44 months): HFMSE scores	–

Abbreviations: ACEND, Assessment of Caregiver Experience with Neuromuscular Disease; AE, adverse event; CGI-I, Global Impression of Change – Improvement; CHOP INTEND, Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders; CMAP, compound muscle action potential; HFMSE, Hammersmith Functional Motor Scale Expanded; HINE-2, Module 2 of the Hammersmith Infant Neurological Examination; IXRS, Interactive Voice/Web-Response System; PedsQL, Paediatric Quality of Life Inventory; RULM, Revised Upper Limb Module; UK, United Kingdom; US, United States; WHO, World Health Organization
Source: ENDEAR: Finkel 2017a(49); Clinicaltrials.gov NCT02193074(50); EPAR(1); CHERISH: Mercuri 2018;(51) CHERISH CSR(52); NURTURE: Bertini 2016(53); DeVivo 2017(54); Clinicaltrials.gov NCT02386553(55); NURTURE CSR(56)

Table 8. Eligibility criteria

Study	Inclusion criteria	Exclusion criteria
ENDEAR	• Signed informed consent of parent(s) or guardian(s); • A genetic diagnosis of 5q-linked SMA due to homozygous gene deletion or compound heterozygote deletion/mutation of *SMN1* • Two copies of the *SMN2* gene; younger than 6 months of age (180 days) at SMA symptom onset • Younger than 7 months of age (210 days) at screening; • Receiving adequate nutrition and hydration (with or without gastrostomy) in the opinion of the site investigator at the time of study entry • Measuring to at least the third percentile in body weight using country-specific guidelines • Adherence to the consensus statement for standard of care in SMA for medical care guidelines • Gestational age of 37–42 weeks • Live within a 9-hour ground travel time from a study centre • Ability to complete all study procedures and parent/guardian has adequate psychosocial support.	• Peripheral oxygen desaturation (oxygen saturation below 96% without ventilation support) during screening • SMA symptoms within the first week of birth • Presence of an active infection requiring systemic antiviral or antibacterial treatment during screening • History of brain or spinal cord disease that would interfere with lumbar puncture, CSF circulation, or safety assessments • Presence of an implanted CSF drainage shunt or central nervous system catheter; abnormalities in haematology or clinical chemistry parameters at screening that would prevent inclusion as assessed by the site investigator • Treatment of SMA with an investigational drug, biological agent, or device within 30 days of screening • History of gene therapy, prior ASO therapy, or cell transplantation • The parent/guardian is unable to understand a basic description of the study or does not agree to comply with the schedule of assessments as defined by the protocol • The infant's caregiver does not adhere to the standard-of-care guidelines • Presence of a medical condition that would interfere with the infant's ability to participate in the study as assessed by the site investigator.

Study	Inclusion criteria	Exclusion criteria
CHERISH	• Signed informed consent of parent(s) or guardian(s) and signed informed assent of child (if indicated per child's age and institutional guidelines) • Genetic documentation of 5q-linked SMA due to homozygous gene deletion, mutation, or compound heterozygote of *SMN1*; • Onset of clinical signs and symptoms consistent with SMA at more than 6 months of age • Age 2 to 12 years inclusive • Able to sit independently but never had the ability to walk independently • HFMSE score of 10 or higher and 54 or lower at screening • Able to complete all study procedures, measurements, and visits and parent or guardian/child had adequately supportive psychosocial circumstances; estimated life expectancy more than 2 years from screening; met age-appropriate institutional criteria for use of anaesthesia/sedation if use was planned for study procedures • For those individuals who may have reached reproductive maturity, females must have had a negative pregnancy test at screening and agree to employ adequate contraceptive measures for the duration of the study, and males were to be abstinent for the duration of the study.	• Respiratory insufficiency at screening (defined by the medical necessity for invasive or non-invasive ventilation for >6 hours during a 24-hour period) • Medical necessity for a gastric feeding tube, where most feeds are given by this route; severe contractures (any contracture that, according to the investigator, could interfere with HFMSE) or severe scoliosis (Cobb Angle >40 degrees) evident on X-ray examination at screening • Hospitalisation for surgery (i.e., scoliosis surgery, other surgery), pulmonary event, or nutritional support within 2 months of screening or planned during the duration of the study • Presence of an untreated or inadequately treated active infection requiring systemic antiviral or antimicrobial therapy at any time during the screening period; history of brain or spinal cord disease, including tumours, or abnormalities by MRI or CT that would interfere with the lumbar puncture procedures or CSF circulation • Presence of an implanted shunt for the drainage of CSF or an implanted CNS catheter • History of bacterial meningitis • Dosing with nusinersen in any previous clinical study; prior injury (e.g., upper or lower limb fracture) or surgical procedure that would impact the child's ability to perform any of the outcome measure testing required in the protocol and from which the child has not fully recovered or achieved a stable baseline • Clinically significant abnormalities in haematology or clinical chemistry parameters or electrocardiogram at screening; treatment with another investigational drug (e.g., oral albuterol/salbutamol, riluzole, carnitine, creatine, sodium phenylbutyrate), biological agent, or device within 1 month of screening or 5 half-lives of study agent, whichever is longer • Treatment with valproate or hydroxyurea within 3 months of screening • Any history of gene therapy, ASO, or cell transplantation • Any ongoing medical condition that would interfere with the conduct and assessments of the study (e.g., medical disability such as wasting or cachexia, and severe anaemia).

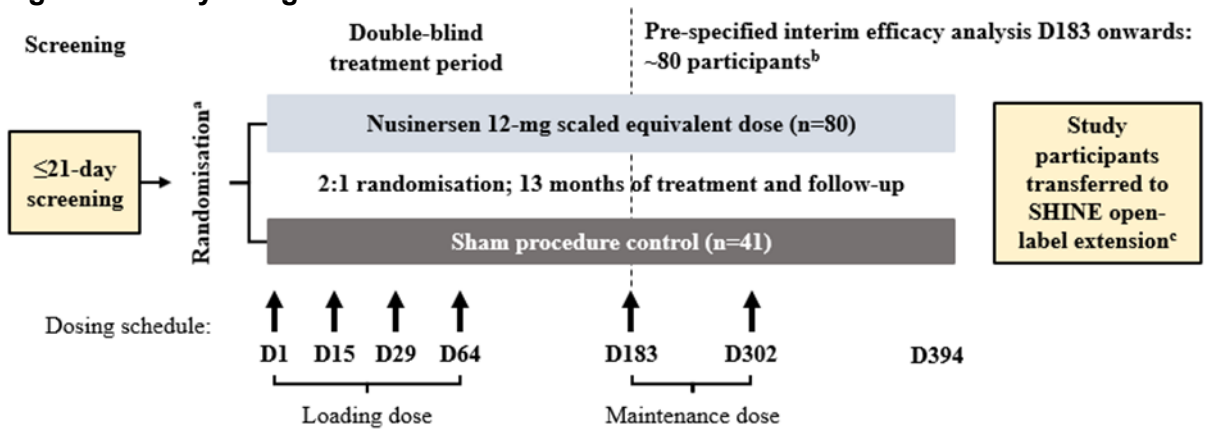
Study	Inclusion criteria	Exclusion criteria
NURTURE	• Age ≤ 6 weeks at first dose • Genetic documentation of 5q SMA homozygous gene deletion or mutation or compound heterozygous mutation • Genetic documentation of 2 or 3 copies of *SMN2* • CMAP ≥1 mV at baseline • Gestational age of 37–42 weeks for singleton births; gestational age of 34–42 weeks for twins • Able to complete all study procedures, measurements and visits, and parent(s) or guardian(s)/subject has adequately supportive psychosocial circumstances in the opinion of the investigator	• Hypoxaemia (oxygen saturation <96% awake or asleep without any supplemental oxygen or respiratory support) • Any clinical signs or symptoms at screening or immediately prior to the first dosing (day 1) that are, in the opinion of the Investigator, strongly suggestive of SMA • Clinically significant abnormalities in haematology or clinical chemistry parameters • Treatment with an investigational drug given for the treatment of SMA biological agent, or device. Any history of gene therapy, prior ASO treatment, or cell transplantation • Presence of an untreated or inadequately treated active infection requiring systemic antiviral or antimicrobial therapy at any times during the screening period • History of brain or spinal cord disease that would have interfered with the lumbar puncture procedures, CSF circulation or safety assessments • Presence of an implanted shunt for the drainage of CSF or an implanted central nervous system catheter • History of bacterial meningitis or viral encephalitis • Diagnosis of neonatal respiratory distress syndrome requiring surfactant replacement therapy or invasive ventilator support • The subject's parent(s) or legal guardian(s) was unable to understand the nature, scope and possible consequences of the study or was unable to or did not agree to comply with the study requirements • Ongoing medical condition that, according to the investigator, would have interfered with the conduct and assessments of the study; an example is a medical disability that would have interfered with the assessment of safety or would have compromised the ability of the subject to undergo study procedures.

Abbreviations: ASO, antisense oligonucleotide; CSF, cerebrospinal fluid; CMAP, compound muscle action potential CNS, central nervous system; CT, computed tomography; HFMSE, Hammersmith Functional Motor Scale-Expanded; MRI, magnetic resonance imaging; SMA, spinal muscular atrophy; SMN, survival of motor neuron
Source: ENDEAR: Finkel 2017(49) CHERISH: CHERISH: Mercuri 2018(51); NURTURE: Clinicaltrials.gov NCT02386553(55); NURTURE CSR(56)

2.3.2 ENDEAR: Study design and methodology

ENDEAR is the pivotal, phase III, randomised, double-blind, sham-procedure controlled study to assess the clinical efficacy and safety of nusinersen in patients with infantile onset SMA.(49) ENDEAR included a total of 121 symptomatic infants ≤7 months of age, diagnosed with infantile onset SMA (symptom onset before 6 months of age). After a screening period of up to 21 days, eligible infants were randomly assigned in a 2:1 ratio to receive either a scaled-equivalent-12 mg dose of nusinersen or a sham procedure control (Figure 4).

Figure 4. Study design for ENDEAR



Abbreviation: D, day
[a] Randomisation was stratified by disease duration during screening (age at screening minus age at symptom onset): ≤12 vs. >12 weeks
[b] Interim efficacy analysis was conducted on 15 June 2016, once ~80 participants had the opportunity to be assessed at the day 183 visit
[c] All infants completing the end of study visit for ENDEAR had the opportunity to enrol in SHINE (ClinicalTrials.gov, NCT02193074)
Source: Finkel 2017b(57)

Nusinersen was administered as a single intrathecal lumbar puncture injection on study days 1, 15, 29, and 64, followed by maintenance dosing once every 4 months (on days 183 and 302).(49) The nusinersen dose was adjusted according to the estimated volume of CSF for the infant's age on the day of dosing, such that the infant received a dose that was equivalent to a 12 mg dose in a person 2 years of age or older; thus, younger infants were injected with smaller volumes that contained lower doses of the drug.(49)

The sham procedure consisted of a small needle prick to the skin over the lumbar spine, which was covered with a bandage to simulate the appearance of a lumbar-puncture injection.(49) The child was kept in the treatment room for a pre-determined amount of time to mimic the time it took to perform the full procedure.(49) The administration schedule was the same as for the nusinersen treatment arm.(49)

To maintain blinding, nusinersen was administered or the sham procedure was performed by dedicated trial personnel who were aware of the group assignments, whereas the infant's parents and key trial personnel who were responsible for assessments were unaware of the group assignments and were not present for the procedure.(49)

A pre-specified interim analysis was performed by the sponsor and the data and safety monitoring board when approximately 80 infants had been enrolled for at least 6 months (conducted on 15th June 2016).(49) The analysis showed a benefit–risk assessment in favour of nusinersen. This result prompted early termination of the trial. At that time, infants were invited to complete an end-of-trial visit at least 2 weeks after they had received their most recent dose of nusinersen or undergone their most recent sham procedure. The assessments that were scheduled to be performed on day 394 were performed at the end-of-trial visit. Infants who completed the ENDEAR trial were invited to enrol in the open-label extension study SHINE (ClinicalTrials.gov number, NCT02594124). The final analysis was conducted with the use of data collected up to the date of the last patient's last visit (data-cut: November 21, 2016).(49)

2.3.3 ENDEAR: Study endpoints

The trial had 2 primary efficacy endpoints. The first was a motor milestone response, which was defined according to Module 2 of the Hammersmith Infant Neurological Examination (HINE-2). The second primary efficacy endpoint was event-free survival, which was defined as the time to death or the use of permanent assisted ventilation (tracheostomy or ventilatory support for ≥16 hours per day for >21 continuous days in the absence of an acute reversible event).(49)

In accordance with the statistical analysis plan, only the first primary efficacy endpoint (motor milestone response) was statistically assessed in the interim analysis.(49) The second primary efficacy endpoint and all secondary efficacy endpoints were assessed in the final analysis.

The study endpoints are shown in Table 7, with more details provided below.

2.3.3.1 ENDEAR: Motor milestone assessment

As described in Section 1.3.1, even when current standards of care are applied, developmental milestones such as sitting unaided, rolling, crawling, standing or walking are rarely, even partially, achieved as part of the natural history of infantile onset SMA.(58) This is especially true after the onset of the disease as the natural history is for the continual decline of any (partial) motor milestones achieved.(34,58,59)

The HINE is a 3-section, 37-item, quantifiable assessment of overall neurologic function in infants.(60) Module 2 of the HINE (HINE-2) assesses the development of motor function through the achievement of motor milestones; scores on the HINE-2 range from 0–26, with higher scores indicating better motor function.(49) The HINE-2 is a clinically relevant measure of motor function in infants with SMA and was used to assess the achievement of motor milestones in previous studies of infants with SMA.(48) It involves evaluation in 8 motor-milestone categories: voluntary grasp, kicking, head control, rolling, sitting, crawling, standing, and walking (Figure 5).

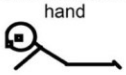
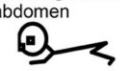
The HINE-2 also allows one to quantify intermediate steps leading to the full achievement of the milestone. Each item provides the opportunity to score the level of development on a 5-

point scale with 0 as absence of the activity. It is important to be able to evaluate these smaller, more easily achieved “sub milestones” because each milestone represents a massive achievement requiring the interaction and coordination of many muscle and motor pathways,(63,64) and therefore the HINE-2 allows for an increased ability to detect change.(58)

A modified version of the HINE-2 that excluded voluntary grasp was used to assess motor milestone responders in the current study.(49) Voluntary grasp, a category in which none of the incremental changes requires movement against gravity, is more developmentally based and was excluded from the analysis as some infants with SMA can acquire all milestones in this category. Additionally, a 2-point increase in the category of ability to kick was used to denote improvement in this category because the lower extremities do not lift off the exam table while kicking horizontally (1 point), and therefore this is not a movement against gravity that signifies a clear increase in strength.

The achievement of motor milestones was assessed as part of the neurological examination conducted by the neurologist at the study centre using the motor milestones portion i.e. HINE-2. HINE-2 motor milestone assessments were performed at screening, and prior to dosing on days 64, 183, 302 and 394.(49) The infants were considered to have a motor milestone response if they met the following 2 criteria: improvement in at least 1 category (i.e., an increase in the score for head control, rolling, sitting, crawling, standing, or walking of ≥1 point, an increase in the score for kicking of ≥2 points, or achievement of the maximal score for kicking) and more categories with improvement than categories with worsening (i.e., a decrease in the score for head control, rolling, sitting, crawling, standing, or walking of ≥1 point or a decrease in the score for kicking of ≥2 points).(49) Infants who died or were withdrawn from the trial were considered to have had no response, regardless of whether they attended the visit on day 183.(49) This method of imputation under-reports the efficacy of nusinersen, but was used to increase the strength and validity of the data.

Figure 5. The HINE-2 used in ENDEAR

Head control	Unable to maintain head upright normal up to 3m	Wobbles normal up to 4m	Maintained upright all the time normal from 5m		
Sitting	Cannot sit	With support at hips  normal at 4m	Props  normal at 6m	Stable sit  normal at 7-8m	Pivots (rotates)  normal at 9m
Voluntary grasp – note side	No grasp	Uses whole hand	Index finger and thumb but immature grasp	Pincer grasp	
Ability to kick in supine	No kicking	Kicks horizontally but legs do not lift	Upward (vertically)  normal at 3m	Touches leg  normal at 4-5m	Touches toes  normal at 5-6m
Rolling	No rolling	Rolling to side (normal at 4m)	Prone to supine (normal at 6 m)	Supine to prone (normal at 6 m)	
Crawling or bottom shuffling	Does not lift head	On elbow  (normal at 3 m)	On outstretched hand  (normal at 4m)	Crawling flat on abdomen  (normal at 8m)	Crawling on hands and knees  (normal at 10m)
Standing	Does not support weight	Supports weight (normal at 4m)	Stands with support (normal at 7m)	Stands unaided (normal at 12m)	
Walking		Bouncing (normal at 6m)	Cruising (walks holding on) (normal at 12m)	Walking independently (normal by 15m)	

Abbreviation: HINE-2, Module 2 of the Hammersmith Infant Neurological Examination
A modified version of the HINE-2 that excluded voluntary grasp was used to assess motor milestone responders
Source: De Sanctis 2016(58)

[redacted]

2.3.3.2 ENDEAR: Event-free survival

Event-free survival was defined as the time to death or the use of permanent assisted ventilation (tracheostomy or ventilatory support for ≥16 hours per day for >21 continuous days in the absence of an acute reversible event).(49) The use of permanent assisted ventilation as of days 91, 182, 273, 364, and 394 was determined on the basis of patient data from parental diaries and hospital records obtained at those visits.(49) All events of permanent assisted ventilation were adjudicated by an independent end-point adjudication committee whose members were unaware of the group assignments.(49)

Event-free survival provides information on the morbidity associated with SMA and accounts for the effects of supportive care on survival.(49) Chronic ventilatory support is internationally

defined in SMA as non-invasive or invasive ventilation for more than 16 hours per day for more of than 14 days in the absence of an acute reversible illness or postoperatively.(65)

2.3.3.3 ENDEAR: CHOP INTEND

The Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders (CHOP INTEND) is a validated 16-item 64-point motor assessment designed specifically to evaluate the motor skills of infants with SMA with higher score indicating greater motor skill.(49,66,67) A CHOP INTEND response was defined as an increase of at least 4 points from baseline in the CHOP INTEND score at the end-of-trial visit (day 183, 302, or 394).(49) An increase of ≥4 points in CHOP INTEND score from baseline was chosen as the definition of a responder for this endpoint because an increase of ≥4 points is generally considered to be outside the range of test variability.(49)

Figure 6. CHOP INTEND overview

Item	Graded response range (0-4)
1 Spontaneous upper extremity movement	No movement of limbs (0) - Moving elbow off surface in supine position (4)
2 Spontaneous lower extremity movement	No movement of limbs (0) - Moving feet/knees off surface in supine position (4)
3 Hand grip	No attempt to maintain grasp (0) - Maintains hand grip with shoulder off bed (4)
4 Head movement	Head falls to the side, no attempts to regain midline (0) - Rotates from maximum rotation to midline (4)
5 Hip abductors	No attempt to maintain kness off surface (0) - Keeps knee off surface of bed >5 seconds or lifts foot off surface (4)
6 Rolling from legs	Pelvis lifted passively off support surface (0) - When traction is applied at the end of manoeuvre, rolls to prone with lateral head righting (4)
7 Rolling from arms	Head turns to the side; body remains limp or shoulder lifts passively (0) - Rolls to prone with lateral head righting (4)
8 Shoulder and elbow flexion and horizontal abduction	No attempt (0) - Clears hand from surface with antigravity arm movement (4)
9 Shoulder and elbow flexion	No attempt to lift arm (0) - Abducts or flexes shoulder to 60º (3), makes contact with toy (4)
10 Knee extension	No visible knee extension (0) - Extends knee to >45º (4)
11 Hip flexion and foot dorsiflexion	No active hip, knee, or ankle motion (0) - Hip flexion or knee flexion >30º (4)
12 Head control	No response; head hangs (0) - Attains head upright from flexion and turns head side to side (4)
13 Elbow flexion score with item 14	No visible contraction (0) - Flexes elbow (4)
14 Neck flexion score with item 13	No muscle contraction (0) - Lifts head off bed (4)
15 Head/neck extension, Landau reflex	No head extention (0) - Extends head to horizontal plane or above (4)
16 Spinal incurvation, Galant reflex	No response (0) - Twists pelvis towards stimulus off axis (4)

Abbreviation: CHOP INTEND, Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders

[redacted]

2.3.3.4 ENDEAR: CMAP responders

CMAP is an electrophysiological technique that can be used to determine the approximate number of motor neurons in a muscle or group of muscles as a complementary, objective

endpoint to support functional outcome measures. CMAP is a validated method for tracking disease progression in neuromuscular disorders such as SMA and has been proposed as a potential biomarker of a therapeutic effect in SMA.(1,68–70)

One effect of decreased SMN is early abnormalities in synaptic input to muscle fibres from motor neurons within the spinal cord. Motor units, defined as a motor neuron and all associated muscle fibres that it innervates, are the basic functional units of skeletal muscle.(71) CMAP measures the output of the motor units supplying a particular muscle or group of muscles and CMAP size is determined by the size and number of depolarized muscle fibres following supramaximal nerve stimulation.(72) CMAP amplitudes in SMA patients correlate with clinical severity, age, and function, and patients with milder disease often have normal CMAPs. On the other hand, in patients with infantile onset SMA, CMAP amplitude is abnormally low and does not improve after symptom onset. Correlation of CMAP size and function in patients with SMA highlights the potential to use CMAP as a biomarker for prognosis. CMAP measures may provide sensitive indicators of the health of motor neurons which are complementary to functional outcome measures because some subjects with CMAP declining values are often quite stable in terms of overall functional status.(69)

CMAP response was defined as an increase in the peroneal CMAP amplitude to at least 1 mV (or maintenance of an amplitude of ≥1 mV) at the end-of-trial visit (day 183, 302, or 394).(49) CMAP measurements of ulnar nerve function in the abductor digiti minimus muscle and peroneal nerve function in the anterior tibialis muscle were performed or supervised by a clinical electromyographer at the study centre.(1)

[redacted]

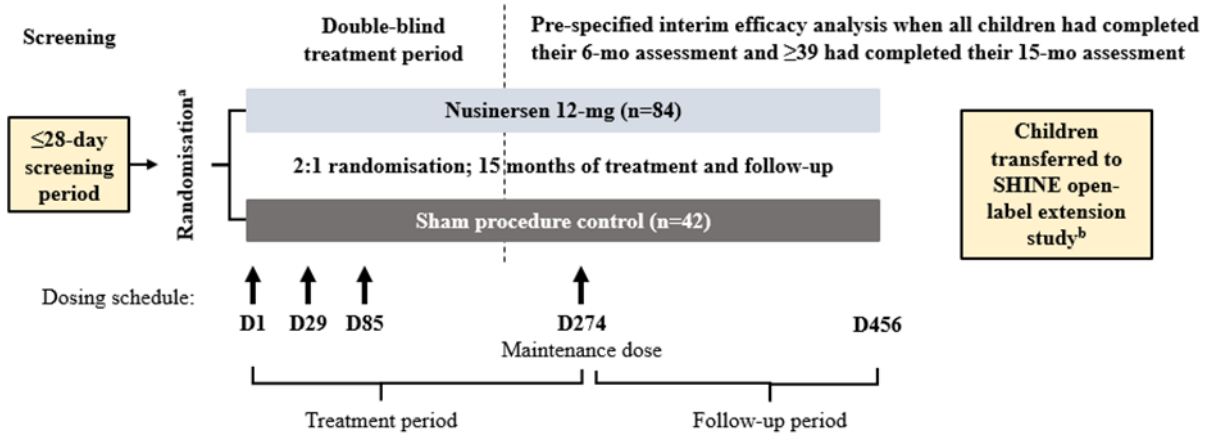
Of note, in the trial, CMAP was performed by highly specialised technicians under clinical trial conditions, however in the real world there are not enough of these specialised technicians to allow for this to be a routine biomarker.

2.3.4 CHERISH: Study design

CHERISH is a pivotal, phase III, randomised, double-blind, sham-procedure controlled study to assess the clinical efficacy and safety of nusinersen.(51) A total of 126 patients with later onset (those who have or who are most likely to develop types II and III) SMA were randomised and dosed to assess the clinical efficacy, safety, tolerability, and pharmacokinetics of nusinersen.(51)

Eligible patients were randomised in a 2:1 ratio to either a 12 mg dose of nusinersen or a sham-procedure control (Figure 7). Randomisation was stratified based on the patient's age at screening (<6 years vs. ≥6 years) and conducted as described for ENDEAR (see Section 2.3.2).

Figure 7. Study design for CHERISH



Abbreviation: D, day
[a] Randomisation was stratified based on age at screening (<6 vs. ≥6 years)
[b] All infants completing the end of study visit for CHERISH had the opportunity to enrol in SHINE (ClinicalTrials.gov, NCT02193074)
Source: Mercuri 2017(73)

Nusinersen was administered intrathecally as a single lumbar puncture injection using a loading dose on study days 1, 29 and 85, followed by maintenance dosing 6 months thereafter (on day 274) (Figure 7).(51) Depending on institutional guidelines, anaesthesia or sedation could be used for the lumbar puncture procedure. The sham-control procedure was also administered on days 1, 29, 85, and 274 using the same procedure as described for ENDEAR (Section 2.3.2).

Blinding was conducted as per the approach described for ENDEAR (Section 2.3.2) with the additional consideration that in CHERISH if anaesthesia or sedation was used for the nusinersen administration in that institution, minimal sedation was also used for the sham procedure.

An interim analysis was conducted at the data cut-off date of August 31, 2016, when 126 patients had received treatment. CHERISH was stopped shortly after at the recommendation of the data and safety monitoring board, following positive statistical analysis of the primary endpoint at the interim analysis.(2,51) The final analysis had a cut-off date of 3rd March 2017.

2.3.5 CHERISH: Study endpoints

The CHERISH study endpoints are shown in Table 7, with more details provided below. The primary endpoint was change from baseline in Hammersmith Functional Motor Scale – Expanded (HFMSE) score at 15 months.

2.3.5.1 CHERISH: HFMSE score

The HFMSE is a tool used to assess motor function in children and has been validated for use in SMA.(74) The scale has 20 scored activities for use in children with later onset SMA (types II and III) and limited ambulation, as well as an additional module of 13 items to allow evaluation of ambulatory patients (Figure 8).(75,76) Each motor skill item is scored on a 3-point Likert scale from 0 (no response) to 2 (full response), with a total score range of 0 to 66.

The scale provides objective information on motor ability and clinical progression, and is therefore a clinically relevant measure of treatment efficacy in later onset SMA patients. A phase 1 study of nusinersen reaffirmed that the HFMSE is sensitive to change,(77) with a 3-point change in score considered clinically meaningful and demonstrated that a child could improve on at least 2 HFMSE motor skills.(78,79)

Figure 8. The HFSME tool

	Motor function	Items	Score range
	Sitting	1-4	Item scores: 0 = no response to 2= full response
	Rolling	5-9	
	Transitions/crawling	10-17	
	Standing/stepping	18-20	
	Transitions/kneeling	21-27	
	Squat/jump	28-29	
	Stairs	30-33	
	Total	**33**	**Total score: 0-66** **Higher score indicates better function**

Abbreviation: HFSME, Hammersmith Functional Motor Scale-Expanded
Source: Schneider 2017(76)

It should be noted that each activity included in the HFMSE has been related to activities of daily living, and therefore the HFMSE is also clinically meaningful to patients and their caregivers.(43,80) (Table 9) For example, to name but a few, sitting meant being able to sit on a normal chair, in the car and on the toilet, rolling meant the caregiver would not have to wake up to turn their child; other activities included being able to play, read a book, dress, wash and eat.(80)

Table 9. HMFSE activities and their relationship to activities of daily living

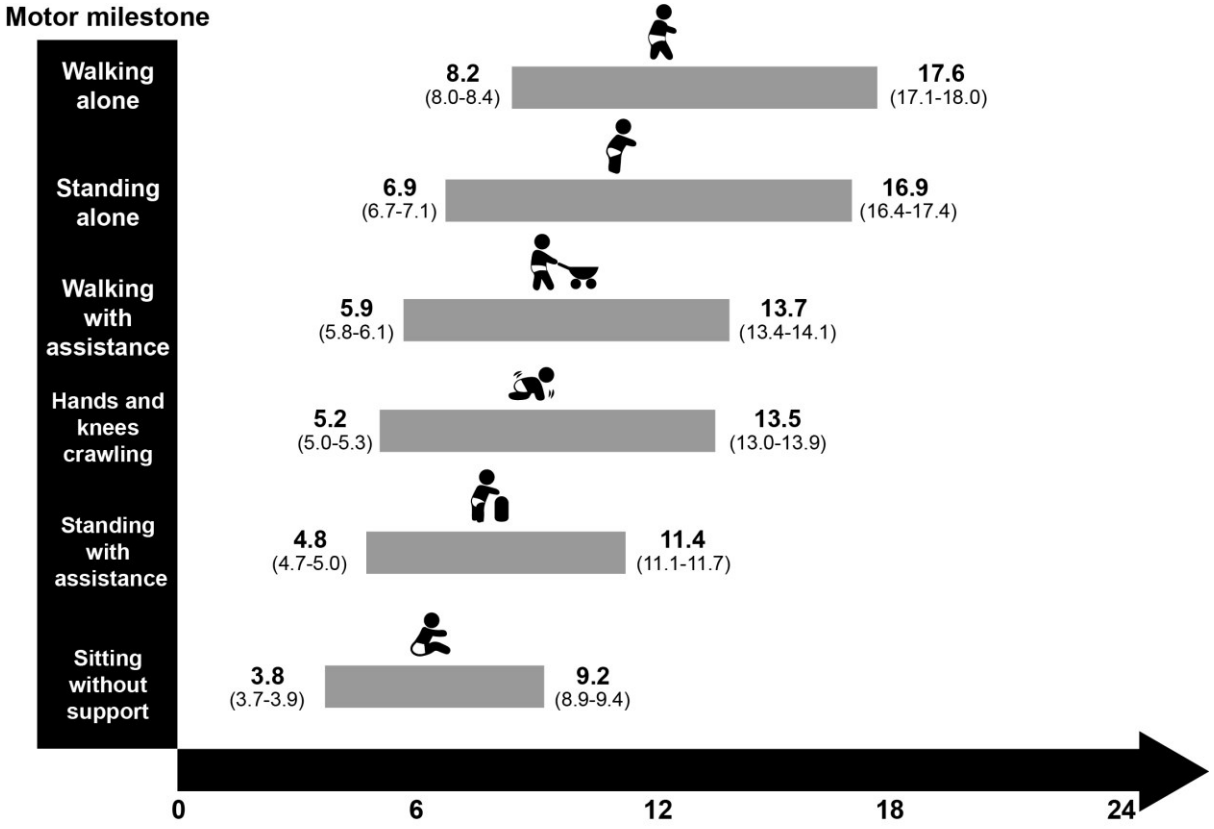
HMFSE Item	HMFSE activities	Activities of daily living
1	Able to sit on chair or with legs off bed with or without hand support	Sitting on normal school chair or public spaces (stools in restaurant); sitting on toilet; sitting in car; independence out of the house; dress by herself/himself
2	Able to sit on floor cross legged or legs stretched in front	Play on floor with siblings; sit on lounge chair, deck-chair; picnic; travel with less equipment; inclusion in activities
3	Able to bring hands to face at eye level	Wash face; brush and style; eat; put on eye glasses; answer telephone; blow nose
4	Able to bring hands to head	Scratch head; wash, brush, style hair; put on hat; dress upper body
5	Roll to side	Sleep by myself in my own room; caregiver does not have to wake up to turn him/her; help during dressing lying down; not having to turn head to see
6-7-8-9	Roll	Play; sleep well; sunbathe; experience space; reach for something at sides when lying down
10	Able to lie down from sitting	Independence: lie down and rest when tired; fun movement when falling; rest on the back; safety: fall in a controlled way (avoid head trauma)
11	Able to raise head when lying prone	Turn head react to stimulus, visual exploration of surroundings; read a book; not be afraid of choking; watch tv; on beach not get sand in face
12-13	Able to prop on forearms or extend arms	Read a book; watch tv; stretch back; sunbathe
14	Able to sit up from lying	No need for assistant; wake up and not have to wait for someone to sit me up; independence; sit up and drink at night
15	Able to four-point knee	Play like an animal in school; hiding; be able to fit under small spaces
16	Able to craw	Move around; experience space; go get objects; play on floor
17	Lift head from supine	Change head position; drink at night; read; watch tv; check the clock or alarm
18	Stand with support	Use toilet standing (boy); use full length mirror, perceive body dimensions and proportions; shower properly; climb in car; use kitchen burners, cook
19	Stand without support	Public spaces: wait for bus, stand in queue; cook; use normal sink; dress; reach something on a shelf
20	Able to walk	Freedom; go where and when you please; get to places; not to have to rely on wheelchair batteries
21-22	Able to flex hip from supine	Dress (pants, socks); scratch legs; change position
23-24-25-26	Able to half knee	Pick up object on floor; tie shoe laces; put away object on low surfaces; pet a dog; play; kneel in church; talk with a kid
27	Able to go from standing to sitting	Not get hurt when falling or not fall in an embarrassing way; sit on grass or sand; pet a dog; sit beside a friend in same position/play on floor; pick up something from floor
28	Able to squat	Sit when needed; pick up objects on floor; pee; tie shoes; pull up trousers
29	Able to jump	Have fun, play; dance, gymnastics; avoid obstacles; normality; go to friends' home regardless of where they live; stay and live in my own home
30-31-32-33	Go up and down stairs	Absence of barriers; normality; go to friends' home regardless of where they live; stay and live in my own home

Abbreviation: HFSME, Hammersmith Functional Motor Scale-Expanded
Source: Pera 2017(80)

2.3.5.2 CHERISH: Motor milestones with WHO criteria

The WHO motor milestones are a set of 6 gross motor milestones (sitting without support, standing with assistance, hands and knees crawling, walking with assistance, standing alone, walking alone) that are expected to be attained by 24 months of age in healthy children (Figure 9).(76,80)

Figure 9. WHO motor development milestones: windows of achievement in healthy children in months



Abbreviations: WHO, World Health Organization; CI, confidence interval
Horizontal bars represent normal variation in the age at which milestones are achieved in healthy children. Values to the left of each bar represent the first percentile (95% CI) and to the right of each bar the 99th percentile (95% CI) age in months, respectively
Source: Schneider 2017(76)

2.3.5.3 CHERISH: RULM

The RULM is a validated SMA-specific outcome measure that assesses upper limb functional abilities in individuals with SMA, including young children and non-ambulatory young children and weaker individuals who have a floor effect (i.e when patients score at the bottom/lower limit [floor effect] of the scale) or very low score on the HFMSE.(81) The original test consists of 9 items, but the revised version of the test consists of 19 scorable items: 18 items scored on a 0 (unable) to 2 (full achievement) scale, as with the HFMSE, and one item that is scored from 0 (unable) to 1 (able). These item scores are summed to give a total score ranging from 0–37 points with lower scores reflecting poorer ability.(80) The RULM consists of upper limb

performance items that are reflective of reachable space and activities of daily living (i.e., raise a can to mouth as if drinking, take a coin and place it in a box, remove the lid of a container, being able to lift a weight [200 g to 1 kg]. Patients with SMA and their caregivers were involved iteratively throughout the process to establish clinical meaningfulness and relevance of individual RULM items to activities of daily living.(80) The RULM is quickly administered, well tolerated by children of 30 months of age to adults, suitable for use in multicenter settings, and has been evaluated in individuals with SMA.(80)

Table 10. Details of the items included in the final version of the Revised Upper Limb Module

Entry item
Bring hands from lap to table
Complete the path bringing the car to the finish line without stopping or taking pencil off of paper?
Pick up coins/tokens
Place coin/token into cup: On table: horizontal At shoulder height: vertical
Reach to the side and touch the coin/token: Bring hand at shoulder height and above
Push button light with one hand
Tearing paper
Open Ziploc container
Raise 200-g cup to mouth
Lift 200-g weight and bring it from 1 circle to the other (midline to outer circle on tested side) without sliding
Lift 500-g weight and bring it from 1 circle to the other (midline to outer circle on tested side) without sliding
Lift 200-g weight and bring it from one circle to the other (inner to outer circle on opposite side) without sliding across midline
Bring 500-g sand weight from lap to table or eye level
Bring both arms above head - Shoulder abduction
Bring 500-g weight above shoulder height - Shoulder abduction
Bring 1-kg weight above shoulder height - Shoulder abduction
Bring hand above shoulder height - Shoulder flexion
Bring 500-g weight above shoulder height - Shoulder flexion
Bring 1-kg weight above shoulder height - Shoulder flexion

Source: Mazzone 2017(81)

Upper limb function is very important to these patients. They want to be able to carry out self care activities such as brushing their teeth and wheelchair transfers, fine motor activities such as writing and controlling motorised wheel chairs and activities of daily living such as bringing food and drink to their mouths.(43) The impact on quality of life of the ability to perform daily life actions (including the type of actions that are represented by the RULM and the HFMSE) was reported in a large survey of patients with later onset SMA (type II and III) (N=822 patients or carers).(44) For patients who were able to achieve the given actions, the following 5 actions appear to have a major impact on their quality of life: use the restrooms alone (72%, use restroom on own), have a wash by themselves (63.6%, wash on own), perform transfers on their own (60.5%, transfer on own), self-feeding (60%), and dressing alone (55.5%, dress on own). Because patients can lose motor milestones and upper limb function, patients also greatly value stabilisation of these functions. For patients who reported inability to achieve the given actions, the following 5 actions were having a major impact on their HRQL: Use the restrooms alone (70.7%), self-feeding (65.4%), turn on her/his own in the bed (59.8%, turn in bed), have a wash by themselves (59.6%), and perform transfers on their own (58.4%).

2.3.5.4 CHERISH: CGI Scale

The CGI assessment is based on a 7-point ordinal scale from 1 (very much improved) to 7 (very much worse).

2.3.5.5 CHERISH: PedsQL

The Paediatric Quality of Life Inventory (PedsQL) Measurement Model is a modular, self-report and parent proxy-report approach to measuring HRQL in children and adolescents (2–18 years of age).

The PedsQL GCS includes assessment of physical functioning, emotional functioning, social functioning, and academic functioning. The PedsQL NMM was designed to measure HRQL dimensions specific to children 2–18 years of age with neuromuscular disorders, including SMA. For both the GCS and the NMM, higher scores (total scores range from 0–100) indicate better HRQL or less severe health issues.

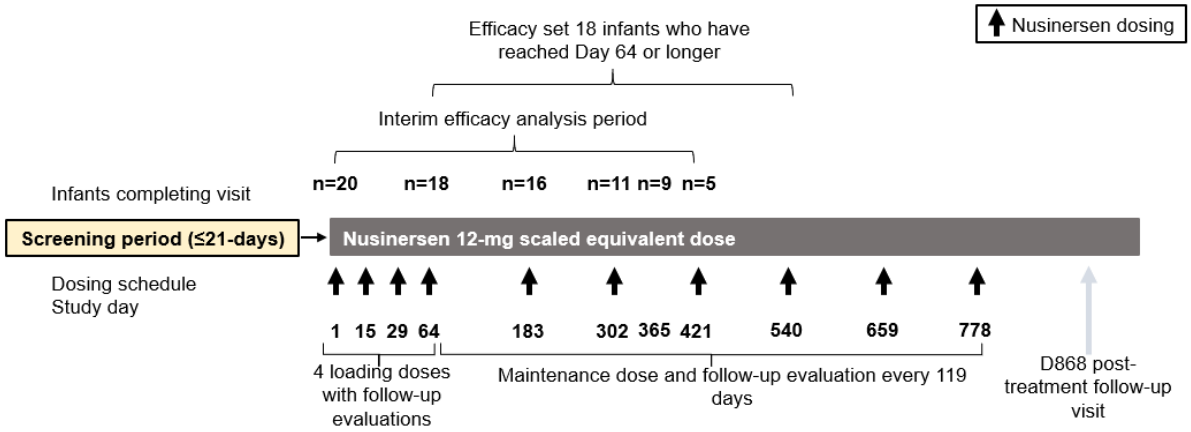
2.3.5.6 CHERISH: ACEND

The ACEND was designed to quantify the caregiver burden experience by parents of children affected with severe muscular diseases, including children with SMA.(83) The domains include assessing physical burden (including: feeding/grooming/dressing; sitting/play; transfers; and mobility) and general caregiver burden (including time, emotion and finance).

2.3.6 NURTURE: Study design

NURTURE is an on-going phase II open-label, multicentre, multinational, single-arm study to assess the efficacy and safety of nusinersen in pre-symptomatic infants genetically diagnosed with SMA (2 or 3 *SMN2* copies) who were enrolled at 6 weeks of age or younger with CMAP ≥1 mV.(53) Patients in this study were deemed most likely to develop type I or II SMA. Intrathecal nusinersen (12-mg equivalent dose) was administered by lumbar puncture.(84) The dosing schedule is: loading doses on day 1, 15, 29, 64; maintenance dose on day 183, 302, 421, 540, 659 and 778 (Figure 10).

Figure 10. Study design for NURTURE



Source: Crawford 2017(45)

At the time of the most recent interim analysis (cut-off date 31 October 2016), a total of 20 patients (out of the 25 planned) had been enrolled and received at least 1 dose of nusinersen (intention to treat [ITT] set). The efficacy set comprised 18 patients who had received all 4 loading doses or had the opportunity to complete the day 64 visit (Figure 10). All patients are continuing in the study.(45)

The study endpoints are shown in Table 7. The primary endpoint is the time to respiratory intervention or death (respiratory intervention is defined as invasive or non-invasive ventilation for ≥6 hours/day continuously for ≥7 days, or tracheostomy).

In NURTURE, if a subject has a sibling with SMA, and if consent is given, data for the untreated sibling are being collected, too (see Section 2.6.13.2 for sibling concordance data).

2.3.7 Baseline characteristics

2.3.7.1 ENDEAR: Baseline demographics

The demographic and baseline disease characteristics and SMA history of the ITT population were consistent with a population highly likely to develop SMA type I (infantile onset).

At baseline, patients in the nusinersen group had a younger age of SMA symptom onset (consistent with poorer prognosis) than the control group (mean of 7.9 vs. 9.6 weeks), required more ventilatory support (26 vs. 15%) and exhibited more severe symptoms of SMA (Table 11).(49)

Table 11. Baseline demographics of the ITT population

Characteristic	Nusinersen (N=80)	Sham control (N=41)
Female, n (%)	43 (54)	24 (59)
[redacted]	[redacted]	[redacted]
Mean (range) age at first dose, day	163 (52, 242)	181 (30, 262)
Mean (range) age at symptom onset, week	7.9 (2, 18)	9.6 (1, 20)
Mean (range) age at SMA diagnosis, week	12.6 (0, 29)	17.5 (2, 30)
Mean (range) disease duration at screening, week	13.2 (0, 25.9)	13.9 (0, 23.1)
[redacted]	[redacted]	[redacted]
SMA symptoms, n (%)		
Hypotonia	80 (100)	41 (100)
Developmental motor delay	71 (89)	39 (95)
Paradoxical breathing	71 (89)	27 (66)
Pneumonia or respiratory symptoms	28 (35)	9 (22)
Limb weakness	79 (99)	41 (100)
Swallowing or feeding difficulties	41 (51)	12 (29)
Other	20 (25)	14 (34)
Use of a ventilation support, n (%)	21 (26)	6 (15)
Use of a gastrointestinal tube, n (%)	7 (9)	5 (12)
Total HINE-2 score, mean (SD)	1.29±1.07	1.54±1.29
CHOP INTEND score at baseline, mean (SD)	26.63 (8.13)	28.43 (7.56)
CMAP amplitude, mV, mean (SD)		
Ulnar nerve	0.226 (0.19)	0.225 (0.12)
Peroneal nerve	0.371 (0.31)	0.317 (0.29)

Abbreviations: CHOP INTEND, Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders; CMAP, compound muscle action potential; ITT, intention to treat; SD, standard deviation; SMA, spinal muscular atrophy
Source: Finkel 2017a(49); *ENDEAR CSR(85)

The groups were generally similar in their baseline CHOP INTEND total scores, HINE-2 total score and baseline values for the CMAP measures (Table 11). Imbalance was seen with regard to the patients' history of SMA symptoms as of the start of the study: a greater percentage of infants in the nusinersen group had a history of paradoxical breathing (nusinersen vs. control: 89 vs. 66%), pneumonia or respiratory symptoms (35 vs. 22%) and more patients required ventilator support at baseline in the nusinersen group than the control group (26 vs. 15%) (Table 11). Therefore, the nusinersen group had a worse prognosis at baseline than the sham-procedure control group.

The groups were generally similar in their baseline motor milestone achievements with minor differences in individual categories that did not favour either group overall. In the nusinersen and sham-control groups at baseline, 82% and 78% of patients were unable to maintain their head upright; 96% and 98% were unable to sit; 70% and 78% were unable to kick; and 99% and 88% could not roll. No subject was able to crawl, stand, or walk.(49)

2.3.7.2 CHERISH: Baseline characteristics

Overall, the demographics and baseline disease characteristics of the ITT set (N=126), including SMA and medical history, were consistent with a population highly likely to develop later onset SMA (type II or III).

Baseline demography was well balanced between the groups, with only slight differences in gender and race (Table 12). Patients in the nusinersen group were slightly older than in the control group (median age at screening: 4 years vs. 3 years). The nusinersen and control groups were balanced with respect to age at symptom onset, time from disease onset to enrolment, age SMA was diagnosed, time from diagnosis to enrolment, disease duration and *SMN2* copy number (Table 12). However, there was an imbalance in the proportion of patients who had ever achieved a milestone, with 13% of patients in the nusinersen group and 29% in the control group having stood without support, and 24% of patients in the nusinersen group and 33% in the control group having walked with support (Table 12). In addition, more patients in the nusinersen group (76%) used a wheelchair than in the control group (69%). Furthermore, there was an imbalance in median time from disease onset to enrolment i.e. a longer delay to receiving therapy in the nusinersen group. Overall, the nusinersen group is likely to have a worse prognosis at baseline.

At baseline, the mean WHO and RULM total scores were similar between groups; the HFMSE total score was slightly higher in the nusinersen group.

Table 12. Baseline demographics in the ITT population for CHERISH

Characteristic	Nusinersen (N=84)	Sham-procedure control (N=42)
Female, n (%)	46 (55)	21 (50)
White, n (%)	64 (76)	30 (71)
Median (range) age at screening, years	4.0 (2–9)	3.0 (2–7)
Median (range) age at symptom onset, months	10.0 (6–20)	11.0 (6–20)
Median (range) time from disease onset to enrolment, months	39.3 (8–94)	30.2 (10–80)
Median (range) age at SMA diagnosis, months	18.0 (0–48)	18.0 (0–46)
Median (range) time from diagnosis to enrolment, months	27.8 (2–86)	26.0 (2-72)
Median (range) disease duration, months	39.3 (8–94)	30.2 (10–80)
SMN2 copy number, 2/3/4/unknown, %	7/88/2/2	10/88/2/0
Children who have ever achieved motor milestone, n (%) Sat without support Walked with support Stood without support Walked ≥15 ft independently	 84 (100) 20 (24) 11 (13) 0	 42 (100) 14 (33) 12 (29) 0
Children using a wheelchair, n (%)	64 (76)	29 (69)
Mean (SD) HFMSE total score [a]	22.4 (8.3)	19.9 (7.2)
Mean (SD) WHO total score [a,b]	1.4 (1.0)	1.5 (1.0)
Mean (SD) RULM total score [a,c]	19.5 (6.2)	18.4 (5.7)

Abbreviations: ft, feet; HFMSE, Hammersmith Functional Motor Scale Expanded; ITT, intention to treat, n, number; RULM, Revised Upper Limb Module; SD, standard deviation; SMA, spinal muscular atrophy; WHO, World Health Organization

[a] Baseline is defined as the last nonmissing value before the first dose of nusinersen or sham-procedure control.

[b] If the baseline value as defined above was missing, then baseline was imputed as the median of the nonmissing values of the stratum to which the child belongs: age<6 or ≥6 years.

[c] One child had a missing value and this was imputed as the median baseline value of the child across all the multiply imputed datasets.

Source: Mercuri 2018;(51)

The interim efficacy set (IES) were defined as infants in the ITT set who were assessed at the day 183, 302 or 394 visit and had a time difference of at least 190 days between the date of first dose and the data cut-off date of the interim analysis (June 15, 2016). The IES baseline characteristics were similar to that observed in the ITT set.(86)

2.3.7.3 NURTURE: Baseline characteristics

In the ITT set, most patients were male, had 2 *SMN2* copies, were younger than 1 month of age at enrolment and were enrolled in the United States (Table 13). The baseline CHOP INTEND, HINE total motor milestone score, ulnar and peroneal CMAP amplitude are shown in Table 13. All patients had a CMAP amplitude ≥1 mV. No patients had achieved WHO motor milestones at baseline due to their age (≥42 days old).

Infants with infantile onset SMA (type I) usually have 2 or 3 copies of *SMN2*, with 2 copies as the most common genotype (80% of type I SMA patients have 2 copies), while type II is usually associated with 3 copies (82% of type II SMA patients).(87) Individuals with fewer copies of *SMN2* will on average produce less functional SMN protein and are therefore more likely to develop a more severe form of SMA.(88) In NURTURE, most subjects (N=13) have 2 *SMN2* copies and would therefore be expected to develop a more severe SMA phenotype than subjects with 3 *SMN2* copies. However, it is noted that *SMN2* copy number cannot be used to definitively determine the type of SMA an individual will have as other genetic modifiers can affect how much SMN protein is made, including sequence variation of the *SMN2* gene, trans-regulatory splicing factors or epigenetic modifiers acting on *SMN2*, or expression of the *plastin 3* gene.(89,90) Therefore, depending on their genetic background, it is possible for an individual with 2 copies of *SMN2* to have type I, type II or type III SMA.

Table 13. NURTURE: Baseline characteristics

Characteristic	2 *SMN2* copies N=13 [a]	3 *SMN2* copies N=7	Total N=20
Age at first dose, days, n			
≤14	6	2	8
>14 to ≤28	5	3	8
>28	2	2	4
Range	3–41	10–42	3–42
Mean CHOP INTEND total score	48.0	53.8	49.6
Median (range) [b]	50.0 (25–60) [c]	56.0 (40–60) [d]	54.0 (25–60) [e]
Mean HINE total motor milestones	2.5	4.2	3.0
Median (range) [b]	3.0 (0–5) [c]	4.0 (2–7) [d]	3.0 (0–7) [e]
Mean ulnar CMAP amplitude	2.62	3.96	2.99
Median (range), mV [b]	2.15 (1.0–6.7) [c]	4.00 (2.7–4.9) [d]	2.85 (1.0–6.7) [e]
Mean peroneal CMAP amplitude	2.47	4.88	3.27
Median (range), mV [b]	2.65 (0.2–4.2) [f]	4.40 (4.0–7) [d]	3.20 (0.2–7.0) [g]
Male, %			55
Region, n			
North America			13
Europe			4
Asia-Pacific			3

Abbreviations: CHOP INTEND, Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders; CMAP, compound muscle action potential; HINE, Hammersmith Infant Neurological Examination; NURTURE study interim analysis data cut-off date: October 21, 2016.
[a] Included 1 set of twins each with 2 *SMN2* copies

[b] Based on efficacy set of patients who completed the day 64 visit or longer (N=18)
[c] N=13. [d] N=5. [e] N=18. [f] N=10. [g] N=15
Source: Crawford 2017(45)

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

A summary of the statistical analysis is shown in Table 14.

Table 14. Summary of statistical analyses

Trial name	Hypothesis objective	Statistical analysis	Sample size, power calculation	Data management, patient withdrawals
ENDEAR	• The null hypothesis was that nusinersen and sham-procedure control groups have the same 'survival' function.	• A hierarchical testing strategy was used to control the overall type I error rate at 0.05; in the final analysis, endpoints were ranked and tested for statistical significance in a hierarchical order • The difference between the nusinersen group and the control group in the proportion of infants who had a motor milestone response was analysed with the use of Fisher's exact test. • Event-free survival and overall survival were assessed with the use of a log-rank test that was stratified according to disease duration at screening (≤12 weeks or >12 weeks). • The median time to death or the use of permanent assisted ventilation in each group and associated 95% CI were estimated with the use of the K-M product-limit method; probability of survival was estimated with the use of the K-M method. A hazard ratio for death or the use of permanent assisted ventilation and a HR for death were calculated with the use of a Cox proportional-hazards model that was adjusted for disease duration at screening in each infant. A hazard ratio of less than 1.00 indicated a lower risk of	• For the primary endpoint of motor milestone response, the power was estimated to be approximately 60% to detect a statistically significant difference between treated and sham groups at the time of the interim analysis (N ~80 subjects), under the assumptions of having 3 responders in the sham group (3/26 = 11.5%) and 20 responders in the nusinersen group (20/52 = 38.5%), and alpha = 0.035. • At the final analysis, with alpha = 0.03, 111 subjects would provide approximately 78% power to differentiate a response rate of 38.5% for the nusinersen group vs. a response rate of 11.5% for the sham group. • In addition, the sample size for this study was estimated based on a doubling of median time to death or permanent ventilation for the nusinersen group compared to that of the sham-procedure control group. Based on limited available natural-history data for the target population, it was estimated that the median time to death or permanent ventilation of the	• For the interim analyses, the analysis populations were the ITT set, the IES, and for the final analyses, the analysis populations were the ITT set, and the efficacy set (see Table 15). • An interim analysis was planned for when approximately 80 subjects had the opportunity to be assessed at the day 183 visit and was conducted with a clinical cut-off date of 15 June 2016. The study was stopped prematurely due to the efficacy observed in the nusinersen-treated group compared to the sham-control group during an interim analysis. • At the interim analysis only the first primary endpoint, proportion of milestone responders, was tested. To control the type I error rate across the interim and potential final analysis, this was pre-specified to be tested at an alpha of 0.032 based on the Lan-DeMets alpha spending function. The second primary efficacy endpoint was not tested since it was

Trial name	Hypothesis objective	Statistical analysis	Sample size, power calculation	Data management, patient withdrawals
		an event in the nusinersen group than in the control group. • A number of sensitivity analyses were conducted to test the uncertainty in the primary and secondary outcomes.(1) Further details of the sensitivity analyses are included in Appendix M. • A pre-specified subgroup analysis (age at onset of SMA symptoms and disease duration [≤12 weeks and >12 weeks]) was analysed according the above methods.(91)(50)	sham-procedure control arm is 5–6 months from date of randomisation. With 2:1 randomisation and 13 months follow-up time, 111 subjects would provide approximately 80% power to detect a doubling in median time to death or permanent ventilation for the nusinersen group vs. the sham-procedure control group at an overall 2-sided 5% significance level.	expected that too few events would have occurred to formally evaluate time to death or permanent ventilation and survival rate. • Initially, the main efficacy analysis presented for assessment were the percentages of motor milestones responders in the IES. The analysis was based on non-missing values at the later of the day 183, day 302, and day 394 assessments. Subjects who died or withdrew from the study were counted as non-responders.

CHERISH	• The null hypothesis was that nusinersen and sham-procedure control groups have the same change from baseline HFSME score at 15 months.	• To control the overall type I error rate at 0.05 across the interim and final analyses for the primary and secondary endpoints, a hierarchical strategy with independent alpha spending functions for primary and secondary endpoints was applied • Because the P value for the primary endpoint was significant in the interim analysis, this end point was not formally tested for significance • All secondary efficacy endpoints were assessed in the final analysis. • The prespecified interim analysis of the primary end point was performed in the ITT population; this analysis was conducted when all the children had been enrolled for at least 6 months and at least 39 children had completed their 15-month assessment. Because some children would not have completed the 15-month assessment by the time of the interim analysis, the analysis was performed with the use of a multiple-imputation method to account for missing data on HFMSE scores obtained after baseline. LS mean values are reported.	• A total of 70 patients in the nusinersen group and 35 patients in the control group provided at least 90% power to detect a 3-point difference between the control and nusinersen groups in the change from baseline HFMSE with a standard deviation of 4.4, using a 2-sided test with an alpha level of 0.05. A planned enrolment of 117 patients ensured that a small dropout rate would not affect the power of the primary efficacy analysis.	• For the interim analysis, the analysis populations were the ITT set, and the IES, and for the final analysis, the analysis populations were the ITT set. • An interim analysis was planned when all subjects had completed the 6-month assessment and at least 39 subjects had completed the 15-month assessment. At the interim analysis, only the primary efficacy endpoint (change from baseline HFMSE score at 15 months) was tested. • The study was stopped prematurely due to the efficacy observed in the nusinersen-treated group compared to the sham-control group during an interim analysis.

		• In the final analysis, the LS mean changes in the total HFMSE score, the number of WHO motor milestones achieved per child, and the RULM score and LS mean differences in change between groups were based on an ANCOVA, with group assignment as a fixed effect and with adjustment for each child's age at screening and the value at baseline. • The percentage of children with an improvement on the HFMSE (≥3-point improvement) was compared between groups using an adjusted logistic regression model, yielding an odds ratio, 95% CI, and P value. Binomial proportions and corresponding CIs also were presented, and missing data were imputed using multiple imputation. • The LS mean number of new WHO motor milestones per child was compared between groups using ANCOVA, with treatment as a fixed effect and adjustment for each child's age at screening and number of milestones at baseline. Between-group differences in the proportions of children who achieved any new motor milestone, able to stand alone, or able to walk with assistance were compared between the groups		

Trial name	Hypothesis objective	Statistical analysis	Sample size, power calculation	Data management, patient withdrawals
		using exact unconditional CIs, and the P value was based on Fisher's exact test. • Between-group changes from baseline in the RULM score were assessed by ANCOVA with treatment as a fixed effect and adjustment for each child's age at screening and derived total score at baseline. Estimates were constructed from fitting the ANCOVA model to each of the imputed datasets. • Five sensitivity analyses of the primary efficacy variable in the final analysis were conducted to test for potential impacts of differences in modeling approaches (see Appendix M). • Subgroup analyses of the primary and secondary endpoints prespecified in the statistical analysis plan included below and above the randomisation stratification factor for age (i.e., age <6 years vs. age ≥6 years), and disease duration (time from SMA disease onset to screening) by tertiles.		
NURTURE	[redacted]	[redacted]	[redacted]	[redacted]

Trial name	Hypothesis objective	Statistical analysis	Sample size, power calculation	Data management, patient withdrawals
	[redacted]	[redacted]		

Abbreviations: ANCOVA, analysis of covariance; CI, confidence interval; HR, hazard ratio; HFSME, Hammersmith Functional Motor Scale-Expanded; IES, interim efficacy set; ITT, intention to treat; K-M, Kaplan-Meier; LS, least squares; RULM, Revised Upper Limb Module; SD, standard deviation; SMA, spinal muscular atrophy; WHO, World Health Organization

Source: ENDEAR: Finkel 2017a(49); CHERISH: Mercuri 2018(51); NURTURE: NURTURE CSR(56)

2.4.1 ENDEAR: Analysis sets

The populations analysed at the different analyses are summarised in Table 15.

Table 15. ENDEAR: Populations analysed for the different endpoints at interim and final analysis

Analysis	Endpoints	Population	Number of patients	Description
Interim	Motor milestones (HINE-2)	IES	Nusinersen: 51; Sham control: 27	Infants in the ITT set who were assessed at the day 183, 302, or 394 visit and had a time difference of at least 190 days between the date of first dose and the data cut-off date of the interim analysis
Final	Event-free survival, overall survival	ITT set	Nusinersen: 80; Sham control: 41	All patients who were randomised and received ≥1 dose of study drug
Final	Motor milestones, CHOP INTEND, CMAP amplitude	Efficacy set	Nusinersen: 73; Sham control: 37	Infants in the ITT set who were assessed at the day 183, 302, or 394 visit and had a time difference of at least 190 days between the date of the first dose and the data cut-off date of the final analysis

Abbreviations: CHOP INTEND, Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders; CMAP, compound muscle action potential; IES, interim efficacy set; HINE-2, Module 2 of the Hammersmith Infant Neurological Examination; ITT, intention to treat
Source: Finkel 2017a (49)

2.4.1 CHERISH: Analysis sets

The populations analysed are summarised in Table 16.

Table 16. CHERISH: Definitions of the populations analysed for the interim and final analysis

Population	Number of patients	Description
ITT set	Nusinersen: 84 Sham control: 42	All patients who were randomised and received ≥1 dose of study drug or control procedure. Children were analysed in the treatment group to which they were randomised. Used for the change from baseline to month 15 in HFMSE score, percentage of HFMSE responders, and change in RULM score.
IES	Nusinersen: 35 Sham control: 19	A subset of the ITT set who had been assessed at month 15 (i.e. the day 456 visit), which included all children with a day 456 visit and all children with a time difference of at least 463 days (456 days plus a 7-day window) between the date of first dose and the data cut-off date (August 31, 2016) for the interim analysis. Used for the main interim analysis of motor milestones and also as a supportive analysis for the primary and all other secondary efficacy endpoints.
Efficacy set	Nusinersen: 66 Sham control: 34	Subset of children in the ITT set who had the opportunity to be assessed at the day 456 visit (i.e., month 15), which included all children with a day 456 visit and all children with a time difference of at least 463 days (456 days plus a 7-day window) between the date of first dose and the date for the final analysis. Used for the analysis of WHO motor milestones.

Abbreviations: ITT, intention to treat; IES, interim efficacy set
Source: Mercuri 2018(51)

2.4.2 NURTURE: Analysis sets

The populations analysed are summarised in Table 17.

Table 17. NURTURE: Definitions of the populations analysed for the interim analysis

Population	Number of patients	Description
ITT set	Nusinersen: 20	All patients who received ≥1 dose of study drug
Efficacy set	Nusinersen: 18	A subset of the ITT set who had been assessed at day 64 or would have been assessed at day 64 had they not died or discontinued treatment

Abbreviation: ITT, intention to treat
Source: NURTURE CSR(56)

2.4.3 Patient disposition

Patient disposition, including diagrams showing the flow of participants through each stage of the trials for ENDEAR, CHERISH and NURTURE are presented in Appendix D.

2.5 Quality assessment of the relevant clinical effectiveness evidence

Please see Appendix D for a detailed quality assessment for the ENDEAR, CHERISH and NURTURE, which was performed according to the quality appraisal checklist for intervention studies developed by NICE. ENDEAR and CHERISH were completed to the highest standard with adequate randomisation and blinding procedures (Table 19). NURTURE is a single arm trial and therefore randomisation and blinding procedures are not applicable (see Appendix D).

Table 18. Quality assessment results for parallel group RCTs

Trial name	ENDEAR	CHERISH
Was randomisation carried out appropriately?	Yes	Yes
Was the concealment of treatment allocation adequate?	Yes	Yes
Were the groups similar at the outset of the study in terms of prognostic factors?	Partly: Baseline demography was balanced between the nusinersen and control groups. Patients enrolled in the nusinersen treatment group showed greater disease severity compared with the sham-control group.	Partly: Baseline demography was balanced between the nusinersen and control groups. there was an imbalance in the proportion of patients who had ever achieved a milestone, with fewer patients in the nusinersen group than in the control group having stood without support, and having walked with support; more patients in the nusinersen group used a wheelchair than in the control group
Were the care providers, participants and outcome assessors blind to treatment allocation?	Yes	Yes
Were there any unexpected imbalances in drop-outs between groups?	No	No
Is there any evidence to suggest that the authors measured more outcomes than they reported?	No	No
Did the analysis include an ITT analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	Yes	Yes

Abbreviation: CRD, ITT, intention to treat

Source: ENDEAR: Finkel 2017a(49); CHERISH: Mercuri 2018(51)

Note: Potential conflicts of interest were reported by all authors in the manuscript by Finkel 2017a(49)

Adapted from Systematic reviews: CRD's guidance for undertaking reviews in health care (University of York Centre for Reviews and Dissemination)

In England and Wales it is anticipated that nusinersen will be used as a first-line treatment option (in addition to existing symptomatic standard of care) as soon as possible after diagnosis in infantile onset patients (SMA type I), later onset infantile patients (SMA type II and III) and pre-symptomatic patients with multiple (≥2) copies of *SMN2* (see Section 1.3.3). The studies (ENDEAR for infantile onset patients, CHERISH for later onset patients and NURTURE for pre-symptomatic patients) are closely aligned to anticipated clinical practice in England and Wales. The generalisability of the studies to England is discussed in Section 2.13.2.

2.6 Clinical effectiveness results of the relevant trials

2.6.1 ENDEAR: Efficacy results from the interim and final analyses

Infantile onset SMA: ENDEAR

- Patients with infantile onset SMA treated with nusinersen achieved statistically significant and clinically meaningful improvements in motor milestones, as well as sustained and clinically meaningful improvements in event-free survival, overall survival, motor function and motor neuron health.
  - These improvements include attainment of motor milestones such as independent sitting, standing and walking, which are in stark contrast to the steady loss of motor milestones that is the hallmark of SMA type I demonstrated by the sham-control group and natural-history data.

- Compared with the sham-control group, nusinersen-treated infants with infantile onset SMA demonstrated:
  - A significantly greater percentage of patients achieving an improvement in HINE-2 motor milestones* (51 vs. 0%; difference of 50.68% [95% CI, 31.81–66.48%]; P <0.0001).
    - In infants who were alive and still on study on day 394, 77 vs. 0% achieved an improvement in HINE-2 motor milestones*
  - Achievement of motor milestones unexpected for infants with SMA type I including full head control (22 vs. 0%), supine to prone rolling (10 vs. 0%), independent sitting (8 vs. 0%) and standing with support (1 vs. 0%); these are well above the expectations for patients with SMA type I receiving standard of care in natural-history studies.
  - Statistically significant increases in event-free survival (time to death or permanent ventilation; P=0.005) and overall survival (P=0.004).
    - Overall, there was a 47% relative reduction in the risk of death or permanent ventilation compared to sham control.
    - There was a 63% relative reduction in the risk of death compared to sham control
    - Notably, nusinersen-treated patients who were below the median for disease duration at baseline had a markedly decreased risk of death or permanent ventilation (76% reduction in risk) compared to sham-control patients who were below the median, suggesting that early treatment with nusinersen may confer a strong benefit for event-free survival.
  - Greater improvements in motor function and motor neuron health as determined by the CHOP INTEND and the CMAP amplitude, respectively.
    - A significantly higher percentage of infants in the nusinersen group than in the control group had a 4-point increase in CHOP INTEND score (71 vs. 3%, P<0.001).

- In infants who were alive and still on study on day 394, 92% vs 9% of children had a 4-point increase in CHOP INTEND score

- Subgroup analysis (≤12 weeks and >12 weeks) suggested that earlier and greater motor milestone responses and prolonged survival were observed among patients with shorter disease duration at the start of the study compared to patients with a longer disease duration, suggesting that early treatment with nusinersen may confer a stronger benefit.

* ≥2-point increase (or maximal score) in ability to kick, OR ≥1-point increase in the motor milestones of head control, rolling, sitting, crawling, standing or walking, AND improvement in more categories of motor milestones than worsening

Table 19 shows a summary of the results of the interim analysis and for the final analysis. The interim analysis was conducted once ~80 patients had been assessed at the day 183 visit for the primary endpoint of motor milestones, which was the only endpoint with formal statistical analysis at the interim analysis.(1) In the interim analysis, a significantly higher percentage of infants in the nusinersen group than in the control group had a motor milestone improvement, termed responders (see Section 2.3.3.1 for the definition: 41 vs. 0%, P<0.001). These results prompted early termination of the trial, and infants were evaluated at end-of-trial visits.(49)

More details of the results from the primary, secondary and key tertiary endpoints are described in the following sections. Results from a pre-specified subgroup analysis (age above and below the study median disease duration [≤12 weeks and >12 weeks]) are in Section 2.7 and in Appendix D.

Table 19. Summary of results from the interim and final analysis of ENDEAR

Efficacy parameter	Results	
	Nusinersen	Sham control
Interim analysis: primary endpoint of motor milestones (data-cut: 15th June 2016)		
Motor milestones [a]		
Proportion responders (HINE-2), n (%)	21 (41%)	0 (0%)
Difference (95% CI)	41.18 (18.16, 61.20)	
P value	P <0.001	
Final analysis (data-cut: 21st November)		
Primary endpoints		
Motor milestones [b]		
Proportion responders (HINE-2), n (%) [c, d]	37 (51%)	0 (0%)
Difference (95% CI)	[redacted]P	
P value	<0.0001	
Proportion with improvement in total score	49 (67%)	5 (14%)
Proportion with worsening in total score	1 (1%)	8 (22%)
Event-free survival [e]		
Patients who died or received permanent ventilation, n (%)	31 (39%)	28 (68%)
Hazard ratio (95% CI)	0.53 (0.32, 0.89)	
P value	P=0.005	
Secondary endpoints		
CHOP INTEND [b]		
Proportion with ≥4-point improvement, n (%)	52 (71%)	1 (3%)
Difference (95% CI) *	[redacted]P	
P value	<0.001	

Efficacy parameter	Results	
	Nusinersen	Sham control
Proportion with any improvement, n (%)	53 (73%)	1 (3%)
Proportion with any worsening, n (%)	5 (7%)	18 (49%)
Overall survival rate[e]		
Dead, n (%)	13 (16%)	16 (39%)
Alive, n (%)	67 (84%)	25 (61%)
Hazard ratio (95% CI)	0.37 (0.18, 0.77)	
P value	P=0.004	
No use of permanent assisted ventilation [e], n (%)	62 (78%)	28 (68%)
Hazard ratio (95% CI)	0.66 (0.32–1.37)	
P value	P=0.13	
CMAP amplitude [b]		
CMAP responders, n (%)	26 (36%)	2 (5%)
Nominal P value	P=0.001	
Time to death or permanent ventilation in patients below median disease duration		
Hazard ratio (95% CI)	0.24 (0.10, 0.58)	
P value	P<0.001	
Time to death or permanent ventilation in patients above median disease duration		
Hazard ratio (95% CI)	0.84 (0.43, 1.67)	
P value	P=0.4	

Abbreviations: CHOP INTEND, Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders; CI, confidence interval; CMAP, compound muscle action potential; HINE-2, Module 2 of the Hammersmith Infant Neurological Examination

[a] Assessed in the Interim analysis set (nusinersen N=51; Sham control N=27)

[b] At the final analysis, CHOP INTEND, motor milestone and CMAP analyses were conducted using the efficacy set (nusinersen N=73; Sham control N=37)

[c] Assessed at the later of day 183, day 302, and day 394 Study Visit

[d] According to HINE-2: ≥2-point increase [or maximal score] in ability to kick, OR ≥1-point increase in the motor milestones of head control, rolling, sitting, crawling, standing or walking, AND improvement in more categories of motor milestones than worsening, defined as a responder for this primary analysis

[e] At the final analysis, event-free survival, overall survival and permanent ventilation were assessed using the intention to treat population (ITT nusinersen N=80; Sham control N=41)

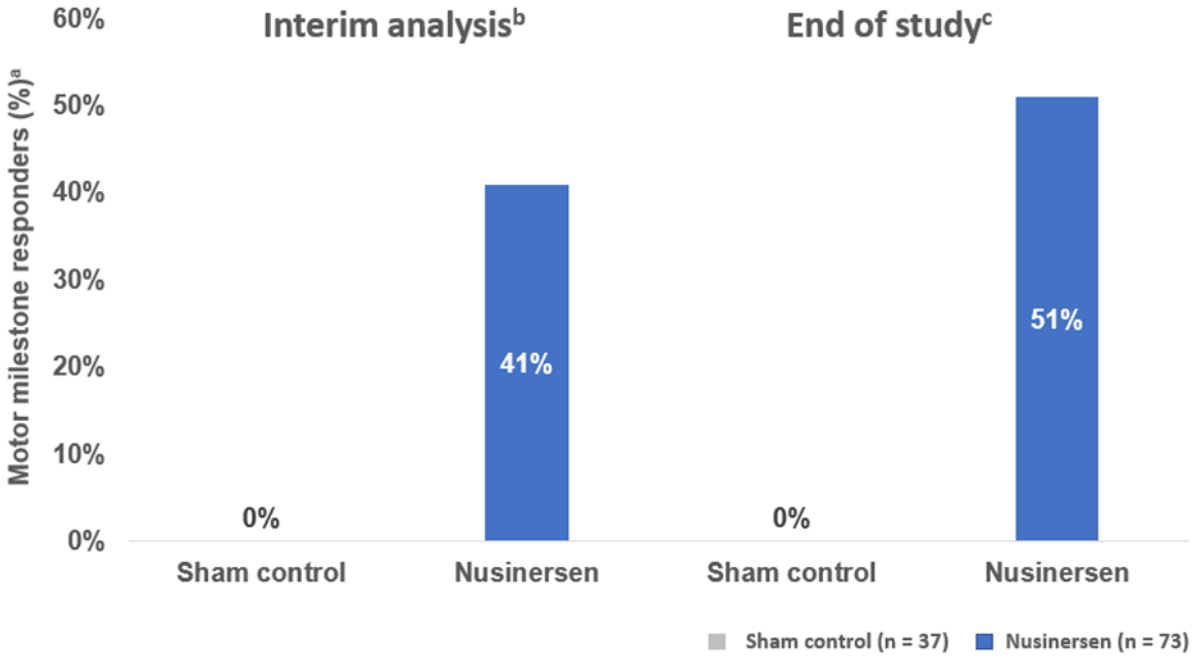
Source: Finkel 2017(49); EPAR(1); SmPC(2); *ENDEAR CSR(85)

2.6.2 ENDEAR: Primary endpoints

2.6.2.1 ENDEAR: Motor milestone responders

At the interim analysis, a clinically and statistically significantly greater percentage of nusinersen-treated infants were HINE-2 motor milestone responders than those who received the sham-procedure control (P <0.001) (Table 19; Figure 11). At the final analysis, nusinersen-treated infants demonstrated continued improvement compared with the control group over the previous interim analysis (P <0.0001) (Table 19; Figure 11). In infants who were alive and still on study on day 394, 63 vs. 0% were HINE-2 motor milestone responders.(92)

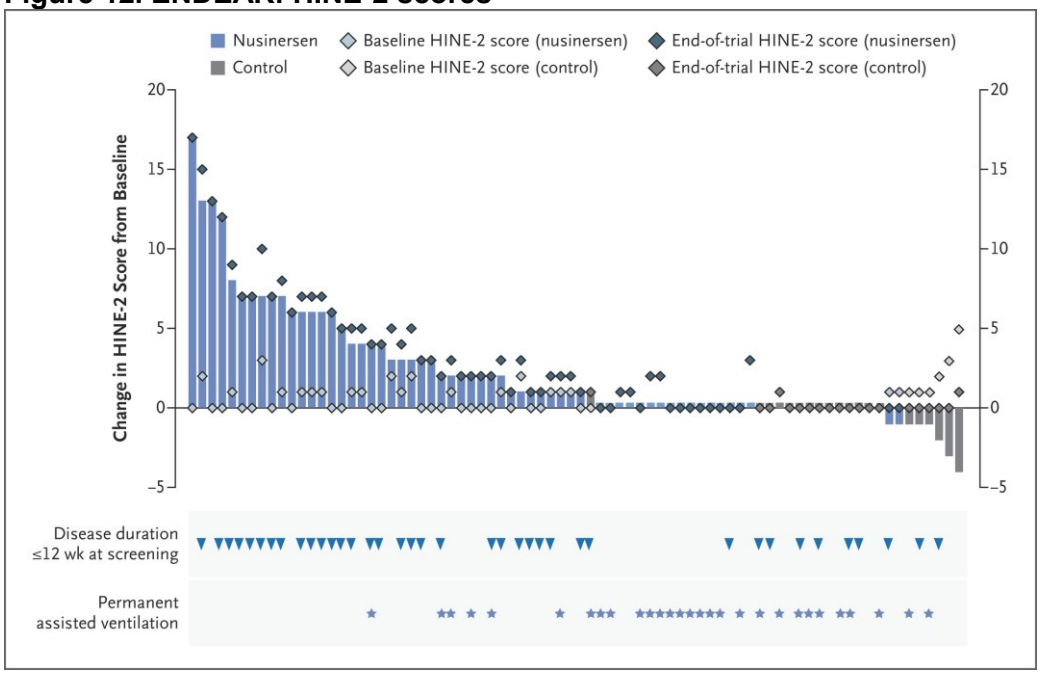
Figure 11. ENDEAR: Proportion of motor milestone (HINE-2) responders in the interim and final analysis



Abbreviation: HINE-2, Module 2 of the Hammersmith Infant Neurological Examination
Responders were defined as: ≥2-point increase (or maximal score) in ability to kick, OR ≥1-point increase in the motor milestones of head control, rolling, sitting, crawling, standing or walking, AND improvement in more categories of motor milestones than worsening
[a] Interim endpoint re-evaluated with final study data with no alpha spending
[b] The interim efficacy analysis was conducted on June 15, 2016, once ~80 participants had the opportunity to be assessed at the day 183 visit; N=78
[c] The end of study analysis was conducted on November 21, 2016. Infants with opportunity for at least a day 183
Source: Finkel 2017b (57)

Figure 12 shows the HINE-2 scores at baseline and at the end-of-trial visit (on day 183, 302, or 394) (diamonds), as well as the change in HINE-2 score from baseline through the end-of-trial visit (bars), for the 78 infants who were alive, attended an end-of-trial visit, and were included in the final analysis.

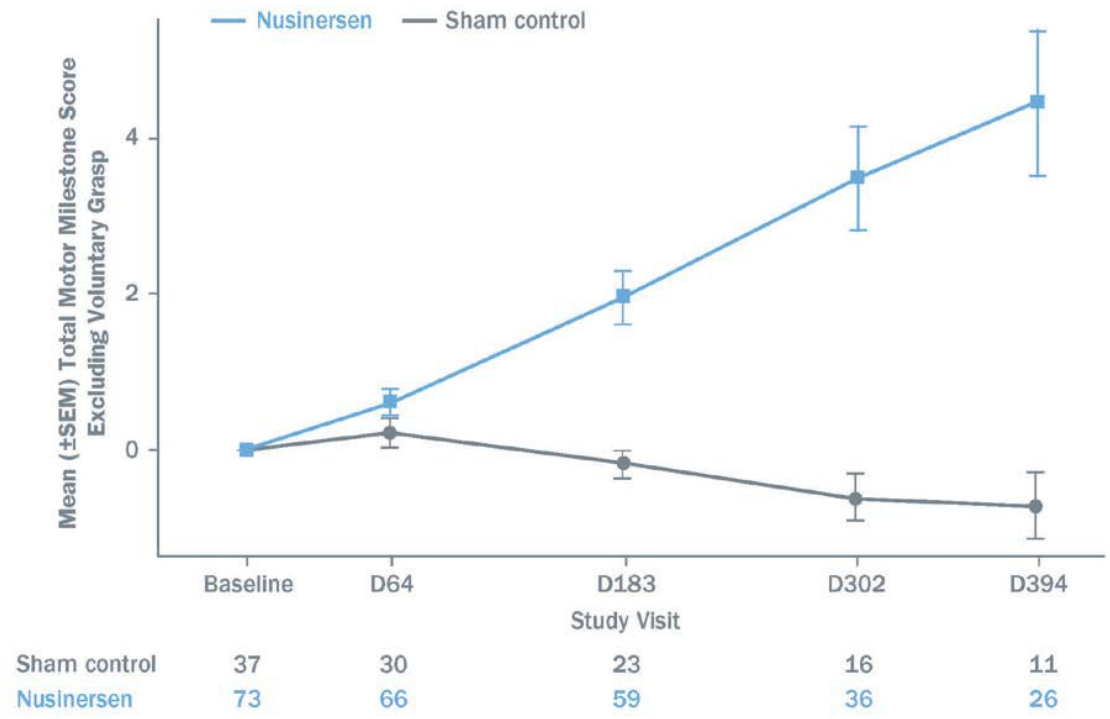
Figure 12. ENDEAR: HINE-2 scores



Abbreviation: HINE-2, Module 2 of the Hammersmith Infant Neurological Examination
Shown are the scores on HINE-2 at baseline and at the end-of-trial visit (on day 183, 302, or 394) (diamonds), as well as the change in HINE-2 score from baseline through the end-of-trial visit (bars), for the 78 infants who were alive, attended an end-of-trial visit, and were included in the final analysis (see Appendix D Section 2.2.1 for reasons for discontinuations). The scores shown here account for 7 of the 8 motor-milestone categories, excluding voluntary grasp. For the infant in the control group who had a 1-point increase, the increase was in the score for kicking, and therefore the infant was not considered to have a motor-milestone response. The shortest bars indicate a value of 0. Triangles indicate infants who had a disease duration of 12 weeks or less at screening. Stars indicate infants who received permanent assisted ventilation during the trial.
Source: Finkel 2017a(49)

Mean changes from baseline in HINE-2 total motor milestone scores obtained at the day 64, 183, 302, and 394 study visits among all infants in the efficacy set are shown in Figure 13. Nusinersen-treated infants demonstrated continued gains without plateau, while sham control infants demonstrated an overall decrease vs. baseline.

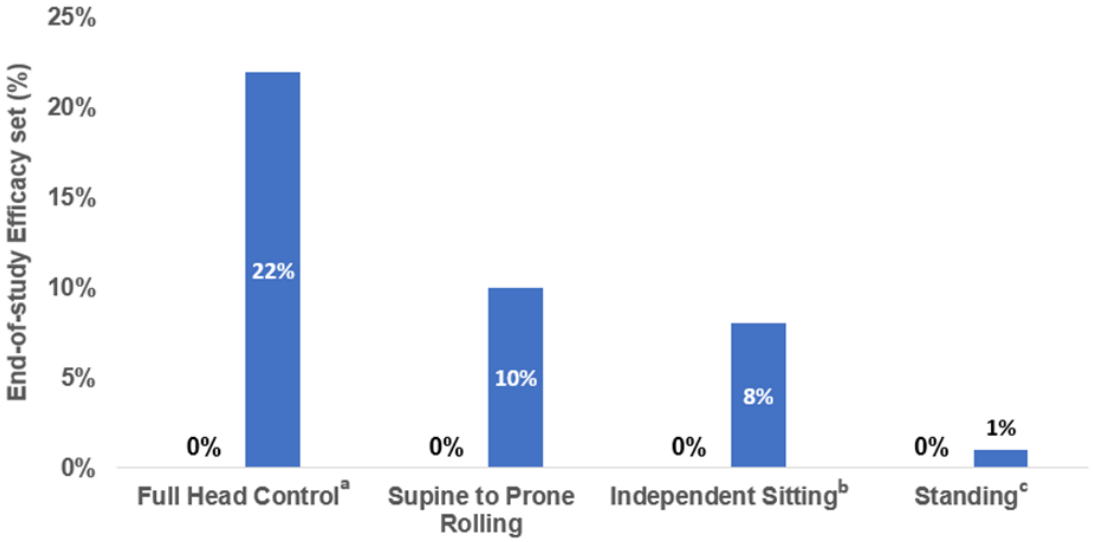
Figure 13. Change in HINE-2 over time



Abbreviation: HINE-2, Module 2 of the Hammersmith Infant Neurological Examination
Source: Finkel 2017a(49)

In the nusinersen group, 22% of the infants achieved full head control, 10% were able to roll over, 8% were able to sit independently, and 1% were able to stand; in the control group, no infants achieved these milestones (Figure 14).

Figure 14. HINE-2 Motor Milestones - Quality of Motor Responses

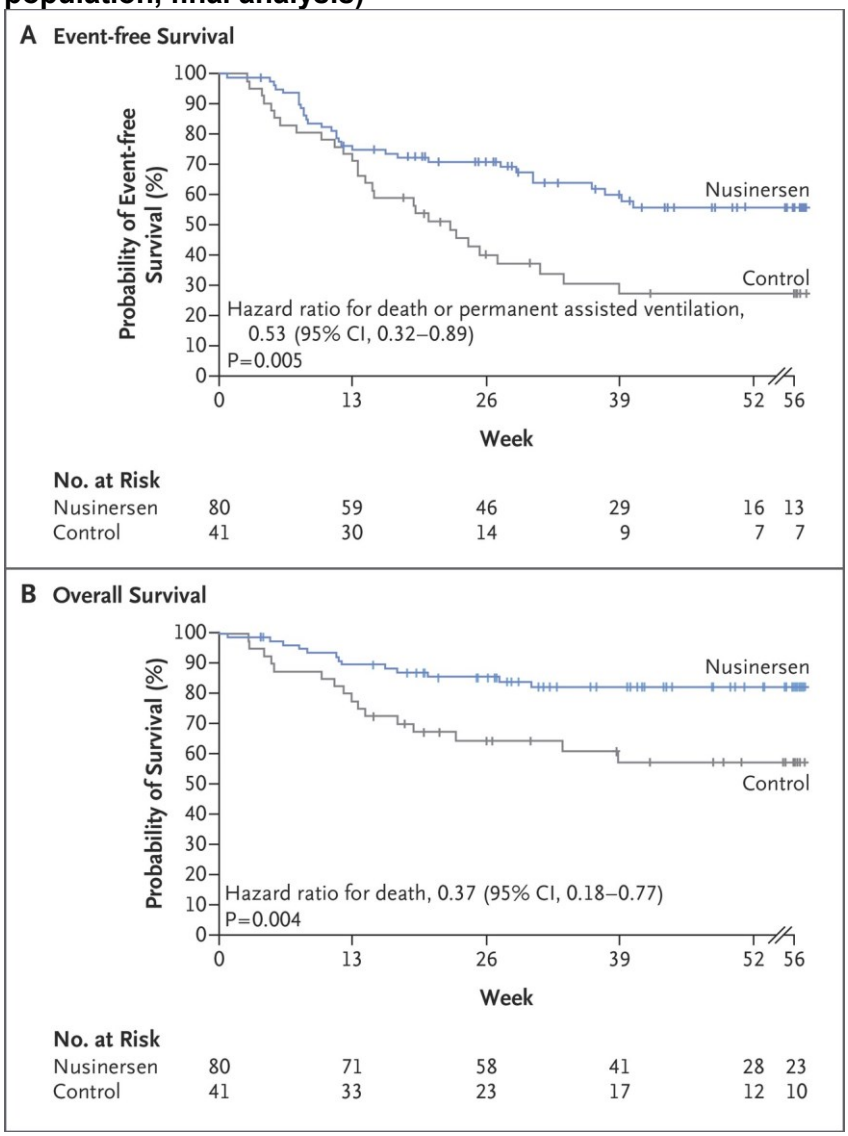


Abbreviation: HINE-2, Module 2 of the Hammersmith Infant Neurological Examination
Source: Finkel 2017a(49)

2.6.2.2 ENDEAR: Event-free survival

The likelihood of event-free survival was significantly higher in the nusinersen group than in the control group. By the cut-off date for the final analysis, 39% of the infants in the nusinersen group and 68% in the control group had died or had received permanent assisted ventilation. The median time to death or the use of permanent assisted ventilation was 22.6 weeks in the control group and was not reached in the nusinersen group. Overall, the risk of death or the use of permanent assisted ventilation was 47% lower in the nusinersen group than in the control group (hazard ratio, 0.53; 95% confidence interval [CI], 0.32–0.89; P=0.005; Figure 15).(49) Of note the event free survival appeared to be improved further by earlier treatment (please see the exploratory endpoint Section 2.6.3.2).

Figure 15. ENDEAR: K-M curves for event-free survival (A) and overall survival (B) (ITT population, final analysis)



Abbreviations: K-M, Kaplan-Meier; ITT, intention to treat
Source: Finkel 2017a(49)

2.6.3 ENDEAR: Secondary endpoints

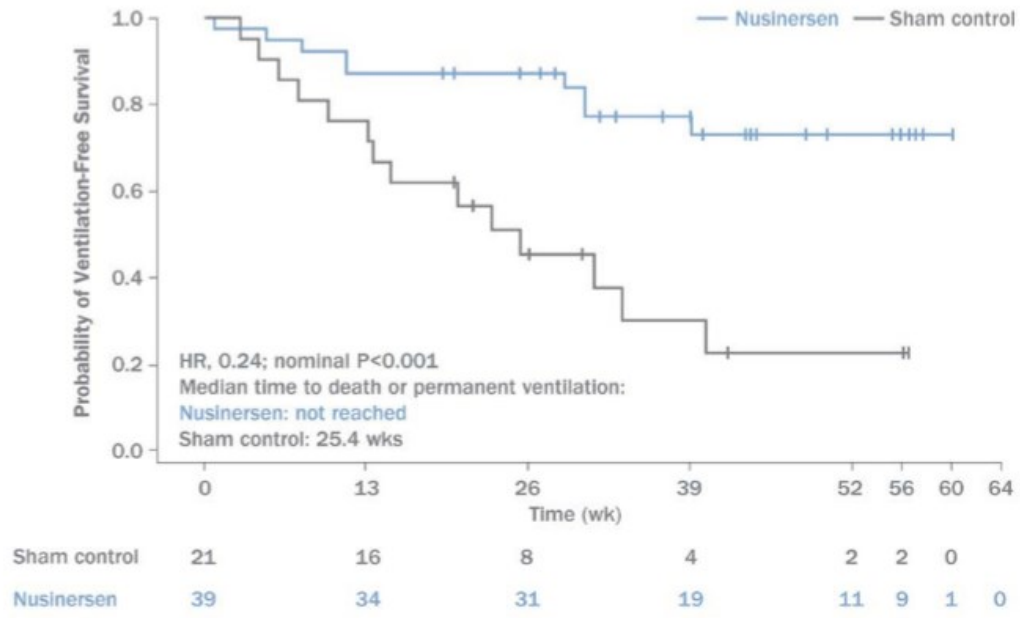
2.6.3.1 ENDEAR: Overall survival

A lower percentage of infants in the nusinersen group than in the control group had died by the end of the trial (16 vs. 39%). The risk of death was 63% lower in the nusinersen group than in the control group (hazard ratio, 0.37; 95% CI, 0.18–0.77; P=0.004; Figure 15).(49). The median time to death was not reached in either group. (49)

2.6.3.2 ENDEAR: Time to death or permanent ventilation in the subgroups of participants below and above the study median disease duration

In the subgroup of infants below the study median disease duration of 13.1 weeks, 23% of nusinersen-treated vs. 67% of sham control infants died or required permanent ventilation (hazard ratio, 0.24; nominal P<0.001; Figure 16). The risk of death or permanent ventilation was 76% lower in nusinersen-treated infants vs. sham control infants in this subgroup, and the median time to death or permanent ventilation was 25.4 weeks in the sham control infants and was not reached in nusinersen-treated infants.(49)

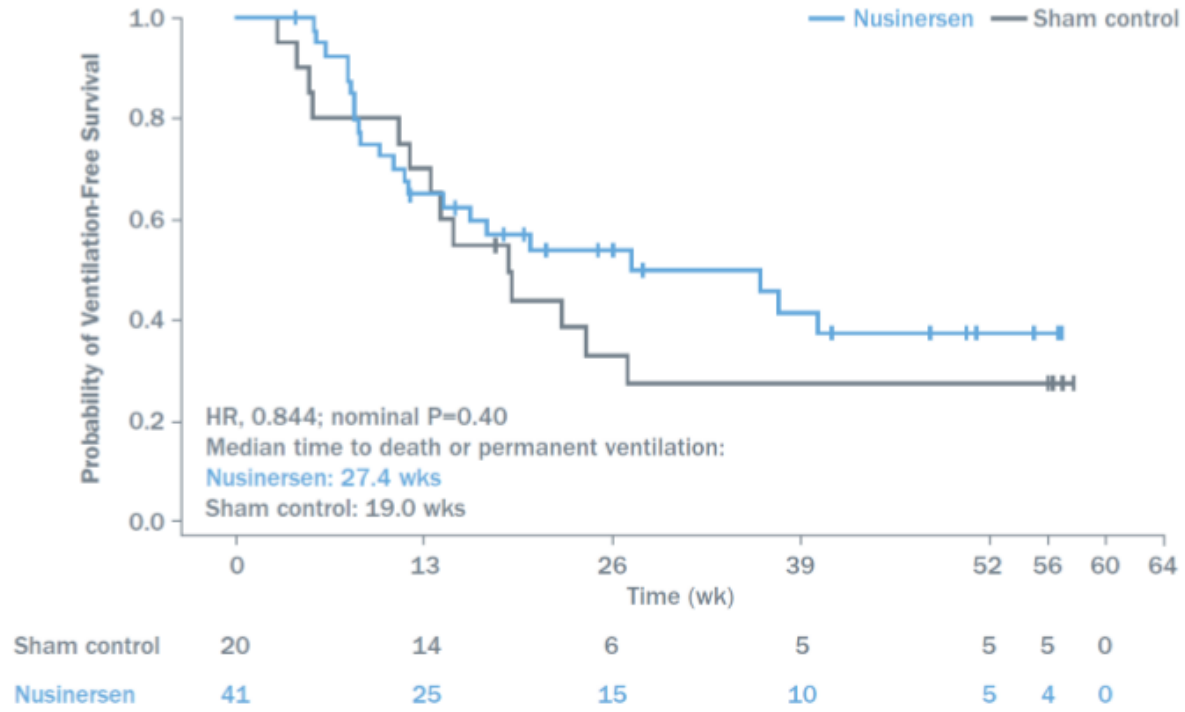
Figure 16. ENDEAR: K-M plot of time to death or permanent ventilation in the subgroup of infants below the median disease duration at screening



Abbreviations: HR, hazard ratio; K-M, Kaplan-Meier
Note: A HR <1 indicates lower risk of event for the nusinersen group. The HR is calculated based on Cox regression adjusted for each infant's disease duration at screening.
Source: Finkel 2017a(49)

Among infants above the study median disease duration, there was no significant difference in the proportion of infants who died or required permanent ventilation between groups (nusinersen, 54%; sham control, 70%; hazard ratio, 0.84; nominal P=0.40; Figure 17).(49)

Figure 17. ENDEAR: K-M plot of time to death or permanent ventilation in the subgroup of infants above the median disease duration at screening

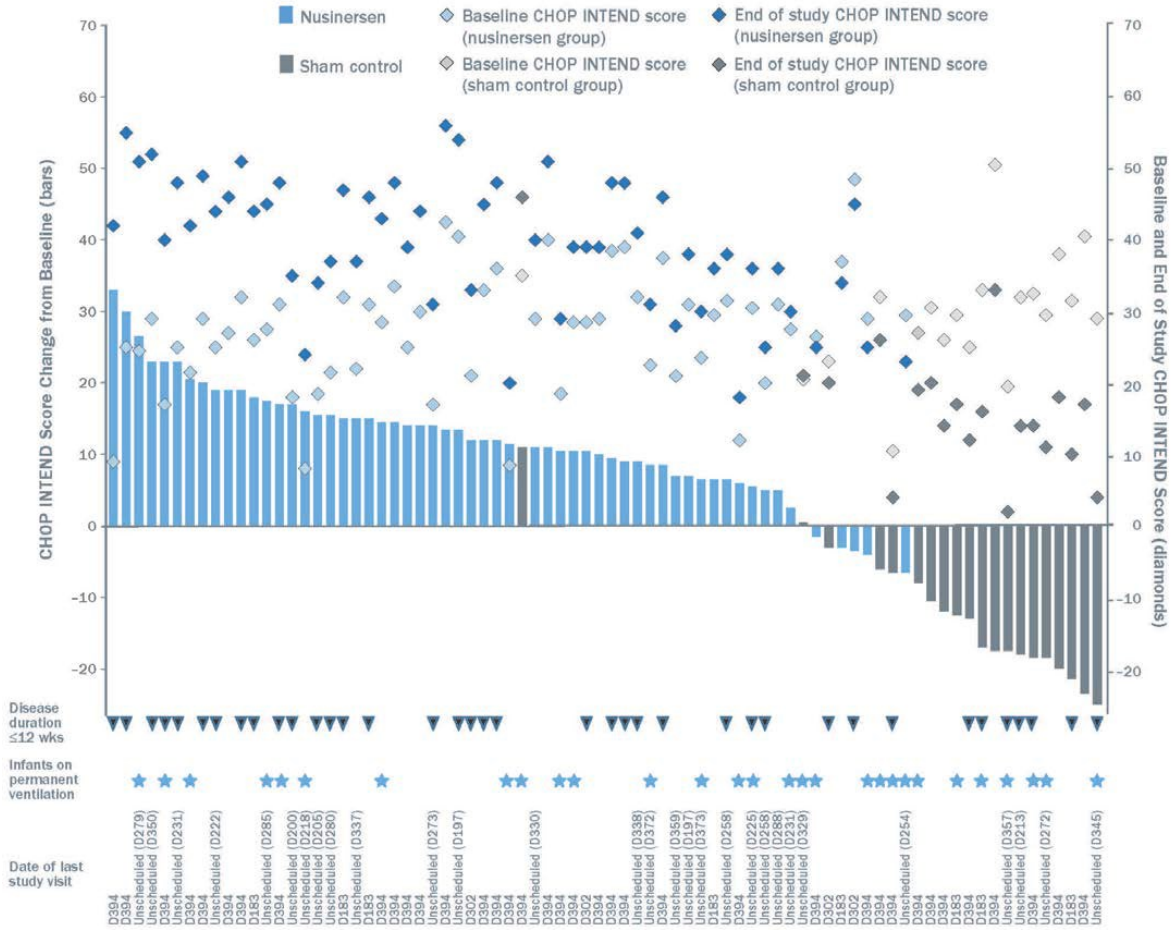


Abbreviations: HR, hazard ratio; K-M, Kaplan-Meier
Note: A HR <1 indicates lower risk of event for the nusinersen group. The HR is calculated based on Cox regression adjusted for each infant's disease duration at screening.
Source: Finkel 2017a(49)

2.6.3.3 ENDEAR: CHOP INTEND motor function scores

A significantly higher percentage of infants in the nusinersen group than in the control group had a 4-point increase in CHOP INTEND score (71 vs. 3%, P<0.001). An increase of at least 1 point from baseline in the CHOP INTEND score was observed in 73% of the infants in the nusinersen group vs. 3% in the control group; a decrease in the score was observed in 7 vs. 49% (Table 19; Figure 18).(49) In infants who were alive and still on study on day 394, 88 vs. 14% of children had a 4-point increase in CHOP INTEND score.(92)

Figure 18. ENDEAR: CHOP INTEND motor function scores at end of the study (efficacy set, final analysis)

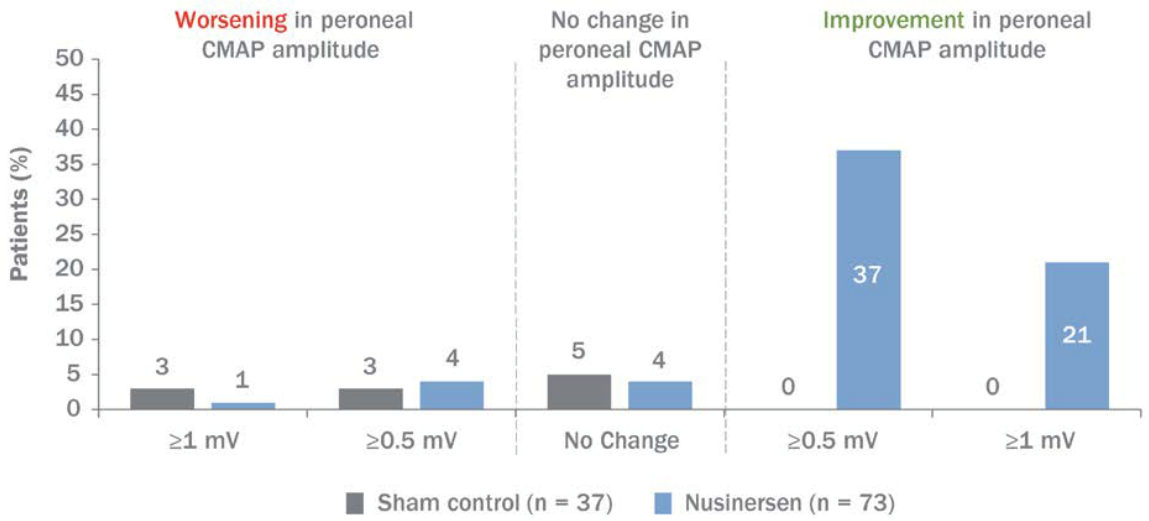


Abbreviations: CHOP INTEND, Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders
Infants with opportunity for at least a 6-month (day 183) assessment were included in the analysis; last available assessment of 6-month (day 183), 10-month (day 302), or 13-month (day 394) was used. Shortest bars indicate zero value. Light diamonds indicate baseline CHOP INTEND scores. Dark diamonds indicate end-of-study CHOP INTEND scores. Triangles indicate infants with disease duration ≤12 weeks at screening. Stars indicate infants who developed the need for permanent ventilation during the course of the study.
Source: Finkel 2017a(49)

2.6.3.4 ENDEAR: CMAP amplitudes

More nusinersen-treated patients had an improvement in peroneal CMAP amplitude at the end of the study than patients who had received the sham procedure. In addition, a greater proportion of nusinersen-treated patients were peroneal CMAP responders (i.e. CMAP amplitude increasing to or maintained at ≥1 mV compared to baseline at the later of the day 183, 302, or 394 study assessments) than sham-control patients (36 vs. 5%, respectively; nominal P=0.001) (Table 11 and Figure 19).(49) Similar improvements in nusinersen-treated patients were also observed in ulnar CMAP amplitude.(49)

Figure 19. Peroneal CMAP amplitude at end of study



Abbreviations: CMAP, compound muscle action potential
Infants with opportunity for at least a 6-month (day 183) assessment were included in the analysis; last available assessment of 6-month (day 183), 10-month (day 302), or 13-month (day 394) was used.
Source: Finkel 2017a(49)

2.6.4 ENDEAR: Key tertiary endpoints

2.6.4.1 ENDEAR: Serious respiratory events

[redacted]

2.6.4.2 ENDEAR: Number of hours of ventilatory support

[redacted]

2.6.4.3 ENDEAR: Number and length of hospitalisations

The adjusted annualised rate of hospitalisation was lower in the nusinersen group: 4.378 (95% CI: 3.636,5.273) hospitalisations/year in the nusinersen group vs. 5.817 (3.636, 5.273) hospitalisations/year in the control group (P=0.0959). In addition, overall time spent hospitalised was significantly lower in the nusinersen vs. sham control group (LS mean: 0.114 vs. 0.207; LS mean treatment difference [95% CI]: -0.093 [-0.151 to -0.034]; P=0.0022).(93).These findings are even more clinically meaningful in light of the poorer prognosis in the nusinersen group based on a more severe history of SMA symptoms at baseline compared with the control group (see Section 2.3.7.1).

2.6.5 ENDEAR: Conclusion

Among infants with SMA, those who received nusinersen were more likely to be alive and have improvements in motor function than those in the control group. Early treatment may be necessary to maximise the benefit of the drug. Despite the trial being ended early the efficacy seen is expected to extend beyond the limits of the randomization. Please see Section 2.13 for further discussion of the clinical efficacy results in ENDEAR in infantile onset SMA patients.

2.6.6 CHERISH: Efficacy results from the interim and final analyses

- Nusinersen showed significant and clinically meaningful improvement in motor milestones, enabling patients to achieve and/or maintain developmental motor milestones, which is a deviation from the natural history.
- Compared with the sham-control group, nusinersen-treated patients with later onset SMA demonstrated:
    - A significant improvement in motor function as measured by HFMSE scores from baseline to month 15 compared with a decline in HFMSE score in the control group at the interim analysis (P<0.001) and the final analysis (nominal P value: P=0.0000001).
        - Nusinersen-treated children who had shorter disease durations generally showed the greatest improvements in HFMSE from baseline; this is consistent with the idea that early initiation of treatment may lead to greater improvements.
    - A higher proportion of responders achieving a clinically meaningful change (defined as 3 points or more) in the HFMSE score than the control group (57 vs. 26%).
    - Patients in the nusinersen group showed sustained improvements in HFSME scores and because the improvement had not yet plateaued by 15 months patients may be expected to further improve.
    - Greater improvements in World Health Organization (WHO) motor milestones (20 vs. 6%); while there were patients in the control group who lost motor milestones at 15 months, there were no motor milestones lost in the nusinersen group.
    - More patients with improvements (“much improved” or “having any improvements”) at all time points in the investigator and caregiver CGI of change assessment.

The results in Table 20 represent the final analysis (data cut-off: 3 March 2017) and the interim analysis of the primary endpoint of the study, which was the only endpoint formally tested for the interim analysis (data cut-off: 31 August 2016). As previously noted, CHERISH was stopped on the request of an external impartial ethics board following positive statistical analysis of the primary endpoint at the interim analysis due to a statistically significantly

improvement in HFMSE scores as compared with patients in the sham-control group (P=0.0000002).

Table 20. Summary of primary and secondary results from the interim and final analysis of CHERISH

Efficacy parameter	Results	
	Nusinersen (N=84)	Sham control (N=42)
Interim analysis: Primary endpoint (data cut: 31st August 2016)		
HFMSE score		
Change from baseline in HFMSE (95% CI)	4.0 (2.9, 5.1)	-1.9 (-3.8, 0.0)
LSM change difference (95% CI)	5.9 (3.7, 8.1)	
P value	P<0.001	
Final analysis (data cut: 3rd March 2017)		
Primary endpoint		
HFMSE score		
Change from baseline in HFMSE (95% CI)	3.9 (3.0, 4.9)	-1.0 (-2.5, 0.5)
LSM change difference (95% CI)	4.9 (3.1, 6.7)	
Nominal P value[a]	P=0.0000001	
Secondary endpoints		
Change in HFMSE score of ≥3 points		
Proportion of children with change in HFMSE score of ≥3 points, % (95% CI)	57 (46, 68)	26 (12, 40)
Odds ratio (95% CI)	6 (2, 15)	
P value	P=0<0.001	
Motor milestones at 15 months (WHO criteria)		
% who achieved ≥1 new motor milestone (95% CI)	20 (11, 31)	6 (1, 20)
Difference in proportions (95% CI)	14 (-7, 34)	
P value	P=0.08	
LSM number of new motor milestones achieved per child (95% CI)	0.2 (0.1, 0.3)	-0.2 (-0.4, 0.0)
LSM difference (95% CI)	0.4 (0.2, 0.7)	
Nominal P value[b]	P=0.0001	
% who achieved standing alone (95% CI)	2 (0, 8)	3 (0, 15)
Difference in proportions (95% CI)	-1 (-22, 19)	
Nominal P value[b]	P >0.9999	
% who achieved walking with assistance (95% CI)	2 (0., 8)	0 (0, 10.)
Difference in proportions (95% CI)	1.5 (-19.1, 22.0)	
Nominal P value[b]	P >0.9999	
RULM		
Change from baseline at 15 months (95% CI)	4.2 (3.4, 5.0)	0.5 (-0.6, 1.6)
LSM difference (95% CI)	3.7 (2.3, 5.0)	
Nominal P value	P=0.0000001	

Abbreviations: CI, confidence interval; HFMSE, Hammersmith Functional Motor Scale Expanded; LSM, least squares mean; RULM, Revised Upper Limb Module; WHO, World Health Organization

[a]Because the P value for the primary endpoint was significant in the interim analysis, this endpoint was not formally tested for significance in the final analysis. The exploratory P value is not reported in the full publication and is from Mercuri et al. 2018(51)

[b]To control the overall type I error rate at 0.05 across the interim and final analyses for the testing of primary and secondary endpoints, a hierarchical strategy was used, in which significance of the primary endpoint was required before inferential conclusions could be drawn about the secondary endpoints. If an endpoint failed to

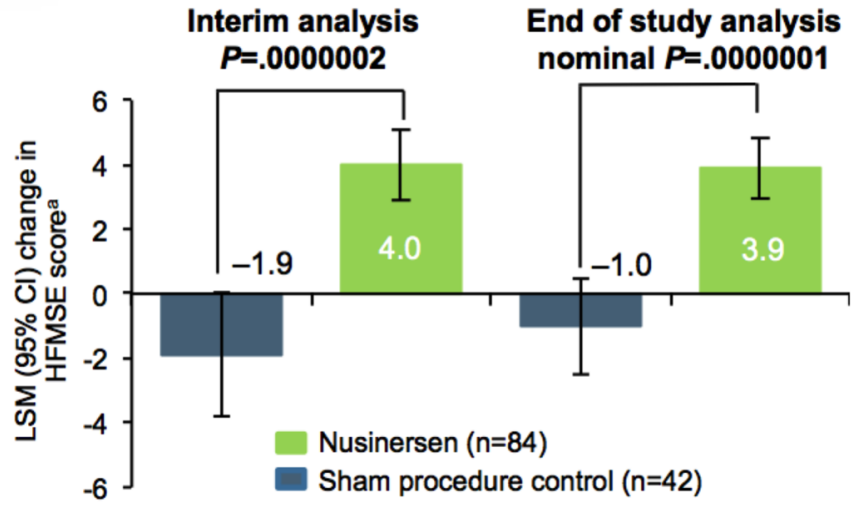
reach significance, subsequent endpoints were not tested within the hierarchical analysis. Secondary endpoints are listed in hierarchical order. Because the P value for the second secondary endpoint was not significant, all subsequent endpoints analysed in the hierarchical testing strategy were considered to be exploratory. The exploratory P values are not reported in the full publication and are from Mercuri et al. 2018(51)
Source: Mercuri 2018 (51);

2.6.7 CHERISH: Primary endpoints

2.6.7.1 CHERISH: HFMSE score

As shown in Table 20 and Figure 20, in the prespecified interim analysis, there was an LS mean increase from baseline to month 15 in the HFMSE score in the nusinersen group and an LS mean decrease in the control group, resulting in a significant between group difference favouring nusinersen (LS mean difference in change, 5.9 points; 95% CI, 3.7 to 8.1; P<0.001). In the final analysis, there was an LS mean increase from baseline to month 15 in the HFMSE score in the nusinersen group and an LS mean decrease in the control group (LS mean difference in change, 4.9 points; 95% CI, 3.1 to 6.7) (Figure 20). Similar results favouring nusinersen were observed in all sensitivity analyses for the primary endpoint (see Appendix M).

Figure 20. CHERISH: Primary endpoint: mean change from baseline to month 15 in HFMSE score



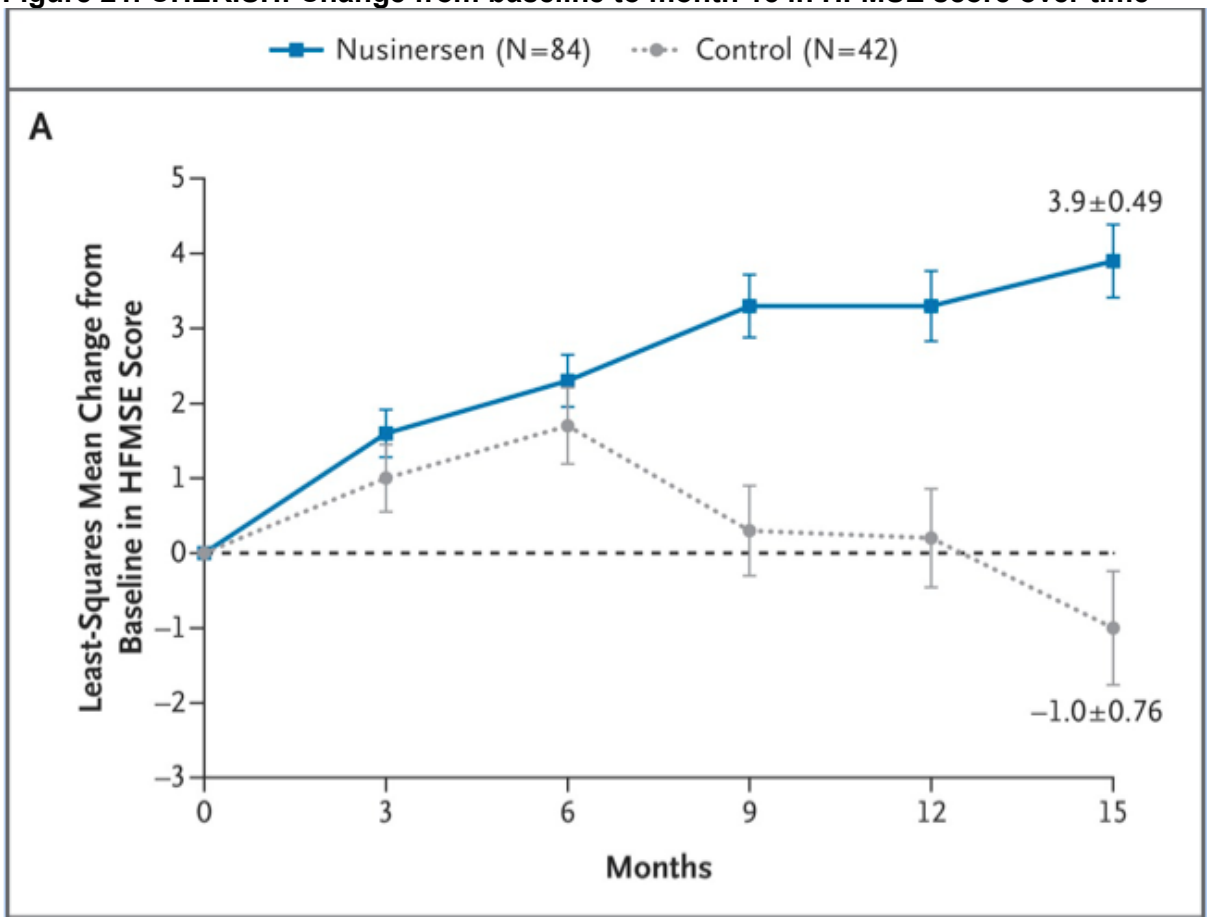
Abbreviations: CI, confidence interval; HFMSE, Hammersmith Functional Motor Scale Expanded; LSM, least squares mean

[a] From baseline to month 15. Interim analysis: observed - sham-procedure control, N=19; nusinersen, N=35; imputed - sham-procedure control, N=23; nusinersen N=49. End of study analysis: observed - sham-procedure control, N=34; nusinersen, N=66; imputed - sham-procedure control N=8, nusinersen N=18.
The P value in the Mercuri 2018 NEJM publication differs from that presented here (P<0.001 vs P=0.0000002) due to journal style and rounding guidelines.
Source: Mercuri 2017(73)

Mean change of HFMSE scores from baseline over time is shown in Figure 21. The results showed a greater improvement in HFMSE scores in the nusinersen group compared with the sham-control group at all time points. At month 3 the LS mean difference between the 2 groups was 0.6, which increased to 3.0 by month 9 and 3.1 by month 12. By month 15, the patients in the control group were showing a decline in HFSME scores from baseline (-1.0) while the

patients in the nusinersen group continued to show an improvement, with an LS mean difference in scores of 4.9. Therefore, patients in the nusinersen group showed sustained improvements in HFSME scores and because the improvement had not yet plateaued by 15 months patients may be expected to further improve.

Figure 21. CHERISH: Change from baseline to month 15 in HFMSE score over time



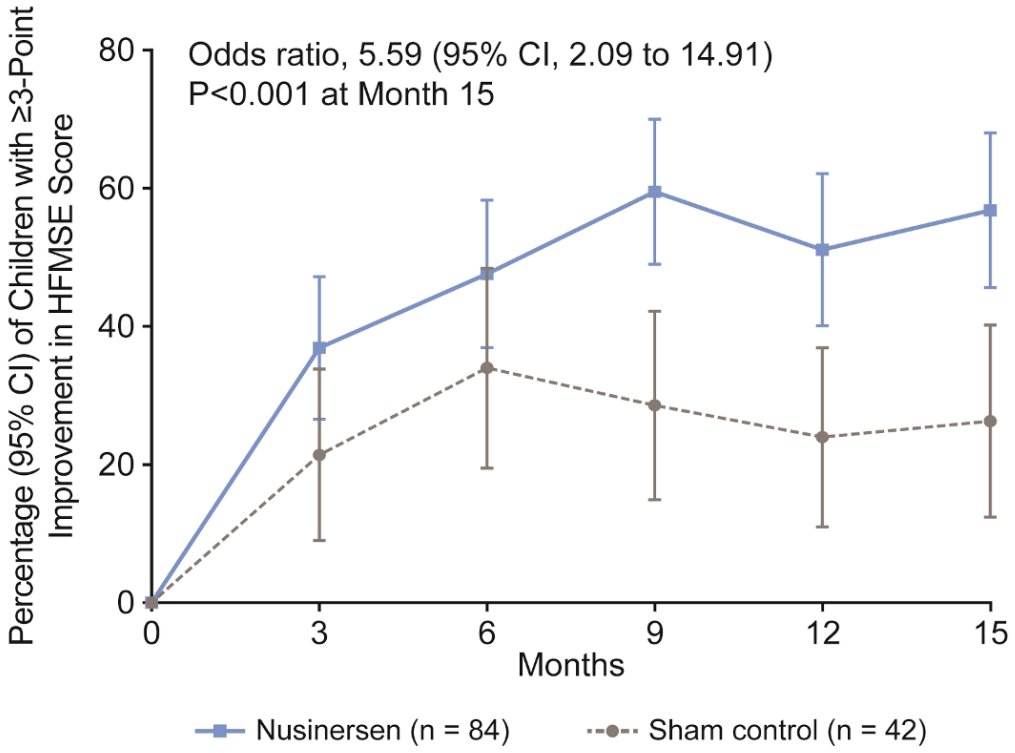
Abbreviations: HFMSE, Hammersmith Functional Motor Scale Expanded; LSM, least squares mean; SE, standard error
Source: Mercuri 2018(51)

2.6.8 CHERISH: Secondary endpoints

2.6.8.1 CHERISH: Proportion of patients with a ≥3-point increase in HFMSE score

A higher percentage of children in the nusinersen group than in the control group had an increase from baseline to month 15 in the HFMSE score of at least 3 points (57 vs. 26%, P<0.001) (Table 20 and Figure 22).(51) Results from the IES supported the primary analysis.

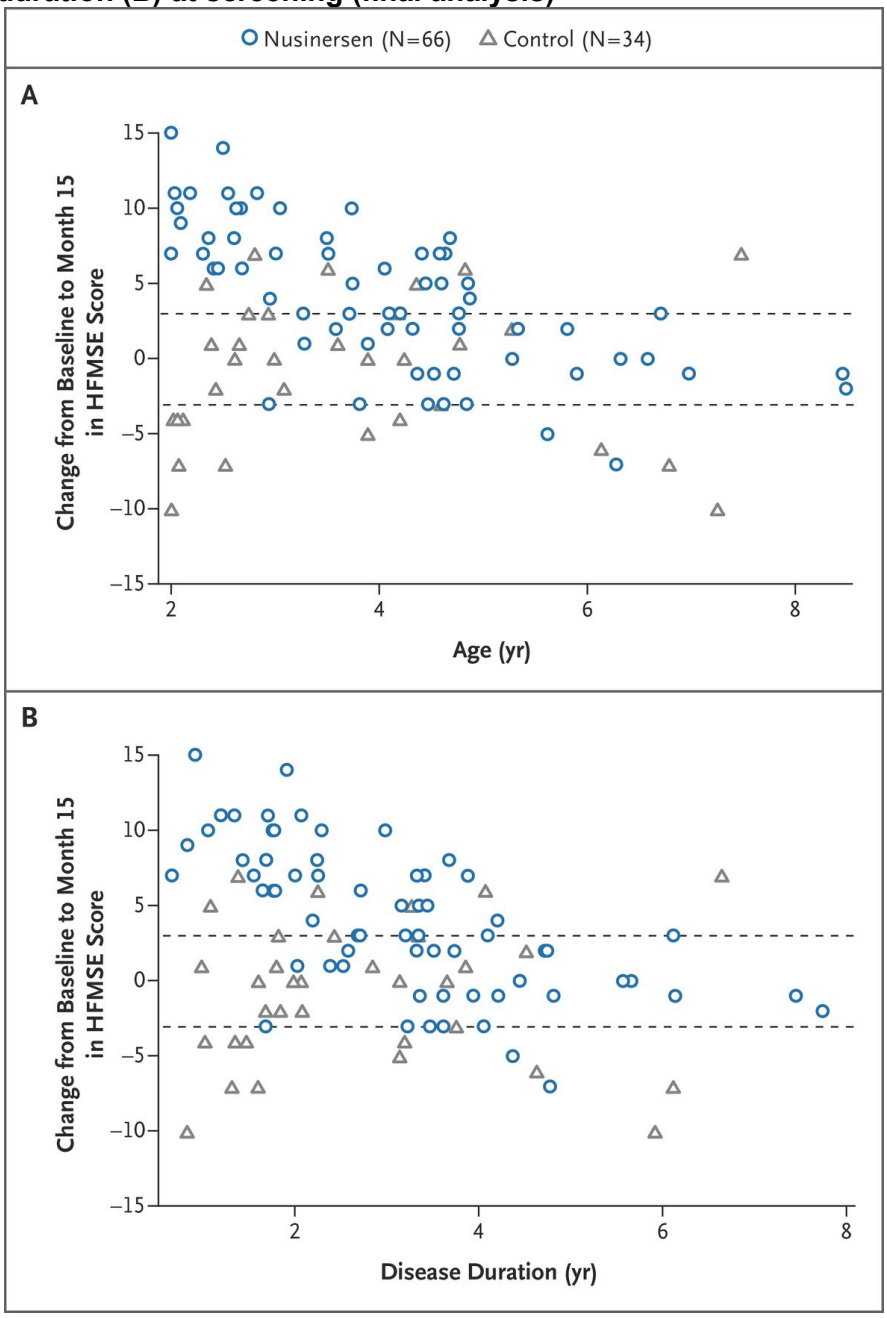
Figure 22. CHERISH: Proportion of HFMSE responders (≥3-point change in score from baseline) at each visit based on the final analysis (ITT population)



Abbreviations: CI, confidence interval; HFMSE: Hammersmith Functional Motor Scale Expanded; ITT, intention to treat
Source: Mercuri 2018(51)

Analyses of the change from baseline to month 15 in the HFMSE score according to age and disease duration revealed greater improvements in younger children and in those who received treatment earlier in their disease course, respectively (Figure 23).These data are consistent with the idea that early initiation of treatment may lead to greater improvement over a period of time.

Figure 23. Change from baseline in total HFMSE score according to age (A) and disease duration (B) at screening (final analysis)



Abbreviations: HFMSE, Hammersmith Functional Motor Scale Expanded; yr, year
Disease duration is a child's age at screening minus the age at symptom onset. The analyses included children in the ITT population who did not have missing data for the 15-month assessment (66 in the nusinersen group and 34 in the control group). Dotted lines represent a ±3-point change in HFSME score, which is considered to be clinically meaningful
Source: Mercuri 2018(51)

2.6.8.2 CHERISH: Motor milestones (WHO criteria)

As can be seen in Table 21, more patients in the nusinersen group (20%) gained new motor milestones compared to those in the control group (6%). At month 15, there was an LS mean

increase from baseline in the number of new WHO motor milestones achieved per child in the nusinersen group (by 0.2) and an LS mean decrease in the control group (by –0.2).

While there were patients in the control group who lost WHO motor milestones at 15 months, there were no motor milestones lost in the nusinersen group (Table 21). At the end of the study, there were a few patients in both treatment groups who could stand alone, and 1 subject in the nusinersen group who was able to walk with assistance. Evaluations at different time points (i.e. 6, 9 and 12 months) were supportive of the main analysis of all the motor milestones secondary endpoints.

Table 21. CHERISH: WHO motor milestone achievement

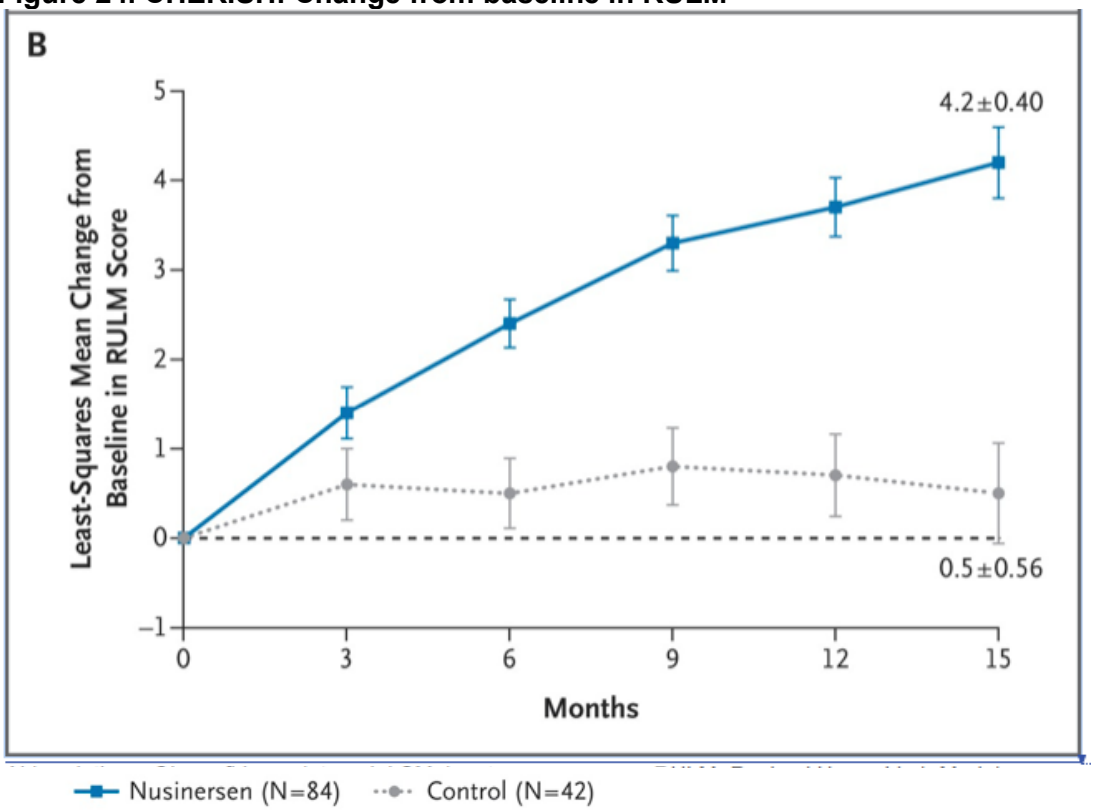
WHO motor milestone	Nusinersen (N=66)			Sham control (N=34)			Difference in % change at month 15 (nusinersen minus sham control)
	Baseline n (%)	Month 15 n (%)	Change at month 15 %	Baseline n (%)	Month 15 n (%)	Change at month 15 %	
Sitting without support	65 (98)	66 (100)	+2	34 (100)	34 (100)	0	+2
Hands and knees crawling	13 (20)	20 (30)	+10	7 (21)	1 (3)	-18	+28
Standing with assistance	5 (8)	9 (14)	+6	6 (18)	4 (12)	-6	+12
Walking with assistance	4 (6)	5 (8)	+2	2 (6)	2 (6)	0	+2
Standing alone	2 (3)	3 (5)	+2	1 (3)	2 (6)	+3	-1
Walking alone	0	1 (2)	+2	0	0	0	+2

Abbreviations: WHO, World Health Organization
Source: Mercuri 2017b(73)

2.6.8.3 CHERISH: RULM test at 15 months

Overall improvements were seen in the RULM for both groups, but the nusinersen group had a greater improvement (LS mean change of 4.2) than the control group (LS mean change of 0.5; difference of 3.7) (Table 20 and Figure 24). The results from the IES support the primary analysis. The trends in RULM scores by visit based on observed values and the IES were generally similar to those based on imputed values.

Figure 24. CHERISH: Change from baseline in RULM



Abbreviations: CI, confidence interval; LSM, least squares mean; RULM, Revised Upper Limb Module
Observed data: sham-procedure control, N=34; nusinersen, N=66
Source: Mercuri 2018 (51)

2.6.9 CHERISH: Key tertiary endpoints

[redacted]

Table 22. CGI assessment (investigator and caregiver) at month 15

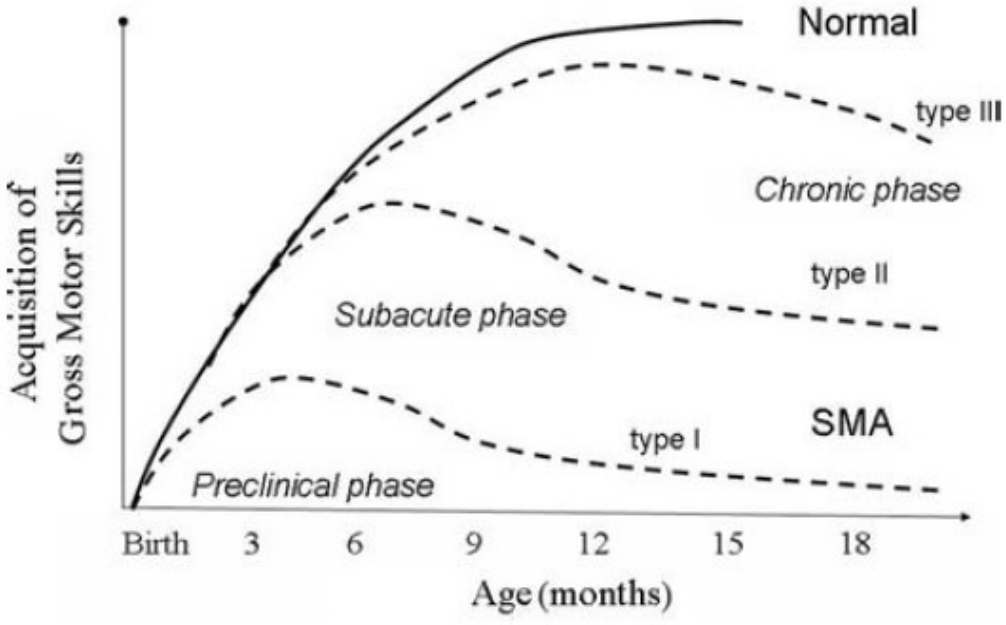
	Investigator assessment		Caregiver assessment	
CGI assessment N (%)	[redacted]	[redacted]	[redacted]	[redacted]
Very much improved	[redacted]	[redacted]	[redacted]	[redacted]
Much improved	[redacted]	[redacted]	[redacted]	[redacted]
Minimally improved	[redacted]	[redacted]	[redacted]	[redacted]
No change	[redacted]	[redacted]	[redacted]	[redacted]
Minimally worse	[redacted]	[redacted]	[redacted]	[redacted]
Much worse	[redacted]	[redacted]	[redacted]	[redacted]
Very much worse	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: CGI = Clinical Global Impression
Source: CHERISH CSR(86)

[redacted]

Additionally, consideration should be given to the natural history of the disease whereby patients achieve motor milestones but then either plateau or decline and subsequently lose milestones as portrayed in Figure 25.

Figure 25. Relationship between gross motor milestones acquisition and loss over time



Source: Swoboda 2007(94)

When these month 9 results are taken in the context of the disease trajectory, starting at 12 months, subjects in the nusinersen group had a greater mean change compared to a decline in the control group.

[redacted]

[redacted]

[redacted]

The limitations and challenges of HRQL data in infants and children with SMA are discussed in Section 2.13.4 and Section 3.4.

2.6.10 CHERISH: Conclusion

In the CHERISH study, nusinersen demonstrated significant and clinically meaningful improvements in motor function vs. sham procedure, as assessed by the HFMSE from baseline to month 15. Improvements for nusinersen vs. sham procedure also were observed in the number of new WHO motor milestones achieved per child and in upper limb function. These improvements are likely to have a significant impact on the daily lives and HRQL of patients and their carers/families (see Section 2.3.5 for the relationship between these motor milestone scales and activities of daily living/HRQL). It should also be noted that stabilisation of a patient's current clinical state has been reported to represent a therapeutic progress for patients and carers.(43,44) In a large survey of patients with later onset SMA (type II and III) (N=822 patients or carers) the majority of respondents (81.3%) felt that a medicine which would stabilise their disease course would represent an important progress and almost all of the respondents a progress (96.5%, moderate or important).(44) Of particular importance is stabilisation in muscular strength (including those that would be evaluated by the HFMSE and RULM), which would allow patients to preserve functions such as self-feeding, having a wash independently, use the bathroom independently and performing transfers alone (Table 23).(44)

Table 23. Survey results - priority of functions to be stabilised

Stabilisation	Number (%) of respondents (N=822)
Self-feeding	301 (36.6)
Wash on own	227 (27.6)
Use restroom on own	206 (25.1)
Transfer on own	164 (20.0)
Use a keyboard	212 (25.8)
Turn in bed	183 (22.3)
Write with a pen	200 (24.3)
Brush own teeth	149 (18.1)
Dress on own	149 (18.1)
Brush own hair	71 (8.6)

Participants were asked to choose 3 functions, ranked 1–3 in decreasing order of priority, they would most like to stabilise. All numbers are the number of the respective answers received. The percentages given express the proportion of the total answers selecting the given function, irrespective of the priority order, among the 822 replies to the questionnaire.
Source: Rouault 2017(44)

Please see Section 2.13 for further discussion of the clinical efficacy results in CHERISH in later onset SMA patients.

2.6.11 NURTURE (supportive study): Efficacy results

- Benefits with nusinersen treatment have been reported in the interim analysis (31st October 2016: median time on study 317.5 (2–524) days) of an ongoing phase II trial in pre-symptomatic infants (NURTURE), demonstrating that early initiation of treatment with nusinersen is beneficial, enabling infants to develop motor milestones above what might be expected for those with infantile or later onset SMA.
- All infants were alive without requiring chronic respiratory support and were exhibiting improvements in motor function and/or motor milestones
- Most infants achieved motor milestone and growth parameter gains not regularly acquired by infants with infantile and later onset SMA and generally more consistent with normal development, such as head control, independent sitting, standing and walking independently
- Nusinersen-treated infants achieved motor milestones beyond those achieved by their sibling with infantile and later onset SMA
    - These results are inconsistent with the natural history of sibling pairs with SMA in which most siblings (87%) have concordant phenotypes
- These results suggest that early initiation of nusinersen provides clinical benefits in patients who begin treatment in the pre-symptomatic stage of SMA

2.6.12 NURTURE: Primary endpoint: Time to death or respiratory intervention

At the time of the interim analysis (data-cut: 31 October 2016), infants had been on study for a median (range) of 317.5 (2–524) days. All infants were alive and none had required respiratory intervention (invasive or non-invasive ventilation for ≥6 hours/day continuously for ≥7 days or tracheostomy).(45)

2.6.13 NURTURE: Secondary endpoints

2.6.13.1 NURTURE: HINE motor milestone achievements

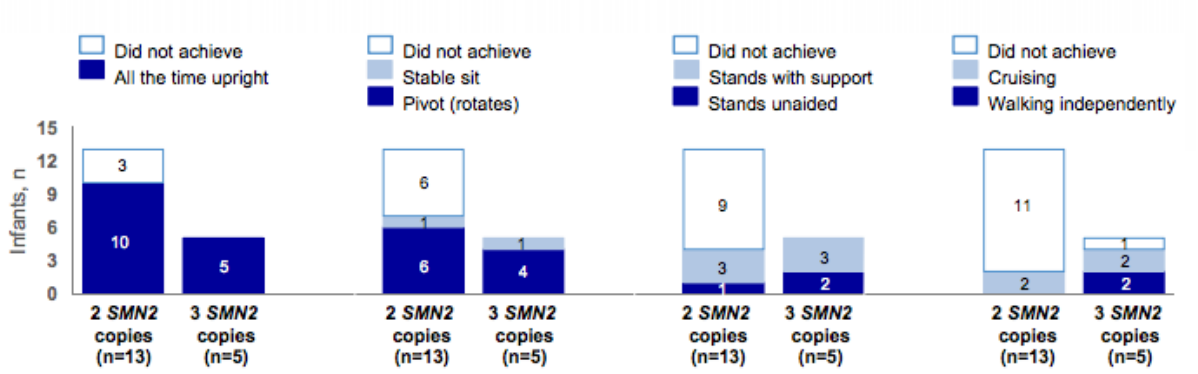
Subjects achieved milestones beyond what would be expected in SMA type I or II and more consistent with normal development. Compared to baseline, improvements in HINE motor milestones were achieved in 16 out of 18 (89%) subjects in the efficacy set. At the data cut-off, 12 subjects were sitting independently, 9 were standing with or without support, and 6 were walking with or without support (Table 24). Three of 9 infants ≥12 months of age had achieved standing unaided (expected age, 12 months) and 2 infants ~13 months of age had achieved independent walking (expected age, 15 months).

Table 24. NURTURE: HINE motor milestone achievements

Motor function	Full head control	Independent sitting (stable sit, pivot [rotates])	Stands with support/stands unaided	Cruising[a] /walking
Total infants achieving, n	15	12	9	6
Expected age of attainment, months	5	7	8	11
Infants achieving at expected age, n/N (%)	15/16 (94%)	10/12 (83%)	7/11 (64%)	5/9 (56%)

Abbreviation: HINE, Hammersmith Infant Neurological Examination
Data-cut: 31 October 2016 interim efficacy set
[a] Cruising = walks while holding on (e.g to furniture/baby walker)
Source: DeVivo 2017(54)

Figure 26. NURTURE: HINE motor milestone achievement



Abbreviation: HINE, Hammersmith Infant Neurological Examination, IES, interim efficacy set
Among 18 Infants with day 64 Assessment (IES)
See Section 2.3.7.3 for details of SMN copy number
Cruising = walks while holding on (e.g to furniture/baby walker)
Source: DeVivo 2017(54)

2.6.13.2 NURTURE: HINE motor milestone achievements from sibling pairs

For this interim analysis, treated subjects were compared to untreated siblings in terms of achieving age-appropriate motor milestones of sitting (at approximately 6 months of sage [day 183]) and walking (at approximately 14 months of age [day 421]). The natural history of SMA suggests that most siblings (87%) have concordant phenotypes (i.e. the presence of the same symptoms/severity of disease [subtype of SMA]).(95)

Thirteen siblings in NURTURE who were evaluable at day 183 had ≥1 sibling with SMA. Of the thirteen, 8 of the NURTURE nusinersen treated infants had a sibling who had not achieved independent sitting. Of these eight, 6 NURTURE nusinersen treated subjects were ≥7 months

of age (normal age to sit at). Of these six, 5 NURTURE nusinersen treated subjects had achieved independent sitting. This is contrary to what would be expected by the natural history of sibling concordance.(45)

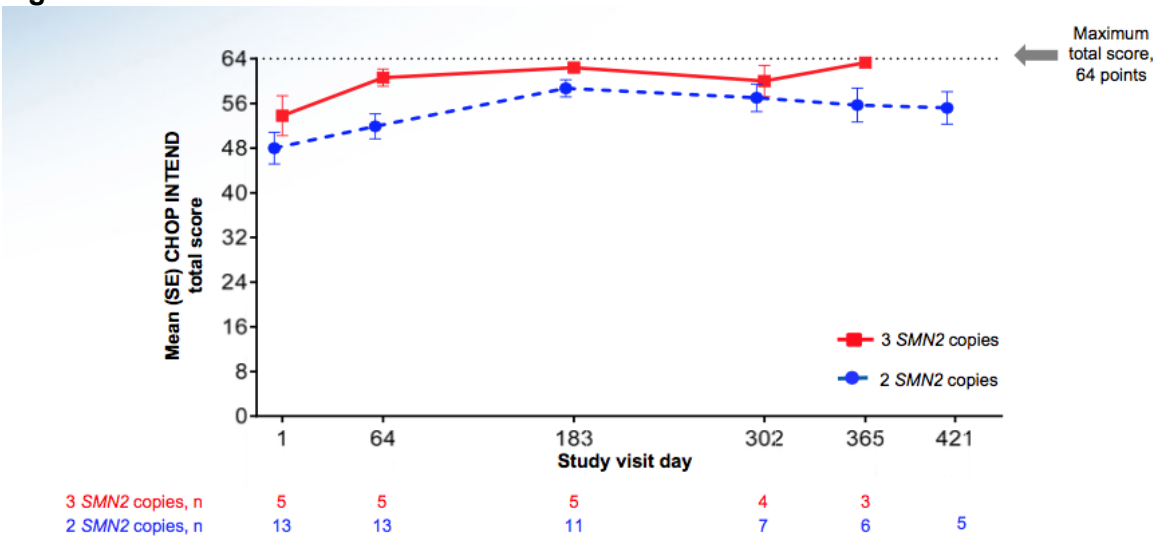
Of the thirteen sibling pairs, 5 NURTURE nusinersen treated infants had a sibling who achieved independent sitting but not walking. Of those five, 2 NURTURE nusinersen treated infants had achieved independent walking. This is also contrary to what would be expected by the natural history of sibling concordance.

These data suggest that patients treated with nusinersen exhibit development that is discordant with their untreated sibling and are able to achieve motor milestones that are not regularly acquired by patients with SMA.

2.6.13.3 NURTURE: CHOP INTEND

From baseline to last study visit, 16 of 18 subjects (89%) in the efficacy set achieved and maintained improvements in the CHOP INTEND total score, which with the balance of probabilities is inconsistent with the natural history of SMA (Figure 27). The majority of subjects (61%, N=11/18) had an increase of ≥4 points in the CHOP INTEND total score compared to baseline over the duration of the study. Overall, 39% subjects (N=7/18) achieved the highest attainable CHOP INTEND score at the data cut-off date for this interim analysis, which is not achievable in untreated patients who are affected by SMA.

Figure 27. NURTURE: Mean CHOP INTEND total score over time



Abbreviations: CHOP INTEND, Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders; SE, standard error
Data-cut: 31 October 2016
Source: Crawford 2017(45)

2.6.13.4 NURTURE: WHO motor milestone achievement

Achievement of WHO motor milestones increased steadily from baseline, and all subjects who gained a WHO motor milestone from baseline retained the motor milestone until the last study visit for this data cut-off. At the last observed visit, 71% of patients had achieved sitting without support, 59% had achieved standing with assistance, 29% walking with assistance, 18% standing alone, and 12% walking alone (Table 25).

Table 25. NURTURE: WHO motor milestone achievement

WHO motor milestone	2 *SMN2* copies N=12	3 *SMN2* copies N=5	Total N=17
Sitting without support (sits up straight for ≥10 seconds), n (%)	7 (58)	5 (100)	12 (71)
Standing with assistance (stands with assistance for ≥10 seconds), n (%)	5 (42)	5 (100)	10 (59)
Hands and knees crawling (stomach does not touch surface during ≥3 continuous movements), n (%)	2 (17)	4 (80)	6 (35)
Walking with assistance (child takes ≥5 supported steps), n (%)	2 (17)	3 (60)	5 (29)
Standing alone (child stands alone for ≥10 seconds, n (%)	1 (8)	2 (40)	3 (18)
Walking alone (child takes ≥5 independent steps), n (%)	0	2 (40)	2 (12)

Abbreviation: WHO, World Health Organization
Last observed visit: Data-cut: 31 October 2016 (interim efficacy set)
Source: Crawford 2017(45)

2.6.13.5 NURTURE: Growth parameters

All but 1 subject gained weight over time, [redacted]

Four patients (out of 16) had manifestations of SMA symptoms observed up to 6 months of age based on growth failure, including 1 subject who had a percutaneous gastric tube placement to assist with feeding.(45) However, many factors unrelated to SMA may contribute to early growth failure in infants. In this regard, the pre-symptomatic status of the patients in NURTURE confounds the assessment of whether growth failure is a true manifestation of SMA symptom onset.(1)

[redacted]

2.6.14 Conclusion

In infants with pre-symptomatic SMA nusinersen demonstrated beneficial effects on survival and achievement of motor milestones not normally acquired by infants with SMA type I or II. Please see Section 2.13 for further discussion of the clinical efficacy results in NURTURE in pre-symptomatic SMA patients, and the benefits of early treatment with nusinersen.

2.7 Subgroup analysis

Subgroup analysis from the 2 pivotal trials ENDEAR and CHERISH, in addition to data from NURTURE, have consistently shown that a shorter period between disease onset and treatment demonstrates on average a better outcome, suggesting that early treatment with nusinersen may confer the greatest benefits.

2.7.1 ENDEAR

The main analyses of event-free survival, motor milestones, CHOP INTEND, and overall survival results were evaluated for the following pre-specified subgroups:

- Age at symptom onset (≤12 weeks, >12 weeks [N=94, N=16])
- Disease duration at screening (≤12 weeks, >12 weeks [N=48, N=62])

Statistical analysis was as for the primary and secondary endpoints (Section 2.4). As described, statistical analyses, sample size and study power were based around the primary efficacy endpoints. The ENDEAR study was therefore not powered to assess differences between nusinersen and sham control in subgroups. In addition, the numbers of patients in the age of symptom onset >12 weeks was small (N=16), meaning results of this subgroup analyses in particular should be interpreted with caution.

See Appendix E for the results of subgroup analyses. Overall, nusinersen demonstrated benefit in all subgroups and greater efficacy in infants with disease duration ≤12 weeks and ≤12 weeks of age.(85,91) Therefore, early treatment with nusinersen may confer the greatest benefits. In addition to the ITT population, the economic analysis has been conducted based on these subgroups (Section 3.9).

2.7.2 CHERISH

A pre-specified subgroup analysis based on disease duration (<25 months; ≥25 months; <44 months and ≥44 months) and age at screening (<6 years vs. ≥6 years) was performed. It should be noted that the stratum that included children younger than 6 years of age was larger than the stratum that included children 6 years of age or older. See Section 2.4 for the statistical analysis; the CHERISH study was not powered to detect differences. Analyses of the change from baseline to month 15 in the HFMSE score according to age and disease duration revealed greater improvements in younger children and in those who received treatment earlier in their disease course, respectively (Figure 23 Section 2.6.8.1 and Appendix E). Waterfall plots showing HFMSE and RULM score at months 15, which depict the age and disease subgroups, are shown in Appendix E, showing that younger children and those who received treatment earlier in their disease course tend to have greater improvements. Subgroup analysis has not been conducted in the economic analysis due to the small sample size within the CHERISH trial.

2.8 Meta-analysis

A meta-analysis was not considered appropriate due to the different SMA populations across the trials. A summary of the principal findings from ENDEAR, CHERISH and NURTURE are

described in Section 2.13.1, including a comparison of motor milestone achievement among the patients with symptomatic infantile onset SMA and pre-symptomatic SMA (Figure 29). Overall, nusinersen has consistently been shown to increase motor milestone achievement in all SMA patient populations that it has been trialled.(1) This is in contrast to the natural history of SMA where a decline in motor milestones would be expected (see Section 1.3.1) and where patients have reported that disease stabilisation would be a positive outcome. (43,44)

2.9 Indirect and mixed treatment comparisons

Due to a lack of relevant active comparators, because supportive care may vary across regions and the choice of supportive care is based on the patients' physical status, no indirect or mixed treatment comparisons were conducted. Any such indirect or mixed treatment comparison would not have been informative and potentially not fully representative of clinical practice in England.

2.9.1 Uncertainties in the indirect and mixed treatment comparisons

Non-applicable.

2.10 Adverse reactions

2.10.1 Integrated safety analysis

An integrated safety analysis of nusinersen from unblinded data from 8 completed or ongoing studies (all sham-controlled or uncontrolled studies) has been conducted, as reported as a poster presentation by Mercuri et al. 2017.(96) The studies included the pivotal clinical studies ENDEAR and CHERISH, together with other phase I and II trials in the following patient populations:

- Infantile onset SMA
    - ENDEAR: Pivotal phase III, randomised, double-blind, sham-controlled study; dose 12 mg × 6 over 302 days; N=121 (nusinersen group n=80; sham-control group n=41) (see Section 2.3.2 for details of the study design)
    - CS3A: Phase II, open-label, single arm study; dose 6 mg × 3 then 12 mg × 9 or 12 mg × 12 over 1,261 days; data cut January 26, 2016; N=20 (see Appendix L)
- Later onset SMA
    - CHERISH: Pivotal phase III, randomised, double-blind, sham-controlled study; dose 12 mg × 4 over 274 days; data cut April 30, 2016; N=126 (nusinersen group n=84; sham-control group n=42) (see Section 2.3.4 for study design)
    - Phase I, open-label, single arm studies: CS1 and CS10 (extension of CS1), CS2 and CS12 (extension of CS2 and CS10: over 533 days; data cut April 7, 2016) (N=56 overall) (see Appendix L)
- Pre-symptomatic SMA
    - NURTURE: Phase II, open-label, single arm study; dose 12 mg × 18 over 1,730 days; ongoing; data cut October 31, 2016; N=20 (see Section 2.3.6 for study design)

2.10.2 Safety population and treatment exposure

Across the 8 unblinded studies, 260 infants and children were treated with nusinersen for a total of 355 patient-years, including 100 patients with infantile onset SMA for a total of 91.2 patient-years and 140 patients with later onset SMA for a total of 247.6 patient-years (Table 26).

Table 26. Exposure to nusinersen

Patients [a]	Infantile onset SMA	Later onset SMA	Pre-symptomatic SMA	All nusinersen-treated patients
Study	ENDEAR and CS3A	CHERISH and CS1, CS2, CS10, CS12	NURTURE	ENDEAR, CHERISH, NURTURE, CS3A, CS1, CS2, CS10, CS12
No. of patients dosed with nusinersen	100	140	20	260
Median (range) exposure, days	308 (6–994)	453 (31–1,536)	329 (6–531)	397 (6–1,536)
Total no. of patient-years	91.2	247.6	16.5	355.3
Median (range) no. of doses received	5 (1–9)	4 (1–8)	6 (1–7)	4 (1–9)

Abbreviations: No., number; SMA, spinal muscular atrophy
[a] Patients were considered to be exposed to study treatment from the time the very first dose was administered to the last day of follow-up
Source: Mercuri et al. 2017(45)

2.10.3 Adverse events

All AEs leading to treatment discontinuation were observed in the infantile onset SMA studies, and were events with fatal outcomes that were consistent with those typically observed for infantile onset SMA (usually respiratory in nature) (Table 27).(45)

Treatment-related AEs (i.e. assessed by the investigator as related to the study drug) occurred in only 1 patient with later onset SMA [redacted] and in no patients with infantile onset SMA or pre-symptomatic SMA (Table 27).(45)

The majority of patients reported an AE(s) – 95% of nusinersen-treated patients and 99% of sham-control-treated patients. The most commonly reported AEs were consistent with events typically observed in patients with SMA or complications of lumbar puncture (headache, vomiting, back pain and post-lumbar puncture syndrome) (Table 27). Lumbar puncture-related events, such as headache and post lumbar puncture syndrome, were reported more commonly in children than in infants, and this most likely reflects the higher verbal communication skills present in children appropriate for their age.(1) Of note, the incidence of post lumbar puncture syndrome when administering nusinersen could be reduced by using a non cutting needle and a needle with smaller diameter.(97)

Pre-symptomatic infants treated with nusinersen experienced fewer AEs compared with symptomatic infants, which is most likely due to their healthier baseline condition, which they maintained throughout participation in the study (Table 27).

Table 27. Adverse event summary from integrated safety analysis of nusinersen

N (%)	Nusinersen-treated patients				Sham-control-treated patients
	Infantile onset SMA	Later onset SMA	Pre-symptomatic SMA	All nusinersen-treated patients	
	ENDEAR & CS3A (N=100)	CHERISH & CS1, 2, 10 & 12 (N=140)	NURTURE (N=20)	ENDEAR, CHERISH, NURTURE, CS1, 2, 3A, 10 & 12 (N=260)	ENDEAR & CHERISH (N=83)
Summary of AEs					
AEs leading to discontinuation [a]	16 (16)	0 (0)	0 (0)	16 (6)	16 (19)
Treatment-related AEs	0 (0)	1 (<1)	0 (0)	1 (<1)	0 (0)
Common AEs No. of events No. of patients	 1,627 97 (97)	 1,187 134 (96)	 141 16 (80)	 2,955 247 (95)	 909 82 (99)
AEs by preferred term, with an incidence of >10% in nusinersen-treated patients					
Pyrexia	59 (59)	49 (35)	5 (25)	113 (43)	39 (47)
Upper respiratory tract infection	36 (36)	50 (36)	8 (40)	94 (36)	25 (30)
Nasopharyngitis	21 (21)	33 (24)	4 (20)	58 (22)	15 (18)
Vomiting	22 (22)	33 (24)	0 (0)	55 (21)	8 (10)
Headache	0 (0)	51 (36)	0 (0)	52 (20)	0 (0)
Constipation	37 (37)	0 (0)	2 (10)	50 (19)	14 (17)
Back pain	0 (0)	44 (31)	0 (0)	45 (17)	0 (0)
Cough	15 (15)	26 (19)	3 (15)	44 (17)	17 (20)
Pneumonia	30 (30)	0 (0)	2 (10)	41 (16)	14 (17)
Respiratory distress	28 (28)	0 (0)	0 (0)	31 (12)	12 (14)
Scoliosis	11 (11)	18 (13)	0 (0)	29 (11)	0 (0)
Diarrhoea	16 (16)	0 (0)	0 (0)	27 (10)	7 (8)
Respiratory failure	26 (26)	0 (0)	0 (0)	27 (10)	16 (19)
Post-lumbar puncture syndrome	0 (0)	26 (19)	0 (0)	26 (10)	0 (0)

Abbreviations: AE, adverse event; SMA, spinal muscular atrophy
[a] All AEs leading to study discontinuation were events with fatal outcomes
Source: Mercuri et al. 2017(96)

2.10.4 Serious adverse events and deaths

The incidence of serious AEs reported in the clinical trials was consistent with the severity of SMA and associated symptoms. In the consolidated safety analysis, 39% of nusinersen-treated patients reported serious adverse events (SAEs). A higher number of patients (50/83; 60%) reported SAEs in the sham-control arms of ENDEAR and CHERISH compared with SAEs for nusinersen-treated patients in the same trials (96/240; 40%). Overall, 39% of nusinersen-treated patients reported SAEs. The majority of the SAEs were respiratory in

nature (Table 28).(45) No SAEs were considered by the investigator to be related to study treatment and the types of SAE were consistent with manifestations of the effects of SMA.

Table 28. Serious adverse event and death summary from integrated safety analysis of nusinersen

N (%)	Nusinersen-treated patients				Sham-control-treated patients
	Infantile onset SMA	Later onset SMA	Pre-symptomatic SMA	All nusinersen-treated patients	
	ENDEAR & CS3A (N=100)	CHERISH & CS1, 2, 10 & 12 (N=140)	NURTURE (N=20)	ENDEAR, CHERISH, NURTURE, CS1, 2, 3A, 10 & 12 (N=260)	ENDEAR & CHERISH (N=83)
Patient death	17 (17)	0 (0)	0 (0)	17 (7)	16 (19)
Incidence of SAEs	77 (77)	19 (14)	6 (30)	102 (39)	50 (60)
SAEs					
Respiratory, thoracic, and mediastinal disorders	63 (63)	4 (3)	2 (10)	69 (27)	33 (40)
Infections and infestations	60 (60)	13 (9)	4 (20)	77 (30)	29 (35)
Cardiac disorders [a]	12 (12)	0 (0)	0 (0)	12 (5)	7 (8)
Metabolism and nutrition disorders [b]	10 (10)	0 (0)	2 (10)	12 (5)	7 (8)
Gastrointestinal disorders	7 (7)	1 (<1)	1 (5)	9 (3)	7 (8)
General disorders and administrative site conditions	7 (7)	1 (<1)	1 (5)	9 (3)	1 (1)
Injury, poisoning, and procedural complications [c]	3 (3)	3 (2)	0 (0)	6 (2)	3 (4)
Investigations [d]	3 (3)	0 (0)	0 (0)	3 (1)	3 (4)
Nervous system disorders	3 (3)	0 (0)	0 (0)	3 (1)	0 (0)
Vascular disorders	2 (2)	0 (0)	0 (0)	2 (<1)	0 (0)
Immune system disorders	0 (0)	1 (<1)	0 (0)	1 (<1)	-
Musculoskeletal and connective tissue disorders	1 (1)	0 (0)	0 (0)	1 (<1)	-
Skin and subcutaneous tissue disorders	1 (1)	0 (0)	0 (0)	1 (<1)	0 (0)

Abbreviations: SAE, serious adverse event; SMA, spinal muscular atrophy

[a] This class is partly based on anatomy (endocardial, myocardial and pericardial disorders, coronary artery disorders, and valve disorders) and partly on pathophysiology (neoplasia, arrhythmia, cardiac failure, congenital cardiac disorders, and cardiac signs and symptoms)

[b] Includes disorders in the handling of specific substances by the body (e.g., purine and pyrimidine metabolism disorders, inborn errors or metabolism, and lipid metabolism disorders), conditions associated with nutritional disorders in general (e.g., appetite and general nutritional disorders, vitamin-related disorders), and medical conditions that may not be associated with a specific metabolic or nutritional pathogenesis (e.g. acid-base disorders, electrolyte and fluid balance conditions)

[c] Covers cases where an injury, poisoning, procedural or device complication factor is significant in the medical event being reported, and includes: post-lumbar puncture syndrome; procedural pain, nausea, complication, headache, or site reaction; post-procedural swelling, complication of discomfort
[d] Includes clinical laboratory tests, radiological tests, physical examination parameters, and physiological tests
Source: Mercuri et al. 2017(96)

Overall, the fatality rate of the nusinersen-treated patients was less than half that of the sham-control patients (7 vs. 19%) (Table 28).(96) There were no deaths reported in the pre-symptomatic infants or in the later onset SMA patients.(96) Deaths were reported in the infantile onset SMA studies, both for nusinersen-treated and sham-control patients, and the causes of death were all consistent with those typically observed for infantile onset SMA (usually related to respiratory failure) and considered to be unrelated to nusinersen by the study investigator.(96) In the pivotal study in infantile onset SMA (ENDEAR), 13 (16%) patients in the nusinersen group died compared with 16 (39%) of the control group; the main causes of death were respiratory disorders (9 vs. 29%, respectively), consistent with causes of death typically observed in the setting of this rapidly progressive and fatal form of SMA.(49)

2.10.5 Additional safety issues

Thrombocytopaenia and coagulation abnormalities, including acute severe thrombocytopaenia, have previously been observed after administration of other ASOs for other therapeutic indications via subcutaneously or intravenously route. However, in the integrated safety analysis of nusinersen, in the 8 studies described above, no cases of sustained or severe thrombocytopaenia, nor bleeding-related AEs associated with decreased platelet counts were reported in the nusinersen-treated population.(96) The SmPC states that if clinically indicated, platelet and coagulation laboratory testing is recommended prior to administration of nusinersen based on this potential class effect.(2)

Renal toxicity has also previously been observed with other ASOs. However, proteinuria was similar between nusinersen- and sham-control-treated patients in the integrated safety analysis of the 8 studies.(96) There is no indication that nusinersen causes renal toxicity. As a precautionary measure and in view of the potential class effect the SmPC states that if clinically indicated, urine protein testing (preferably using a first morning urine specimen) is recommended. For persistent elevated urinary protein, further evaluation should be considered.(2)

Adverse reactions associated with the administration of nusinersen by lumbar puncture have been observed.(2) The majority of these are reported within 72 hours of the procedure. The incidence and severity of (2) these events were consistent with events expected to occur with lumbar puncture.(96) No serious complications of lumbar puncture, such as serious infections, have been observed in the clinical trials of nusinersen.

Potential difficulties with lumbar puncture as a route of administration may be seen in very young patients and those with scoliosis. The use of ultrasound or other imaging techniques to assist with intrathecal administration can be considered at the physician's discretion.(2)

Adverse reactions have been identified during post-approval use of nusinersen.(2) Among patients treated with nusinersen, complications associated with lumbar puncture including

serious infection have been observed. The frequency of these reactions is not known as they have been reported from the post marketing setting.

Please note that in the post-marketing setting cases of meningitis have been noted following the administration of nusinersen.(2) [redacted]

The immunogenic response to nusinersen was determined in 148 patients with baseline and post-baseline plasma samples evaluated for anti-drug antibodies (ADAs).(2) Overall, the incidence of ADAs was low, with 7 patients (5%) in 148 patients developing treatment-emergent ADAs, of which 2 were transient and 2 were considered to be persistent, and 3 were unconfirmed. There was no apparent effect of ADA development on clinical response, AEs, or the pharmacokinetic profile of nusinersen.

2.10.6 Post-authorisation requirements

Biogen Idec is committed to complete the following post-authorisation measures outlined in Table 29. The post-marketing plan consists of a number of on-going clinical studies, including an open-label pre-symptomatic study (NURTURE), an open-label extension study (SHINE) and a study in patients who were not eligible to participate in either of the sham-controlled clinical studies (EMBRACE). Recognising the rare nature of the disease and the difficulties in setting up specific product registries, Biogen has been collaborating with a number of key academic disease registries. The scientific objectives of these collaborations are to describe and characterise the natural history of SMA disease and nusinersen exposure, effectiveness, and safety.

Table 29. Post-authorisation measures

Description	Status
Studies	
PAES: In order to evaluate the long-term efficacy and safety of nusinersen in symptomatic patients with SMA, results will be reported from the SHINE study (CS11; phase III, open-label extension study)	Submission of final study results: August 2023
PAES: In order to evaluate the long-term efficacy and safety of nusinersen in pre-symptomatic patients with SMA, results will be reported from the NURTURE study (CS5; phase II, open-label study)	Submission of final study results: April 2023
EMBRACE (SM202): Post-authorisation commitment - Pharmacovigilance. Phase 2, randomised, double-blind*, sham-procedure controlled* study to assess the safety, tolerability, pharmacokinetics, and efficacy in patients who were not eligible to participate in ENDEAR or CHERISH *In light of emergent data, Part 1 of the study was terminated early and all subjects were rolled over into the open-label Part 2 of the study	Target study completion: 2019
Registry initiatives	
MDA US Neuromuscular Disease Registry	On-going registry
International SMA Consortium (ISMAC) natural history study	On-going registry
TREAT-NMD Alliance registries	On-going registry

Abbreviations: PAES, Post-authorisation efficacy study; SMA, spinal muscular atrophy

2.10.7 Safety conclusion

Across the nusinersen clinical trial programme in pre-symptomatic, infantile onset, and later onset SMA, nusinersen demonstrated a favourable safety profile.(96) The majority of AEs and SAEs reported in infants and children exposed to nusinersen were consistent with the nature and frequency of events typically occurring in the context of SMA or lumbar puncture procedure. All AEs leading to treatment discontinuation were observed in the infantile onset SMA studies, and were events with fatal outcomes that were consistent with those typically observed for infantile onset SMA (usually respiratory in nature). Comparing the nusinersen- and sham-procedure control–treated groups in the 2 randomised controlled trials, ENDEAR and CHERISH, no abnormal patterns or trends in clinical laboratory parameters were observed with nusinersen. Please also see Appendix F for AEs in ENDEAR and CHERISH i.e not in the integrated safety analysis.

2.11 Ongoing studies

SHINE (NCT02594124) is the ongoing extension study for patients who previously participated in ENDEAR, CHERISH, CS12 and CS3A.(47) The primary objective is to evaluate the long-term safety and tolerability of nusinersen administered intrathecally. Secondary objectives are to examine the long-term efficacy of nusinersen. A summary of ongoing nusinersen trials is shown in Table 30.

Table 30. Summary of ongoing nusinersen trials

Study title and number	Title	Design	Subject population	Treatment groups	Interim analyses	Ongoing /updated analyses
SHINE NCT02594124(47)	A Study for Participants With Spinal Muscular Atrophy (SMA) Who Previously Participated in Nusinersen (ISIS 396443) Investigational Studies.	Open-label extension study	Infantile and later onset SMA patients from ENDEAR and CHERISH, CS12 and CS3A	Nusinersen	Estimated dates for interim analyses: Q1 2018 Data cut-off: 30 June 2017	Estimated study completion: August 1, 2022
NURTURE NCT02386553(55)	A Study of Multiple Doses of Nusinersen (ISIS 396443) Delivered to Infants With Genetically Diagnosed and Pre-symptomatic Spinal Muscular Atrophy (NURTURE)	Open-label, phase II	Genetically diagnosed and pre-symptomatic SMA	Nusinersen	Estimated dates for interim analyses: Q1/Q2 2018 Data cut-off: June 2017	Estimated study completion: January 26 2022
EMBRACE NCT02462759(48)	A Study to Assess the Safety and Tolerability of Nusinersen (ISIS 396443) in Participants With Spinal Muscular Atrophy (SMA). (EMBRACE)	Phase II, randomised, double-blind, sham-procedure controlled study	Patients with SMA who are not eligible to participate in the clinical studies ENDEAR and CHERISH	Nusinersen and Sham	Estimated dates for interim analyses: Part 1: August 10, 2017	Estimated study completion: April 1, 2019

Abbreviations: SMA, spinal muscular atrophy, Q, quarter

2.12 Innovation

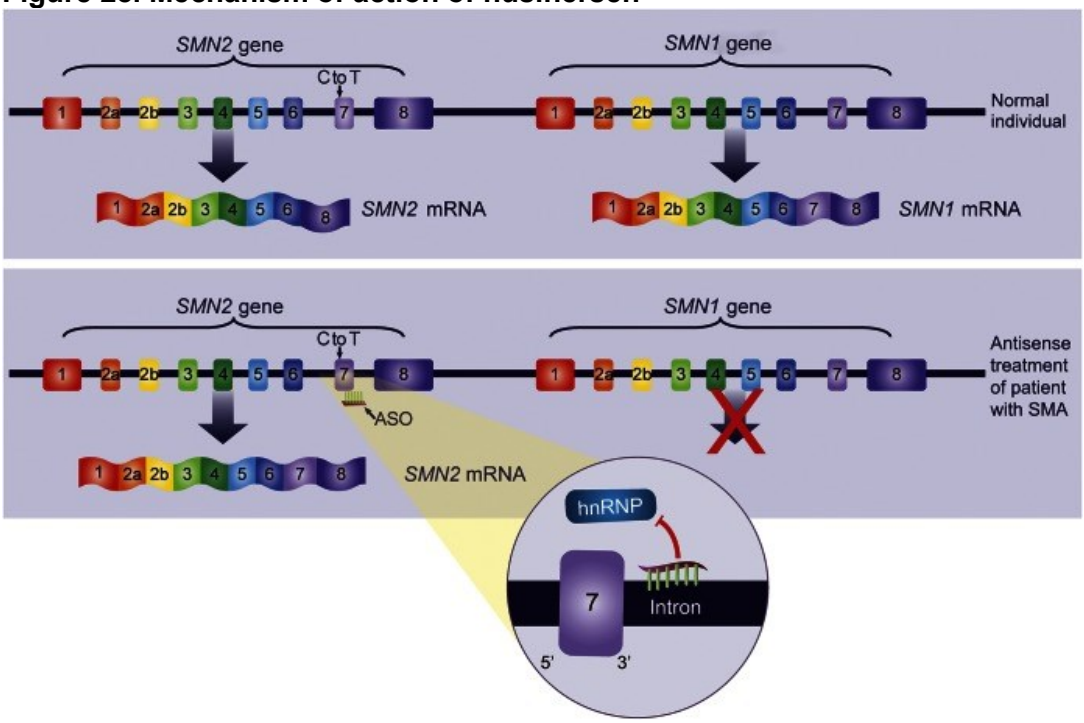
In 2017, Biogen and Ionis won the Prix Galien USA Award for Best Biotechnology Product for nusinersen, an award that recognises scientific innovation through the improvement of the state of human health.(98) This breakthrough and innovation has been recognised by many countries in reimbursement discussions since the Prix Galien submission. In Germany, nusinersen became only the third drug ever, and the first orphan drug to receive the highest benefit score from the G-BA – 'major added benefit'. Nusinersen 'confers an unprecedented large improvement in therapy-relevant benefit, primarily because of a major increase in survival time, alleviation of typical symptoms of the disease, and reduction of serious side effects.' for type I and 'the observed benefit consists of unprecedented attenuation of serious symptoms and appreciable alleviation of the disease' for type II.(99) In France, reimbursement has been endorsed by Commission de Transparence with a 'substantial benefit status' receiving an ASMR III for SMA type I and and type II.(100) Only 2 applications out of 579, have received such a high ranking over the past 3 years.

The outlook for SMA patients, even the most severely affected children, has improved in terms of crude survival, albeit with severe disability, due to advances in nutritional and respiratory care.(101) However, there is no evidence that such management strategies alter the basic neuropathological process and neuromuscular function, and the effects are necessarily very limited in modifying the motor milestones and natural history of the disease.(101) The unmet need and transformational nature of nusinersen was recognised by the EMA who granted marketing authorisation based on accelerated approval process.(5)

A detailed understanding of the molecular genetic basis of SMA has allowed for the development of the first targeted therapy i.e. nusinersen. In SMA, inactivating mutations in the *SMN1* gene can be partially compensated for by limited expression of SMN protein from a variable number of copies of the *SMN2* gene.(101) The advent of this tailored molecular therapy for SMA, based on modulating the splicing behaviour of the *SMN2* gene (Figure 28) provides, for the first time, a treatment which alters the natural history of motor neuron degeneration.

Data from ENDEAR demonstrate that a consequence of the step change in therapy represented by nusinersen is that infants will achieve motor milestones normally associated with less severe types of SMA (for example, sitting, standing) and are likely to survive beyond the point where they would have previously succumbed to respiratory failure without invasive ventilation. Data from CHERISH demonstrate that children will achieve clinically meaningful improvements in motor function inconsistent with the natural history of children with later onset SMA. In addition, data from NURTURE suggest that nusinersen will have benefits in pre-symptomatic SMA patients. Given the impact of SMA on patients and carers, the findings are of substantial value to patients with SMA and their families/carers, demonstrating that for the first time a treatment for SMA can transform the course of disease.

Figure 28. Mechanism of action of nusinersen



Nusinersen is a 2′-O-(2-methoxyethyl) modified ASO drug designed to target an hnRNP-A1/A2–dependent splicing silencer, ISS-N1, in intron 7 of the SMN2 pre-mRNA. Nusinersen displaces hnRNP proteins from the ISS-N1 site on the *SMN2* pre-mRNA, facilitating accurate splicing of *SMN2* transcripts (e.g., increasing the synthesis of transcripts containing exon 7) and resulting in increased production of full-length SMN protein.
Abbreviations: ASO, antisense oligonucleotide; hnRNP, heterogenous nuclear ribonucleoprotein; ISS, intronic splicing silencer; mRNA, messenger RNA; SMA, spinal muscular atrophy; SMN, survival of motor neuron.
Source: Chiriboga 2016(77)

2.13 Interpretation of clinical effectiveness and safety evidence

2.13.1 Principal findings from the clinical evidence

The benefits and harms of nusinersen in patients with symptomatic infantile onset SMA and later onset SMA were evaluated in 2, phase III randomised double-blind, sham-controlled trials: ENDEAR and CHERISH. A sham control was used as there are no relevant active comparators. The sustained and clinically meaningful benefits compared with a sham procedure resulted in the early termination of both studies and the transition of all ongoing patients to an open-label, extension trial (SHINE).(47)

Both ENDEAR and CHERISH demonstrated clinically meaningful efficacy and a favourable safety profile of nusinersen compared with the sham procedure. These findings are of substantial value to patients with SMA and their carers, demonstrating that for the first time a treatment for SMA can transform the course of disease. Currently patients in England who are not included in the nusinersen EAP only have access to supportive care, which can extend survival and manage symptoms, but not prevent progressive motor function decline.

2.13.1.1 Clinical benefits for infantile onset SMA

Patients with infantile onset (type I) SMA by definition fail to gain independent sitting and as a rule do not achieve motor skills beyond those which are present at the time of diagnosis, despite symptomatic treatment.(102) Infantile onset is also associated with respiratory failure and extremely high mortality, with infants rarely surviving beyond 2 years.(18,22,102)

Patients with infantile onset SMA who received nusinersen in the ENDEAR study showed statistically significant (P <0.0001) and clinically meaningful improvement in motor function (as measured by HINE-2), and were more likely to be alive without the use of permanent assisted ventilation compared with patients who underwent the sham procedure. These findings support the CS3A phase II, open-label study of nusinersen in infantile onset SMA (see Appendix L).(49) Sustained and clinically meaningful improvements were also demonstrated in motor function (CHOP INTEND) and motor neuron health (CMAP), compared with patients who received the sham procedure; thus confirming that nusinersen improves neuromuscular function. Patients receiving nusinersen had a significantly higher likelihood of event-free survival (time to death or permanent ventilation) and overall survival than infants who underwent a sham procedure, despite the fact that more infants in the nusinersen group than in the control group were receiving ventilatory support at baseline. In addition, early treatment with nusinersen appeared to confer a strong benefit for event-free survival.

Some infants who received nusinersen developed motor milestones that are inconsistent with infantile onset SMA, including the ability to stand. These findings were supported by sensitivity analyses, which demonstrated the robustness of these results and the strong treatment effect, both clinically and statistically, of nusinersen (Appendix M).

The consistent treatment benefit across efficacy endpoints is especially meaningful in light of the fact that patients in the nusinersen treatment group began the study with a worse prognosis (based on an earlier age of symptom onset at baseline) and more severe SMA symptoms (based on a greater percentage of patients requiring ventilatory support and higher incidence of paradoxical breathing, pneumonia or respiratory symptoms, and swallowing or feeding difficulties at baseline) than the patients in the control group.

No serious safety concerns were identified during the close monitoring that followed the intrathecal injections in the trials.

Patients from ENDEAR have been transitioned to the SHINE open-label extension study to assess the effects of longer treatment duration on motor function and HRQL when using nusinersen in patients with SMA.(49) This study is currently enrolling patients with an estimated final completion date of August 2022 (see Section 2.11 for more details of ongoing studies, including SHINE).

2.13.1.2 Clinical benefits for later onset SMA

Patients with later onset SMA include those with type II and the less severe type III. Patients with type II SMA have a longer life expectancy than those with type I SMA, but often develop scoliosis, which leads to increased risk for respiratory compromise and subsequently a

shortened life expectancy than the general population.(6,22) In patients with SMA type III, life expectancy is not reported to be significantly less than in a normal population.(14,104) However, SMA patients experience a loss of motor function over time and numerous secondary complications.(89) As a result, SMA children with SMA type III can walk independently, although starting to walk may be delayed in some patients.(1) Due to the progressive nature of SMA, many patients would value stabilisation of their disease.(43)

Patients with later onset SMA who received nusinersen in the CHERISH study realised clinically meaningful benefits as compared to patients who received a sham procedure. These benefits included statistically significantly greater gains in motor function (measured by HFMSE; P<0.001), as well as greater improvements in the number of new WHO motor milestones achieved per child such as the ability to walk in children with type II SMA.(51) In comparison, children who received the sham procedure had a decline in motor function (evaluated as a decline in HFMSE score), and lost WHO motor milestones at 15 months. Statistically significant greater improvements in upper limb function (measured through RULM score; P=0.0000001) were also observed in the nusinersen-treated children compared with those who received the sham procedure. All the outcomes observed are inconsistent with the natural history of children with later onset SMA.(86)

The consistent treatment benefit across efficacy endpoints is especially meaningful since fewer patients in the nusinersen treatment group had achieved a WHO motor milestone at or before baseline compared with the control group.

Patients from CHERISH have been transitioned to the SHINE open-label extension study to evaluate the long-term efficacy, safety and tolerability of nusinersen to patients with SMA,(105) as per the ongoing patients from ENDEAR.

Overall, the results demonstrate the clinical benefit of nusinersen in later onset SMA patients who have a high unmet need for a disease-modifying treatment.

2.13.1.3 Benefits with earlier treatment

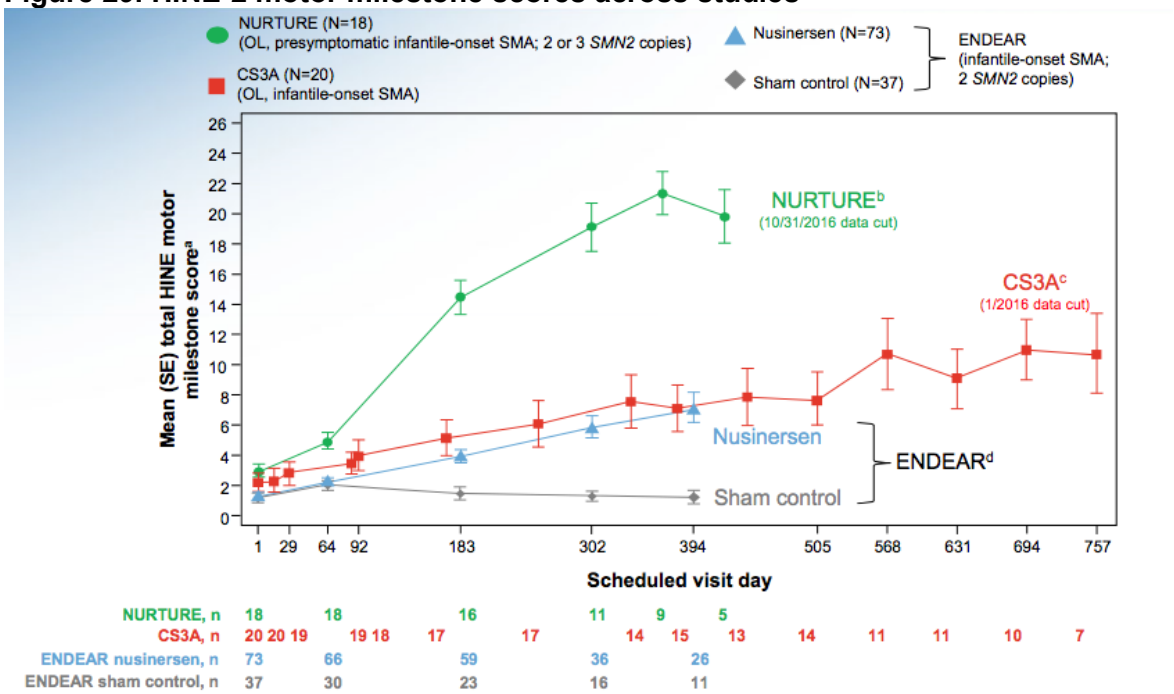
An ongoing phase II study (NURTURE) is evaluating the benefit of nusinersen in pre-symptomatic infantile onset and later onset patients.(55,56) As of the interim analysis all infants are alive without requiring chronic respiratory support and are exhibiting improvements in motor function and/or motor milestones. Most infants (16 of 18 patients) maintained age-appropriate growth and achieved developmental milestones unexpected in type I or II SMA; these milestones were more consistent with normal development, and in some cases included the ability to walk. This included improvements, compared to baseline, in HINE motor milestones in 16 patients (89%) and a ≥4-point improvement in CHOP INTEND total score in 16 patients (89%).

The limited data available to date from the NURTURE study support the findings from ENDEAR and CHERISH. Taken together with the clinical evidence for symptomatic patients (CS3A, ENDEAR and CHERISH studies), these data demonstrate that nusinersen has consistently produced meaningful benefits across a range of SMA phenotypes. Most importantly, it points towards the need for early treatment with nusinersen.

The benefits with earlier treatment of nusinersen were also highlighted through subgroup analyses conducted for the later onset population of CHERISH and the infantile onset population of ENDEAR. In the infantile onset population, earlier and greater motor milestone responses and prolonged survival were observed among patients with shorter disease duration at the start of the study (≤12 weeks) compared to patients with a longer disease duration (>12 weeks), suggesting that early treatment with nusinersen may confer a stronger benefit. In CHERISH, nusinersen-treated children who were younger and had shorter disease durations generally showed the greatest improvements in HFMSE from baseline; older children and those with longer disease durations demonstrated stabilisation of HFMSE scores in comparison to a decline seen in the sham arm; this is consistent with the idea that early initiation of treatment may lead to greater improvements.

The benefits with nusinersen treatment are also apparent in a comparison of the motor milestone scores of patients with symptomatic and pre-symptomatic infantile onset SMA. As shown in Figure 29, patients who received nusinersen in ENDEAR, NURTURE and a supporting phase II trial (CS3A; see Appendix L) had higher mean total motor milestones scores (as measured with HINE) after day 64, than those who received the sham control. Furthermore, motor milestones scores appear to be higher in pre-symptomatic patients, than symptomatic patients, from day 183 onwards, suggesting greater benefit for patients with earlier treatment.

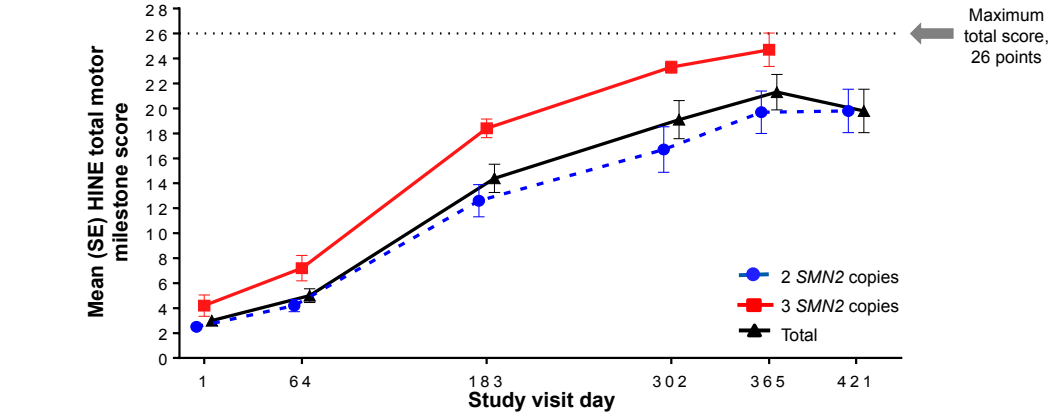
Figure 29. HINE-2 motor milestone scores across studies



Abbreviations: HINE-2, Module 2 of the Hammersmith Infant Neurological Examination; OL, open label; SE, standard error, SMA, spinal muscular atrophy
Populations: NURTURE (232SM201) = interim efficacy set; CS3A = all dosed infants; ENDEAR (CS3B) = interim efficacy set. For each study, visits with n <5 are not plotted.
[a] Maximum total milestone score 26.
[b] Median (range) age at first dose: 19.0 (3–42) days.
[c] Median (range) age at enrolment: 155 (36–210) days.
[d] Median (range) age at first dose: 175.0 (30–262) days.
Source: Crawford 2017(45)

Please note that the pre-symptomatic infants in NURTURE had 2 or 3 copies of *SMN2* (most likely to develop either infantile-onset or later-onset SMA), whereas in ENDEAR and CS3A all patients were infantile-onset with 2 copies of *SMN2*. However, as can be seen from Figure 30, the improvement in HINE-2 motor function in NURTURE was similar in pre-symptomatic children with 2 or 3 copies of *SMN2* (NB the black line in Figure 30 is equivalent to the green line in Figure 29). Therefore, when comparing only patients with 2 copies of *SMN2*, motor milestones scores still appear to be higher in pre-symptomatic patients than symptomatic patients from day 183 onwards. It is also noted that the downward bend of the NURTURE line is due to no children with 3 copies of *SMN2* reaching 421 days in the NURTURE trial. Thus the 421-day data point represents only the results of children with 2 copies of *SMN2*.

Figure 30. HINE-2 motor milestone scores in NURTURE according to *SMN2* copy number



Abbreviations: HINE-2, Module 2 of the Hammersmith Infant Neurological Examination; SE, standard error

2.13.1.4 Safety

The overall nusinersen exposure across the different clinical studies allows for an adequate assessment of safety in the context of this disease. The majority of AEs and SAEs reported in infants and children exposed to nusinersen were consistent with the nature and frequency of events typically occurring in the context of SMA or lumbar puncture procedure. Overall, nusinersen appeared to have a manageable safety profile and was well tolerated, and no specific safety concerns have been identified in the overall safety profile of nusinersen.

Across the 8 studies there was only 1 treatment-related AE (i.e. assessed by the investigator as related to study drug) which occurred in a patient with later onset SMA in the CHERISH trial (one event of nausea post sedation); no treatment-related AEs were reported in patients with infantile onset SMA or pre-symptomatic SMA.

All AEs leading to treatment discontinuation were observed in the infantile onset SMA studies, and were events with fatal outcomes that were consistent with those typically observed for infantile onset SMA (usually respiratory in nature).

There may be some risks stemming from the application procedure (lumbar puncture), but no specific major risks have been attributed to nusinersen itself.

Overall, across the nusinersen clinical trial programme in pre-symptomatic, infantile onset and later onset SMA, nusinersen demonstrated a favourable safety profile.

2.13.2 Applicability to clinical practice in England

Of the 31 study centres in ENDEAR, 2 were from England.(106) [redacted] These patients are likely to be representative of the English SMA population from the perspective of patient demographics.

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]Of note, the SMA REACH network is currently providing

and designing training for the above motor milestones ready for real world data gathering of SMA patients.(107)

2.13.3 Strengths of the clinical evidence

[redacted]

All key findings for ENDEAR were supported by sensitivity analyses, which demonstrated the robustness of the results and the strong treatment effect, both clinically and statistically, of nusinersen.(49) [redacted]

[redacted]

The consistent treatment benefit across efficacy endpoints is especially meaningful in light of the fact that subjects in the nusinersen treatment group of ENDEAR began the study with a worse prognosis (based on an earlier age of symptom onset at baseline) and more severe SMA symptoms (based on a greater percentage of subjects requiring ventilatory support and higher incidence of paradoxical breathing, pneumonia or respiratory symptoms, and swallowing or feeding difficulties at baseline) than the subjects in the control group.(49) [redacted]

[redacted]

Initial data from patients with infantile onset SMA (N=36) enrolled in the EAP in Europe also confirm the benefits of nusinersen to date (after 2 months of treatment).(108) At the first visit,

the maximum motor acquisition using HINE-2 scale was the sitting position with help (n=3) and rolling to the side (n=10). The mean (SD) CHOP INTEND score was 28.1 ± 10.6. No major severe events were reported during the injections. At the time of the first follow-up visit (2 months) the mean CHOP INTEND score improved with 16% (± 24%) and one patient acquired autonomous sitting position.

2.13.4 Limitations of the clinical evidence

Despite the high quality of ENDEAR and CHERISH, both trials were subject to a number of difficulties and limitations consistent with conducting clinical trials in a rare disease and a paediatric patient population.

One of the limitations relating to the paediatric population is that infants and young children are often unable to cooperate with testing of strength or motor function or may tire easily. While CHOP INTEND has been validated for SMA, HINE has not been specifically validated. Therefore, for example, the primary motor milestones endpoint (HINE) in ENDEAR may not be as sensitive to improvements as CHOP INTEND.(102) However, the limitation would apply to both treatment arms, thereby not leading to any bias with the nusinersen outcomes. Overall, most of the measures on the HINE assessment were readily reproducible, and using a combination of functional tests rather than a single test helped to provide a more meaningful indication of response. The HINE-2 in particular has been shown to be clinically meaningful to patients and carers, with the outcomes of relevance to activities of everyday living.(43,80) Conducting clinical trials in infants, such as those in the infantile onset population, is particularly challenging from the perspective of collecting HRQL data.(109–113) No HRQL data were collected for the infantile onset SMA population due to the difficulties assessing this outcome in infants and a lack of validated measures of HRQL in SMA before 2 years of age. While HRQL data, including PedsQL, were collected in the CHERISH study, the impact of treatment on HRQL is still difficult to capture in these young patients with later onset SMA (median age at screening: 4 years vs. 3 years in the nusinersen and control group, respectively). As children at this age lose a lot of their motor function before the age of setting down long term memories they don't usually have memories of what those motor functions are like and have come more readily to accept their condition. The limitations of the HRQL are further discussed in more detail in Section 3.4.

Enrolling patients who have a rare disease and a wide spectrum of subtypes can also introduce a number of limitations. In particular, the CHERISH study had a mixed, heterogenous patient population representing different stages of disease. Untreated SMA patients have rapid disease progression once symptoms start to appear, meaning that even a few months can make a big difference in functional ability. Therefore, an individual's response to a therapeutic intervention may vary depending on the phase of their illness. For example, in the initial stage of later onset SMA when patients are showing the first clinical indication of weakness, there is usually a slowing in the rate of acquisition of new motor milestones rather than a clear loss of motor function. This is followed by a much slower yet progressive decline in functional abilities over time. Thus, enrolment in a clinical trial alongside other symptomatic children in a more advanced phase of their illness may confound expected results of a specific therapeutic intervention for the entire cohort, depending on which outcome

measure is used to indicate efficacy. Therefore, it is not surprising that only a few patients in either treatment group achieved the milestones of standing alone or walking with assistance. To minimise this limitation, patients were randomised to the different treatment groups and subgroup analyses were conducted, where possible. However, due to the rare nature of SMA, and consequent small patient population in the trial, it was difficult to conduct subgroup analyses evaluating a wide range of disease stages with sufficient power.

[redacted] Further data will be collected post approval to confirm the effect of nusinersen on these groups.(1) The EMA have concluded that an effect of nusinersen can reasonably be assumed in these patients based on the outcomes of the CHERISH study and the same underlying mechanism of action throughout 5q SMA, which is altered by nusinersen.

Due to blurring of diagnostic criteria between infant onset and later onset patients (the classification of SMA into discrete subtypes [i.e type I, II, III etc] is arbitrary in what is a spectrum disorder), there is a risk that some of the enrolled patients may have been more appropriate for the later onset category and vice versa. To minimise this risk, *SMN2* copy number was only included as an inclusion criterion for ENDEAR and NURTURE to improve the homogeneity of the study population.

Finally, there is a lack of long-term data from the pivotal studies, and therefore, it is not yet known whether the effects of nusinersen will be maintained in the longer term, or whether nusinersen may be able to provide a cure in some of the SMA patients.(1) Longer-term data are available from the phase II study CS3A and the phase I studies CS2 and its extension C12(1) (of note, long-term data from CS3A, CS2 and CS12 have been used in the economic model): As of the data cut-off date for CS3A (26 January 2016), the time on study ranged from 62 to 988 days, with a median of 670 days and a total of 32.9 subject-years on study. Overall, 15 subjects were on study for at least 505 days (72 weeks). Fifteen of 20 subjects (75%) were alive and continuing in the study at the time of the data cut-off. Of these 15 subjects, all were >24 months of age, 7 were >30 months of age, and 2 were >36 months of age. Thirteen subjects (65%) were alive, free from permanent ventilation, and continuing in the study at the time of data cut-off. A median time to event-free survival could not be estimated due to an insufficient number of events. These data support the maintenance of effect with long-term treatment beyond the age of 24 months. In addition, across both CS2/CS12, subjects received a median of 6 doses (range 1–7); median time on study is approximately 1050 days (range 31–1219). (see Appendix L for more details of these studies). More information on the long-term efficacy will also become available with time from the SHINE clinical trial. Furthermore, whilst there is as yet no evidence of permanence of effect, there has also been no evidence of lessening of effect over time.

2.13.5 End-of-life criteria

End-of-life criteria may apply to infantile onset SMA (Table 31) but not for the later onset population.

Table 31. End-of-life criteria

Criterion	Data available	Reference in submission (section and page number)
Nusinersen, an antisense oligonucleotide (ASO) injection for intrathecal administration, is indicated for patients with a short life expectancy, normally less than 24 months	Survival is highly dependent upon the nature and extent of supportive care, which may vary by country, institution and physician and patient preference. The median age for death or permanent respiratory support (a composite endpoint used in clinical trials and natural history studies in this population) is approximately 9–13 months.(18) [redacted]	See below
There is sufficient evidence to indicate that nusinersen offers an extension to life, normally of at least an additional 3 months, compared with current NHS treatment	Infants in the ENDEAR study who received nusinersen had a significantly higher likelihood of event-free (final analysis: hazard ratio for death or the use of permanent assisted ventilation, 0.53; P=0.005) and overall survival (hazard ratio for death, 0.37; P = 0.004) than infants who underwent a sham procedure, despite the fact that more infants in the nusinersen group than in the control group were receiving ventilatory support at baseline. The median time to death or the use of permanent assisted ventilation was 22.6 weeks in the control group and was not reached in the nusinersen group; the median time to death was not reached in either group (ITT population at end of study). In addition, at the latest data cut-off, all pre-symptomatic children in NURTURE (including those with 2 *SMN2* copy number) are still alive.	Section 2.6.2.2, Section 2.6.3.1, Section 0 and below

Abbreviations: ITT, intention to treat; NHS, National Health Service; SMA, spinal muscular atrophy

Infantile onset SMA has one of the highest mortality rates among genetic diseases. Patients may require the use of assistive equipment, pain management and surgery to manage their symptoms, however none of the standard of care interventions stop the decline in motor function and patients have a low quality of survivorship.

As far as we are aware, there are no published studies on the natural history of SMA in English (or UK) populations. Changes in standard of care over time, variable use of tracheostomy and invasive mechanical ventilation and small study populations lead to considerable differences in reported survival rates (Table 32). Death predominantly occurs as a result of respiratory compromise, and survival is highly dependent upon the nature and extent of supportive care, which may vary by country, institution and physician and patient preference.(11,22) Studies have shown that “proactive” supportive care can prolong survival, often due to dependence upon gastrostomy tube for nutritional support and non-invasive ventilation or tracheostomy/ventilator support (Table 32).(22,92,93,97) In Oskoui (2007), the median survival time was 8.5 months for patients born in 1980 – 1994 (with limited supportive care) and indeterminate for those born in 1995 – 2006 (when proactive supportive care was commonly provided).(35) The survival rate at 2 years was 30.8 vs 73.9%, respectively.

[redacted]

In addition, a study looking at current care practice in 25 countries reported that in the UK only 3/83 SMA type I patients were invasively ventilated.(22)

More recent natural-history studies have focused upon a combined survival endpoint of age at death or a surrogate of survival free of permanent ventilation, generally accepted as intubation or tracheostomy with mechanical ventilation or >16 hours/day non-invasive ventilation support for >14 consecutive days (16+/14+) in the absence of an acute reversible illness or following surgery. That is, the assumption is that the infant would have died without such support and a sufficient time period was allowed to ensure that the infant would not wean to <16 hours/day of non-invasive support.(102) This endpoint may be more relevant to the situation in England, where permanent ventilation may not be provided to patients; [redacted]

In Finkel 2014, the median age at reaching the combined endpoint of either death or requiring at least 16 hours/day of non-invasive support for at least 14 days in the absence of an acute reversible illness or perioperatively (as a surrogate for death) was 13.5 months (interquartile range 8.1–22.0 months) (Table 1).(34) In Oskoui 2007 median survival time using death or ventilation for more than 16 hours/day as the event was 7.5 months for patients born in 1980 – 1994 and 24.0 months for those born in 1995 – 2006; ventilation for more than 16 hours/day, use of a mechanical insufflation/exsufflation device, and gastrostomy tube feeding showed a significant effect in reducing the risk of death.(35)

Table 32. Natural-history studies reporting survival in SMA type I

Study Years when data were collected Country	N	Supportive care provided	Survival	Age at death (months): Mean (M) and median (m) (range)
Oskoui, 2007(35) 1980-1994 1995-2006 Mainly USA	N = 143	1980–94: Limited (n = 65) Tracheostomy: 24.6% Ventilation (NIV and invasive): 30.8% Ventilation>16hr/d: 21.5% MI-E: 7.7% GT feeding: 40%	Death Median = 8.5 months Survival rate: 1 yr = 36.9% 2 yr = 30.8% 4 yr = 26.2% 10 yr = 24.6%	M = 19.1, m = 7.3 (1.0–193.5)
			Death or ventilation Median = 7.5 months Survival rate: 1 yr = 26.2% 2 yr = 18.5% 4 yr = 3.8% 10 yr = 10.8%	-
		1995–2006: Proactive (n = 78) Tracheostomy: 29.5% Ventilation (NIV and invasive): 82.1% Ventilation>16hr/d: 43.6% MI-E: 62.8% GT feeding: 78.2%	Median = indeterminate Survival rate: 1 yr = 79.3% 2 yr = 73.9% 4 yr = 65.1% 10 yr = 50.3%	M = 22.1, m = 10.0 m (2.5–112.0)
			Death or ventilation Median = 24 months Survival rate: 1 yr = 58.6% 2 yr = 47.0% 4 yr = 28.2% 10 yr = 15.7%	-
Finkel, 2014(34) 2005–09 enrolment USA	N = 34	Proactive: 76% with both GT and NIV/TV	Combined endpoint: Type IB, m = 11.9 Type IC, m = 13.6	Death (n = 9): m = 9 (2–14) Death or requiring >16 hours of BiPAP/day: 13.5 m (IQR: 8.1–22)
Other cohort studies				
Farrar, 2013(14) 1995–2010 Australia	N = 20	Minimal 5% with GT and NIV	Survival at 1 yr = 40% 2 yr = 25% 4 yr = 6% 10 yr = 0	95% died, m = 7.4 (3–56)

Study Years when data were collected Country	N	Supportive care provided	Survival	Age at death (months): Mean (M) and median (m) (range)
Petit, 2011(36) France	N = 45	Minimal None of the survivors >2 years had prior GT or NIV/TV support	9/34 (26%) survived to 2 yr	Mortality in 76%, M = 10.7 (10 days to 6.5 years)
Lemoine et al., 2012(37) 2002–09 USA	N = 49	2 groups: Proactive: NIV BiPAP at night and daytime sleep, and cough-assist device use at least twice daily Supportive: respiratory support, such as supplemental oxygen and suctioning	4-year survival: Proactive: 72% Supportive: 33%	Proactive care (n = 23; 6 deaths): m=7.6 (IQR 6.5,10.5) Supportive care (n = 26; 16 deaths), m = 8.8 (IQR 4.7, 23.7)
Rudnik-Schoneborn, 2009(38) 2000–05 diagnosis Germany	N = 66	Variable NIV/TV, strong NG/GT support	Alive at 2: Overall: 6%	Mortality in 57 (86.3%): All patients: M = 7.3 (few days to 34 months), m = 6.1
Mannaa, 2009(39) 1989–2005 USA	N = 13	Proactive: MI-E: 10 (77%) Mechanical ventilation: 10 (77%) Tracheostomy: 3 NIV: 7	53% survivors: 2 yr = 62% 4 yr = 62% 10 yr = 8%	Data not available
Cobben, 2008(13) 1996–99 Netherlands	N = 34	Minimal	26% survive to 1 yr	Entire group: M = 6 (CI: 5–7), m = 10
Gregoretti 2013(11) 1992 -2010 Italy	N = 194	Tracheostomy and invasive mechanical ventilation (N=42)	2 yr: 95%	-
		Non-invasive respiratory muscle aid (N=31)	2 yr: 68%	-
		No treatment “letting nature take its course” (N=121)	2 yr: 1.3%	-

Abbreviations: BiBAP, Bi-level airway positive pressure; GT, gastrostomy tube; IQR, interquartile range (25–75% percentile); M, mean (standard deviation); m, median (range, X–Y); MI-E, mechanical insufflation– exsufflation device; NG, nasogastric; NIV, non-invasive ventilation; TV, tracheostomy with ventilator; yr, year;
Proactive: both nutritional (NG tube or GT) and respiratory support (NIV or TV).

In the ENDEAR trial (a 13-month RCT of nusinersen vs. sham-control in infantile onset patients) patients were managed proactively with supportive care. Of the 121 subjects treated, 27 (22%) required ventilatory support at baseline, with a greater percentage of subjects in the nusinersen group requiring such support (26 vs. 15%).(49) [redacted]

Event-free survival (defined as time to death or permanent ventilation [tracheostomy or ≥16 hours ventilatory support per day for >21 days]) was a co-primary endpoint in the ENDEAR trial. The median time to death or the use of permanent assisted ventilation was 22.6 weeks in the control group and was not reached in the nusinersen group. Overall, the risk of death or the use of permanent assisted ventilation was 47% lower in the nusinersen group than in the control group (hazard ratio, 0.53; 95% CI, 0.32–0.89; P = 0.005).(49)

Overall survival was analysed as a secondary endpoint in the ENDEAR trial. Even though subjects randomised to nusinersen were younger at symptom onset (earlier age of onset of symptoms is generally associated with shorter survival)(115) and had more swallowing or feeding difficulties at baseline, a lower percentage of subjects in the nusinersen group died compared with the control group (P = 0.004). As of the final analysis (data cut 21st November 2016), 13 subjects (16%) in the nusinersen group and 16 subjects (39%) in the control group had died. Overall, the risk of death was 63% lower in nusinersen-treated subjects than in those who received the sham procedure (hazard ratio, 0.37 [95% CI: 0.18, 0.77]).(49)

The percentage of infants requiring permanent ventilation was also evaluated as a secondary endpoint. Even though a greater percentage of subjects randomised to nusinersen required respiratory support and had a history of pulmonary disease at baseline, there was a trend toward a lower percentage of subjects in the nusinersen group requiring permanent ventilation during the study compared to the control group. An estimated 15% of the infants in the nusinersen group and 8% in the control group had received permanent assisted ventilation at 3 months, and an estimated 31% and 48%, respectively, had received permanent assisted ventilation at 13 months. Overall, 23% of the infants in the nusinersen group and 32% in the control group received permanent assisted ventilation (hazard ratio, 0.66; P=0.13). Overall, the risk of permanent ventilation was 34% lower in nusinersen-treated subjects than in those who received the sham procedure.(49)

In support of data from ENDEAR, all pre-symptomatic infants in NURTURE (including those with 2 copies of *SMN2*) were alive and none had required respiratory intervention (invasive or non-invasive ventilation for ≥6 hours/day, continuously for ≥7 days or tracheostomy).(45)

In summary, nusinersen is associated with significantly prolonged event-free and overall survival. Biogen believe that within the context of clinical practice in England, nusinersen should be considered as an end-of-life treatment.

B.3 Cost effectiveness

3.1 Published cost-effectiveness studies

An SLR(116) found no economic evaluations relevant to SMA. Other than nusinersen, there are currently no other disease-modifying treatments for SMA. Consequently, no comparable cost-effectiveness analyses have been conducted.

3.2 Economic analysis

SMA is a complex disease that, for infantile onset, has severe consequences for and impact on the patient and caregivers. Patients, and by proxy their carers, may benefit from treatment with nusinersen through extended overall survival and the achievement of significant motor milestones (such as the ability to sit, stand and walk); however, translation into quality-adjusted life year (QALY) gains is problematic. The nature of the patient (with disease onset at less than 6 months) means that elucidation of utilities is difficult and may be misleading. In later onset disease, heterogeneity of baseline status of the patient and lack of data relating to utility estimation for standards of care make QALY derivation less robust.

While nusinersen has a marketing authorisation for all categories (types 0 to IV) of 5q SMA, the economic models consider only the type I (infantile onset) and types II and III (later onset) SMA patients because these were studied in the pivotal phase III ENDEAR and CHERISH trials, respectively. These have been handled separately in the two de novo economic models due to the different natural history of SMA by disease category. Pre-symptomatic patients were excluded from consideration in the economic analysis because, despite being studied in the NURTURE trial, type I and type II patients were difficult to distinguish, meaning that an economic assessment would be speculative in nature.

3.2.1 Patient population

The patient populations for the infantile and later onset economic models are based on the ITT population of the pivotal phase III ENDEAR (type I) and CHERISH (types II and III) trials. Starting ages for infantile and later onset patients in the economic models were 5.6 months and 43.7 months, respectively. Fifty five percent of infantile onset patients were female compared with 53% of later onset patients.(49)

To reflect the expectation that the earlier the nusinersen intervention is given, the better the outcome will be, the infantile and later onset economic models include subgroups based on disease duration. Subgroups in the infantile onset model are: (i) patients with disease duration ≤ 12 weeks; and (ii) patients with disease duration >12 weeks. Subgroups in the later onset model are: (i) patients with disease duration <25 months; and (ii) patients with disease duration ≥25 months

3.2.2 Model structure – infantile onset SMA

The infantile onset model adopted a Markov structure composed of 7 health states based on the HINE assessment and the absorbing state ***Dead***. The model structure (Figure 31) consists of health states representing milestone achievement normally observed in patients with

infantile onset SMA (***No Milestone Achieved [No Milestones], Mild Milestones, Moderate Milestones*** [HINE score description included under the model diagram]) and a section dividing patients into health states defined by motor milestones that are not observed in patients with infantile onset SMA (***Sits Without Support, Stands With Assistance, Walks With Assistance, and Stands/Walks Unaided*** health states). To facilitate the use of the long term data of the CS3A study after trial follow-up, the model assigns a mean CHOP INTEND score to each health state and uses the mean rate of CHOP INTEND score change observed in the ENDEAR trial to calculate transitions after trial follow-up.

The model is consistent with the clinical pathway as it relates to the therapy areas involved in the management of SMA. In terms of health states, motor function and motor milestones are the focus of the model to reflect the benefits of nusinersen observed in the ENDEAR clinical trial. In comparison with the clinical pathway which patients follow under symptomatic care, there is less emphasis on respiratory care, which has usually been the central concern of clinical management, but was not the main focus of the clinical trial programme.

3.2.2.1 Definition of health states

The motor milestone health states included in the model are based on the final results of the 13-month ENDEAR trial and 26-month data from the phase 2 open-label study (CS3A) in symptomatic subjects with infantile-onset SMA showing that some patients receiving nusinersen achieved motor milestones typical of later SMA types.

HINE is a clinically-rated neuromuscular assessment of infants up to 24 months of age.(60) The assessment comprises 7 milestone categories (i.e., head control, sitting, ability to kick in supine position, rolling, crawling, standing, and walking) with 3–5 progressively more difficult items for each milestone category. The total milestones score is calculated as the sum of individual milestone scores; each category is scored 0–4 according to whether or not each milestone is not yet attained (0), partially attained (1–2), or fully mastered (3–4).

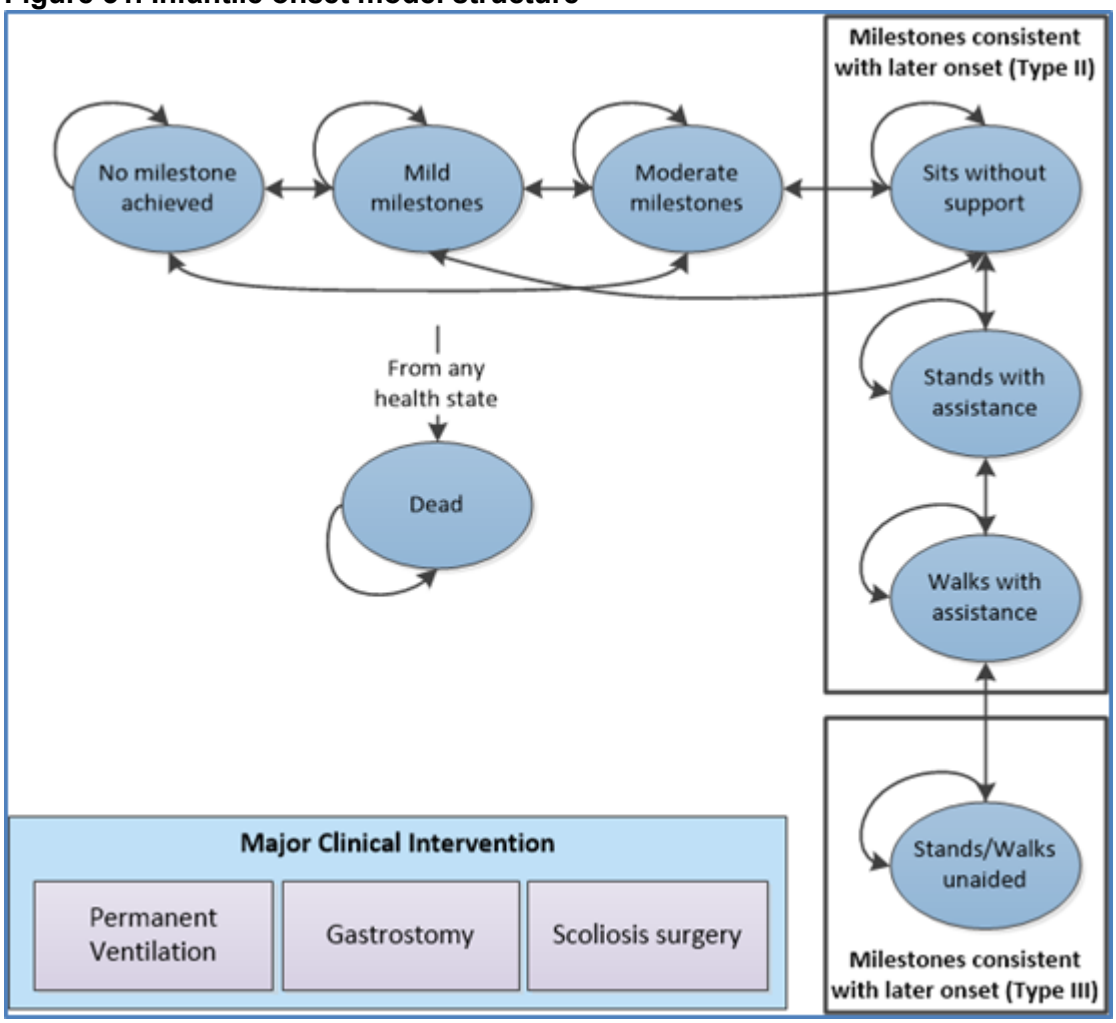
The achievement of motor milestones was assessed as part of the neurological examination conducted by the neurologist at the study centre using HINE-2, the motor milestones portion of the HINE. HINE-2 motor milestone assessments were performed at screening, and prior to dosing on days 64, 183, 302 and 394.

As described in section 2.3.3.3, the CHOP INTEND infant motor function scale, designed specifically to evaluate the motor skills of infants with SMA (49,66,67), is comprised of 16 test items, nine of which are scored 0, 1, 2, 3, or 4 with greater scores indicating greater muscle strength, five are scored as 0, 2, or 4, one is scored as 0, 1, 2, or 4, and one as 0, 2, 3, or 4. This can result in a worst possible total score of 0 and a best possible total score of 64. The CHOP INTEND was assessed by physical therapists at screening (baseline), and pre-dose on days 64, 183, 302, and 394.(49)

Achievement of the motor milestones defining the health states ***Sits without Support***, ***Stands with Assistance***, ***Walks with Assistance*** and ***Stands/Walks Unaided*** is not normally observed for patients with type I SMA under standard of care. Rather, as supported by a survey of paediatric NMD centres (where the maximum motor milestone achieved was ‘sits

without support at hips' in a minority of patients),(117) these states are associated with later onset SMA and the health resource utilisation corresponding to those states. The first 3 states are associated with type II SMA while ***Stands/Walks Unaided*** is associated with type IIIa SMA. The model grouped the motor milestones of standing unaided and walking unaided in the same health state because only a small proportion of patients receiving nusinersen in the CS3A study reached those milestones and because it is believed that there are similarities between the two categories in terms of resource use (although the link is perhaps less strong with HRQL).

Figure 31. Infantile onset model structure



Health state HINE score descriptions: (1) No milestones: Patients have a score of 0 in all HINE items. Voluntary grasp any score. (2) Mild milestones: Patients have a score of 1 in at least one of the following items: head control, ability to kick, or crawling. Patients have a score of 0 in other items. Voluntary grasp any score. (3) Moderate milestones: Patients have any of the following scores in at least one of the following items: Head control = 2; Sitting = 1; Ability to kick = 2 or 3; Rolling = 1 or 2; Crawling = 2; Standing = 1. Patients have a score of 0 in walking. Voluntary grasp any score. (4) Sits without support. Patients have a score of 2 or 3 in Sitting ability and a score <2 in Standing ability. Any score in other items except walking. (5) Stands with assistance. Patients have a score of 2 in standing ability. Any score in other items except walking. (6) Walks with assistance. Patients have a score of 2 in Walking. Any score in other items. (7) Stands/Walks unaided: Patients have a score of 3 either in Standing or Walking ability. Any score in other items.
Abbreviation: HINE, Hammersmith Infant Neurological Exam

Health state transitions over trial follow-up

Over the period of trial follow-up, patients move between health states based on patient-level assessments of motor milestones according to the HINE scale (i.e. transitions within the trial follow-up period were estimated using patient counts).

Patients can move to the state of ***Dead*** from any of the other health states. Numbers of patients still alive in the model were based on overall survival reported in the ENDEAR trial. Model schematics showing health state transitions over the period of trial follow-up and after the end of the trial are illustrated in Appendix N and the transition probability matrices under base case assumptions are provided in Appendix O.

Based on trial observations, patients in the nusinersen arm can access the **Sits Without Support** health state from any of the infantile onset health states, while only one patient in the sham arm reached the **Sits Without Support** health state from the **Moderate Milestones** health state at day 64 and then progressed to the **Moderate Milestones** health state at day 302. After reaching the ***Walks with Assistance*** health state, patients can transition to the ***Stands/Walks Unaided*** health state.

Timing of health state transitions and cycle length

Nusinersen is administered in the model on the schedule used in the ENDEAR trial. The cycle length for the first 5 cycles is dictated by the motor function/motor milestone assessment time points at days 1, 64, 183, 302 and 394 as assessed in the ENDEAR study. The 4 loading doses are administered during the first cycle of the model (the first 2 months) at days 1, 15, 30 and 60, compared with days 1, 15, 29 and 64 in the ENDEAR study. Maintenance doses were administered at days 183 and 302 days matching cycles 2 (6 months) and 3 (10 months). After the end of trial follow-up (13 months), it is assumed that a maintenance dose is administered at 14 months and every 4 months thereafter (Table 33). A half-cycle correction has been applied in the model. Key features of the economic analysis are presented in Table 34.

Table 33. Cycle length - infantile onset model

Cycle	Month (end of cycle)	Dosing schedule
1	2	4 loading doses
2	6	1 maintenance dose
3	10	1 maintenance dose
4	13[1]	-
5	14	1 maintenance dose
6 onwards	18 and every 4 months thereafter	1 maintenance dose

[1]End of trial follow-up

Key features of the economic analysis and their justification are presented in Table 34.

Table 34. Key features of the economic analysis - infantile onset

	Previous appraisals	Current appraisal	
Factor	**TAXXX**	**Chosen values**	**Justification**
Time horizon	N/A	Lifetime (modelled as 40 years in the base case)	The standard approach used in economic evaluation. A lifetime time horizon in chronic conditions ensures that the period of the analysis is long enough to reflect all important differences in costs or outcomes between the technologies being compared, in line with the NICE reference case. Extrapolation of survival beyond the trial period using natural history data indicates that a 40-year modelling period is required in nusinersen patients using base case assumptions.
Treatment waning effect?	N/A	For overall survival, a HR of 1 is assumed between treatment arms after the end of trial follow-up. Motor function is assumed to continue improving in nusinersen patients and deteriorating in control patients in line with CHOP INTEND findings in the ENDEAR study	Applying a HR of 1 is a conservative approach to the extrapolation of survival in the treatments being compared (the other possible scenarios assume that the trial HR continues indefinitely or that it tapers over a period of time, respectively). It avoids double counting in the presence of continued changes in motor function beyond the trial. These are supported by the finding that no diminution of the effect occurred over the trial period and expert clinical opinion that patients receiving nusinersen can take on the characteristics of later onset patients.
Source of utilities	N/A	PedsQL data collected in the CHERISH study in later onset patients, mapped on to EQ-5D using a published algorithm and adapted	The NICE reference case recommends a cost utility analysis. No utilities relevant to infantile SMA were found in the literature while a case vignette study commissioned specifically for the economic analysis produced results considered by

		to infantile onset patients.(118)	an expert UK expert panel to lack face validity.(33) The advisory board expressed a preference for the use of PedsQL data. At the same time, reservations have been expressed about the PedsQL scale (see section 3.4.5) and the mapping to EQ-5D was based on data collected in later onset patients using an algorithm not directly relevant to this patient group. The approach adopted was the most appropriate among a limited range of options.
Source of costs	N/A	NHS reference costs for lumbar puncture. Bastida et al. (2016)(119) for general health care management costs (which drew on the NHS Payment by Results tariffs).	Reference costs are relevant to the NHS in England. Bastida et al. (2016) collected data on health and social care costs in 4 European countries, including the UK. The only alternative source(26) is restricted to the German setting and was therefore included only as a possible scenario analysis.

Abbreviations: EQ-5D European Quality of Life-5 Dimensions; HR, hazard ratio; NICE, National Institute for Health and Care Excellence; NHS, National Health Service; PedsQL, Paediatric Quality of Life Inventory;

3.2.3 Intervention technology and comparators

Nusinersen was modelled as a first-line therapy, with symptomatic care applied according to patient health state (representing clinical need) to real world care (RWC) as is described in the ENDEAR and CHERISH trials and according to the marketing authorisation. Symptomatic care or RWC, the term used in the economic model, was used as a comparator including respiratory, nutritional, gastrointestinal and orthopaedic interventions. This is consistent with the decision problem set out in section 1.1. As previously stated in the decision problem section, the proposed population is narrower than the marketing authorisation (which includes all patients with 5q SMA) because the evidence base on nusinersen is limited to patients with pre-symptomatic and symptomatic infantile onset and later onset SMA

Although no patients in the ENDEAR study discontinued treatment with nusinersen, it was considered appropriate to introduce an assumption related to treatment response as a criterion for discontinuation of treatment over the patient lifetime. As the SmPC states, “the need for continuation of therapy should be reviewed regularly and considered on an individual basis depending on the patient’s clinical presentation and response to the therapy.”(2)

In the model, discontinuation of treatment was dependent on milestone achievement, with patients who move into the ***No Milestones*** health state discontinuing treatment (after 13 months). This assumption was supported by a UK expert panel (at the time of the panel, the ***No Milestones*** health state was named ***Worsened***).(33) In addition, discontinuation of treatment is dependent on receipt of scoliosis surgery, which can render lumbar puncture unviable. As few patients with infantile onset SMA survive to their teens under RWC, the assumed proportions of patients experiencing scoliosis and undergoing surgery are not well supported by evidence. In infantile onset SMA, 1% of patients are assumed to undergo scoliosis surgery(22) at year 12 (non-ambulant)(21) or year 15 (ambulant), as preserved standing ability can decelerate the progression of scoliosis.(21) Twenty percent of patients are assumed to discontinue treatment after scoliosis surgery.

3.3 Clinical parameters and variables

3.3.1 Data sources

ENDEAR is the pivotal, phase III, randomised, double-blind, sham-procedure controlled study to assess the clinical efficacy and safety of nusinersen in patients with infantile onset SMA.(49) ENDEAR included a total of 121 symptomatic infants ≤7 months of age, diagnosed with infantile onset SMA (symptom onset before 6 months of age). After a screening period of up to 21 days, eligible infants were randomly assigned in a 2:1 ratio to receive either a scaled-equivalent-12 mg dose of nusinersen or a sham-procedure control. Study methods and results are reported in sections B.2.3.2 and B.2.6.1.

To fill evidence gaps for data not collected in ENDEAR and to identify data on which to base extrapolation beyond the time horizon of the trial, 2 SLRs(116,120) were conducted and, where required, supplemented with targeted parameterisation searches.

As overall survival was reported in ENDEAR, the analysis did not rely on linking of intermediate with final outcomes. The model structure, clinical validity and base case inputs were validated with expert opinion, including as part of a UK clinical advisory board.(33)

In addition to CHOP INTEND and HINE-2 assessments, the following clinical and cost end-points were reported in the ENDEAR trial:

- Event-free survival (time to death or permanent ventilation);
- Overall survival;
- CMAP;
- Number of serious respiratory events;
- Number of hours of ventilation support;
- Number and length of hospitalisations.

As reported in section B.2.6.1, the ENDEAR study reported that nusinersen can alter the course of disease vs. the control group:

- A significantly greater percentage of patients achieving a motor milestone response as measured by HINE-2 (51 vs. 0%; difference of 50.68% [95% CI, 31.81–66.48%]; P <0.0001).
- Achievement of motor milestones unexpected for infants with SMA type I including full head control (22 vs. 0%), supine to prone rolling (10 vs. 0%), independent sitting (8 vs. 0%) and standing with support (1 vs. 0%); these are well above the expectations for patients with SMA type I receiving standard of care in natural-history studies.
- Statistically significant increases in event-free survival (time to death or permanent ventilation; P=0.005) and overall survival (P=0.004).
    - Overall, there was a 47% reduction in the risk of death or permanent ventilation compared to sham control.
    - There was a 63% reduction in the risk of death compared to sham control.
    - Notably, nusinersen-treated patients who were below the median for disease duration at baseline had a markedly decreased risk of death or permanent ventilation (76% reduction in risk) compared to sham-control patients who were below the median, suggesting that early treatment with nusinersen may confer a strong benefit for event-free survival.
- Greater improvements in motor function and motor neuron health as determined by the CHOP INTEND and the CMAP amplitude, respectively.

Subgroup analysis (≤12 weeks and >12 weeks) suggested that earlier and greater motor milestone responses and prolonged survival were observed among patients with shorter disease duration at the start of the study relative to patients with a longer disease duration, suggesting that early treatment with nusinersen may confer a stronger benefit.

As reported in section 2.6.4, a lower annualised rate of serious respiratory events was observed in patients who received nusinersen (2.570 vs. 4.031 serious respiratory events per year).(85) A lower mean percentage of time on ventilatory support was recorded in the nusinersen group (29.8%) compared with the control group (37.2%) after adjusting for each subject's disease duration at screening and age at symptom onset.(85)

In addition, the adjusted annualised rate of hospitalisation was lower in the nusinersen group at 4.378 hospitalisations/year compared with 5.817 hospitalisations/year in the control group.(85) During the time on study, patients in the nusinersen group spent a lower proportion of time in hospital (12.23%) compared with controls (19.13%) after adjusting for each patient's disease duration and age at symptom onset. These findings were not applied to the costings in the model to avoid double counting of cost differentials arising from differences in the achievement of motor milestones between nusinersen and RWC groups. However, they take on greater clinical significance in light of the increased severity of symptoms demonstrated in the nusinersen group at baseline compared with the control group (see section 2.3.7.1), as confirmed by clinical expert opinion.(33)

Modelled outcomes

The key outputs of the model are life years, utilities, QALYs gained and time spent in each health state. Methods of extrapolation beyond trial follow-up are described in the following

sections for survival (3.3.4) and motor function (3.3.5) as well as methods of utility assessment (3.4) and cost analysis (3.5).

Clinical expert input

Input to the design of the models was provided by the following expert reviews:

- A UK clinical expert (Dr Chiara Bettolo) from the John Walton Muscular Dystrophy Research Centre reviewed the model-specification slides for the infantile onset model on January 6, 2017.(121) The model structure was presented and there were pre-prepared questions via slides.
- An advisory discussion with 1 UK clinical expert (Dr Imelda Hughes, a consultant paediatric neurologist) and 1 senior UK health economist (Professor Alan Brennan, a Professor of Health Economics and Decision Modelling) was held on February 17, 2017.(122) Prepared questions were discussed via a slide deck. Professor Brennan was chosen as someone who understands the NICE process but had no conflicts of interest because he was not a member of any NICE committee and had no direct involvement with an Evidence Review Group.
- An expert panel was held on 11th September 2017.(33) The expert panel considered a number of aspects of the model including the definitions of health states, extrapolation of survival and health state utilities.
- A survey of 9 UK paediatric NMD treatment centres, including 6 from England and Wales. The survey evaluated aspects related to the epidemiology, burden of disease and resource use associated with SMA in the UK setting.(117)

3.3.2 Analysis of survival

As overall survival data from the ENDEAR trial are not fully mature (58.1% survival probability in the sham-treatment arm and 82.7% in the nusinersen arm), extrapolation on the basis of external data was considered more appropriate than extrapolating on the basis of a survival function fitted to the Kaplan-Meier curve.

A 3-phase extrapolation of the data was conducted. Firstly, survival functions were fitted to the Kaplan-Meier data from ENDEAR and hazard rates taken from the trial data up to the end of trial follow-up. After the end of trial follow-up, survival curves were fitted to external study data and the predicted hazard rate at the end of the external data estimated. At the end of follow-up of the external data, a model was fitted to the UK general population mortality data and used to estimate the hazard rate for patients with the mean age of those at the end of follow-up of the external data.

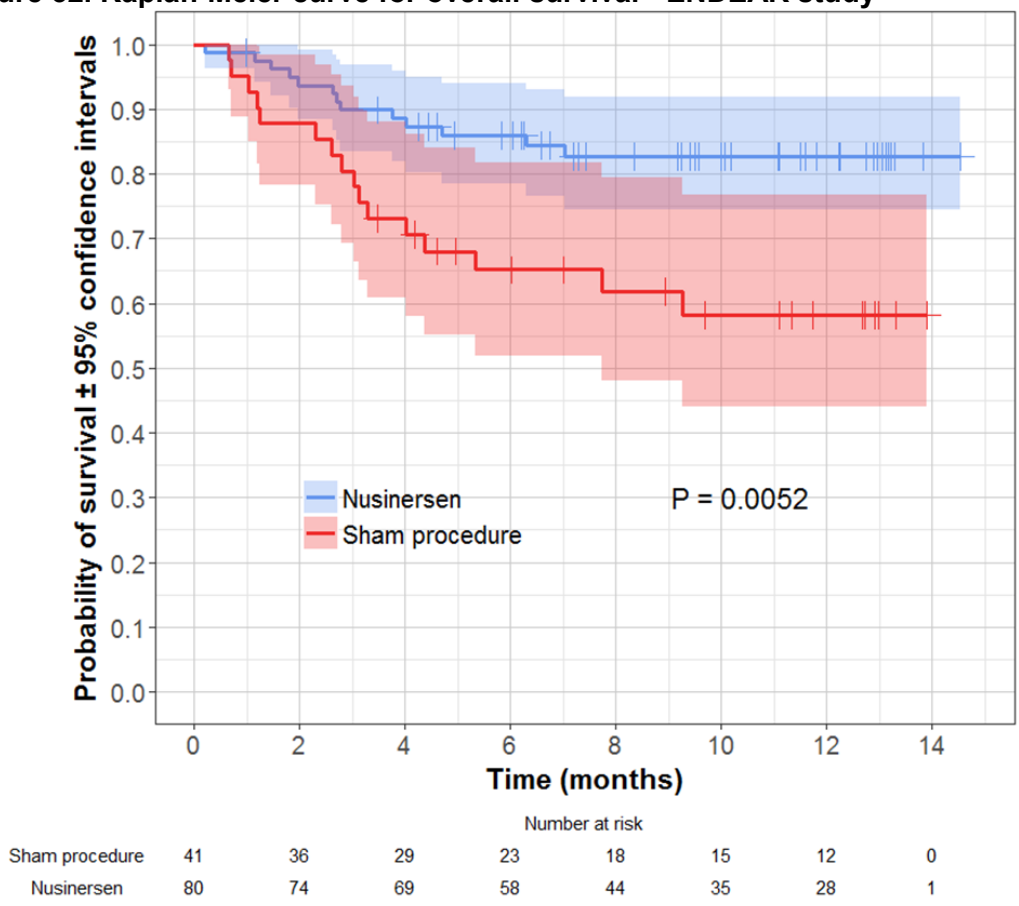
The analysis carried out for infantile onset SMA is summarised below, including the treatment of mortality among infantile onset patients who achieve motor milestones characteristic of later onset patients. Further details are provided in Appendix P which describes the fitting of survival curves to the ENDEAR trial data, external data and the general population data.

3.3.3 Analysis of survival over trial follow-up: ENDEAR

The ITT dataset was used to model the survival over the ENDEAR trial follow-up. No imputation was conducted for missing observations other than the censoring of incomplete observations. Overall survival represented by the Kaplan-Meier curve for infantile onset patients (Figure 32) was modelled using bootstrapped Kaplan-Meier and Cox models, a range of conventional parametric functions, including exponential, Weibull and Gompertz functions, as well as more flexible spline-based models(123) and hybrid models (combining Kaplan-Meier data with fitted functions). Details are provided in Appendix O. Where possible, 2 sets of functions were fitted:

- treatment included as a covariate (scale parameter allowed to vary by treatment);
- stratified models where all parameters (scale and shape) are allowed to vary by treatment. This is equivalent to fitting separate models by treatment, but it enables the creation of a single fit statistic. Stratification is described in the survival analysis literature.(124)

Figure 32. Kaplan-Meier curve for overall survival - ENDEAR study



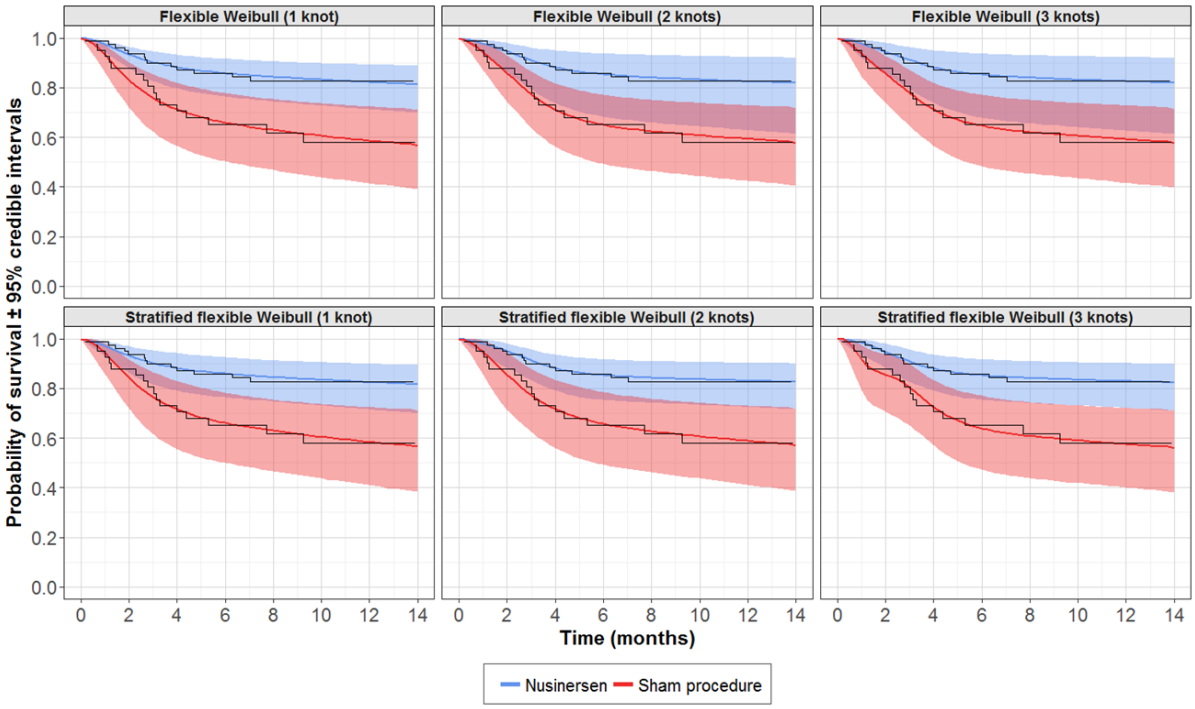
Model fit was assessed as follows:

- testing of –log(–log(survival)) plot and significance to assess the proportional hazards assumptions;

- estimation of smoothed hazard rates to investigate how the hazard rates and ratios change over time;
- graphical comparison of the predicted curve from a given survival function to the Kaplan-Meier curve;
- comparison of the Akaike information criterion (AIC) statistic, the Bayesian information criterion (BIC) statistic, and integrated Brier score (IBS) through bootstrap cross-validation;
- assessment of the clinical plausibility of the extrapolated portion of the survival curves.

The models that gave the best visual fit to the ENDEAR data were the Gompertz model and the spline-based Weibull models with 1–3 knots. Model fit and validation showed that the Gompertz model and the unstratified spline-based Weibull models with 1–2 knots gave the best fit. While the bootstrap cross-validation showed that there was some uncertainty in how reliable model predictions were, the finding that the parametric models behaved in a similar way to the Cox model and Kaplan-Meier estimates was an important factor. The Gompertz model and unstratified spline-based Weibull models with 1–2 knots fit the data well and preserved the proportional hazard assumption which appeared to have been met with these data. The flexible spline-base Weibull with 1 knot was chosen in the base case. Figure 33 illustrates the fitting of flexible spline-based Weibull models to ENDEAR.

Figure 33. Flexible spline-based models applied to ENDEAR



3.3.4 Modelling of external data

Three candidate sets of data were identified for extrapolating beyond the end of trial follow-up. Two of these, Gregoretti et al. (2013)(11) and Zerres and Rudnik-Schöneborn (1995),(125) were implemented in the model, the first as the base case and the second as a scenario. A third study by Oskoui et al. (2007)(35) was considered but reconstruction of the data at a

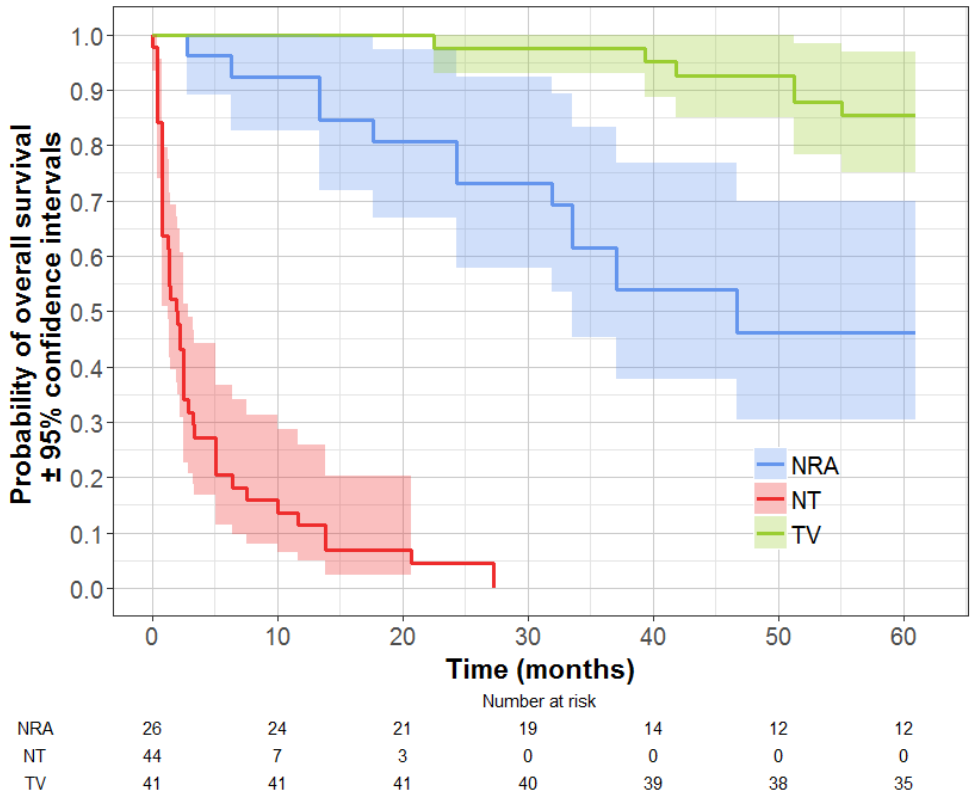
patient level was problematic because the number of patients at risk at each time point was not reported.

The study by Gregoretti et al. (2013)(11) was a retrospective chart review of 194 infantile onset SMA patients followed by 4 Italian centres between October 1, 1992 and December 31, 2010. It provided subgroup data according to the respiratory management strategy patients received. The strategies were a 'no treatment'/'let nature take its course' option (NT, 121 patients); elective tracheostomy and invasive mechanical ventilation (VT, 42 patients); and non-invasive respiratory aid (NRA, 31 patients) consisting of non-invasive bilevel ventilation and mechanically assisted coughing.

Figure 34 illustrates the adjusted survival estimates matching the ENDEAR trial data for each of the 3 groups in the study. A UK expert panel agreed that the NRA graph best reflected the UK standard of care.

All the survival functions fitted to NRA data gave a good visual fit but only the exponential, Weibull, and hybrid models gave plausible long-term predictions. The exponential model was selected in the base case to predict the hazard rates after follow-up of the ENDEAR trial data as model fit and validation showed it to give the best fit.

Figure 34. Kaplan Meier estimates based on Gregoretti et al. (2013) adjusted for mean age of patients at the start of the ENDEAR trial

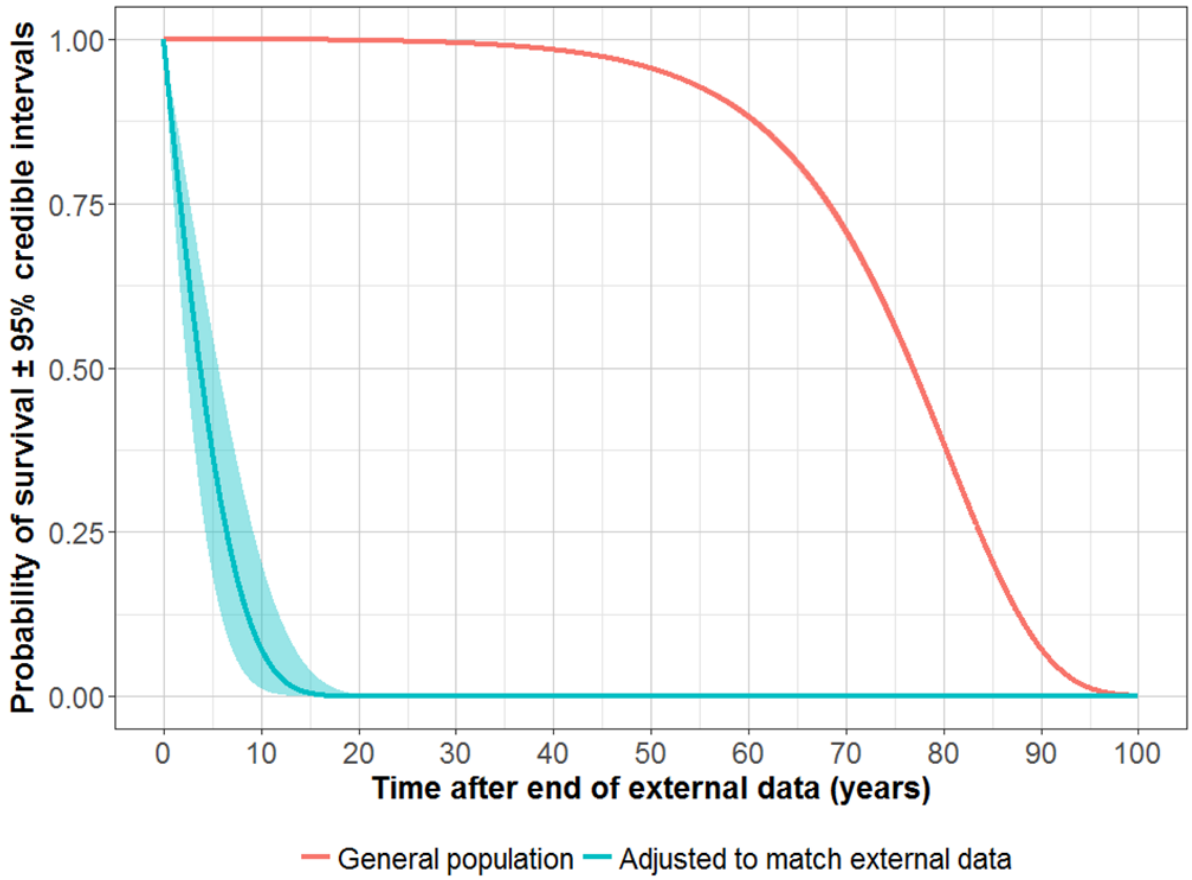


Abbreviations: NRA, non-invasive respiratory aid; NT, no treatment; TV, tracheotomy and invasive mechanical ventilation.

3.3.4.1 Extrapolation beyond external data

To project survival beyond the end of the follow-up period in Gregoretti et al. (2013), the predicted hazard rate was estimated and compared with the hazard rate for patients with the mean age of patients at the end of follow-up from a model fitted to general population data. General population mortality data were drawn from The Office for National Statistics database(126) and average life table data for males and females used. A similar curve fitting exercise was conducted with the general population data as for the ENDEAR and Gregoretti et al. (2013) data. Weibull, Gompertz and flexible spline-base Weibull models with 1, 2 and 3 knots were fitted to the general population data.

Figure 35. Predicted survival from the hazard ratio adjusted model compared with the unadjusted model fitted to general population data using data from the end of follow-up of NRA patients in Gregoretti et al. (2013)



Abbreviation: NRA, non-invasive respiratory aid

The models that gave the best visual fit were the Gompertz distribution and the spline-based Weibull models with 1 or 2 knots. Model fit (AIC and BIC) showed that the spline-based Weibull model with 2 knots gave the best fit. However, cross-validation showed that the Gompertz distribution gave the most reliable model. Because these models gave a similar fit, the choice of model is unlikely to have a noticeable effect on mean survival. The Gompertz model is the simplest model of those fitted and has a good theoretical justification, that is, an exponentially

increasing hazard rate as patients age, which is typically seen in a healthy population. Therefore, this model was chosen to perform the extrapolation after the follow-up time of the Gregoretti et al. (2013) study.(11) Comparison of the hazards at the end of Gregoretti et al. (2013)(11) and the general population at the same age (age 5.08 years) gave a ratio of 5,184.8. This was applied to general population mortality to give an adjusted survival curve for a population matching that of Gregoretti et al. (2013) as illustrated in Figure 35.

For the extrapolation of the treatment effect observed in the ENDEAR trial, a conservative hazard ratio of 1 was assumed after the end of trial follow-up to avoid overstating benefits given that an adjustment was made to the mortality of infantile onset patients who achieve later onset motor milestones. It was assumed that the mortality of these patients would fall between that of type I and type II patients, with an adjustment applied to a survival function fitted to data from the study by Zerres et al. (1997)(104) in type II patients. Drawing on clinical expert opinion(122) that infantile onset patients achieving later onset milestones could also experience later onset mortality, the adjustment factor was set to 0.9 in the base case where a factor of 0 applies the mortality of type I patients and a factor of 1 applies the mortality of type II patients. Sensitivity analyses were conducted demonstrating a high degree of sensitivity to mortality assumptions.

3.3.5 Transition probabilities after the end of trial follow-up

After the end of trial follow-up, there is a high level of uncertainty around the transition probabilities. The assumption made in the base case was that, except for those who stop treatment, patients in the nusinersen arm continue to improve, and therefore move to better health states, in line with improvements in CHOP INTEND observed over the period of trial follow-up. As motor function improvements seen in the clinical studies did not exhibit a plateau and, on the grounds of nusinersen's action on the underlying cause of disease, an expectation of continued improvement was supported by a panel of expert UK clinicians.(33) The option of introducing a plateau with some of those patients progressing as in the RWC arm was included in the model as a scenario. In contrast with those in the nusinersen arm, patients receiving symptomatic care are expected to follow natural history, whereby patients experience a decline in motor function as measured by the CHOP INTEND.(34) Hence, patients in the RWC arm either remain in their health state or transition to worse health states after trial follow-up.

To derive transitions for the base case scenario, the model assigns a CHOP INTEND score to each health state based on the mean CHOP INTEND score of the patients in each health state throughout the ENDEAR trial follow-up (i.e. mean score including all assessments). The mean scores for the ***No Milestones, Mild Milestones, Moderate Milestones, and Sits without Support*** health states were calculated using the CHOP INTEND scores for each arm. Only one measurement was available for the ***Sits without Support*** health state in the RWC arm. Mean CHOP INTEND scores for patients standing and walking were calculated from the scores of the [redacted] patients in the CS3A trial able to stand and walk and from the scores of the [redacted] patients in the CS3A trial able to stand but not walk, respectively (Table 35). An alternative scenario analysis assigns the mean CHOP INTEND scores for both arms combined.

Table 35. Mean CHOP INTEND scores throughout the ENDEAR trial

Health state	Nusinersen		RWC		Source
	Mean (SE) CHOP INTEND score	N	Mean (SE) CHOP INTEND score	N	
No Milestones: each arm	24.6 (0.93)	96[a]	20.2 (1.07)	79[a]	ENDEAR trial
Mild Milestones: each arm	33.0 (0.78)	94[a]	26.8 (1.43)	30[a]	ENDEAR trial
Moderate Milestones: each arm	41.4 (0.90)	59[a]	37.1 (2.37)	14[a]	ENDEAR trial
Sits without Support: each arm	46.7 (1.43)	24[a]	48.0[b]	1[a]	ENDEAR trial
Stands with assistance: *Nusinersen arm*	52.7 (0.67)	3[c]	52.7 (0.67)	3[c]	CS3A trial
Walks with assistance: *Nusinersen arm*	63.0 (1.00)	2[c]	63.0 (1.00)	2[c]	CS3A trial

Abbreviations: CHOP INTEND, Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders

[a] Measurements throughout the trial follow-up

[b] Assumed to be fixed in the probabilistic sensitivity analysis

[c] Last visit assessment in the CS3A single arm trial for patients receiving nusinersen. Patients in the RWC arm of the ENDEAR trial did not achieve the stands with assistance or walks with assistance milestone. The model assumes the same score as for those receiving nusinersen.

In the nusinersen arm, the model uses the mean rate of CHOP INTEND increase, as observed in the ENDEAR trial for patients treated with nusinersen ([redacted]), to calculate the transition probability to the next best health state. In the RWC arm, the model uses the mean rate of CHOP INTEND decrease, as observed in the ENDEAR trial for the sham arm ([redacted]), to calculate the transition probability to the next worst health state. A more conservative mean rate of decrease observed by Finkel et al. (2014)(34) of 0.11 points per month can be used in scenario analysis. Transitions to ***Dead*** were governed by the survival function after trial follow-up. Model schematics showing transitions observed over the trial period and modelled transitions beyond the end of trial follow-up are illustrated in Appendix N, with the transition matrices presented in Appendix O.

For patients receiving nusinersen, the calculation of transition probabilities beyond the end of trial follow-up can be illustrated as follows. The transition probability to the next best health state from the health state ***Stands with Assistance*** is given by:

$$transition\ probability_{standing\ to\ walking}$$
$$= Min\left(1, \left(\frac{Rate\ of\ CHI\ increase_{per\ month} \times Cycle\ length}{CHI_{walking} - CHI_{standing}}\right)\right)$$
$$= Min(1, ([redacted]))$$
$$= 42\%, transition\ probability_{standsing\ with\ assistance\ to\ walks\ with\ assistance}$$
$$= Min\left(1, \left(\frac{Rate\ of\ CHI\ increase_{per\ month} \times Cycle\ length}{CHI_{walks\ with\ assistance} - CHI_{stands\ with\ assistanceing}}\right)\right)$$
$$= Min(1, ([redacted])) = 42\%,$$

$transition\ probability_{standing\ to\ standing} = 1 - transition\ probability_{standing\ to\ walking} = 58\%, transition\ probability_{stands\ with\ assistance\ to\ stands\ with\ assistance} = 1 - transition\ probability_{stands\ with\ assistance\ to\ walks\ with\ assistance} = 58\%,$

where *CHI* is the mean CHOP INTEND score. The model assumes that the probability of transitioning from the ***Walks with Assistance*** health state to the ***Stands/Walks Unaided*** health state is the same as the transition probability from the ***Stands with Assistance*** health state to the ***Walks with Assistance*** health state.

For patients receiving RWC, the transition probability to the next worse health state is calculated in a similar way. For example, from the health state ***Walks with Assistance***, the transition probability is given by:

$transition\ probability_{walking\ to\ standing} = Min\left(1, \left(\frac{Rate\ of\ CHI\ decrease_{per\ month} \times Cycle\ length}{CHI_{walking} - CHI_{standing}}\right)\right) = Min(1, ([redacted])) = 61\%, transition\ probability_{walks\ with\ assistance\ to\ stands\ with\ assistance} = Min\left(1, \left(\frac{Rate\ of\ CHI\ decrease_{per\ month} \times Cycle\ length}{CHI_{walks\ with\ assistance} - CHI_{stands\ with\ assitance}}\right)\right) = Min(1, [redacted]) = 61\%,$

$transition\ probability_{walking\ to\ walking} = 1 - transition\ probability_{walking\ to\ standing} = 39\%, transition\ probability_{walks\ with\ assitance\ to\ walks\ with\ assitance} = 1 - transition\ probability_{walks\ with\ assistance\ to\ stands\ with\ assistance} = 39\%,$

where *CHI* is the mean CHOP INTEND score. The model assumes that the probability of transitioning from the ***Walks with Assistance*** health state to the ***Stands with Assistance*** health state is the same as the transition probability from the ***Stands/Walks Unaided*** health state to the ***Walks with Assistance*** health state.

3.4 Measurement and valuation of health effects

HRQL assessments are particularly challenging in SMA due to the nature of the condition and the age of the patient population. The well documented issues with conceptualising and measuring HRQL in children and young people(109,127) mean that QALYs may not capture

a fully rounded view of the value of therapy. Proxy assessments of patient HRQL may be useful and necessary in this context but nevertheless may fail to provide a balanced assessment of HRQL in SMA. In SMA, the situation is further complicated by issues specific to the condition. For example, the relationship between motor function and HRQL does not necessarily conform with intuitive expectations (e.g. improvements in motor function do not always lead to predictable improvements in HRQL).

As no utility measurements were included in the pivotal ENDEAR trial, nor were any suitable utilities identified by an SLR(116), other approaches were explored including a case vignette study undertaken to obtain utilities for each of the modelled health states in infantile onset SMA. The health state utilities incorporated into the model were ultimately derived from a mapping algorithm applied to PedsQL data collected in the CHERISH trial. While mapping is an accepted method in economic evaluation,(128) and had the advantage in this analysis of enabling QALYs to be based on EQ-5D in accordance with the NICE reference case,(129) the approach had the disadvantage that the underlying HRQL data were obtained from a patient group different from the target population. The vignette and mapping studies, along with other sources considered for utilities, are summarised below and presented in detail in Appendix H.

3.4.1 Case vignette study

This study(130) involved interviews (4 in person and 1 by telephone) with 5 UK clinical experts who were asked to describe a typical child with different types of SMA (symptoms, physical limitations and HRQL), the typical course of the disease and the available treatments for SMA. Interview results and a literature review were used to draft case studies describing a child in each of the health states in the economic model.

Five experts responded to requests for interviews to value the case studies, including 2 who had participated in the initial case study development interviews. The experts completed the EQ-5D Youth version (EQ-5D-Y) for all case studies and the Peds-QL-NMM for 2 baseline states. In the absence of a tariff for the EQ-5D-Y, the EQ-5D-Y data were scored using the adult EQ-5D 3-level scale (EQ-5D-3L) tariff. The results of the valuation exercise are reported in Appendix H.

It was found in this study that the majority of health states were assigned negative values, which is not commonly observed with EQ-5D, and that the rankings of some utilities were counterintuitive. These utilities were therefore subject to further expert scrutiny as part of a UK expert panel.(33) As a result of the reservations expressed about this set of utilities by paediatric NMD specialists from SMA treatment centres across the UK, other sources of data were considered.

3.4.2 Health-related quality of life data from clinical trials

The experts' preferred dataset was that collected using the PedsQL measure as part of the CHERISH study among later onset patients. The PedsQL scores collected in the trial were mapped on to the EQ-5D using a published algorithm(118). Although the health states defined for infantile onset differed from those defined for later onset SMA, they were regarded as sufficiently similar to justify adapting the utilities generated for later onset patients.

3.4.2.1 Mapping

The algorithm(118) developed to map from PedsQL to EQ-5D was estimated on the basis of data from a cross-sectional survey conducted in 4 secondary schools in England amongst children aged 11–15 years of age. Predictive ordinary LS models for EQ-5D based on PedsQL GCS were internally validated on an estimation dataset that included complete PedsQL GCS and EQ-5D scores for 559 respondents. In addition, a validation exercise was conducted on a separate dataset for 337 respondents. The best predictive accuracy was obtained with models using PedsQL subscale scores, their squared terms and interactions with and without age and gender. Both models generated higher prediction errors for children in poorer health states. The authors consider the predicted EQ-5D utilities to be robust for children aged 11–15 years in attendance at secondary school but acknowledge that the algorithms remain to be evaluated in populations differing in age or clinical characteristics.

The utilities derived in this way were adapted in the base case for infantile patients, on the basis of an assumed correspondence between health states defined in later onset and infantile onset patients, especially as infantile onset patients (when treated with nusinersen) are expected to become more like a type II later onset patient, as confirmed during the UK expert panel.(33) Patient utilities for each infantile onset health state along with the corresponding later onset health state are presented in Table 36. Each infantile onset health state was assigned the utility from the closest comparable health state in later onset.

Table 36. Patient utilities - infantile onset

Health state	Patient utility	Equivalent later onset health state
No Milestones	[redacted]	***Sits without Support but does not Roll***
Mild Milestones	[redacted]	***Sits and Rolls Independently***
Moderate Milestones	[redacted]	***Sits and Rolls Independently***
Sits without Support	[redacted]	***Sits and Crawls with Hands and Knees***
Stands with Assistance	[redacted]	***Stands/Walks with Assistance***
Walks with Assistance	[redacted]	***Stands Unaided***
Stands/Walks Unaided	[redacted]	***Walks Unaided***

It should be noted that the mapping exercise produced results for the later onset patients that may lack face validity: the ***Stands Unaided*** health state utility ([redacted]) was less than that for ***Stands/Walks with Assistance*** ([redacted]). These two states were therefore allocated the higher of the two utilities. The ***Stands/Walks Unaided*** health state was allocated the ***Walks Unaided*** health state from the later onset population.

3.4.2.2 Carer utilities

The default approach to estimating carer QALYs was analogous to the method for estimating patient QALYs, being based on patient life years but multiplied by a carer utility rather than a

patient utility. This raises a question about the appropriate utility from the carer's perspective as the patient's health state varies but also of whether improvements in survival for the patient are a satisfactory proxy for the impact on the carer of earlier or later death of the patient. This approach was felt to overstate carer QALY gains, and that a more logical approach to reflect carer burden was to apply a decrement or disutility relative to the general population.

For each health state, the method compares the carer utility obtained from the PedsQL mapping with a general population EQ-5D utility. If the carer utility is greater than the general population figure, no decrement is applied. If the carer utility is less than the general population estimate, the difference between the carer utility and the general population utility is calculated (a negative number) and multiplied by patient life years. The carer utilities in this calculation were derived by applying the carer utility obtained by Bastida et al. (2016)(119) to the ***Sits and Rolls Independently*** health state and, for each health state, adjusting by the difference between the patient utility for that health state and the patient utility for ***Sits and Rolls Independently*** from the PedsQL mapping. The values for health states ***Walks with Assistance*** and ***Stands/Walks Unaided*** were capped to that of the ***Stands with Assistance*** health state. Table 37 reports the calculations for carer utilities in infantile onset SMA. Base case utility decrements are presented in Table 38.

Table 37. Approach to carer utilities - infantile onset SMA

Health states	Caregiver's health state utility values	Methodology
No Milestones	[redacted]	Applying the difference between ***Sits and Rolls Independently*** ([redacted]) and ***Sits without Support but does not Roll*** ([redacted]) health states from the PedsQL mapping study to the Bastida utility value gives a utility of [redacted]
Mild Milestones	[redacted]	Assumption based on infantile onset point estimate from Bastida: the value from the study is assumed to best reflect this health state or the ***No Milestones*** health state, and the selection of this health state was chosen as it seems implausible that the ***No Milestones*** health state would have such a high utility value
Moderate Milestones	[redacted]	The same as ***Mild Milestones*** health state (no difference in patient utilities)
Sits without Support	[redacted]	Applying the difference between ***Sits and Rolls Independently*** ([redacted]) and ***Sits and Crawls with Hands and Knees*** ([redacted]) health states in the PedsQL mapping study to the Bastida utility value gives a utility of [redacted]
Stands with Assistance	[redacted]	Applying the difference between ***Sits and Rolls Independently*** ([redacted]) and ***Stands/Walks with Assistance*** ([redacted]) health states in the PedsQL mapping study to the Bastida utility value gives a utility of [redacted]
Walks with Assistance	[redacted]	The same as ***Stands with Assistance*** (no difference in patient utilities)
Stands/Walks Unaided	[redacted]	Assumed to be the same as ***Stands with Assistance***

The general population EQ-5D utility was based on a predictive equation(131) with coefficients on age, the square of age and the proportion who are female. This gave a utility of 0.915. Carer disutilities relative to this reference point are given in Table 38. Additionally, bereavement of the carer was assigned a negative utility based on Song et al. (2010).(132)

Table 38. Base case carer disutilities, infantile onset SMA

Health state	Carer disutility
No Milestones	[redacted]
Mild Milestones	[redacted]
Moderate Milestones	[redacted]
Sits without Support	[redacted]
Stands with Assistance	[redacted]
Walks with Assistance	[redacted]
Stands/Walks Unaided	[redacted]

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

3.4.3 Health-related quality of life studies

An SLR(116) for HRQL and utilities identified 5 HRQL studies but no studies reporting utility values specific to patients with SMA. All 5 reported HRQL assessed by parents or caregivers whether through the parent proxy element of the PedsQL or through an HRQL issues questionnaire and semantic differential scales. An update to the review identified a further 5 studies, of which 3 used the PedsQL measure, 1 used the SF-36 measure and 1 used the EQ-5D. The latter study was a published report on the Spanish results (133) of the Bastida et al. (2016) study(119) previously cited. One study which assessed PedsQL was a poster reporting the case vignette study already described.(130) The other 9 studies are summarised below and details of all 10 are given in Appendix H. For future clinical studies, researchers will have access to the Spinal Muscular Atrophy Health Index (SMA-HI) which is being developed jointly by Biogen and Rochester University.(24)

Bach et al. (2003).(134) The care providers of 53 SMA type I children managed in 1 US NMD clinic were sent Likert-scale surveys of 6 HRQL issues and 10 polar-adjective pairs. The HRQL estimations were compared with those of 67 clinicians and with those of 30 parents considering their unaffected children.

Iannaccone and Hynan (2003).(135) Thirty-eight children with SMA who fulfilled inclusion and exclusion criteria were enrolled at 5 US paediatric centres for a reliability study. Thirty-four patients and 7 evaluators completed the study. Thirteen patients were aged 2–4 years and 21 were 5–17 years. The Gross Motor Function Measure was completed by 34 subjects. Six variables for pulmonary function tests were measured in 20 subjects. Quantitative muscle testing was performed on 21 subjects in 8 muscle groups. Thirty-three subjects completed the PedsQL NMM for Parents.

Iannaccone et al. (2009).(136) 176 children with SMA and their parents completed the PedsQL Generic Core Scales (GCS) and PedsQL NMM. The PedsQL demonstrated feasibility, reliability, and validity in the SMA population. Consistent with the conceptualisation of disease-specific symptoms as causal indicators of generic HRQL, the majority of

intercorrelations among the NMM scales and the GCS were in the medium to large range, supporting construct validity.

Kocova et al. (2014)(137) conducted a survey using the PedsQL NMM among 35 children with genetically proven SMA and their parents.

Wong et al. (2007).(138) The authors conducted a randomised, double-blind, placebo-controlled trial on 55 patients aged 2–18 years with SMA. Patients aged younger than 5 years received 2 g/day of creatine/placebo for 6 months. Patients aged 5 years and older received 5 g/day. The primary outcome measure was the Gross Motor Function Measure. Secondary outcome measures were Quantitative Muscle Testing, Parent Questionnaire for the PedsQL NMM, and Pulmonary Function Tests.

Bastida et al. (2016)(119) conducted a cross-sectional study of patients with SMA in France, Germany, Spain and the UK. Data on HRQL were collected from questionnaires that were completed by patients' caregivers. HRQL was measured with the EQ-5D-3L parent proxy for children/adolescents and the EQ-5D-5L to assess the general health of caregivers. In addition to EQ-5D values, self-ratings on the visual analogue scale (VAS) were recorded. In scenario analysis, the upper and lower patient EQ-5D VAS values reported in the study can be applied as constant utilities across health states. The limits which can be explored in scenario analysis are 0.731 (95% CI: 0.403–0.954, beta) and 0.817 (95% CI: 0.37–0.999, beta).

Klug et al. (2016)(26) assessed PedsQL, either self- or proxy-reported, among a cross-section of 189 type I, II and III SMA patients in Germany.

Voos et al. (2015)(139) studied 12 children with type I SMA and 12 matched controls. In addition to figure and colour association and number and letter association tasks, children were assessed with CHOP INTEND, Pediatric Evaluation of Disability Inventory (PEDI) and PedsQL. Children with type I SMA scored 3-40% on CHOP INTEND, 5-20% on PEDI and 29-50% on PedsQL.

Kruitwagen-Van Reenen et al. (2016)(140) assessed HRQL among 62 adult patients with SMA (4 with type I, 21 with type II, 33 with type III and 4 with type IV) using the validated Dutch version of the SF-36. All patients scored low on the "physical functioning" domain. Scores on the other domains were within the limit of 1.5 standard deviations. Patients with SMA types IIIb/IV scored markedly lower than patients with SMA types I-IIIa in the "role emotional" and "mental health" domains.

3.4.4 Adverse reactions

AEs were not modelled in the base case or scenario analyses as the ENDEAR trial did not observe any treatment-related AEs. The SmPC lists only those AEs associated with the lumbar puncture procedure that occurred with an incidence at least 5% higher in patients treated with nusinersen compared with sham procedure control patients (headache, vomiting and back pain). Additionally, it states that AEs commonly associated with lumbar puncture (e.g. headache and back pain) could not be assessed in the infant population exposed to nusinersen due to limited communication appropriate for that age group, highlighting difficulties of assessment in a paediatric population. Since the AEs connected with the mode

of administration are short lived, it was considered reasonable to exclude them from the cost and HRQL estimates.

3.4.5 Health-related quality of life data used in the cost-effectiveness analysis

The difficulties of exploring subjective HRQL in this group of patients means that obtaining a set of utilities which are truly reflective of the patient experience and aspects of the condition that most affect patients' HRQL is problematic. Testing of the approach to HRQL and utilities with the UK clinical advisory board suggests that there may be no single measure which provides a rounded assessment of the relative importance of different aspects of the disease and nusinersen on the patient's HRQL. Therefore, the information on motor function, motor milestones and other endpoints in ENDEAR is likely to provide additional insight into the patient's HRQL but is beyond the scope of a NICE reference case cost-effectiveness analysis.

When presented with the utilities based on the PedsQL measure, the advisory panel felt, on the one hand, that they exhibited a realistic degree of variation across health states. The experts reasoned that the differences between health states would be limited due to a lack of experience and perception of life without disease, a lack of cognition regarding disease states and expectations concerning long-term outcomes as well as coping and supportive technologies. On the other hand, health states which are defined in terms of gross motor milestones could miss fine motor tasks ranging from communication ability (enabling greater social independence and peer group acceptance) to the ability to play a musical instrument. In addition, an emphasis on motor function downplays the importance of respiratory function. In young infants, it was felt that in type I patients, respiratory function and comfort (the patient not feeling that they're suffocating) is a key contributor to defining HRQL. Days in hospital and level of respiratory intervention might be a good indicator of HRQL in young infants while, as the child ages, motor function, particularly as it affects the ability to engage with the environment including communication ability, becomes more important.

Evidence on the PedsQL instrument from the literature illustrates the difficulties of assessing HRQL in this patient group. A systematic review of health outcomes in children with neurodisability (including disability where motor functioning is affected by central nervous system impairments) found it to be lacking in many areas although there was good evidence for structural validity.(28) There was no evidence of qualitative work done to determine content validity with children and young people for the PedsQL. Test-retest reliability results were inconclusive, not all domain scales reached acceptable criteria for internal consistency and evidence for their psychometric robustness in younger children was weak. General concerns were raised about the candidate patient-reported outcomes measures (PROMs) identified in this systematic review, none of which were found adequately to capture all of the important health outcomes for young people, parents and professionals. A separate systematic review has raised concerns about the overall lack of evidence for responsiveness and measurement error for the PedsQL (amongst other instruments).(27)

Against this, PedsQL has been used frequently in SMA, and has been validated by the American Spinal Muscular Atrophy Randomized Trials group for use in patients with SMA who are 2–18 years of age.(31) Although the mapped PedsQL data from the CHERISH study were obtained from later onset, rather than infantile onset patients, their use in both groups was

based on the similarities in health states between the two models. In contrast, PedsQL data from previous studies could not be converted into utilities for each of the health states in the economic model in a straightforward way. Patient and carer health state utilities and carer utility decrements were based on the CHERISH PedsQL, with adjustments to the infantile onset population as described above (Table 36, Table 37 and Table 38). These are presented together with confidence intervals while carer utility decrements are presented in Table 39. As there was no basis for varying utilities by age of the patient, something which the UK advisory panel noted would be useful, utilities are assumed to be constant over time. As a scenario, utilities from Bastida et al. were considered the most relevant to include as a scenario because they were based on EQ-5D.

Table 39. Summary of utility values used in the analysis

Health state	Utility value: mean (standard error)		95% CI	Reference in submission (section and page number)	Justification
Patients				**Mapping**	
No Milestones	[redacted]		[redacted]	p. 131	See text
Mild Milestones	[redacted]		[redacted]	p. 131	See text
Moderate Milestones	[redacted]		[redacted]	p. 131	See text
Sits without Support	[redacted]		[redacted]	p. 131	See text
Stands with Assistance	[redacted]		[redacted]	p. 131	See text
Walks with Assistance	[redacted]		[redacted]	p. 131	See text
Stands/Walks Unaided	[redacted]		[redacted]	p. 131	See text
	[redacted]				
Carers	[redacted]	**Decrement**	**95% CI for utilities**	**Carer utilities**	
No Milestones	[redacted]	[redacted]	[redacted]	p. 131	See text
Mild Milestones	[redacted]	[redacted]	[redacted]	p. 131	See text
Moderate Milestones	[redacted]	[redacted]	[redacted]	p. 131	See text
Sits without Support	[redacted]	[redacted]	[redacted]	p. 131	See text
Stands with Assistance	[redacted]	[redacted]	[redacted]	p. 131	See text
Walks with Assistance	[redacted]	[redacted]	[redacted]	p. 131	See text
Stands/Walks Unaided	[redacted]	[redacted]	[redacted]	p. 131	See text

Abbreviation: CI, confidence interval

3.5 Cost and healthcare resource use identification, measurement and valuation

3.5.1 Intervention and comparators' costs and resource use

Evidence on treatment costs in SMA was drawn from the UK data collected by Bastida et al. (2016),(119) from which only the Spanish results(133) have been published to date. This survey of patients and carers in a number of European countries was considered to be the most relevant to the decision problem defined in this appraisal. A second study by Klug et al. (2016)(26) and identified by one of the SLRs(120) estimated HRQL and costs associated with SMA in Germany. This study was incorporated into the model for the purposes of scenario analysis. None of the other studies have been included.

Base case costs include health and social care costs and exclude transport, informal care, lost productivity and other out-of-pocket costs. Informal care and transport costs are considered from a societal perspective.

Nusinersen costs consist of drug acquisition costs and administration costs. A 12mg/ 5ml vial of nusinersen (one dose) is priced at £75,000. Nusinersen is administered by lumbar puncture, either in the inpatient, outpatient or day-case setting. The unit costs of lumbar puncture using 2015/16 NHS reference costs are presented in Table 40. The procedure codes used do not correspond exactly to lumbar puncture for the administration of nusinersen but were the closest available proxies. The cost of nusinersen in the first year of treatment (6 doses consisting of 4 loading doses and 2 maintenance doses) is £450,000 for a full year. Annual costs thereafter for 4 maintenance doses are £300,000. The weighted average costs of administering a dose of nusinersen by lumbar puncture are £1,359 in those aged 5 years and under, £1,295 in those aged 6-18 years and £606 in those aged 19 years and above.

Table 40. Drug and administration costs for nusinersen (£2016)

Parameter	Value	Source
Drug-acquisition costs (£)		
Nusinersen (per vial)	75,000	Biogen
Administration costs (£)(141)		
Inpatient lumbar puncture		
19 years and over	918	NHS reference costs 2015/16 (EL - HC72A)
6–18 years	1,658	NHS reference costs 2015/16 (EL - HC72B)
5 years and under	1,690	NHS Reference costs 2015/16 (EL - HC72C)
Outpatient lumbar puncture		
19 years and over	204	NHS reference costs 2015/16 (OPROC - HC72A, service code 400)
6–18 years	560	NHS reference costs 2015/16 (OPROC - HC72B, service code 421)
5 years and under	577	NHS reference costs 2015/16 (OPROC - HC72C, service code 421)
Day case lumbar puncture		
19 years and over	593	NHS reference costs 2015/16 (DC - HC72A)
6–18 years	1,546	NHS reference costs 2015/16 (DC - HC72B)
5 years and under	1,700	NHS reference costs 2015/16 (DC - HC72C)

Abbreviation: DC, day case; EL, elective; HC72A, Diagnostic Spinal Puncture, 19 years and over; HC72B, Diagnostic Spinal Puncture, between 6 and 18 years; HC72C, Diagnostic Spinal Puncture, 5 years and under; NHS, National Health Service; OPROC, outpatient procedures;

Bastida et al. (2016)(119) is listed in Appendix K as part of the checklist of confidential information. In brief, the main caregivers of children/adolescents diagnosed with SMA completed a self-administered questionnaire providing information related to sociodemographics, the costs of professional private care, the need for informal care, expenditure and resource utilisation related to SMA. Data on unit costs was collected from the relevant sources in each country (France, UK, Germany and Spain). In the UK, the Payment by Results (PbR) tariff was used for health care costs. Across all the countries studied, costs were expressed in €2014. In addition to cost data, the survey collected HRQL and EQ-5D from patients and caregivers. Data was collected from 167 patients with SMA and their caregivers, of which 34 (7 type I, 20 type II, 7 type III) were from the UK.

The cost analysis is based on estimates of annual costs of managing patients with infantile onset SMA according the main therapeutic areas involved in the care of this patient group (respiratory, gastrointestinal, nutritional and orthopaedic care). These costs are derived from a more detailed breakdown of costs by category of resource use according to motor milestones achieved (those characterising types I, II and III patients, respectively) provided in Bastida et al. (2016).(119) The categories of resource use covered in that study (from a health and social care perspective), together with examples of items within each category, are as follows:

- **Drugs:** e.g. creatine, gabapentin, hydroxyurea, vitamin supplements, calcium;

- **Clinical tests:** e.g. Blood test, urinalysis, chest X-ray, electrocardiogram, magnetic resonance imaging, back X-ray, hip X-Ray, range of motion tests, breathing tests (spirometry);
- **Medical visits:** e.g. urologist, neurologist, psychiatrist, dermatologist, nephrologist, respiratory consultant, nutritionist, occupational therapists, traumatologist, specialist in palliative care, respiratory physiotherapist;
- **Hospitalisation;**
- **General practitioner (GP) & emergency**; GP health centre, GP domiciliary, nurse health centre, nurse domiciliary, emergency health centre, emergency domiciliary;
- **Health material:** e.g. prosthesis, wheelchair, orthoses, adjustable bed, vehicle adaptation, portable oxygen, food supplements, cannulas for gastric feeding button, humidifiers, pulse oximeter, shower chair, communication aids;
- **Social services:** e.g. day centre, occupational centre, respiratory physiotherapy, occupational physiotherapy, psychosocial care for family, residential centres;

Table 41 reports estimates of average annual costs per patient for type I, II and III patients by these categories of costs in the original €2014 and in £2016 on the basis of the same exchange rate used by Bastida et al. (2016)(119) and inflation as measured by changes in consumer prices between 2014 and 2016. Interim results from a survey of UK NMD centres, while also exhibiting a gradient in costs from type I to type III, suggest that the Bastida et al. (2016)(119) costs may be conservative.

Table 41. Annual costs by category of resource use in type I, II and III SMA patients

	Type I		Type II		Type III	
	€2014	£2016	€2014	£2016	€2014	£2016
Drugs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Medical tests	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Medical visits	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Hospitalisations	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
GP & emergency	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Health material	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Social services	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Source: Bastida 2016(119)

These costs were allocated to the 4 main therapy areas according to the proportions set out in Table 42. For example, drug costs are split 50/50 between respiratory care and gastrointestinal care.

Table 42. Allocation of therapy costs by type of resource

Cost item	Respiratory care	Gastrointestinal care	Nutritional care	Orthopaedic care	Reference
Direct health care costs (Bastida et al., 2016)					
Drugs	50%	50%	0%	0%	Assumption
Medical tests	25%	25%	25%	25%	Assumption
Medical visits	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Hospitalisations	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
General practitioner and emergency	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Health materials	25%	25%	25%	25%	Assumption
Social services	25%	25%	25%	25%	Assumption

Applying these proportions to the costs for type I patients in Table 41 gives annual health care costs by resource category and therapy area for patients achieving milestones consistent with infantile onset as shown in Table 43.

Table 43. Annual costs by therapy area/resource category for infantile onset patients

	Respiratory Care	Gastrointestinal care	Nutritional Care	Orthopaedic Care
Drugs	[redacted]	[redacted]	[redacted]	[redacted]
Medical tests	[redacted]	[redacted]	[redacted]	[redacted]
Medical visits	[redacted]	[redacted]	[redacted]	[redacted]
Hospitalisations	[redacted]	[redacted]	[redacted]	[redacted]
General practitioner and emergency	[redacted]	[redacted]	[redacted]	[redacted]
Health materials	[redacted]	[redacted]	[redacted]	[redacted]
Social services	[redacted]	[redacted]	[redacted]	[redacted]
Total	[redacted]	[redacted]	[redacted]	[redacted]

Source: Bastida 2016(119)

Allocating the costs for type II and III patients in the same way gives annual costs by therapy area for all 3 patient types as shown in Table 44. All 3 columns are applicable to the infantile onset model while only the second and third columns are relevant to the later onset model. The guidelines identified(6) do not differentiate the amount of care required by patients at different levels of the HINE scale or by CHOP INTEND response. Therefore, in the model it was assumed that patients in the health states consistent with SMA type I accrue the costs of patients with SMA type I, that patients in health states consistent with SMA type II accrue the costs of patients with SMA type II, and that patients in health states consistent with SMA type III accrue the costs of patients with SMA type III. Clinical experts agreed with the assumption that improved motor milestones would require reduced resource use due to fewer complications.(33,121,122)

Table 44. Annual health care and social care costs according to motor milestones achieved (£2016)

	Milestones consistent with infantile onset	Milestones consistent with later onset (type II)	Milestones consistent with later onset (type III)
Respiratory care	[redacted]	[redacted]	[redacted]
Gastrointestinal care	[redacted]	[redacted]	[redacted]
Nutritional care	[redacted]	[redacted]	[redacted]
Orthopaedic care	[redacted]	[redacted]	[redacted]

Source: Bastida 2016(119)

The same annual costs by therapy area are applied to both nusinersen and RWC patients. This is regarded as a conservative approach as resource use data collected as part of the ENDEAR trial suggests that nusinersen is associated with reduced hospitalisation and ventilation costs compared with sham-procedure patients. On the other hand, allowing for the differentials in use of hospitalisation and ventilation could represent double counting if they are already reflected in the variation in costs according to achievement of motor milestones. Table 45 reports base case costs together with 95% confidence intervals.

Table 45. Unit costs associated with the technology in the economic model (£2016)

Items	Intervention (95% CI)	Reference in submission	RWC (CI)	Reference in submission
Technology cost				
Mean cost of technology treatment	£75,000 per vial	Table 40		Table 40
Administration cost (£2015/16)				
Inpatient lumbar puncture				
19 years and older	918; (CI: 884–951)	Table 40	As intervention	Table 40
6-18 years	1,658; (CI: 1,472–1,844)	Table 40	As intervention	Table 40
5 years and younger	1,690; (CI: 1,504–1,876)	Table 40	As intervention	Table 40
Outpatient lumbar puncture				
19 years and older	204; (CI: 176–231)	Table 40	As intervention	Table 40
6-18 years	577; (CI: 358–797)	Table 40	As intervention	Table 40
5 years and younger	593; (CI: 367–819)	Table 40	As intervention	Table 40
Day case lumbar puncture				
19 years and older	593; (CI: 588–598)	Table 40	As intervention	Table 40
6-18 years	1,546; (CI: 1,467–1625)	Table 40	As intervention	Table 40
5 years and younger	1,700; (CI: 1,600–1,799)	Table 40	As intervention	Table 40
Health state costs (£ per year): nusinersen arm				
SMA type I				
Drugs	[redacted]	Table 41	As intervention	Table 41

Items	Intervention (95% CI)	Reference in submission	RWC (CI)	Reference in submission
Medical tests	[redacted]	Table 41	As intervention	Table 41
Medical visits	[redacted]	Table 41	As intervention	Table 41
Hospitalisations	[redacted]	Table 41	As intervention	Table 41
GP & emergency	[redacted]	Table 41	As intervention	Table 41
Health materials	[redacted]	Table 41	As intervention	Table 41
Social services	[redacted]	Table 41	As intervention	Table 41
SMA type II	[redacted]			
Drugs	[redacted]	Table 41	As intervention	Table 41
Medical tests	[redacted]	Table 41	As intervention	Table 41
Medical visits	[redacted]	Table 41	As intervention	Table 41
Hospitalisations	[redacted]	Table 41	As intervention	Table 41
GP & emergency	[redacted]	Table 41	As intervention	Table 41
Health materials	[redacted]	Table 41	As intervention	Table 41
Social services	[redacted]	Table 41	As intervention	Table 41
SMA type III	[redacted]			
Drugs	[redacted]	Table 41	As intervention	Table 41
Medical tests	[redacted]	Table 41	As intervention	Table 41
Medical visits	[redacted]	Table 41	As intervention	Table 41
Hospitalisations	[redacted]	Table 41	As intervention	Table 41
GP & emergency	[redacted]	Table 41	As intervention	Table 41
Health materials	[redacted]	Table 41	As intervention	Table 41
Social services	[redacted]	Table 41	As intervention	Table 41

Abbreviations: RWC, real-world care; CI, confidence interval;

Table 46 reports annual costs across health states grouped into three categories according to motor milestones achieved for these 3 groups of health state (types I, II and II SMA). These estimates exclude the costs of nusinersen.

Table 46. Annual costs by health state (£2016)

	No Milestones, Mild Milestones, Moderate Milestones	***Sits without Support, Stands with Assistance, Walks with Assistance***	***Stands/Walks Unaided***
Drugs	[redacted]	[redacted]	[redacted]
Medical tests	[redacted]	[redacted]	[redacted]
Medical visits	[redacted]	[redacted]	[redacted]
Hospitalisations	[redacted]	[redacted]	[redacted]
GP & emergency	[redacted]	[redacted]	[redacted]
Health material	[redacted]	[redacted]	[redacted]
Social services	[redacted]	[redacted]	[redacted]
Total	[redacted]	[redacted]	[redacted]

3.5.2 Adverse reaction unit costs and resource use

As no serious AEs were reported in either arm of ENDEAR and no AEs were considered by trial investigators to be related to treatment in ENDEAR (see section 2.10), they were excluded from consideration in the model. Although the incidence and severity of AEs associated with the lumbar puncture procedure was consistent with events expected to occur with lumbar puncture, they are not associated with cost or QALY adjustments in the model because of their limited impact and short-term nature.

3.5.3 Miscellaneous unit costs and resource use

There are no additional costs or items of health care resource use which have not been covered elsewhere.

3.6 Summary of base case analysis inputs and assumptions

3.6.1 Summary of base case analysis inputs

The base case methods, as summarised in Table 47, were broadly consistent with the NICE reference case.

Table 47. Elements of the analytical approach compared with the NICE reference case

Element of health technology assessment	Approach adopted
Defining the decision problem	To appraise the clinical and cost effectiveness of nusinersen within its marketing authorisation for treating SMA as specified in the scope developed by NICE
Comparator	Best supportive care as listed in the scope developed by NICE
Perspective on outcomes	QALYs for patients and carers
Perspective on costs	Health and social care
Type of economic evaluation	Cost-utility analysis with incremental analysis
Time horizon	Lifetime
Synthesis of evidence on health effects	Health effects based on pivotal clinical trials. A systematic review of the literature was not required due to the limited body of evidence
Measuring and valuing health effects	QALYs based on EQ-5D (mapped from PedsQL)
Source of data for measurement of HRQL	PedsQL reported by patients with later onset SMA adapted to infantile onset
Source of data for valuation of changes in HRQL	UK EQ-5D value set
Equity considerations	All QALYs are valued equally
Evidence on resource use and costs	Resource use was based on responses by UK participants in a European survey which asked about health and social care utilisation. The PbR tariff was used to value health care resources.
Discounting	3.5% per annum was used for both costs and QALYs

Abbreviations: EQ-5D European Quality of Life-5 Dimensions; HR, hazard ratio; HRQL, Health-related quality of life; NICE, National Institute for Health and Care Excellence; PbR, Payment by Results; PedsQL, Paediatric Quality of Life Inventory; QALY, Quality-adjusted life year; SMA, spinal muscular atrophy;

For evidence on health effects of treatment, the methods diverged from the NICE reference case in that it was not considered necessary to undertake a systematic review of the literature as nusinersen is a recently approved product supported by a well-known body of evidence. The pivotal phase III ENDEAR trial provides the most robust evidence on the health effects of nusinersen and is therefore considered to be the most relevant basis on which to model cost-effectiveness. Long-term data was not collected in the trial as the early achievement of the primary endpoint led to the trial being stopped, with patients being given the option of being treated as part of the SHINE study. Data not available in ENDEAR were obtained from 2 SLRs undertaken to identify costs(116,120) and utility data(116), supplemented with targeted parameterisation searches where required for the model.

Base case inputs and allowance for uncertainty

Table 48 summarises the input variables for which a statistical approach to uncertainty was adopted. This primarily involved assigning a sampling distribution which was used to explore uncertainty associated with each parameter in probabilistic sensitivity analysis (PSA). Variables excluded from PSA were those which cannot be sampled (such as the time horizon) or for which a modelling assumption was required in the absence of data (such as variables governing the extrapolation of survival beyond the end of trial follow-up). Variables included in PSA were additionally included in one-way sensitivity analysis (OWSA) with default upper and lower values 20% above and below the base case figure except where this was potentially inappropriate (e.g. utilities cannot exceed 1) or there was a natural upper or lower bound (e.g. a hazard rate of 1 for mortality). Appendix P provides a list of variables tested in OWSA and the ranges of values used. Discount rates were not varied in sensitivity analysis in accordance with NICE's recommended approach.

The ranges of values used in OWSA and confidence intervals around variables included in PSA relate to base case methodological approaches or data sources where it is possible to select one of a number of options in the model. The impact on the results of selecting different data sources or methods for particular variables (e.g. health state utilities or treatment costs) is explored in scenario analysis. One variable, namely general population mortality, was based on a population rather than a sample and was therefore excluded from uncertainty analysis.

Table 48. Summary of variables subject to probabilistic sensitivity analysis in the economic model

Variable	Base case value	Measurement of uncertainty and distribution (95% confidence limits unless otherwise stated)	Section
Mean age (months)	5.6	95% CI: 5.3–5.9 (normal)	3.2.1
Percentage female	55%	95% CI: 46–64% (beta)	3.2.1
Population subgroup	ITT	Uncertainty around the transition matrices was calculated using the method of Briggs et al. (2003)(142)	3.9

Variable	Base case value	Measurement of uncertainty and distribution (95% confidence limits unless otherwise stated)	Section
OS to end of trial follow-up	Flexible spline-based Weibull (1 knot)	Variance-covariance matrix (Cholesky decomposition)	3.3.2
OS prediction after end-of-trial follow-up for RWC arm	Exponential curve fitted to Kaplan-Meier from Gregoretti et al. (2013)	Variance-covariance matrix (Cholesky decomposition)	3.3.2
Age-specific mortality, HR for SMA type I vs. general population (after end of trial follow-up)	5184.8	95% CI: 3021.3–8897.7 (log HR normally distributed)	3.3.2
Type II specific mortality	Flexible spline-based Weibull (2 knots) fitted to Kaplan-Meier from Zerres et al. (1997)	Variance-covariance matrix (Cholesky decomposition)	3.3.2
Hazard ratio at the end of trial follow-up	0.372	95% CI: 0.18–0.77 (normal)	3.3.2
Percentage of patients who discontinue after scoliosis surgery	20%	95% CI: 13–28% (beta)	3.2.3
Percentage of patients having scoliosis surgery: nusinersen	1%	95% CI: 0.03–4.4% (beta)	3.2.3
Percentage of patients having scoliosis surgery: RWC	1%	95% CI: 0.03–4.4% (beta)	3.2.3
Year after which patients have scoliosis surgery (non-ambulant): nusinersen	12	95% CI: 7–17 (normal)[a]	3.2.3
Percentage of patients having scoliosis surgery (non-ambulant): RWC	10	95% CI: 6–14 (normal)[a]	3.2.3
Year after which patients have scoliosis surgery (ambulant): nusinersen	15	95% CI: 9–21 (normal)[a]	3.2.3
Percentage of patients having scoliosis surgery (ambulant): RWC	15	95% CI: 9–21 (normal)[a]	3.2.3
Mean monthly rate of CHOP INTEND increase: nusinersen	[redacted]	[redacted]	3.3.5
Mean monthly rate of CHOP INTEND decrease: RWC	[redacted]	[redacted]	3.3.5
Mean CHOP INTEND score per health state	ITT population: each arm	Normal	3.3.5
Administration costs (£2016)			

Variable	Base case value	Measurement of uncertainty and distribution (95% confidence limits unless otherwise stated)	Section
Inpatient lumbar puncture			
19 years and older	918	95% CI: 884–951 (normal)	3.5.1
6-18 years	1,658	95% CI: 1,472–1,844 (normal)	3.5.1
5 years and younger	1,690	95% CI: 1,504–1,876 (normal)	3.5.1
Outpatient lumbar puncture			
19 years and older	204	95% CI: 176–231 (normal)	3.5.1
6-18 years	577	95% CI: 358–797 (normal)	3.5.1
5 years and younger	593	95% CI: 367–819 (normal)	3.5.1
Day case lumbar puncture			
19 years and older	593	95% CI: 588–598 (normal)	3.5.1
6-18 years	1,546	95% CI: 1,467–1,625 (normal)	3.5.1
5 years and younger	1,700	95% CI: 1,600–1,799 (normal)	3.5.1
Percentage of patients having an inpatient procedure	40%	SE = 0.08 (Dirichlet)	3.5.1
Percentage of patients having an outpatient procedure	30%	SE = 0.06 (Dirichlet)	3.5.1
Percentage of patients having a day case procedure	30%	SE = 0.06 (Dirichlet)	3.5.1
Health state costs (£2016 per year)			
SMA type I			
Drugs	[redacted]	[redacted]	3.5.1
Medical tests	[redacted]	[redacted]	3.5.1
Medical visits	[redacted]	[redacted]	3.5.1
Hospitalisations	[redacted]	[redacted]	3.5.1
GP & emergency	[redacted]	[redacted]	3.5.1
Health materials	[redacted]	[redacted]	3.5.1
Social services	[redacted]	[redacted]	3.5.1
SMA type II	[redacted]	[redacted]	
Drugs	[redacted]	[redacted]	3.5.1
Medical tests	[redacted]	[redacted]	3.5.1
Medical visits	[redacted]	[redacted]	3.5.1
Hospitalisations	[redacted]	[redacted]	3.5.1
GP & emergency	[redacted]	[redacted]	3.5.1
Health materials	[redacted]	[redacted]	3.5.1
Social services	[redacted]	[redacted]	3.5.1
SMA type III	[redacted]	[redacted]	
Drugs	[redacted]	[redacted]	3.5.1
Medical tests	[redacted]	[redacted]	3.5.1
Medical visits	[redacted]	[redacted]	3.5.1

Variable	Base case value	Measurement of uncertainty and distribution (95% confidence limits unless otherwise stated)	Section
Hospitalisations	[redacted]	[redacted]	3.5.1
GP & emergency	[redacted]	[redacted]	3.5.1
Health materials	[redacted]	[redacted]	3.5.1
Social services	[redacted]	[redacted]	3.5.1
End-of-life costs (£/patient)	11,839	95% CI: 7,662–16,911 (gamma)	3.5.1
Health-state utility values: patients			
No Milestones	[redacted]	[redacted]	3.4.5
Mild Milestones	[redacted]	[redacted]	3.4.5
Moderate Milestones	[redacted]	[redacted]	3.4.5
Sits without Support	[redacted]	[redacted]	3.4.5
Stands with Assistance	[redacted]	[redacted]	3.4.5
Walks with Assistance	[redacted]	[redacted]	3.4.5
Stands/Walks Unaided	[redacted]	[redacted]	3.4.5
Health-state utility values: carers	[redacted]	[redacted]	
No Milestones	[redacted]	[redacted]	3.4.5
Mild Milestones	[redacted]	[redacted]	3.4.5
Moderate Milestones	[redacted]	[redacted]	3.4.5
Sits without Support	[redacted]	[redacted]	3.4.5
Stands with Assistance	[redacted]	[redacted]	3.4.5
Walks with Assistance	[redacted]	[redacted]	3.4.5
Stands/Walks Unaided	[redacted]	[redacted]	3.4.5

Abbreviations: CHOP INTEND, Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders; CI, confidence interval; GP, general practitioner; HR, hazard ratio; OS, overall survival; RWC, real-world care; SMA, spinal muscular atrophy;

[a] Standard error assumed to be 20% of the mean value.

[b] The standard error was calculated from the mean weekly rate of increase from the weekly 95% confidence interval.

3.6.2 Assumptions

Assumptions used in the model in the absence of data primarily centered on the extrapolation of treatment effects beyond the time horizon of the trial and are summarised in Table 49.

Table 49. Variables for which a modelling assumption was made (in the absence of data)

Variable	Base case assumption and allowance for uncertainty	Rationale
Factor to adjust type II mortality risk	A factor of 1 applies the mortality rates of type II patients to infantile onset patients in motor milestones characteristic of later onset and a factor of 0 applies the mortality rates of type I patients. A factor of 0.9 is applied in the base case (varied between 0.72 and 1 in OWSA and between 0.5 and 1 in scenario analysis).	The clinical expert panel(33) supported the proposition that, if the population was becoming more like a type II population following nusinersen treatment, then the nusinersen survival curve could become more like that observed in type II patients by Zerres et al. (33)
HR for treatment effect on overall survival after the end of trial follow-up	The HR beyond the end of trial follow-up is assumed to be 1. In scenario analysis, the within-trial HR can be applied indefinitely or tapered over a defined period.	Assuming a HR of 1 beyond the end of trial follow-up represents a conservative approach to the benefits of treatment
Treatment discontinuation rule	Dependent on treatment response and receipt of scoliosis surgery. The alternative scenario is that discontinuation is independent of response (a percentage of patients from each health state discontinue treatment).	No patients in trials of nusinersen have discontinued treatment. The discontinuation rule (movement to the ***No Milestones*** health state) was therefore based on expert clinical opinion, supported by the UK expert panel(33)
Month after which patients discontinue from the *No Milestones* health state	13 months in the base case, but can be user-defined (between 13 and 24 is tested in OWSA).	The length of the trial was around 13 months with no discontinuations; a year after entering the ***No Milestones*** state was supported by the UK expert panel(33)
Percentage of patients who discontinue after scoliosis surgery	20% in the base case, varied between 16% and 24% in OWSA but can be user-defined.	Assumption in the absence of knowledge about the requirement for scoliosis surgery in type I patients
Year after which patients have scoliosis surgery (ambulant)	15 years in the base case, varied between 12 and 18 years in OWSA but can be user-defined.	12 years in non-ambulant patients is based on a study(21) which suggests that preserved standing ability can decelerate the progression of scoliosis in patients with type III SMA. The survey of NMD centres indicated that type III patients undergo scoliosis surgery later than type II patients in whom surgery is performed later than in type I patients
Mean monthly rate of CHOP INTEND increase: nusinersen	[redacted] in the base case, varied between [redacted] in OWSA but can be user-defined. A	The model uses the mean rate of increase/decrease from the ENDEAR trial and the mean scores of patients throughout

Variable	Base case assumption and allowance for uncertainty	Rationale
	scenario allows a proportion of patients still on treatment to reach a plateau. The model allows a proportion of those reaching a plateau to progress as in the RWC arm.	the trial or at last visit from the CS3A trial. The observation that motor function in the clinical studies had not plateaued out and clinical expert opinion(33) (in view of nusinersen's mechanism of action) supported the extrapolation of effects seen in clinical studies over time
Mean monthly rate of CHOP INTEND decline: RWC	[redacted] in the base case, varied between [redacted] in OWSA but can be user-defined.	

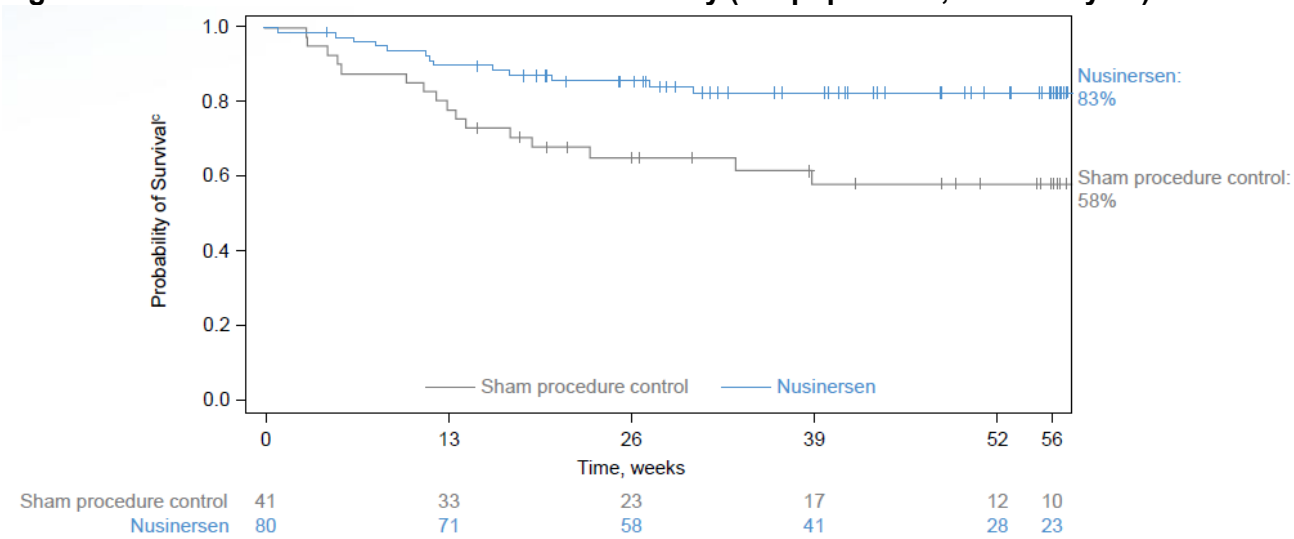
Abbreviations: CHOP INTEND, Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders; HR, hazard ratio; NMD, Neuromuscular disease; OS, overall survival; OWSA, One-way sensitivity analysis; RWC, real-world care; SMA, spinal muscular atrophy;

3.7 Base case results

3.7.1 Base case incremental cost-effectiveness analysis results

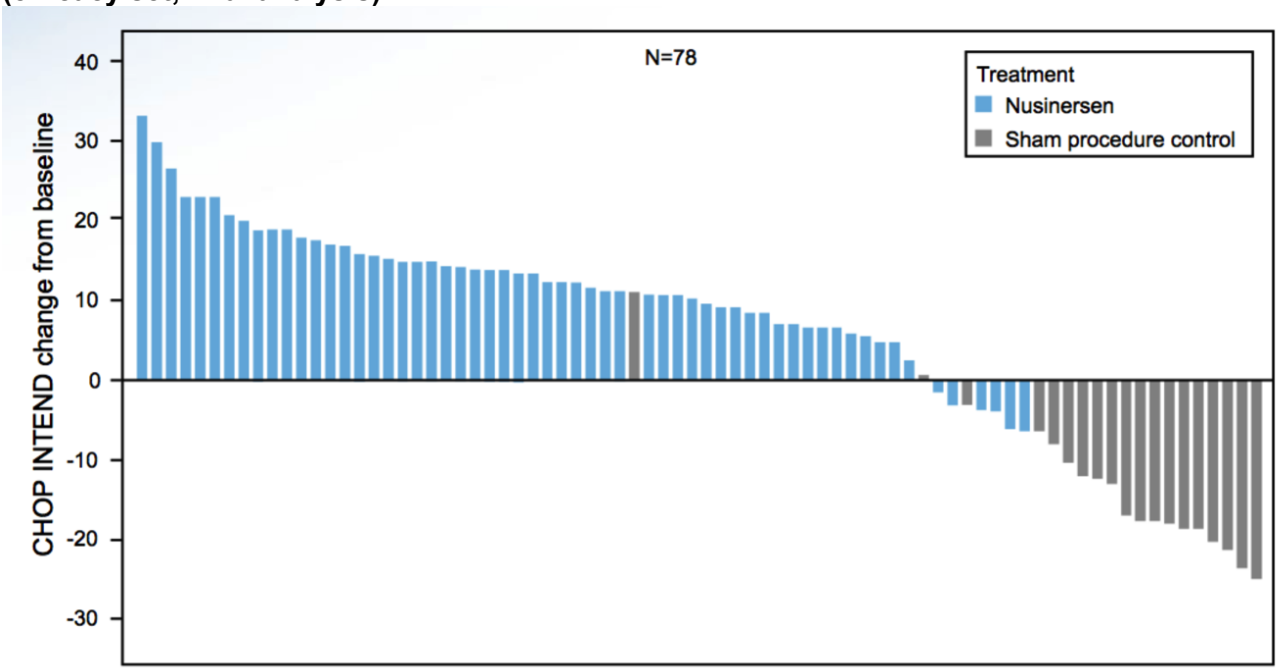
The modelled gains in life years and QALYs with nusinersen are based primarily on the survival and CHOP INTEND results from the ENDEAR study. These are illustrated by the Kaplan-Meier curves for overall survival (Figure 36) and the waterfall plot for the CHOP INTEND results (Figure 37). The results of the ENDEAR study are also summarised in section B.2.6.1.

Figure 36. ENDEAR: overall survival at end of study (ITT population, final analysis)



Abbreviation: ITT, intention to treat

Figure 37. ENDEAR: CHOP INTEND motor function scores at the end of the study (efficacy set, final analysis)



Abbreviation: CHOP INTEND, Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders

Table 50 reports the deterministic results for lifetime costs, life years gained and patient QALYs per patient for nusinersen vs. RWC and the associated incremental cost-effectiveness ratios (ICERs). As with other high cost drugs for small patient populations, the ICER, at around £408,000 per QALY gained, is in excess of NICE's conventional reference points of £20-30,000 per QALY gained/£50,000 when applying end-of-life criteria. The utility decrements for carers give a small reduction in QALYs in nusinersen and RWC groups as life years are multiplied by a negative number in each health state. As patients receiving nusinersen transition over time into health states with better HRQL than those experienced by RWC patients, the QALY penalty is higher with RWC than nusinersen, giving a small incremental carer QALY gain with nusinersen. This reduces the ICER marginally (Table 51).

Table 50. Base case results – infantile onset SMA, patient QALYs

Technology	Total costs (£)	Total LYG	Total QALYs	Inc. costs (£)	Inc. LYG	Inc. QALYs	ICER vs. base-line (£/QALY)	ICER inc. (£/QALY)
RWC	71,540	3.39	2.49					
Nusinersen	2,258,852	9.34	7.86	2,187,311	5.95	5.37	407,605	407,605

Abbreviations: ICER, incremental cost-effectiveness ratio; inc., incremental; LYG, life years gained; QALYs, quality-adjusted life years; RWC, real-world care; SMA, spinal muscular atrophy

Table 51. Base case results – infantile onset SMA, patient and carer QALYs

Technology	Total costs (£)	Total LYG	Total QALYs	Inc. costs (£)	Inc. LYG	Inc. QALYs	ICER vs. base-line (£/QALY)	ICER inc. (£/QALY)
RWC	71,540	3.39	2.17					
Nusinersen	2,258,852	9.33	7.61	2,187,311	5.95	5.44	402,361	402,361

Abbreviations: ICER, incremental cost-effectiveness ratio; inc., incremental, LYG, life years gained; QALYs, quality-adjusted life years; RWC, real-world care; SMA, spinal muscular atrophy

As the breakdown of costs in Table 52 shows, the costs of treatment are driven by the price of nusinersen. Cost offsets in respiratory care are partially counterbalanced by increases in gastrointestinal, nutritional and orthopaedic care but overall these make a minor impact on the costs of treatment.

Table 52. Breakdown of costs by therapy area – infantile onset SMA

Infantile onset SMA	Nusinersen	RWC	Incremental
Total healthcare costs	2,258,852	71,540	2,187,311
Of which:			
Nusinersen acquisition costs	2,153,436		2,153,436
Nusinersen administration costs	35,858		35,858
Respiratory care	42,219	46,661	-4,442
Gastrointestinal care	7,948	6,447	1,501
Nutritional care	4,790	3,104	1,686
Orthopaedic care	6,591	5,099	1,492
End-of-life costs	8010	10,230	-2,220

Abbreviations: RWC, real-world care; SMA, spinal muscular atrophy

As drug costs form by far the most significant element of total healthcare costs for those receiving nusinersen, the cost-effectiveness results are sensitive to changes in the vial price. Other than the cost of nusinersen, the group of variables to which the results are most sensitive is dominated by those governing survival and HRQL impacts. Uncertainty is generated by a lack of long term data on survival in patients receiving nusinersen and by the absence of a well established approach to utility assessment and application (e.g. a positive utility or utility penalty for carers). In addition, reducing the benefits of nusinersen to a single figure can inhibit a full understanding of the way in which nusinersen affects the lives of patients and carers. The following section therefore re-emphasises the range of impacts associated with nusinersen, both as reported in the ENDEAR trial and those which are outputs of the model.

ENDEAR trial – motor skills and milestones

Table 53 summarises the results of the ENDEAR trial in terms of motor milestones and motor skills according to the HINE and CHOP INTEND measures as well as overall survival and the

use of permanent ventilation. In all cases, the advantage in favour of nusinersen is marked, particularly in relation to the HINE and CHOP INTEND measures. A significantly greater proportion of patients in the nusinersen group achieved a motor milestone response on HINE at the planned interim analysis (after which the trial was stopped due to a positive outcome) and the motor milestone response continued to increase in patients receiving nusinersen up to the final analysis. This finding, together with expert clinical opinion, was used as the basis for extrapolation beyond the end of trial follow-up.

Table 53. ENDEAR trial results - infantile onset

ENDEAR (13 months)	Nusinersen	RWC
Motor milestones		
Responders (%): HINE-2	51%	0%
Proportion with improvement in total score (%)	67%	14%
Proportion with worsening in total score (%)	1%	22%
CHOP INTEND		
Proportion with ≥4 improvement (%)	71%	3%
Proportion with ≥4 worsening (%)	3%	46%
Overall survival rate (%)	84%	61%
Patients not requiring permanent ventilation (%)	61%	32%

Abbreviations: CHOP INTEND, Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders; HINE, Hammersmith Infant Neurological Examination; RWC, real-world care
Source: Kuntz 2017(143); Finkel 2017d(49); SmPC(2);

Most nusinersen-treated patients achieved progressive and sustained increases in total motor milestones over time compared with baseline, whereas control group patients showed a slight improvement at the first assessment (day 64) followed by a decrease over time. The loss of motor milestones gained prior to symptom onset, as seen in the control group, is consistent with the natural history of SMA type I, while a gain in motor milestones after symptom onset, as seen in the nusinersen group, is highly inconsistent with the natural history of SMA type I. In the nusinersen group, 16 of 73 patients (22%) achieved full head control, 6 of 73 patients (8%) achieved independent sitting, and 1 of 73 patients (1%) achieved standing. None of the patients in the control group achieved any of these milestones. In relation to CHOP INTEND, a significantly greater proportion of those in the nusinersen group achieved a response.

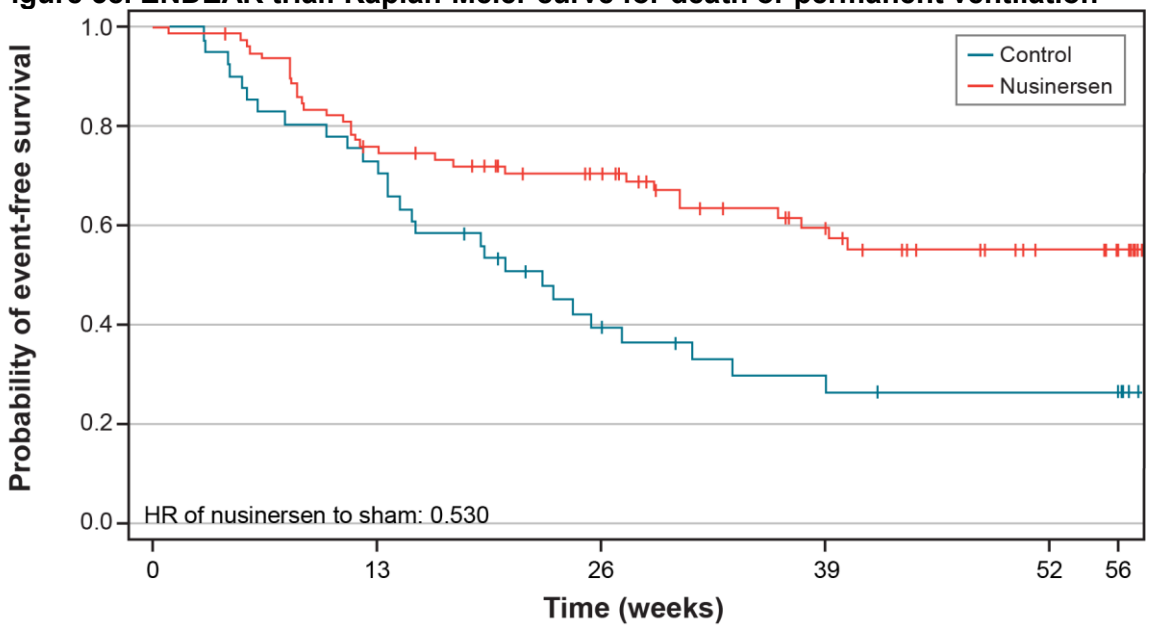
ENDEAR trial – mortality and ventilation

Overall, there was a reduction in the risk of death or permanent ventilation in the nusinersen group compared with the control group (39% versus 68%; hazard ratio[HR], 0.53; P=0.0046), a reduction in the risk of death overall (16% versus 39%; HR, 0.372; P=0.0041), and a 34% reduction in the risk of permanent ventilation (HR, 0.66).(57)

A significantly prolonged event-free survival (time to death or permanent ventilation) was observed in the nusinersen group compared with the control group (P=0.0046). As of the data cut-off date, 31 patients (39%) in the nusinersen group and 28 patients (68%) in the control

group had died or required permanent ventilation (Figure 38). The Kaplan-Meier estimate of the percentage of patients who died or required permanent ventilation by 3 months (day 91) was similar in the 2 groups, but by 6 months (day 182) the Kaplan-Meier curves had separated. This separation between the treatment groups is most apparent after day 91, in the period after the loading doses for nusinersen had been completed.

Figure 38. ENDEAR trial: Kaplan-Meier curve for death or permanent ventilation



Control	41	30	14	9	7	7
Nusinersen	80	59	46	29	16	13

Modelled outcomes

The modelled survival outcomes underlying the cost per QALY estimates give a survival of 9.3 discounted life years in nusinersen patients compared with a mean discounted background survival of 3.4 years in those receiving RWC. Undiscounted, mean survival is estimated at 13.0 years in nusinersen patients compared with 3.9 years under RWC. Alongside this improvement in survival, mean utility is estimated to increase from 0.74–0.84 with nusinersen. To provide an illustration of what this means for patients in terms of motor function and motor milestones, the charts below show the distribution of patients by health state over time for patients receiving nusinersen (Figure 39) and RWC (Figure 40), respectively. In addition to improved survival, the comparison reveals the greater period of time spent in the better health states under nusinersen.

Whereas most nusinersen patients are still alive at 12 years and the majority of those have transitioned to the ***Stands/Walks Unaided*** state, most patients in the RWC group have died and, among those still alive, the ***No Milestones*** health state dominates. The maximum percentage of patients ever achieving later onset (type II) milestones was 55.2% in the nusinersen arm compared with 2.6% of the RWC arm in the model. The maximum percentage of patients achieving later onset (type III) milestones was 56.8% in the nusinersen arm compared with no patients in the RWC arm.

Caution should be taken when interpreting these results because of the small numbers in some of the health states especially at later time points of trial follow-up. In some cases, transition probabilities are 100% because they are based on only 1 observation. Nevertheless, these findings help to put into context the summary cost-effectiveness ratios estimated for nusinersen.

Figure 39. Distribution of patients by health state - infantile onset, nusinersen patients

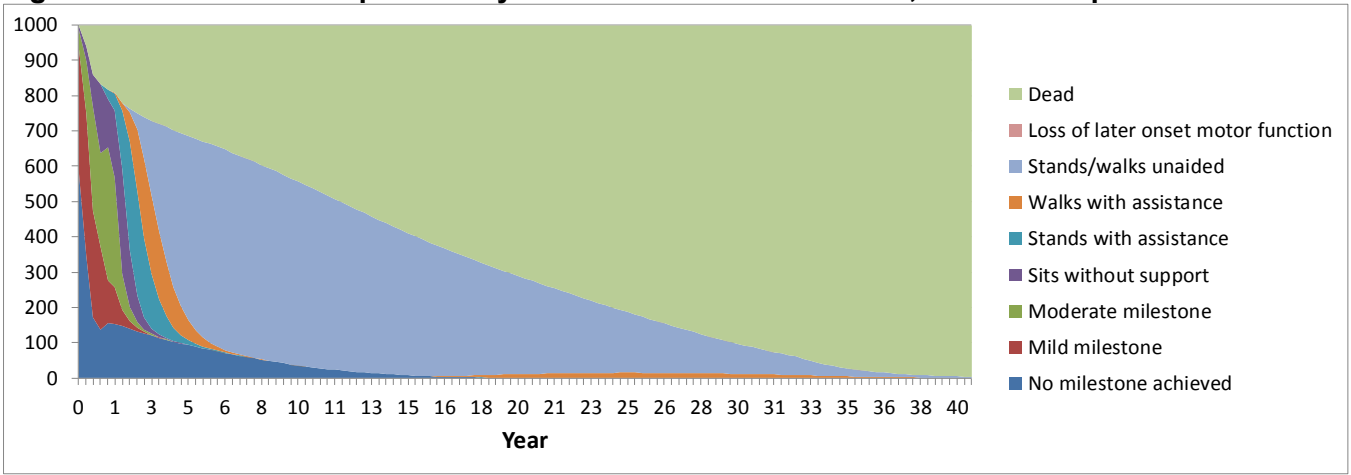
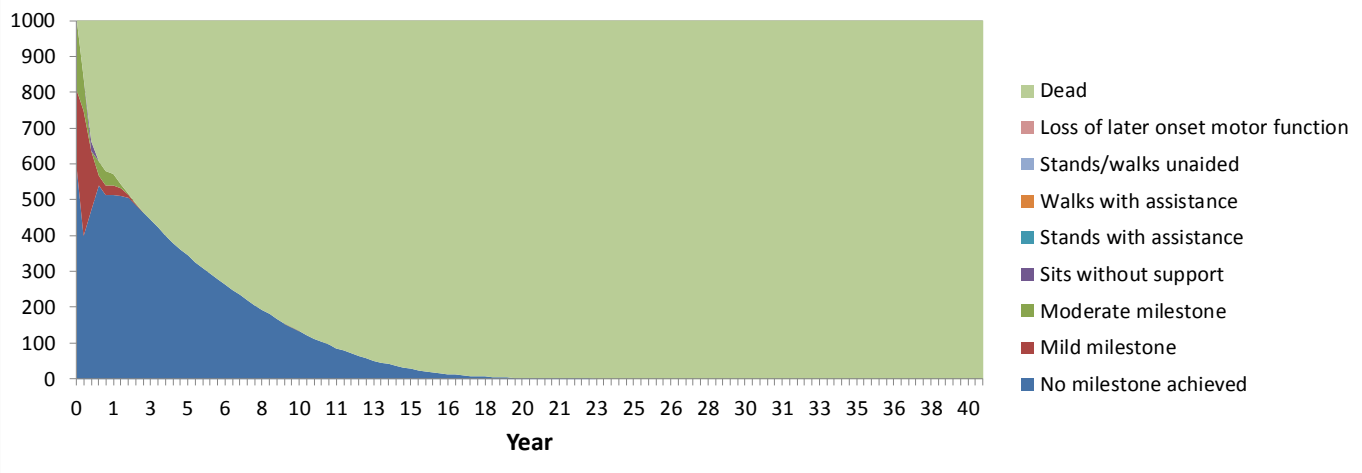


Figure 40. Distribution of patients by health state - infantile onset, RWC patients



Abbreviation: RWC, real-world care

3.8 Sensitivity analyses

3.8.1 Probabilistic sensitivity analysis

To explore the impact of variation in all sample parameters simultaneously, PSA was based on the uncertainty in the source data (where data availability permitted), in accordance with good practice for PSA. Wherever possible, parameter distributions are characterised in terms of their mean and standard error by data from the ENDEAR clinical trial or other sources. Distributions were applied as appropriate for the type of variable concerned. As Briggs

(2005)(144) notes, distributions for individual parameters are generally selected from a small group of candidate options.

Since the beta distribution is restricted to the range 0–1, it lends itself naturally to probabilities, proportions and positive utilities. The gamma distribution is frequently used to represent single cost distributions (which tend to be positively skewed). Where data were available, alpha and beta parameters of beta and gamma distributions were based on base case (mean) values and standard errors. Examples of parameters included in PSA in the current analysis include the following:

- Survival function parameters are sampled from correlated distributions defined by their mean, standard error and covariance.
- Negative utility weights are converted to decrements and sampled from a gamma distribution, the parameters of which are defined by the mean and standard error.
- Positive utility weights are sampled from a beta distribution, the parameters of which are defined by the mean and standard error.
- Mean costs are sampled from a gamma distribution, the parameters of which are defined by the mean and standard error.

For some variables, an assumption was required about the magnitude of the standard error to be applied in PSA, which was set to 20% as a default.

For those variables subject to probabilistic analysis in the infantile onset model, Table 48 reports the mean and standard error (where applicable), together with the approach to exploring uncertainty (generally the distribution applied). The table relates to the base case approach for each variable. The distributional assumptions around, for example, non-base case sources of utilities, are not reported.

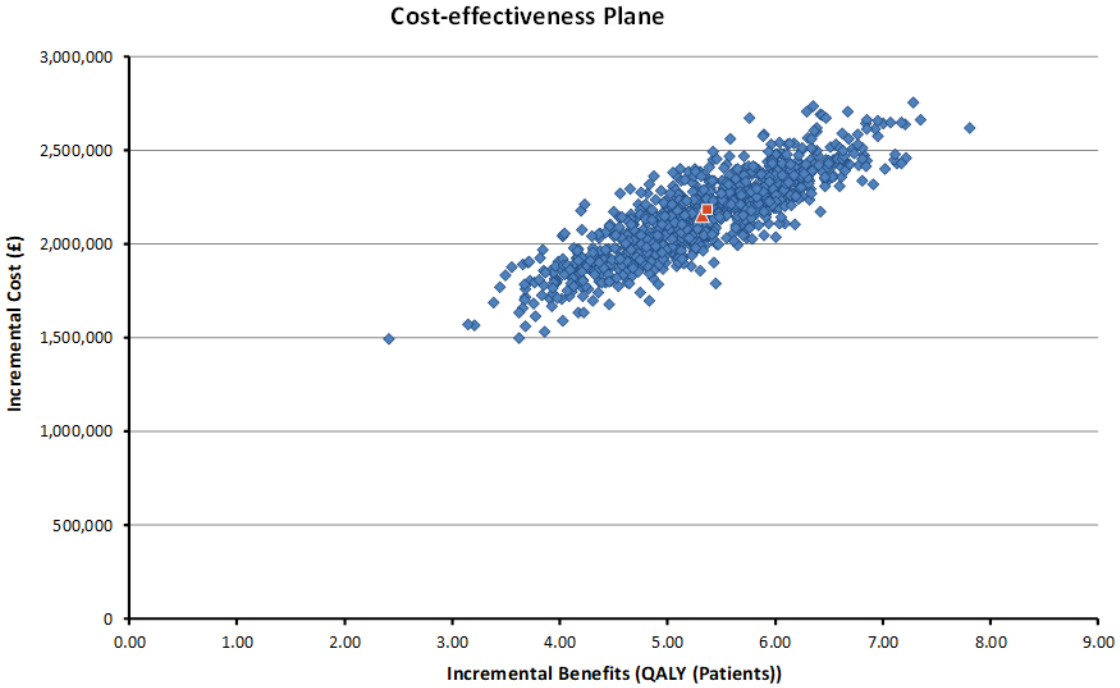
Table 54 reports the probabilistic results in the same format as the deterministic results. The probabilistic costs, life years and QALYs are the mean of 1,000 iterations of the model. Figure 41 shows the 1,000 simulations of incremental costs and QALYs as a scatter plot on the cost-effectiveness plane. Each simulation is shown by a blue diamond while the deterministic and probabilistic means are shown by a red square and red diamond, respectively. Due to the magnitude of the ICER, it was not thought useful to present the cost-effectiveness acceptability curve relative to NICE's conventional reference points of cost-effectiveness.

Table 54. Probabilistic results - infantile onset, patient QALYs

Technology	Total costs (£)	Total LYG	Total QALYs	Inc. costs (£)	Inc. LYG	Inc. QALYs	ICER vs. base-line (£/QALY)	ICER inc. (£/QALY)
RWC	70,869	3.28	2.42					
Nusinersen	2,228,131	9.19	7.73	2,157,262	5.90	5.32	405,792	405,792

Abbreviations: ICER, incremental cost-effectiveness ratio; inc., incremental; LYG, life years gained; QALYs, quality-adjusted life years; RWC, real-world care

Figure 41. Scatter plot - infantile onset SMA



Abbreviations: QALY, quality-adjusted life years

3.8.2 Deterministic sensitivity analysis

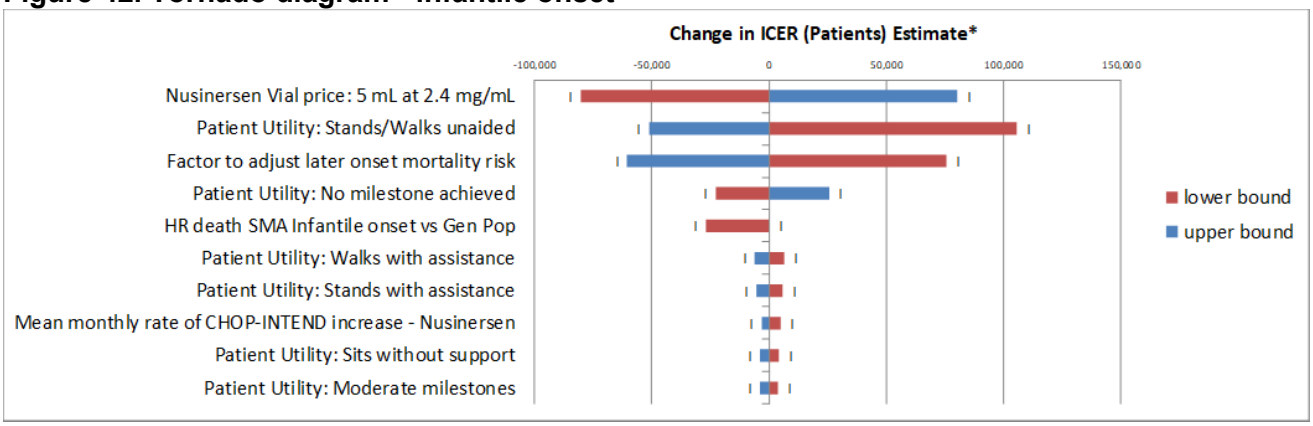
Table 55 reports the OWSA for the 10 variables which have the largest ranges of impact on the ICER from a patient perspective, excluding the discount rates on costs and outcomes (which are the 2 most important variables overall). For each variable, the table reports the base case value, the upper and lower bounds used in OWSA and the ICERs at the upper and lower bounds of the variable. Figure 42 presents the same information graphically in the form of a tornado diagram. Appendix Q lists all variables subject to OWSA.

Table 55. One-way sensitivity analysis - infantile onset

Parameter	Base case	Lower bound	Upper bound	ICER at variable's	
				Lower bound	Upper bound
Nusinersen vial price: 5 mL at 2.4 mg/mL	75,000	60,000	90,000	327,347	487,864
Patient utility: Stands/Walks unaided	[redacted]	[redacted]	[redacted]	513,324	356,400
Factor to adjust later onset mortality risk	[redacted]	[redacted]	[redacted]	483,335	347,082
Patient Utility: No milestone achieved	[redacted]	[redacted]	[redacted]	384,853	433,217
HR death SMA Infantile onset vs Gen Pop	[redacted]	[redacted]	[redacted]	380,713	407,605
Patient utility: Walks with assistance	[redacted]	[redacted]	[redacted]	414,046	401,362
Patient utility: Stands with assistance	[redacted]	[redacted]	[redacted]	413,270	402,094
Mean monthly rate of CHOP-INTEND increase – Nusinersen	[redacted]	[redacted]	[redacted]	412,405	404,354
Patient utility: Sits without support	[redacted]	[redacted]	[redacted]	411,646	403,644
Patient Utility: Moderate milestones	[redacted]	[redacted]	[redacted]	411,339	403,939

Abbreviations: CHOP INTEND, Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders; ICER, incremental cost-effectiveness ratio; RWC, real-world care;

Figure 42. Tornado diagram - infantile onset



*The quadrant where the ICER falls is shown in the graph: I = quadrant 1; II = quadrant 2 (intervention dominated); III = quadrant 3 (less expensive and less effective); IV = quadrant 4 (intervention dominates)
Abbreviations: ICER, incremental cost-effectiveness ratio; RWC, real-world care

3.8.3 Scenario analysis

The exploration of uncertainty related to choice of methods or data sources was categorised as scenario analysis. For example, Zerres and Rudnik-Schöneborn (1995)(125) was used to extrapolate survival beyond the time horizon of the trial as an alternative to Gregoretti et al. (2013)(11). While the latter was used in the base case as it provided subgroup data that more accurately reflected that of the standard of care in the UK, Zerres and Rudnik-Schöneborn

(1995)(125) was considered due to its size (445 patients) and duration of follow-up (20 years). Table 56 reports a range of scenario analyses for infantile onset SMA, indicating the base case approach, scenarios investigated and the associated estimates of cost per QALY gained on the basis of patient and combined patient and carer perspectives. The ICERs can be compared against the base case incremental costs per patient QALY gained and cost per patient and carer QALY gained of £407,605 and £402,361, respectively. The results including carer QALYs are included here for completeness although they are only slightly lower than those using the patient perspective alone.

Table 56. Scenario analysis - infantile onset SMA

Input parameter	Base case analysis setting	Scenarios	ICER (£) Patient perspective (upper), combined patient and carer perspective (lower)
Base case ICER			**407,605** **402,361**
Time horizon (years)	Lifetime (60 years)	10	564,659 543,695
		20	436,278 428,375
		30	410,888 405,315
Cost perspective	Health and social care	Societal	419,253 413,851
Efficacy Setting			
Apply higher long-term risk of death based on SMA type I - adjusted general mortality rates	Apply	Don't Apply	380,658 376,357
OS beyond trial follow-up	Gregoretti 2013 -NRA	Zerres 1995 + 2 knots & 60-year time horizon	379,804 376,289
OS treatment effects	Apply HR =1.00 after trial follow-up	Taper to 1.0 over a defined period (12 months)	405,766 400,680
Health states from which patients discontinue	***No Milestones*** (I)	***No Milestones and Mild Milestones***	406,096 402,138
Apply type II mortality rates from Zerres et al. 1997 to patients in motor milestones characteristic of later onset	Apply	Don't apply	872,257 802,469
Mortality risk factor	0.9	0.5	578,554 556,339
		1.00	347,082 345,578
Assumption that proportion of patients on treatment reach a plateau	No	Yes 0%	417,355 412,445

Input parameter	Base case analysis setting	Scenarios	ICER (£) Patient perspective (upper), combined patient and carer perspective (lower)
% of patients reaching an improvement plateau which start getting worse			
Assumption that proportion of patients on treatment reach a plateau % of patients reaching an improvement plateau which start getting worse	No	Yes 10%	421,445 417,806
Source for RWC arm CHOP INTEND rate of decline	ENDEAR	Finkel et al. 2012	407,315 402,328
Drug administration cost settings			
Inpatient/outpatient/day case	40% 30% 30%	100% 0% 0%	409,438 404,170
		0% 0% 100%	409,015 403,752
Health state cost settings			
Scenarios for health state costs	From published sources	Cost major clinical events only	442,838 437,140
Cost source	Bastida et al. 2016	Klug et al. 2016	405,194 399,980
Utility settings			
Patient	PedsQL type 2 (ITT)	Vignettes	421,703 394,298
		Bastida upper bound	450,353 476,099
		Bastida lower bound	503,295 788,019
		PedsQL type 2 (<25 months disease duration)	387,628 364,333

Abbreviations: CHOP INTEND, Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders; HINE, Hammersmith Infant Neurological Examination; HR, hazard ratio; ICER, incremental cost-effectiveness ratio; OS, overall survival; PedsQL, Paediatric Quality of Life Inventory; RWC, real-world care; SMA, spinal muscular atrophy;

3.8.4 Summary of sensitivity analyses results

OWSA primarily illustrates the significance of utility estimates as a source of uncertainty in the cost-effectiveness estimates. In particular, the utility for the ***Stand/Walks Unaided*** health state, in which the nusinersen cohort spends an average of 9.60 years per patient (undiscounted) compared with 0 years under RWC, generates the largest range of ICERS in OWSA. Extrapolation of survival beyond the time horizon of the ENDEAR trial was another area of considerable uncertainty. The mortality rate applied to infantile onset patients achieving later onset motor milestones generated a wide range of ICERs. However, at the upper end of its range in OWSA (and its most favourable possible value with mortality

equivalent to that of type II patients), this variable gave an ICER which remained above £350,000 per QALY gained. A 20% reduction in the vial price of nusinersen reduced the ICER below £330,000 although, as this parameter is effectively fixed, it should arguably be excluded from uncertainty analysis.

Similarly, in scenario analyses, there were few parameters for which the scenario reduced the ICER below £400,000 per QALY gained, primarily those related to mortality. This was observed when not applying a higher long-term mortality risk from other causes relative to the general population, and when applying data from Zerres and Rudnik-Schöneborn (1995)(125) rather than Gregoretti et al. (2013)(11) to extrapolate survival beyond the end of follow-up in the ENDEAR trial. For extrapolation beyond the ENDEAR study in infantile onset SMA, the latter scenario reduces the ICER to around £380,000. The scenario showing that patients achieving later onset motor milestones share the mortality experience of type II patients replicates the results of OWSA on this variable.

The scenario using the utilities obtained from the case vignette study, because of the linkage between the variation in patient utilities and carer utilities, reduces the ICER below £400,000 per QALY when carer QALYs are included. However, what is known about the disease and the burden on carers, including expert clinical advice at the UK advisory board(33), suggests that a utility does not adequately capture the impact on carers and that this approach is likely to understate the benefits of nusinersen.(109–113) More generally, the estimates of cost effectiveness presented here do not address the underlying limitations of the QALY as a single summary measure of benefit. Because of the conceptual and practical difficulties of measuring utilities, and the associated drawbacks of QALYs in this patient group, we caution against reducing the benefit of nusinersen to a single metric.

3.9 Subgroup analysis

Subgroup analysis was conducted for the two pre-specified subgroups based on disease duration in the ENDEAR trial (Table 57). Results from the trial for these subgroups are presented in section 2.7.1 and cost effectiveness was modelled by applying the transition probabilities specific to the patient counts of the subgroups. Overall survival for the subgroups was based on the Kaplan-Meier curves. As the base case overall survival within the trial period was modelled using the flexible spline-based Weibull function with 1 knot fitted to the ITT Kaplan-Meier curve, the results of the subgroups are presented alongside the results for the ITT population using the Kaplan-Meier curve. However, it is also possible to use the ITT survival with the subgroup data. The mean CHOP INTEND score assigned to each health state and the mean rate of CHOP INTEND change used to estimate transition probabilities after trial follow-up are also modified to be subgroup specific.

Results in Table 57 reflect the results of the ENDEAR trial showing a better response in patients treated earlier. The QALYs gained in the “≤12 weeks disease duration” subgroup were double those of the QALYs gained in the “>12 weeks disease duration” subgroup.

Table 57. Subgroup analysis - infantile onset

Population	Mean monthly rate of CHOP INTEND increase/decrease	Mean CHOP INTEND score per health state	Incremental cost (£)	Incremental QALY	ICER (£/QALY gained)
ITT population	Nusinersen: [redacted] / RWC: [redacted]	ITT each arm	2,187,311	5.37 5.44	407,605 402,361
		ITT both arms	2,175,081	5.31 5.38	409,235 404,015
≤12 weeks disease duration	Nusinersen: [redacted] / RWC: [redacted]	≤ 12 weeks each arm	2,207,402	5.49 5.56	402,252 396,884
		≤ 12 weeks both arms	2,202,236	5.47 5.54	402,917 397,566
>12 weeks disease duration	Nusinersen: [redacted] / RWC: [redacted]	> 12 weeks each arm	2,121,407	5.07 5.13	419,927 415,044
		> 12 weeks both arms	2,124,291	5.05 5.11	420,317 415,427

Abbreviations: ICER, incremental cost-effectiveness ratio; QALY, Quality-adjusted life year;

3.10 Validation

Model validation

Model validation was performed in alignment with the International Society for Pharmacoeconomics and Outcomes Research best practice recommendations.(145) This included validation of the model structure, key data sources, and assumptions. It assessed face validity, internal validity and external validity. Expert opinion, for example as expressed at the September 2017 expert panel(33) and clinical expert survey,(117) was sought on data sources to model survival, on appropriate modelling assumptions where these were required to extrapolate beyond the time horizon of clinical trials, and on the application of utility measures. As the SLR did not identify any relevant economic evaluations for treatments used in infantile onset SMA, a cross-validity check was not performed.

Face validity

In the sections of the submission dealing with survival, health state utilities and costs, the most appropriate available data sources were selected, after systematic literature searches to augment the robust clinical effectiveness data from the ENDEAR study. Given the lack of evidence in what is a relatively under-researched disease area, additional research and extensive use of expert clinical opinion (see section 3.3) have been used to generate estimates of cost-effectiveness in line with the NICE reference case.

External validity

Comparisons of model predictions with outcomes from the studies used to build the model (i.e., dependent, external validity) and with outcomes from the studies not used to build the model (i.e., independent, external validity) were performed.

Using different approaches to treatment effect after the end-of-trial follow-up and assuming that long term survival matched that of the non-invasive respiratory aid group in Gregoretti et al. (2013),(11) survival analysis suggested that the conventional parametric and flexible spline-based functions would give reliable predictions. Mean survival times in each treatment arm and differences in survival for all fitted models are compared with predictions from Kaplan-Meier and Cox models, assuming no treatment effect after trial follow-up, in Table 58.

Table 58. Predicted mean survival assuming no treatment effect after follow-up: non-invasive respiratory aid

	Sham procedure	Nusinersen	Difference	
Model	**Mean**	**Mean**	**Mean**	**P Value**
Kaplan-Meier	42.1	58	16.1	0.1612
Cox model	42.3	57.7	15.5	0.1904
Exponential	36.2	54.3	17.9	0.108
Weibull	38.5	55.1	16.8	0.1468
Stratified Weibull	38.1	55.2	17.2	0.15
Gompertz	40.9	57.1	16.1	0.1616
Stratified Gompertz	40.2	56.8	16.9	0.156
Log-normal	40.3	54.4	13.9	0.2088
Stratified log-normal	37.5	55.1	17.6	0.1276
Log-logistic	38.6	54.9	16.3	0.1516
Stratified log-logistic	37.4	55.1	18	0.13
Generalised gamma	43.7	53.9	10.3	0.3888
Flexible Weibull: 1 knot	40.7	56.9	16.4	0.1504
Flexible Weibull: 2 knots	41.3	57.2	15.9	0.1764
Flexible Weibull: 3 knots	41.2	57.3	16.2	0.1632
Stratified: 1 knot	40.7	56.9	16.5	0.1564
Stratified: 2 knots	41.1	57.7	16.6	0.1524
Stratified: 3 knots	40.3	57.5	17.5	0.1476

Model verification and quality assurance

Quality-control procedures for verification of input data and coding were performed by individuals not involved in the model development and in accordance with a pre-specified test plan. These procedures included verification of all input data with original sources and programming validation. Verification of all input data was documented (with the initials of the health economist performing the quality-control procedure and the date on which the quality-control procedure was performed) in the relevant worksheets of the models. Any discrepancies were discussed, and the input data were updated where required. Programming validation included checks of the model's results, calculations, data references, model interface, and Visual Basic for Applications code.

3.11 Interpretation and conclusions of economic evidence

The analysis presented above of nusinersen for the subset of SMA patients falling into the category of infantile onset is based on data as closely aligned as possible with clinical practice in the NHS in England. Its strengths are that it is informed by robust clinical trial data, longer-term data on survival for extrapolation beyond clinical trial follow-up and assumptions tested against expert clinical opinion. Nevertheless, as nusinersen is the first disease modifying therapy in SMA (and this is the first economic evaluation of nusinersen), there are a number of uncertainties, particularly in relation to long-term persistence of treatment effects, assessments of HRQL and health state utilities, and impacts on carers. The cost per QALY ratio which, like other high cost drugs in rare diseases, has a cost-effectiveness ratio in excess of NICE's conventional benchmarks of £20-30,000 per QALY, should therefore be evaluated alongside the range of outcomes generated by nusinersen. From the patient's perspective, the issues highlighted in relation to HRQL and utility assessment make a strong case that gaining a more rounded insight into the impact of SMA and nusinersen requires other outcomes to be considered alongside the QALY. In addition, a fuller understanding of the long-term impacts of nusinersen and the benefits for the carer, which are likely to be understated in this analysis, will help to develop a more informed picture of nusinersen's value. Nusinersen has the potential to meet an urgent unmet need for disease-modifying therapy in what is currently an end-of-life condition. In infantile onset SMA patients, nusinersen has shown significant early promise, with its full impact likely to become apparent only once additional long-term data has been collected.

B.4 Cost effectiveness – later onset

As mentioned previously, in the absence of pre-existing models of cost effectiveness in SMA, two de novo models have been developed, one relating to infantile onset SMA and the other to later onset SMA. These have been handled separately due to the different natural history of SMA by disease category, with this section focussing on later onset. Type II and III SMA were treated as one group due to the characteristics of CHERISH trial patients who were considered by the UK expert panel(33) to represent those at the less severe end of the type II category.

4.1 Published cost-effectiveness studies

A systematic review of the literature(116) failed to identify any existing economic evaluations of nusinersen in SMA.

4.2 Economic analysis

As no previous economic evaluations of nusinersen in SMA have been undertaken, a de novo model was developed on the basis of available data and expert clinical input.

4.2.1 Patient population

As the model was based on the ITT population of the CHERISH trial, the patient population includes those with later onset (types II and III) SMA. This is a subgroup of patients for which nusinersen has a marketing authorisation (all those with 5q SMA). As indicated in the corresponding section dealing with infantile onset SMA, types I, II and III make up the vast majority of patients with SMA. Types 0 and IV are rare and the role of nusinersen is unclear in these groups.

CHERISH was a phase III, randomised, double-blind, sham procedure controlled study of nusinersen conducted at 24 centres worldwide. A total of 126 patients with later onset (those who have or who are most likely to develop types II and III) SMA were randomised and dosed to assess the clinical efficacy, safety, tolerability, and pharmacokinetics of multiple doses of the 12 mg dose of nusinersen. Median age in the nusinersen group was 4 years compared with 3 years in the sham-procedure control group. The starting age of the patient cohort in the model (43.7 months) is the same as the mean age of patients in the CHERISH trial. The proportion of the modelled cohort who are female, of 53%, also reflects the trial population.

As in the infantile onset model, the later onset model includes subgroup analysis based on disease duration: (i) patients with disease duration <25 months; and (ii) patients with disease duration ≥25 months.

4.2.2 Model structure

The later onset model adopted a Markov structure composed of 6 health states and the absorbing state ***Dead***. In the later onset model, the CHERISH trial played a similar role to that of the ENDEAR study in infantile onset.

Whereas the ENDEAR trial used HINE measures, the CHERISH trial assessed motor milestones using the WHO's motor milestone criteria and some levels of the HFMSE scale

(Figure 43). According to the survey of NMD centres,(117) CHOP INTEND is commonly used in clinical practice among type I patients (but not types II and III). Conversely, the HFMSE is commonly used in patients with type II and III SMA but not type I. HINE-2 is used in all 3 groups, but more so in type I patients. The model structures therefore show the degree to which patients improve according to milestones which are meaningful from a clinical perspective.

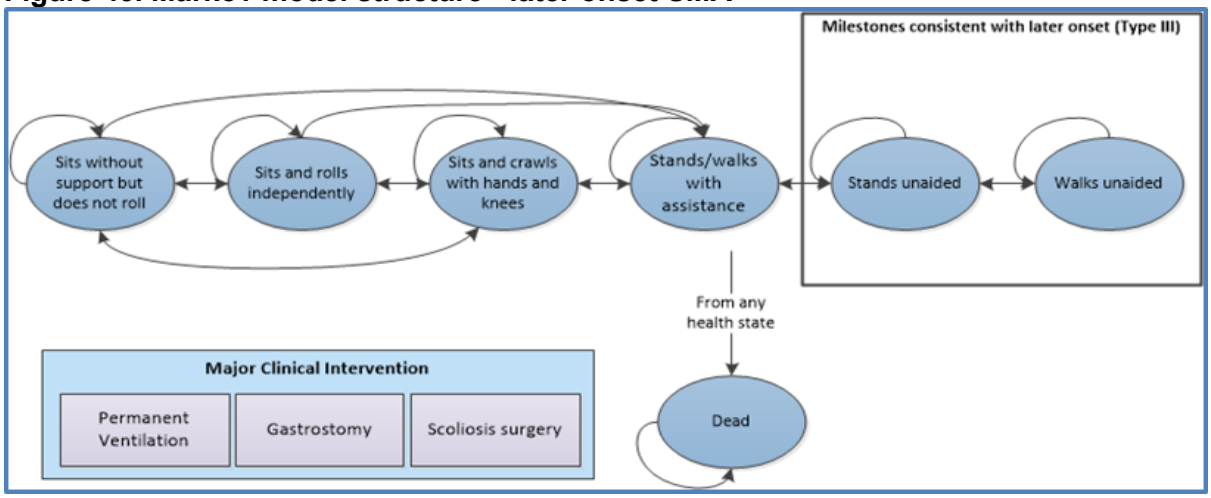
Excluding ***Dead***, the health states in the later onset model consist of the following:

- 4 health states representing milestones normally achieved by patients with later onset SMA type II (***Sits without Support but does not Roll, Sits and Rolls Independently, Sits and Crawls with Hands and Knees,*** and ***Stands/Walks with Assistance***);
- 2 health states representing motor milestones that are not observed in patients with later onset SMA type II (***Stands Unaided***, and ***Walks Unaided***);

The WHO's motor milestone criteria along with the HFMSE item "Rolls prone to supine" were used to determine the proportion of patients in the health states at each time point. The 'stands unaided' and 'walks unaided' milestones were included as separate health states in the model in accordance with clinical expert opinion,(121) which considered that there were significant benefits from being able to walk unaided over standing unaided. Progress to the health states associated with type III milestones, namely ***Stands Unaided*** and ***Walks Unaided*** are possible only once the patient has attained the ***Stands/Walks with Assistance*** health state.

As a meaningful endpoint for patients, HFMSE is a key component of the model as each health state is assigned a mean HFMSE score which is used to estimate transition probabilities after trial follow-up. The CHERISH study showed a greater range of improvement in HFMSE scores, in particular a higher proportion of nusinersen patients increasing their score by >2 points, than had been observed previously with RWC.(75) The UK clinical advisory board(33) observed that the modelled health states, by being focused on gross motor milestones, could miss the fine motor tasks which are important to HRQL. These were considered to include everything from communication ability (enabling greater social independence and peer-group acceptance) to the ability to play a musical instrument.(33)

Figure 43. Markov model structure - later onset SMA



Health state HFMSE and WHO score descriptions: (1) ***Sits without Support but does not Roll***: Patients sit according to the WHO criteria and have a score < 2 in Rolls Prone to Supine right and left in HFMSE score. (2) ***Sits and Rolls Independently***: Patients sit according to the WHO criteria and have a score of 2 in Rolls Prone to Supine right or Rolls Prone to Supine left in HFMSE score. (3***) Sits and Crawls with Hands and Knees*** and higher health states based on WHO criteria.
Abbreviations: HFMSE, Hammersmith Functional Motor Scale-Expanded; WHO, World Health Organization

Health state transitions over the trial period

Transition probabilities were based on overall survival and changes in motor milestones from CHERISH. The model structure and inputs were validated with expert opinion, including as part of a UK advisory board.(33) Subsequently, the model structure was changed based on input of health economists and validated by a Dutch clinician on Friday 10th of November, 2017.

In the CHERISH trial, some patients were observed at screening to be in the ***Stands Unaided*** and ***Walks Unaided*** health states. In the nusinersen arm, 7 and 4% of patients were in these 2 groups compared with 10% of the control group in each health state. Over the period of trial follow-up, allocation of the modelled cohort was governed by counts of trial patients. The transitions between health states during the first 15 months of the model were programmed using patient-level data based on WHO milestones, the HFMSE score of the “Rolls prone to spine” item and survival.

The model schematic showing health state transitions over the period of trial follow-up and after the end of the trial are illustrated in Appendix R and the transition probability matrices under base case assumptions are provided in Appendix S.

Timing of health state transitions and cycle length

The model cycles are defined similarly to infantile onset during the follow-up period of 15 months by the WHO motor milestones and HFMSE assessment time points at days 1, 92, 169, 274, 365, and 456 or approximately 3, 6, 9, 12 and 15 months. In the CHERISH trial, loading doses were administered on days 1, 29 and 85 and maintenance doses on day 274

and every 6 months thereafter. In comparison, the base case settings of the model have 4 loading doses at days 1, 30, 60 and 90 and maintenance doses every 4 months thereafter. As the use of the modelled dosing regimen could lead to greater benefit in clinical practice, the modelled results may represent a conservative estimate of treatment effect. Cycle lengths are presented in Table 59. As in infantile onset SMA, a half-cycle correction was applied. Key features of the economic analysis are summarised in Table 60.

Table 59. Cycle length and maintenance dosing in later onset SMA

Cycle	Month (end of cycle) – later onset	Maintenance dosing
1	3	4 loading doses
2	6	4 maintenance doses (1 every 4 months after month 3)
3	9	
4	12	
5	15[1]	
6	19	
7 onwards	23 and every 4 months thereafter	1 maintenance dose

Abbreviation: SMA, spinal muscular atrophy
[1]End of trial follow-up

Table 60. Features of the economic analysis - later onset SMA

	Previous appraisals	Current appraisal	
Factor	**TAXXX**	**Chosen values**	**Justification**
Time horizon	N/A	Lifetime (modelled as 80 years in the base case)	The standard approach used in economic evaluation. A lifetime time horizon in chronic conditions ensures that the period of the analysis is long enough to reflect all important differences in costs or outcomes between the technologies being compared, in line with the NICE reference case. Extrapolation of survival beyond the trial period using natural history data indicates that an 80-year modelling period is required in nusinersen patients using base case assumptions.
Treatment waning effect	N/A	No deaths were observed in the CHERISH trial. The mean monthly rates of HFMSE increase and decrease in the nusinersen and control arms, respectively, were	Patients receiving RWC are assumed to follow the natural history of the disease in which patients do not walk or stand unaided, may lose the ability to sit unaided and show a decline in motor function as measured by HFMSE. In the nusinersen arm,

		extrapolated beyond the end of trial follow-up. The mortality risk of patients in motor milestones characteristic of later onset (type III) patients is set between that of type II patients and the general population.	improvements in HFMSE had yet to plateau (although the model allows for a plateau). The UK advisory board(33) suggested that the mechanism of action of nusinersen was a strong reason to believe that effects observed in clinical trials could be extrapolated over time.
Source of utilities	N/A	PedsQL data collected in the CHERISH study in later onset patients, mapped on to EQ-5D using a published algorithm.(118)	The NICE reference case recommends a cost utility analysis. No utilities relevant to SMA were found in the literature. The advisory board expressed a preference for the use of PedsQL data.(33)
Source of costs	N/A	NHS reference costs for lumbar puncture. Bastida et al. (2016)(119) for general health care management costs.	Reference costs are relevant to the NHS in England. Bastida et al. (2016) collected data on health and social care costs in 4 European countries, including the UK.

EQ-5D, European Quality of Life-5 Dimensions; HFMSE, Hammersmith Functional Motor Scale-Expanded; NICE, National Institute for Health and Care Excellence; PedsQL, Paediatric Quality of Life Inventory; RWC, real-world care

4.2.3 Intervention technology and comparators

As no patients receiving nusinersen in any of the phase II or phase III trials discontinued treatment, there is no clear stopping rule. Therefore, discontinuation in the model was informed by expert opinion that, as far as treatment response is concerned, only those in the ***Sits without Support but does not Roll*** health state after 1 year would stop treatment. In the model, those transitioning to the ***Sits without Support but does not Roll*** health state ceased treatment (at month 15). In addition, a proportion (20% is assumed in the base case but tested in sensitivity analysis) discontinues treatment after scoliosis surgery due to the inability to receive further lumbar punctures. Forty three percent of patients undergo scoliosis surgery,(22) after 12 years in those who are non-ambulant(21) and an assumed 15 years in those who are ambulant.

4.3 Clinical parameters and variables

The cost-effectiveness model was based on the CHERISH(146) pivotal phase III trial in later onset SMA. To fill evidence gaps for data not collected in CHERISH and to identify data on which to base extrapolation beyond the time horizon of the trial, 2 SLRs(116,120) and targeted parameterisation searches were conducted. Costs were obtained from Bastida et al. (2016) and utility data from CHERISH(146). In addition to survival, HFMSE and motor milestones, the CHERISH study reported the following endpoints:

- The revised version of the ULM, which assesses upper limb function in non-ambulatory patients with later onset SMA. The revised version (RULM) includes the addition of more difficult items to make it applicable to a more general SMA population.
- Achievement of standing alone at 15 months.
- Achievement of walking with assistance at 15 months.
- CGI-I scale (investigator and caregiver assessment). The CGI assessment is based on a 7-point ordinal scale from 1 (very much improved) to 7 (very much worse).
- PedsQL Measurement Module, a modular, self-report and parent proxy-report approach to measuring HRQL in children and adolescents.
- Assessment of Caregiver Experience with Neuromuscular Disease (ACEND) scale.
- Disease-related adverse-events and hospitalisations.

Key results of the CHERISH study were:(2,73,105,147,148)

- Nusinersen patients experienced significant improvement in motor function as measured by HFMSE scores from baseline to month 15 compared with a decline in HFMSE score in the control group (P <0.0001).
- The nusinersen group had a higher proportion of responders achieving an increase of 3 points or more in HFMSE score than the control group (57.3 vs. 20.5%).
- More patients in the nusinersen group gained motor milestones compared with those in the control group (17.1 vs. 10.5%). While there were patients in the control group who lost motor milestones at 15 months (4 of 19, or 21%), there were no motor milestones lost in the nusinersen group.
- A consistently higher proportion of patients in the nusinersen group were rated as much improved or having any improvements compared with the control group at all time points in the investigator and caregiver CGI assessment.

4.3.1 Analysis of survival

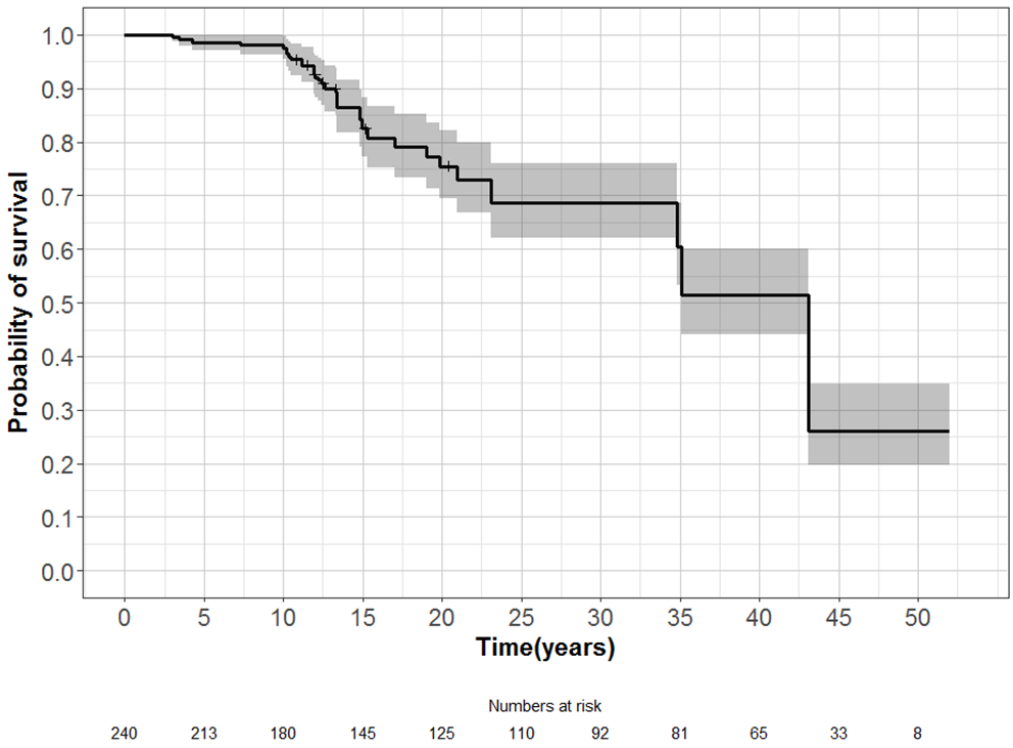
The overall strategy for modelling survival is described in the section of the submission dealing with infantile onset (section 3.3.2). Since there were no deaths in the CHERISH trial, fitting of survival curves to the trial data was not applicable. Therefore, survival is modelled using external data beyond trial follow-up and hazards at the end of the period of external data are compared with general population mortality for longer term extrapolation. Further details are provided in Appendix O.

To extrapolate beyond the trial data in the sham-procedure arm of CHERISH, external data was drawn from the study by Zerres et al. (1997)(104) which is the only long-term dataset identified in later onset patients. The study was conducted among 240 patients with later onset (type II) SMA (those who sat but never walked). One hundred and thirty three patients were recruited from 1985 onwards at German institutes and 107 from 1960 onwards at Polish institutes.

Survival functions were fitted to the reconstructed Kaplan-Meier curve (Figure 44). The models that gave the best visual fit were the Weibull models with and without splines and the

Gompertz distribution (Appendix O). In the base case, the flexible spline-base Weibull with 2 knots was selected as it gave the best fit on the AIC and the BIC (Appendix O).

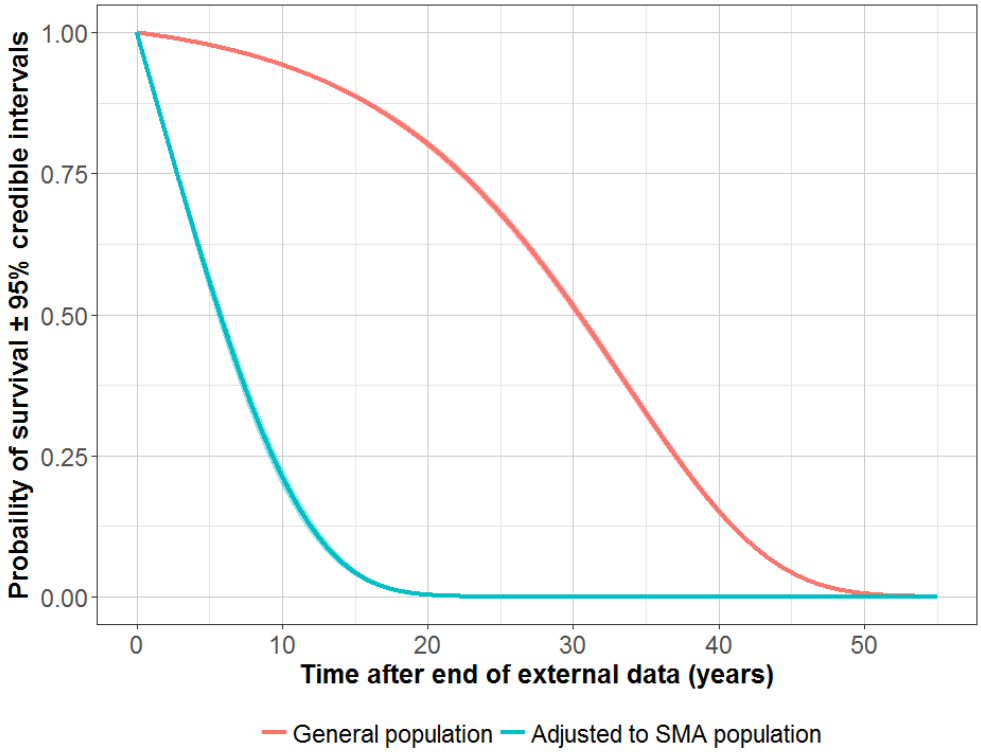
Figure 44. Kaplan-Meier curve based on reconstructed patient-level data from Zerres et al. (1997)



The hazard rate predicted from the flexible spline-based Weibull model with 2 knots fitted to the Zerres et al. (1997) data was estimated for the mean age at the end of follow-up of 53 years. The hazard rate from the Gompertz model fitted to the general population data also was estimated for an age of 53 years. The hazard rates from the Zerres et al. (1997) data was found to be 0.00745, and the hazard rate from the general population was 0.00028. This gave a hazard ratio of 26.4. The Gompertz model was used to predict hazard rates, cumulative hazards, and probability of survival for a population from 53 years of age. The hazard ratio of 26.4 was applied to these hazard rates to give an adjusted survival probability curve that matched the patient population from the Zerres et al. (1997) dataset (Figure 45).

For patients who receive nusinersen, several options for extrapolating treatment effect were considered. In the base case, the assumption was made after the end of follow-up in the CHERISH trial (in which no deaths were observed) that a hazard ratio of 1 would apply (no impact of treatment on overall survival). However, in the base case analysis, it was assumed that patients achieving milestones consistent with SMA type III have a lower risk of death than patients in other health states. In patients with SMA type III, life expectancy is not reported to be significantly lower than that of the general population(14,104). Hence, it is assumed in the model that the risk of death for patients reclassified as type III is between the risk of death for patients with SMA type II (adjustment factor of 0) and the risk of death for the general population (adjustment factor of 1). In the base case, a 0.5 adjustment is applied.

Figure 45. Projected survival from the Gompertz model fitted to the general population data from the end of follow-up of the Zerres et al. (1997) study



Abbreviation: SMA, spinal muscular atrophy

The only source for long-term data in patients with SMA type II who receive nusinersen was the phase I and phase I/IIa CS12 and CS2 trial, which assessed motor function using the HFMSE. In that study, of the 6 who completed an assessment at day 1,050, one patient was able to walk independently.

4.3.2 Transition probabilities after the end of trial follow-up

To derive transitions for the base case scenario after end of trial follow-up, the model assigns a HFMSE score to each health state based on the mean HFMSE score of the patients in each health state throughout the CHERISH trial follow-up (i.e. mean score including all assessments; Table 61). Then, in the nusinersen arm, the model uses the mean rate of HFMSE increase as observed in the CHERISH trial for patients treated with nusinersen ([redacted] points per month) to calculate the transition probability to the next best health state. For the RWC arm, the model uses the mean rate of HFMSE decrease as observed in the CHERISH trial for the sham arm (i.e., [redacted] points per month) to calculate the transition probability to the next worst health state. An alternative scenario analysis uses the mean rate of decrease observed by Kaufmann et al. (2012)(149) (i.e., 0.05 points per month). Appendix R provides the transition matrices for the later onset SMA model. An example calculation of a transition probability after trial follow-up in patients treated with nusinersen is given here.

Table 61. Mean HFMSE scores throughout the CHERISH trial

Health state	Nusinersen		RWC		Source
	Mean (SE) HFMSE score	N	Mean (SE) HFMSE score	N	
Sits without Support but does not Roll each arm	17.7 (0.28)	240[a]	15.9 (0.32)	154[a]	CHERISH trial
Sits and Rolls Independently: each arm	24.6 (0.40)	125[a]	24.0 (0.77)	41[a]	CHERISH trial
Sits and Crawls with Hands and Knees: each arm	34.5 (0.67)	70[a]	26.7 (1.76)[b]	21[a]	CHERISH trial
Stands/walks with assistance: each arm	38.4 (0.71)	42[a]	26.7 (1.76)	21[a]	CHERISH trial
Stands unaided: each arm	40.3 (1.41)	23[a]	31.5 (0.98)	15[a]	CHERISH trial
Walks unaided: each arm	51.0 (10.2)[c]	1	38.8 (3.14)	8[a]	CS12 and CS2 trial; CHERISH trial

Abbreviations: HFMSE, Hammersmith Functional Motor Scale – Expanded

[a] Measurements throughout the trial follow-up

[b] Assumes the same score of the ***Stand/Walks with Assistance*** health state.

[c] Last visit assessment in the CS12 and CS2 trial at day 1050. The mean HFMSE score in the CHERISH trial was 43.3. The score from the CS12 and CS2 trial was used instead of the CHERISH mean because it was associated with a longer follow-up. A higher score is more conservative as it increases the difference between health states.

In patients receiving nusinersen, the probability to the next best health state from the health state ***Stands Unaided*** is calculated as follows:

$$transition\ probability_{standing\ to\ walking} =$$
$$Min\left(1, \left(\frac{Rate\ of\ HFMSE\ increase_{per\ month} \times Cycle\ length}{HFMSE_{walking} - HFMSE_{standing}}\right)\right) =$$
$$Min\left(1, ([redacted])\right) =$$
$$12\%, transition\ probability_{stands\ unaided\ to\ walks\ unaided} =$$
$$Min\left(1, \left(\frac{Rate\ of\ HFMSE\ increase_{per\ month} \times Cycle\ length}{HFMSE_{walks\ unaided} - HFMSE_{stands\ unaided}}\right)\right) =$$
$$Min\left(1, ([redacted])\right) = 10\%,$$

$$transition\ probability_{standing\ to\ standing} = 1 - transition\ probability_{standing\ to\ walking} = 90\%,$$

where *HFMSE* is the mean HFMSE score.

4.4 Measurement and valuation of health effects

4.4.1 Health-related quality of life data from clinical trials

For later onset SMA patient utilities, PedsQL data collected in the CHERISH study were mapped on to the EQ-5D using the published algorithm discussed in relation to the infantile onset model. Details of the mapping are provided in Appendix H and the results summarised below.

Mapping

Patient utilities were based on the PedsQL mapping exercise described in the context of infantile onset SMA, the CHERISH trial providing the underlying data for both infantile and later onset patients.

Patient utilities are reported in Table 62. Carer utilities are based on an analogous approach to that used for infantile onset patients whereby the Bastida et al. (2016) carer utility is adapted to each individual health state using the variation in patient utilities given by the PedsQL mapping. Carer utilities are varied relative to the reference point of ***Sits and Rolls Independently*** which, in later onset patients, is assigned a utility of [redacted] a weighted average of types II and III patients from the UK sample of Bastida et al. (2016). The carer utilities in later onset SMA and the assumptions used to derive them are reported in Table 63. Estimates of carer QALYs are based on carer disutilities (reported in Table 64) relative to a general population utility of 0.915, as used in the infantile onset model. Also in common with the infantile onset model, an adjustment was made to incorporate the impact of bereavement on carers into the model.

Table 62. Patient utilities - later onset SMA

Health state	Patient utility
Sits without Support but does not Roll	[redacted]
Sits and Rolls Independently	[redacted]
Sits and Crawls with Hands and Knees	[redacted]
Stands/Walks with Assistance	[redacted]
Stands Unaided	[redacted]
Walks Unaided	[redacted]

Abbreviation: SMA, spinal muscular atrophy

Table 63. Approach to carer utilities - later onset SMA

Health states	Caregiver's health state utility values	Methodology
Sits without Support but does not Roll	[redacted]	Applying the difference between ***Sits and Rolls Independently*** ([redacted]) and ***Sits without Support but does not Roll*** ([redacted]) health states from the PedsQL mapping study to the Bastida utility value [redacted]
Sits and Rolls Independently	[redacted]	Assumption based on infantile onset point estimate from Bastida: the value from the study is assumed to best reflect this health state or the ***Sits without Support but does not Roll*** health state, and the selection of this health state was chosen as it seems implausible that the ***Sits without Support but does not Roll*** health state would have such a high utility value
Sits and Crawls with Hands and Knees	[redacted]	Applying the difference between ***Sits and Rolls Independently*** ([redacted]) and ***Sits and Crawls with Hands and Knees*** ([redacted]) health states in the PedsQL mapping study to the Bastida utility value [redacted]
Stands/Walks with Assistance	[redacted]	Applying the difference between ***Sits and Rolls Independently*** ([redacted]) and ***Stands/Walks with Assistance*** ([redacted]) health states in the PedsQL mapping study to the Bastida utility value ([redacted]
Stands Unaided	[redacted]	Same as ***Stands/Walks with Assistance*** (no difference in patient utilities)
Walks Unaided	[redacted]	Applying the difference between ***Sits and Rolls Independently*** ([redacted]) and ***Walks Unaided*** ([redacted]) health states in the PedsQL mapping study to the Bastida utility value [redacted]

Abbreviations: SMA, spinal muscular atrophy; PedsQL, Paediatric Quality of Life Inventory;

Table 64. Carer disutilities - later onset SMA

Health states	Caregiver's health state disutility values
Sits without Support but does not Roll	[redacted]
Sits and Rolls Independently	[redacted]
Sits and Crawls with Hands and Knees	[redacted]
Stands/Walks with Assistance	[redacted]
Stands Unaided	[redacted]
Walks Unaided	[redacted]

Abbreviation: SMA, spinal muscular atrophy

4.4.2 Health-related quality of life studies

The corresponding section related to infantile onset SMA provides a summary of the literature and other sources of utility data and Appendix H provides further detail.

4.4.3 Adverse reactions

As no AEs were considered by trial investigators to be related to treatment in CHERISH, they were excluded from consideration in the modelling with respect to both costs and health outcomes. AEs associated with lumbar puncture have been observed but the incidence and severity of these are consistent with events expected to occur with lumbar puncture. No serious AEs were reported in either arm of CHERISH.(86)

4.4.4 Health-related quality of life data used in the cost-effectiveness analysis

The PedsQL data collected from the CHERISH trial was considered the most appropriate data on HRQL as it was collected directly from the patient group relevant to the economic model. As discussed in relation to the infantile onset model, PedsQL has been used frequently in SMA and has evidence for its validity although some reservations have been expressed about its use. The utilities based on PedsQL were considered by the UK expert panel(33) to reflect real life as lived by patients and their families and to exhibit a reasonable level of variation across health states. While little evidence is available on carer impacts, it was thought reasonable to factor the same differentials in utilities between health states into carer utilities, although it is possible that a reduced level of motor function (e.g. being confined to a wheelchair) could be preferable to, for example, being able to walk but with a high level of instability. Patient and carer utilities, with confidence intervals, are summarised in Table 65.

Table 65. Summary of utility values for cost-effectiveness analysis

Health state	Utility value: mean (standard error)		95% CI	Reference in submission (section and page number)	Justification
Patients				**Mapping**	
Sits without Support but does not Roll	[redacted]		[redacted]	p. 173	See text
Sits and Rolls Independently	[redacted]		[redacted]	p. 173	See text
Sits and Crawls with Hands and Knees	[redacted]		[redacted]	p. 173	See text
Stands/Walks with Assistance	[redacted]		[redacted]	p. 173	See text
Stands Unaided	[redacted]		[redacted]	p. 173	See text
Walks Unaided	[redacted]		[redacted]	p. 173	See text
Carers	[redacted]	**Decrement**	**95% CI for utilities**		
Sits without Support but does not Roll	[redacted]	[redacted]	[redacted]	p. 173	See text
Sits and Rolls Independently	[redacted]	[redacted]	[redacted]	p. 173	See text
Sits and Crawls with Hands and Knees	[redacted]	[redacted]	[redacted]	p. 173	See text
Moderate Improvement	[redacted]	[redacted]	[redacted]	p. 173	See text
Stands Unaided	[redacted]	[redacted]	[redacted]	p. 173	See text
Walks Unaided	[redacted]	[redacted]	[redacted]	p. 173	See text

Abbreviations: CI, confidence interval;

4.5 Cost and healthcare resource use identification, measurement and valuation

4.5.1 Intervention and comparators' costs and resource use

Drug costs and administration costs are the same as those presented for infantile onset SMA.

4.5.2 Health-state unit costs and resource use

The health and social care costs by health state are the same for later onset patients as for infantile onset patients. Annual costs associated with types II and III motor milestones (Table 44) are relevant to the later onset model, but not those associated with type I milestones.

Table 66. Annual health care and social care costs (£2016) according to motor milestones achieved

	Milestones consistent with later onset (type II)	Milestones consistent with later onset (type III)
Respiratory care	[redacted]	[redacted]
Gastrointestinal care	[redacted]	[redacted]
Nutritional care	[redacted]	[redacted]
Orthopaedic care	[redacted]	[redacted]
Total	[redacted]	[redacted]

The health states in the model correspond with the achievement of motor milestones, and therefore with the annual costs reported in Table 66, as follows:

- Milestones consistent with type II SMA: ***Sits without Support but does not Roll, Sits and Rolls Independently, Sits and Crawls with Hands and Knees, Stands/Walks with Assistance***
- Milestones consistent with type III SMA: ***Stands Unaided, Walks Unaided***

Annual costs associated with these health states are reported in Table 67.

Table 67. Annual health state-related health and social care costs (£2016)

	Sits without Support but does not Roll, Sits and Rolls Independently, Sits and Crawls with Hands and Knees, Stands/Walks with Assistance	*Stands Unaided, Walks Unaided*
Drugs	[redacted]	[redacted]
Medical tests	[redacted]	[redacted]
Medical visits	[redacted]	[redacted]
Hospitalisations	[redacted]	[redacted]
GP & emergency	[redacted]	[redacted]
Health material	[redacted]	[redacted]
Social services	[redacted]	[redacted]
Total	[redacted]	[redacted]

4.5.3 Adverse reaction unit costs and resource use

As discussed in the context of infantile onset SMA, adverse events were not factored into the model either in the cost or QALY calculations.

4.5.4 Miscellaneous unit costs and resource use

There are no additional costs or items of health care resource use which have not been covered elsewhere.

4.6 Summary of base case analysis inputs and assumptions

4.6.1 Summary of base case analysis inputs

Table 68 summarises the variables subject to probabilistic analysis in the economic model. The table excludes those variables which are common to the infantile onset and later onset models. Variables included in the model and subject to OWSA, their base case values and ranges tested, are listed in Appendix T.

Table 68. Summary of variables applied in the economic model

Variable	Base Case Value	Measurement of uncertainty and distribution (95% confidence limits unless otherwise stated)	Section
Mean age (years)	3.6	95% CI: 3.4–3.9 (normal)	4.2.1
Percentage female	53%	95% CI: 44%–62% (beta)	4.2.1
Population subgroup	ITT	Uncertainty around the transition matrices was calculated using the method of Briggs et al. (2003)(142)	4.9
OS prediction after end-of-trial follow-up for real-world care arm	Flexible spline-based Weibull (2 knots) fitted to Kaplan-Meier from Zerres et al. (1997)	Variance-covariance matrix (Cholesky decomposition)	4.3.1
Age-specific mortality, HR for SMA type II vs. general population (after end of external data follow-up)	26.4	95% CI: 16.1–36.8 (normal)	4.3.1
Percentage of patients who discontinue after scoliosis surgery	20%	95% CI: 13–28% (beta)	4.2.3
Percentage of patients having scoliosis surgery: nusinersen	43%	95% CI: 23–38% (beta)	4.2.3
Percentage of patients having scoliosis surgery: RWC	43%	95% CI: 23–38% (beta)	4.2.3
Mean monthly rate of HFMSE increase: nusinersen	[redacted]	[redacted]	4.3.2
Mean monthly rate of HFMSE decrease: real-world care	[redacted]	[redacted]	4.3.2
Mean HFMSE score per health state	ITT population: each arm	Normal	4.3.2
Health-state utility values: patients			
Sits without Support but does not Roll	[redacted]	[redacted]	4.4.4
Sits and Rolls Independently	[redacted]	[redacted]	4.4.4
Sits and Crawls with Hands and Knees	[redacted]	[redacted]	4.4.4
Stands/Walks with Assistance	[redacted]	[redacted]	4.4.4
Stands Unaided	[redacted]	[redacted]	4.4.4
Walks Unaided	[redacted]	[redacted]	4.4.4
Health-state utility values: carers	[redacted]	[redacted]	

Variable	Base Case Value	Measurement of uncertainty and distribution (95% confidence limits unless otherwise stated)	Section
Sits without Support but does not Roll	[redacted]	[redacted]	4.4.4
Sits and Rolls Independently	[redacted]	[redacted]	4.4.4
Sits and Crawls with Hands and Knees	[redacted]	[redacted]	4.4.4
Stands/Walks with Assistance	[redacted]	[redacted]	4.4.4
Stands Unaided	[redacted]	[redacted]	4.4.4
Walks Unaided	[redacted]	[redacted]	4.4.4

[a] SE was the 15-month rate of increase

[b] SE was for the 15-month rate of decrease

Abbreviations: CI, confidence interval; HR, hazard ratio; HFMSE, Hammersmith Functional Motor Scale-Expanded; ITT, intention to treat; OS, overall survival; RWC, real-world care;

4.6.2 Assumptions

Table 69 lists those parameters of the model for which assumptions were made in the absence of data. As was the case with infantile onset SMA, these relate primarily to extrapolation beyond the end of trial follow-up.

Table 69. Variables for which a modelling assumption was made (in the absence of data)

Variable	Base case assumption and allowance for uncertainty	Rationale
Factor to adjust type III mortality risk	A factor of 1 applies the general population mortality rates to later onset patients in motor milestones characteristic of type III patients. A factor of 0 applies the mortality rates of type II patients. A factor of 0.5 is applied in the base case (varied between 0.4 and 0.6 in OWSA and varied to 1 in scenario analysis).	Mortality in type III SMA has been found to be not significantly different from that of the general population. Expert clinical advice(33) supports the proposition that type II patients who achieve motor milestones associated with type III SMA are likely to experience similar mortality.
OS treatment effect after trial follow-up	The HR beyond the end of trial follow-up is assumed to be 1.	Continuation of the within-trial HR of 1.
Treatment discontinuation rule	Dependent on treatment response and receipt of scoliosis surgery. The alternative scenario is that discontinuation is independent of response.	No patients in trials of nusinersen have discontinued treatment. The discontinuation rule (movement to the ***Sits without Support but does not Roll*** health state) was supported by the UK clinical advisory board.(33)
Month after which patients discontinue from the *Sits without Support but does not Roll* health state	15 months in the base case, but can be user-defined (between 15 and 24 is tested in OWSA).	The length of the trial was around 15 months with no discontinuations
Percentage of patients who discontinue after scoliosis surgery	20% in the base case, varied between 16% and 24% in	Assumption in the absence of knowledge about the

Variable	Base case assumption and allowance for uncertainty	Rationale
	OWSA but can be user-defined.	requirement for scoliosis surgery in type I patients
Year after which patients have scoliosis surgery (ambulant)	15 years in the base case, varied between 12 and 18 years in OWSA but can be user-defined.	12 years in non-ambulant patients is based on a study(21) which suggests that preserved standing ability can decelerate the progression of scoliosis in patients with type III SMA. The survey of NMD centres indicated that type III patients undergo scoliosis surgery later than type II patients in whom surgery is performed later than in type I patients
Mean monthly rate of HFMSE increase: nusinersen	[redacted] points in the base case, varied between [redacted] in OWSA but can be user-defined. A scenario allows a proportion of patients still on treatment to reach a plateau. The model allows a proportion of those reaching a plateau to progress as in the RWC arm	The model uses the mean rate of increase/decrease from the CHERISH trial and the mean HFMSE scores of patients throughout the CHERISH trial. The observation that motor function in the clinical studies had not plateaued out and clinical expert opinion(33) (in view of nusinersen's mechanism of action) supported the extrapolation of effects seen in clinical studies over time.
Mean monthly rate of HFMSE decline: RWC	[redacted] points in the base case, varied between [redacted] in OWSA but can be user-defined.	

Abbreviations: HFMSE, Hammersmith Functional Motor Scale-Expanded; HR, hazard ratio; NMD, Neuromuscular disease; OS, overall survival; OWSA, One-way sensitivity analysis; RWC, real-world care; SMA, spinal muscular atrophy;

4.7 Base case results

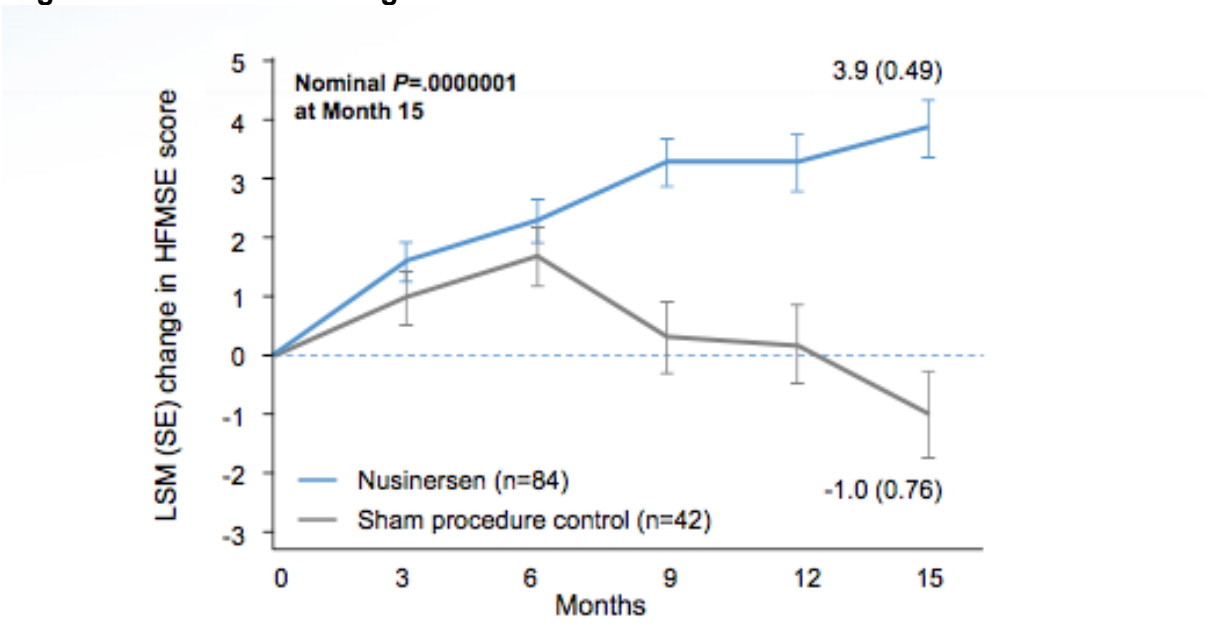
As the later onset model results are critically dependent on the motor function and motor milestone results of the CHERISH study, they are reiterated here. The mean change in HFMSE scores from baseline over time is shown in Figure 21. The results showed a greater improvement in HFMSE scores in the nusinersen group compared with the sham-control group at all time points. At month 3 the LS mean difference between the 2 groups was 0.6, which increased to 3.0 by month 9 and 3.1 by month 12. By month 15, the patients in the control group were showing a decline in HFSME scores from baseline (-1.0) while the patients in the nusinersen group continued to show an improvement, with an LS mean difference in scores of 4.9. Therefore, patients in the nusinersen group showed sustained improvements in HFSME scores and, because the improvement had not yet plateaued by 15 months, patients may be expected to improve further.

Proportion of HFMSE responders

The nusinersen group had a higher proportion of responders (56.8%) achieving an increase of 3 points or more in HFMSE score than the control group (26.3%) at 15 months (difference

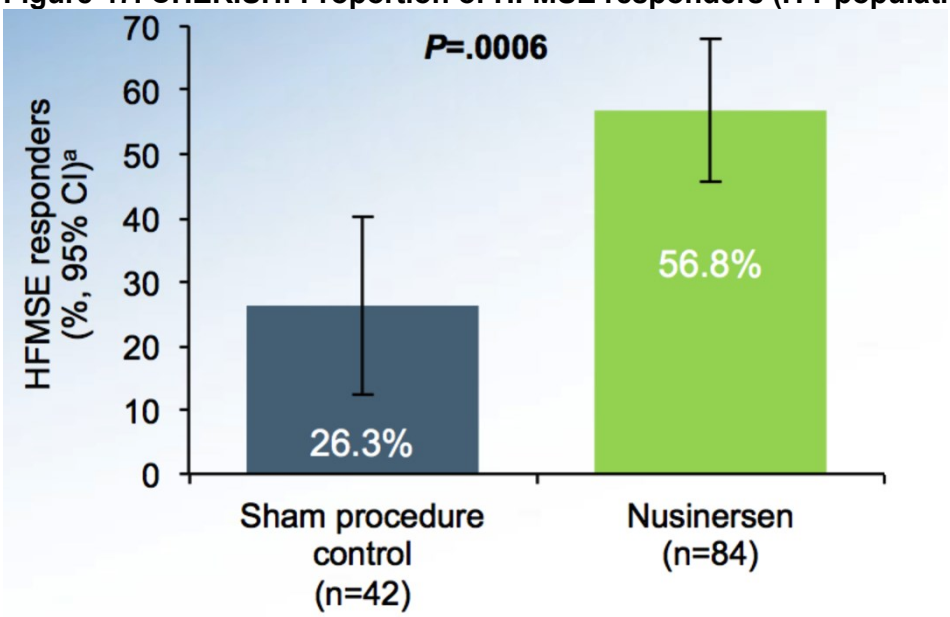
of 30.5%) (Figure 22).(105) Apart from two patients who were six and seven years old at study entry, all other patients who achieved a ≥3-point increase in observed HFMSE score from baseline at 15 months were four years old or younger at study entry, consistent with the idea that early initiation of treatment may lead to greater improvement over a period of time.(86) Results from the IES supported the primary analysis.

Figure 46. CHERISH: Change from baseline to month 15 in HFMSE score over time



Abbreviations: HFMSE, Hammersmith Functional Motor Scale Expanded; LSM, least squares mean; SE, standard error.
Source: Mercuri (2017)(73)

Figure 47. CHERISH: Proportion of HFMSE responders (ITT population, final analysis)



Abbreviations: CI, confidence interval; HFMSE: Hammersmith Functional Motor Scale Expanded; ITT, intention to treat

[a] HFMSE responder was defined as a child with a ≥3-point increase from baseline in HFMSE score at month 15. If a child is discontinued due to treatment failure or death, the child is classified as a non-responder irrespective of imputed value. Observed data: sham procedure control, n=34; nusinersen, n=66.

Source: Mercuri 2017c(105)

Motor milestones (WHO criteria)

As can be seen in Table 70, more patients in the nusinersen group (19.7%) gained new motor milestones compared with those in the control group (5.9%).

While there were patients in the control group who lost motor milestones at 15 months, there were no motor milestones lost in the nusinersen group (Table 70). At the end of the study, there were a few patients in both treatment groups who could stand alone, and one subject in the nusinersen group who was able to walk with assistance. Evaluations at different time points (i.e. 6, 9 and 12 months) were supportive of the main analysis of all the motor milestones secondary endpoints.

Table 70. CHERISH: WHO motor milestone achievement

WHO motor milestone	Nusinersen (N=66)			Sham control (N=34)			Difference in % change at month 15 (nusinersen minus sham control)
	Baseline n (%)	Month 15 n (%)	Change at month 15 %	Baseline n (%)	Month 15 n (%)	Change at month 15 %	
Sitting without support	65 (98)	66 (100)	+2	34 (100)	34 (100)	0	+2
Hands and knees crawling	13 (20)	20 (30)	+10	7 (21)	1 (3)	-18	+28
Standing with assistance	5 (8)	9 (14)	+6	6 (18)	4 (12)	-6	+12
Walking with assistance	4 (6)	5 (8)	+2	2 (6)	2 (6)	0	+2
Standing alone	2 (3)	3 (5)	+2	1 (3)	2 (6)	+3	-1
Walking alone	0	1 (2)	+2	0	0	0	+2

Abbreviations: WHO, World Health Organization

Source: Mercuri et al. 2017b(73)

4.7.1 Base case incremental cost-effectiveness analysis results

Table 71 reports the lifetime costs, life years and QALYs for nusinersen and RWC. The greater costs and lower benefits in later onset patients compared with infantile onset combine to give an ICER of £1.25m per QALY gained. The inclusion of carer QALYs reduces the ICER to around £0.9m per QALY gained.

Table 71. Base case results - later onset SMA, patient QALYs

Technology	Total costs (£)	Total LYG	Total QALYs	Inc. costs (£)	Inc. LYG	Inc. QALYs	ICER vs. base-line (£/QALY)	ICER inc. (£/QALY)
RWC	184,312	19.61	14.52					
Nusinersen	3,148,754	20.99	16.88	2,964,442	1.38	2.37	1,252,991	1,252,991

Abbreviations: ICER, incremental cost-effectiveness ratio; inc., incremental; LYG, life years gained; QALYs, quality-adjusted life years; RWC, real-world care; SMA, spinal muscular atrophy;

Table 72. Base case results - later onset SMA, patient and carer QALYs

Technology	Total costs (£)	Total LYG	Total QALYs	Inc. costs (£)	Inc. LYG	Inc. QALYs	ICER vs. base-line (£/QALY)	ICER inc. (£/QALY)
RWC	184,312	19.61	12.36					
Nusinersen	3,148,754	20.99	15.66	2,964,442	1.38	3.30	898,164	898,164

Abbreviations: ICER, incremental cost-effectiveness ratio; inc., incremental; LYG, life years gained; QALYs, quality-adjusted life years; RWC, real-world care; SMA, spinal muscular atrophy;

Table 73 compares the lifetime costs with nusinersen or RWC. Although nusinersen is associated with a reduction of between 27% and 32% in each of respiratory, gastrointestinal, nutritional and orthopaedic care, the cost of nusinersen again dominates the cost estimates.

Table 73. Cost comparison - later onset SMA

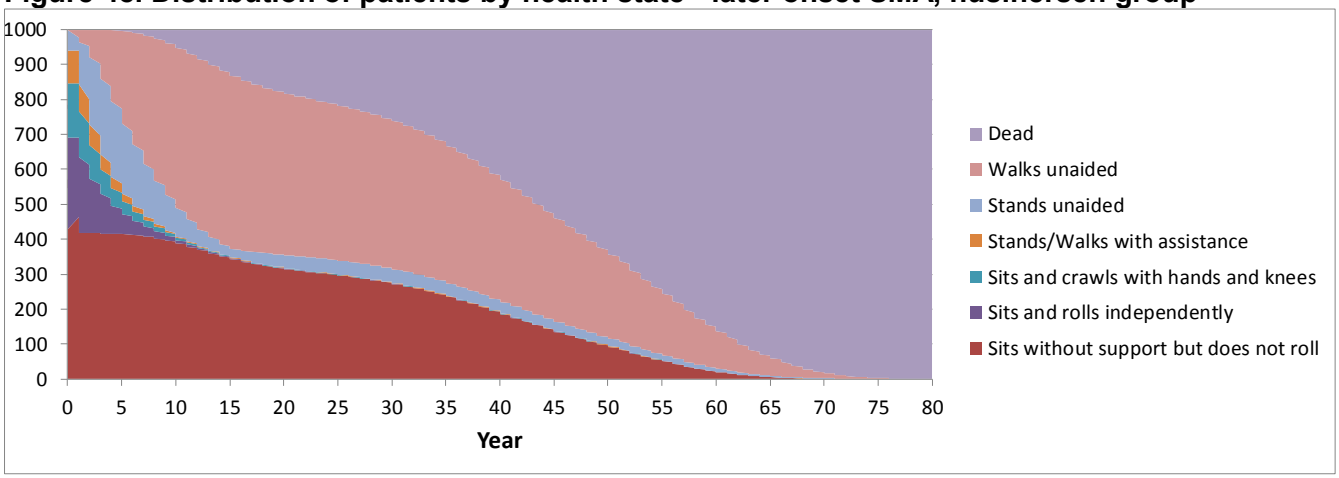
Infantile onset SMA	Nusinersen	RWC	Incremental
Total healthcare costs	3,148,754	184,312	2,964,442
Of which:			
Nusinersen acquisition costs	2,977,654		2,977,654
Nusinersen administration costs	42,085		42,085
Respiratory care	74,170	101,985	-27,815
Gastrointestinal care	21,703	32,702	-10,999
Nutritional care	15,098	22,887	-7,790
Orthopaedic care	18,044	26,737	-8,693
End-of-life costs	-	-	-

Abbreviations: RWC, real-world care; SMA, spinal muscular atrophy;

The results presented in Table 71 and Table 72 are underpinned by CHERISH data on the motor function and motor milestones reported above. The relatively small gain in survival (compared with the benefit in infantile onset patients) of 1.38 discounted life years illustrates

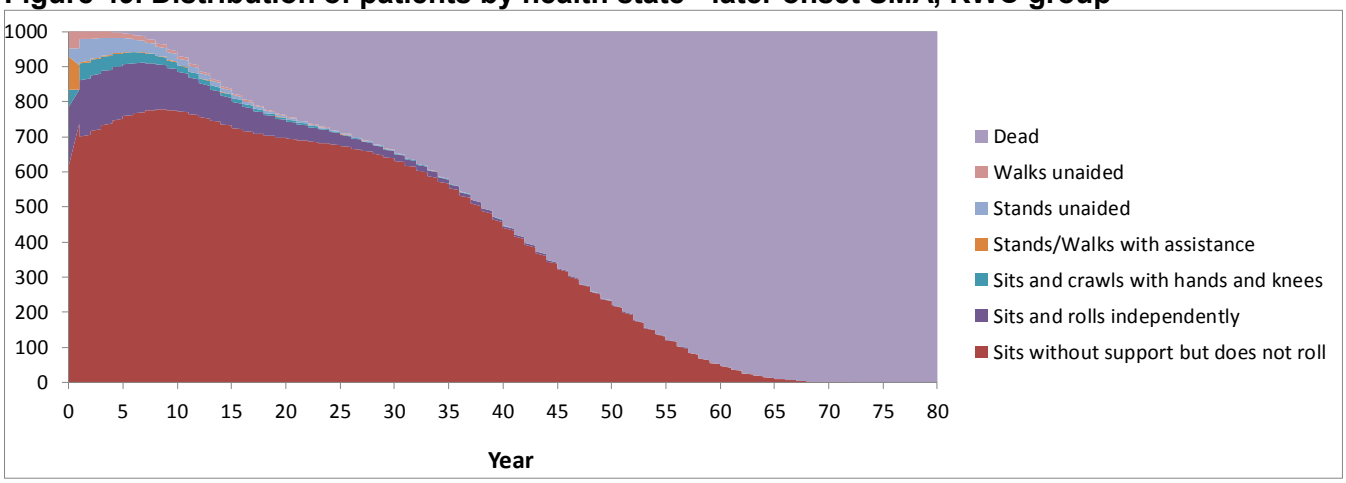
the benefits associated with the expected relationship between the achievement of improved motor milestones and mortality. The larger gain in QALYs serves to illustrate the HRQL gains from the generally better health states experienced with nusinersen compared with RWC. Given some of the drawbacks of QALYs as a summary measure of benefit, Figure 48 and Figure 49 compare the distribution of later onset SMA patients treated with nusinersen or RWC over the lifetime time horizon.

Figure 48. Distribution of patients by health state - later onset SMA, nusinersen group



Abbreviations: HFMSE, Hammersmith Functional Motor Scale-Expanded; SMA, spinal muscular atrophy

Figure 49. Distribution of patients by health state - later onset SMA, RWC group



Abbreviations: RWC, real-world care; SMA, spinal muscular atrophy

The Markov traces show extended survival with nusinersen and the transition over time of nusinersen patients to improved health states compared with RWC patients. For example, those still alive at 30 years are concentrated in the ***Walks Unaided*** health state with nusinersen whereas the corresponding cohort treated with RWC is predominantly located in the ***Sits without Support but does not Roll*** health state. Fifty four percent of nusinersen patients achieved later onset (type III) milestones compared with 10% of RWC patients.

4.8 Sensitivity analyses

4.8.1 Probabilistic sensitivity analysis

The methods of PSA were the same as those used in the infantile onset model.

As with infantile onset, it was not considered meaningful to present the cost-effectiveness acceptability curve based on conventionally accepted willingness to pay benchmarks due to the magnitude of the cost-effectiveness ratio. However, the PSA scatter plot for patient costs and patient QALYs is presented to indicate the parameter-related uncertainty in the model (Figure 50).

Table 74. Probabilistic results - later onset SMA, patient QALYs

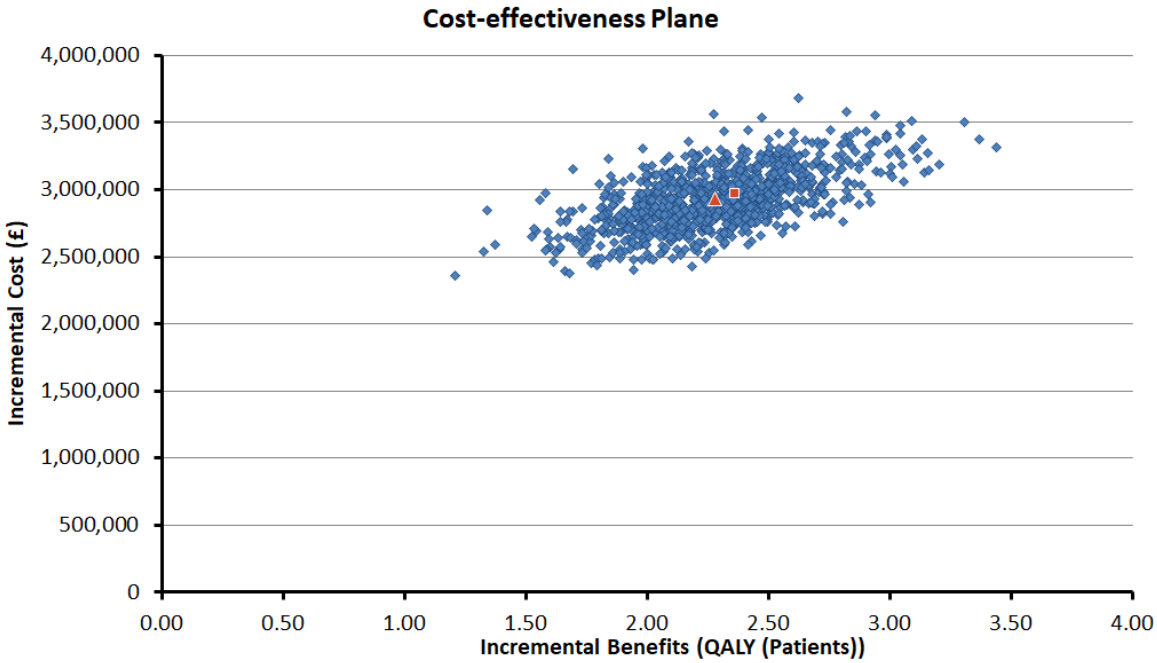
Technology	Total costs (£)	Total LYG	Total QALYs	Inc. costs (£)	Inc. LYG	Inc. QALYs	ICER vs. base-line (£/QALY)	ICER inc. (£/QALY)
RWC	183,177	19.63	14.56					
Nusinersen	3,113,403	20.96	16.84	2,930,226	1.32	2.28	1,284,614	1,284,614

Abbreviations: ICER, incremental cost-effectiveness ratio; inc., incremental; LYG, life years gained; QALYs, quality-adjusted life years; RWC, real-world care; SMA, spinal muscular atrophy;

4.8.2 Deterministic sensitivity analysis

Table 75 reports the 10 variables with the largest range of impact on the ICER in terms of the overall spread between the ICER at the lower and upper bounds of each variable in OWSA. The table gives the base case value of each variable, the lower and upper bounds tested in OWSA and the ICERs associated with those limits. The base case ICER is £1,252,991 per QALY gained (Table 71). The same information is presented as a Tornado diagram in Figure 51.

Figure 50. Scatter plot on the cost-effectiveness plane - later onset SMA



Abbreviations: QALY, quality-adjusted life year; SMA, spinal muscular atrophy;

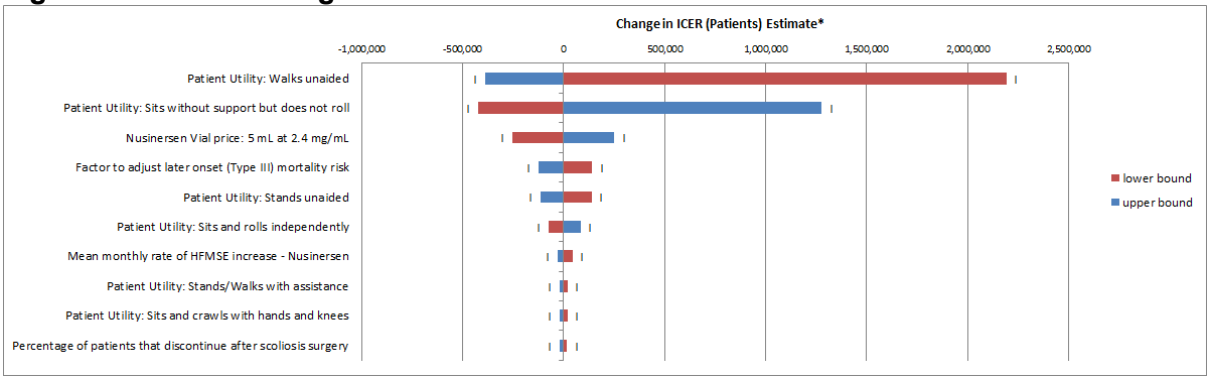
Table 75. One-way sensitivity analysis - later onset SMA

Parameter	Base case	Lower bound	Upper bound	ICER at variable's	
				Lower bound	Upper bound
Patient utility: *Walks Unaided*	[redacted]	[redacted]	[redacted]	3,445,079	867,785
Patient Utility: *Sits without Support but does not Roll*	[redacted]	[redacted]	[redacted]	832,517	2,531,626
Nusinersen vial price: 5 mL at 2.4 mg/mL	75,000	60,000	90,000	1,001,276	1,504,706
Factor to adjust later onset (type III) mortality risk	0.5	0.4	0.6	1,395,430	1,129,421
Patient utility: *Stands Unaided*	[redacted]	[redacted]	[redacted]	1,392,437	1,138,933
Patient Utility: *Sits and Rolls Independently*	[redacted]	[redacted]	[redacted]	1,179,076	1,336,794
Mean monthly rate of	[redacted]	[redacted]	[redacted]	1,300,172	1,223,602

HFMSE increase - nusinersen					
Patient utility: *Stands/Walks with Assistance*	[redacted]	[redacted]	[redacted]	1,274,338	1,232,348
Patient Utility: *Sits and Crawls with Hands and Knees*	[redacted]	[redacted]	[redacted]	1,271,507	1,235,007
Percentage of patients that discontinue after scoliosis surgery	[redacted]	[redacted]	[redacted]	1,270,599	1,236,041

Abbreviations: HFMSE, Hammersmith Functional Motor Scale-Expanded; ICER, incremental cost-effectiveness ratio; SMA, spinal muscular atrophy

Figure 51. Tornado diagram - later onset SMA



*The quadrant where the ICER falls is shown in the graph: I = quadrant 1; II = quadrant 2 (intervention dominated); III = quadrant 3 (less expensive and less effective); IV = quadrant 4 (intervention dominates)
Abbreviations: ICER, incremental cost-effectiveness ratio; HFMSE, Hammersmith Functional Motor Scale – Expanded; SMA, Spinal Muscular Atrophy

4.8.3 Scenario analysis

Scenario analyses explored the impact of varying the methodological approach to or data used to support model inputs, or varied modelling assumptions where data were absent (for example, long term survival). As noted in relation to the cost data, only one other data source was available in addition to the Bastida et al. (2016) study. The alternative to the CHERISH trial data for changes over time in HFMSE was a natural history study in SMA type II and III patients. The scenarios reported here are those which had the most significant impact on the results. Table 76 shows the input parameters which are the subject of scenario analyses, the approach adopted in the base case, the scenario(s) explored and the resulting ICER(s). The ICERs can be compared against the base case incremental cost per patient QALY gained of £1,252,991.

Table 76. Scenario analysis - later onset SMA

Input parameter	Base case analysis setting	Scenarios	ICER (£) Patient perspective (upper), combined patient and carer perspective (lower)
Base case ICER			**1,252,991** **898,164**
Time horizon (years)	Lifetime (80 years)	20	2,394,639 1,473,743
		40	1,528,733 1,027,641
		60	1,280,983 911,199
Cost perspective	Health and social care	Societal	1,150,976 825,038
Efficacy setting			
Apply higher long-term risk of death based on SMA type II adjusted general mortality rates	Apply	Don't Apply	1,227,736 886,694
Apply general population mortality rates to patients in motor milestones characteristic of later onset (type III) patients	Apply	Don't apply	2,324,278 1,285,987
Mortality risk factor	0.5	0.75	969,170 753,553
		1.00	734,749 614,044
Assumption that proportion of patients on treatment reaches a plateau; % of those reaching an improvement plateau who start getting worse	No	Yes 0%	1,371,100 983,437
Assumption that proportion of patients on treatment reaches a plateau; % of those reaching an improvement plateau who start getting worse	No	Yes 10%	1,393,262 997,921
Source for RWC arm HFMSE rate of decline	CHERISH	Kaufmann 2012(149)	1,268,258 911,947
Drug administration cost settings			
Inpatient/outpatient/day case	40% 30% 30%	100% 0% 0%	1,258,656 902,225
		0% 0% 100%	1,255,928 900,269
Health state cost settings			
Scenarios for health state costs	From published sources	Cost major clinical events only	1,276,308 914,878
Cost source	Bastida 2016	Klug 2016	1,258,136 901,852

Abbreviation: HFMSE, Hammersmith Functional Motor Scale-Expanded; ICER, incremental cost-effectiveness ratio; RWC, real-world care;

4.8.4 Summary of sensitivity analyses results

In common with the infantile onset model, the discount rates (excluded from the OWSA results) and nusinersen vial price were among the 5 variables which produced the largest spread around the base case ICER of £1,252,991 per QALY gained in the later onset model. Mortality rates were again important in later onset SMA but utilities had relatively greater prominence compared with the results for infantile onset SMA. The lowest ICER, of £832,517 per QALY, was obtained in OWSA with a utility associated with the ***Sits without Support but does not Roll*** health state of 1 (Table 75).

Shortening the time horizon increased the ICER relative to patient lifetime in the base case, substantially so at a time horizon below 20 years. Adopting a societal rather than a health and social care perspective reduces the ICER marginally in later onset patients. Changing assumptions about the source of health and social care costs, the setting for the administration of nusinersen or the approach to health state costs had a relatively minor impact on the ICER.

In later onset patients, uncertainty around the mortality of type II patients who achieved motor milestones characteristic of later onset (type III) patients resulted in wide variation around the ICER. Given evidence that type III patients have mortality similar to that of the general population, the model allows for a mortality adjustment factor. The following options are possible: the mortality of type II patients in type III milestones is set equal to the mortality of the general population (adjustment factor of 1), the mortality of type II patients (adjustment factor of 0), or somewhere in between. From a base case adjustment of 0.5, shifting the mortality risk of this group closer to that of the general population reduces the ICER and, when equalising it to the general population mortality rates, the ICER falls to around £735,000 per QALY gained from a patient perspective and below £615,000 including carer QALYs.

These scenario analyses serve to illustrate some of the key areas of uncertainty around the cost per QALY estimates. As with infantile onset patients, we reiterate that QALYs here are difficult to interpret and do not necessarily capture the full value of nusinersen.

4.9 Subgroup analysis

Subgroup analysis was conducted for subgroups based on disease duration (Table 77). In the CHERISH trial the subgroups were specified as <25 months, ≥25 months but <44 months, and ≥44 months. The model includes analyses for <25 months disease duration and ≥25 months disease duration. Cost effectiveness was modelled by applying the transition probabilities specific to the patient counts of the subgroups. The mean HFMSE score assigned to each health state and the mean rate of HFMSE change used to estimate transition probabilities after trial follow-up are also modified to be subgroup specific.

Table 77. Subgroup analysis - Later onset

Population	Mean monthly rate of HFMSE increase/decrease	Mean HFMSE score per health state	Incremental cost (£)	Incremental QALY	ICER (£/QALY gained)
ITT population	Nusinersen: [redacted] / RWC: [redacted]	ITT each arm	2,964,442	2.37	1,252,991
		ITT both arms	2,963,298	2.34	1,265,944
<25 months disease duration	Nusinersen: [redacted] / RWC: [redacted]	<25 months each arm	2,947,814	2.33	1,263,457
		<25 months both arms	2,962,710	2.47	1,201,673
≥ 25 months disease duration	Nusinersen: [redacted] / RWC: [redacted]	≥ 25 months each arm	2,944,944	1.72	1,712,437
		≥ 25 months both arms	2,962,045	1.83	1,615,299

Abbreviations: ICER, incremental cost-effectiveness ratio; QALY, Quality-adjusted life year;

A higher rate of HFMSE increase results in faster transitions to the next best health state and a higher rate of HFMSE decrease results in faster transitions to the next worse health state. However, the ICER for the <25 months disease duration subgroup using the each arm scenario is higher than the ICER for the ITT each arm scenario. This is due to the faster transition to worse health states in the <25 months subgroup for those patients in the nusinersen arm discontinuing treatment, which is associated with the higher rate of HFMSE decrease along with a smaller HFMSE score difference between the ***Walking unaided*** and ***Standing unaided*** health states in the RWC arm. If no patient is assumed to discontinue treatment, the ICER for the <25 months each arm subgroup is lower than the ICER for the ITT each arm scenario.

4.10 Validation

4.10.1 Validation of cost-effectiveness analysis

Approaches to model validation have been described in the corresponding section related to the infantile onset model.

4.11 Interpretation and conclusions of economic evidence

The analysis of nusinersen in the subset of SMA patients with the later onset (types II and III) form of the condition shares a number of characteristics with the analysis of infantile onset patients, being based on pivotal clinical trial data on motor function and motor milestones and a number of the same data sources for health state utilities, costs and survival extrapolation. It therefore shares its strengths, in terms of being based on robust data (if of short duration) from a phase III comparison of nusinersen with RWC, as well as weaknesses in terms of the uncertainties around long term benefits and the assessment of health state utilities and carer impacts. Given the problematic nature of utility assessments and other impacts on patients and carers, similar arguments apply concerning the need to take a more rounded perspective of nusinersen's value in addition to the cost per QALY ratio. As the benefit is reduced in later onset SMA, which has a less marked adverse effect on the patient's life compared with infantile onset SMA, and the lifetime costs are increased, the cost per QALY is correspondingly higher than in infantile onset patients. Notwithstanding the divergent ICER estimates, there

remains an unmet need which nusinersen has the potential to meet in both later and infantile onset SMA.

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Single technology appraisal

Nusinersen for treating spinal muscular atrophy [ID1069]

Dear Michael,

The Evidence Review Group, ScHARR, and the technical team at NICE have looked at the submission received on 20th March 2018 from Biogen. In general they felt that it is well presented and clear. However, the ERG and the NICE technical team would like further clarification on the clinical and cost effectiveness data (see questions listed at end of letter).

The ERG and the technical team at NICE will be addressing these issues in their reports.

Please provide your written response to the clarification questions by **5pm** on **26th April 2018**. Your response and any supporting documents should be uploaded to NICE Docs/Appraisals via the same link that you have received this letter.

Two versions of your written response should be submitted; one with academic/commercial-in-confidence information clearly marked and one with this information removed.

Please underline all confidential information, and separately highlight information that is submitted as commercial in confidence in turquoise, and all information submitted as academic in confidence in yellow.

If you present data that are not already referenced in the main body of your submission and that are academic/commercial in confidence, please complete the attached checklist for confidential information.

Please do not embed documents (PDFs or spreadsheets) in your response because this may result in them being lost or unreadable.

If you have any queries on the technical issues raised in this letter, please contact Lulieth Torres, Technical Lead (lulieth.torres@nice.org.uk). Any procedural questions should be addressed to Joanne Ekeledo, Project Manager (joanne.ekeledo@nice.org.uk).

Yours sincerely

Sheela Upadhyaya
Associate Director
Centre for Health Technology Evaluation

Encl. checklist for confidential information

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Section A: Clarification on effectiveness data

A1. **PRIORITY QUESTION.** Company submission (CS), Section 2.1, page 25. The CS states that a systematic review of the clinical efficacy and safety of nusinersen was not undertaken because *"no relevant studies have been conducted outside of Biogen's clinical development programme."* Please clarify what steps were undertaken to ensure that no studies of nusinersen were missed.

A2. **PRIORITY QUESTION.** CS, Section 2.2, page 25. Please clarify why no searches or systematic review were undertaken to identify the comparator in the NICE scope, best supportive care.

A3. CS, Section 2.3.1, page 31. Both the ENDEAR and NURTURE studies include UK patients, however the CHERISH study does not. Please clarify the reasons for this.

A4. CS, Section 2.3.6, page 48. Please clarify how the 20 patients included the NURTURE study were identified and recruited?

A5. **PRIORITY QUESTION.** CS, Section 2.3.2, page 37 and Section 2.3.4. Please clarify why the maintenance dosing was every 4 months in ENDEAR and every 6 months in CHERISH?

A6. **PRIORITY QUESTION.** CS, Section 2.3.2, page 37 and Section 2.3.4. Please clarify whether or not sedation was used for both the administration of nusinersen and the sham procedure in ENDEAR and CHERISH?

A7. CS, Section 2.3.5.4, page 48. In the CHERISH study, please clarify what the CGI scale measured.

A8. CS, Section 2.3.1, page 36. Please clarify what is meant by "pre-symptomatic". Is this referring to specific symptoms e.g. respiratory, sleep disturbance or feeding symptoms?

A9. CS, Section 2.3.6, page 49. Have the results of the interim analysis (31 Oct 2016) of the NURTURE study been published?

A10. CS, Section 2.10.5, page 94. Are any adverse event data from the post-marketing studies available?

A11. CS, Appendix D, Section 2.3. Please clarify which quality assessment checklists were used.

A12. CS, Appendix D, Section 2.2, Figure 2 and Figure 3. In the ENDEAR study, 2 patients withdrew from treatment. In the CHERISH study, 1 patient withdrew from treatment. Please state the reasons for treatment withdrawal.

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A13. CS, Section 2.2, page 26. Are the interim analyses from the SHINE study available?

A14. CS, Section 2.2, page 26. Please provide the Clinical Study Report for the SHINE study if available.

A15. CS, Section 2.2, page 27. Please clarify the inclusion criteria for the EMBRACE study. Why were patients ineligible for the ENDEAR and CHERISH studies?

A16. CS, Section 2.5, page 62, "*ENDEAR and CHERISH were completed to the highest standard with adequate randomisation and blinding procedures (Table 19)*". Please clarify whether this statement relates to Table 18.

A17. Some of the tables in the CS are not fully labelled. The study that the table refers to is not explicitly stated in Table 11 (CS, p.50) and Table 22 (CS, p.82), and the time points of the data in the table are not explicitly stated in Tables 19 (CS, p.65), 20 (CS, p.76), 24 (CS, p.86), 25 (CS, p.88), 27 (CS, p.92) and 28 (CS, p.93). Please clarify.

A18. Please provide the study start dates for ENDEAR and CHERISH.

A19. CS Section 2.6.3, page 70. Please provide separate Kaplan-Meier plots (with number at risk table, and number of events) for subgroups below and above study mean duration, for the outcome of OS for ENDEAR and CHERISH.

Section B: Clarification on cost-effectiveness data

B1. CS, Appendix G. The ERG notes that a combined "economic" search was conducted to identify studies of cost-effectiveness, health-related quality of life (HRQoL) and resource use. Please confirm whether the search terms used to identify studies of each type were sourced from published and validated filters (providing details and citations where appropriate).

B2. CS, Section 3.2.2.1 page 116. The ERG notes that the definition of the health states for the infant model are not exhaustively defined in the footnote to Figure 31. Please clarify:

(a) What health state would a patient be in if they have a HINE-2 score of 1 for walking and a score of 0 for all other HINE-2 items?
(b) With respect to the definition of the health state "Sits without support", why is a score of 4 for sitting not mentioned? Would a patient with a score of 4 for sitting put this patient in a different health state?
(c) Please clarify why the HINE-2 standing item has been included in determining whether a patient is in the "Sits without support" health state?

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B3.**PRIORITY QUESTION.** CS, Section 2.13.5, page 109. Based on the model predictions, mean survival in the modelled RWC group is greater than 2 years in both the infant and later onset cohorts (infant onset = 3.87 undiscounted life years gained [LYGs], later onset = 36.45 undiscounted LYGs). Please provide a rationale for why you consider that nusinersen should be considered as an end-of-life treatment in the infant onset population.

B4. **PRIORITY QUESTION.** CS, Section 1.3.1, page 16. With respect to mortality in Type I SMA, the text states that *"patients rarely survive to their second birthday."* However, the infant onset model predicts that at 18-months following model entry (approximate cohort age = 2 years), around 54% of patients in the RWC group are still alive. The model also predicts that at 114 months following model entry (approximate cohort age = 10 years), around 13% of patients in the RWC group are still alive. Please comment on the validity of these predictions.

B5. CS, Section 3.3.1, page 121. The CS states *"A significantly greater percentage of patients achieving a motor milestone response as measured by HINE-2 (51 vs. 0%; difference of* [redacted] *P <0.0001)."* In contrast, the model suggests that the proportion of surviving patients not in the "no motor milestones" state is 66%. Please comment on this apparent discrepancy.

B6. CS, Section 3.2.1, page 113. The CS states "*the infantile and later onset economic models include subgroups based on disease duration*" (less than or greater than 12 weeks). CS Section 3.9 (Subgroup Analysis, page 159) text states "*As the base case overall survival within the trial period was modelled using the flexible spline-based Weibull function with 1 knot fitted to the ITT Kaplan-Meier curve, the results of the subgroups are presented alongside the results for the ITT population using the Kaplan-Meier curve. However, it is also possible to use the ITT survival with the subgroup data.*" Please clarify how the two subgroups are handled in the model? If this did not involve fitting separate survival models to each subgroup, please comment on how the results would differ, had this approach been taken?

B7. CS, Section 3.3.2, page 122. Please state the method used to fit survival models to the time-to-event data from ENDEAR (e.g. software, method for parameter estimation). The ERG notes that within the model, Sheet "KMT1" refers to "Least Squares".

B8. **PRIORITY QUESTION.** CS, Section 3.3.4.1, page 127. The CS states *"Drawing on clinical expert opinion(122) that infantile onset patients achieving later onset milestones could also experience later onset mortality, the adjustment factor was set to 0.9 in the base case where a factor of 0 applies the mortality of type I patients and a factor of 1 applies the mortality of type II patients."* The reference cited in the CS is an advisory workshop on SMA, the data from which are held as "Data on file." Please explain how this adjustment factor of 0.9 was derived or elicited. Please also explain why this adjustment factor is applied only in the nusinersen group of the model and whether there is any empirical evidence to support this.

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B9. CS, Section 3.3.3, page 123. Please justify why survival modelling has been used to estimate survival probabilities from ENDEAR given that the spline model is not used for extrapolation of outcomes following the trial follow-up period. Why was "clinical plausibility of the extrapolated portion" a criterion for model selection? Why was the Kaplan-Meier estimate of cumulative survival not used?

B10. **PRIORITY QUESTION.** CS, Section 3.3.2, page 122. Type I SMA mortality is modelled using a piecewise approach using three different parametric functions (a spline model fitted to ENDEAR data, an exponential model fitted to adjusted Gregoretti data and a hazard ratio-adjusted Gompertz function fitted to general population mortality).

(a) Why was such a complex approach required and why were simpler standard models not applied for the entire time period?
(b) What is being assumed about the underling hazard of death through the application of the models in a piecewise fashion?

B11. **PRIORITY QUESTION.** CS, Section 3.3.4, page 125, Figure 34. Please provide further details on the use of data from Gregoretti *et al*:

(a) How were the IPD reconstructed?
(b) How were the reconstructed IPD "adjusted for mean age"?
(c) How were the 95% confidence intervals constructed and do these incorporate uncertainty in the adjustment procedure?

B12. CS Section 3.3.4.1 page 126 and CS Appendix P, page 212. Please provide further details on the use of data from Zerres *et al*:

(a) What is meant by "some uncertainty as to the number of risk" (a number of risk table was not provided in the paper)?
(b) How were the IPD reconstructed?
(c) How do the characteristics of this population compare with that of ENDEAR? Was any adjustment to the original KM made (as with the Gregoretti data)?

B13. CS, Section 4.3.1, page 170. The CS states *"The hazard rate predicted from the flexible spline-based Weibull model with 2 knots fitted to the Zerres et al. (1997) data was estimated for the mean age at the end of follow-up of 53 years."* Please explain how this was done, given that covariate information is not available for the reconstructed Zerres data.

B14. CS Appendices 12.1.2.3. Page 186. Results are provided for a "Bayesian simultaneous model" for the combined ENDEAR trial data and external Gregoretti non-invasive respiratory aid (NRA), for event free survival (EFS). Was this conducted for OS as well, given that OS is needed for the model and the method provides a more consistent approach to extrapolation than the multi-stage procedure defined? Please provide the model and relevant OS data.

B15. Model, Worksheet Country Specific Sheet T1 cell I867. The text in the model cell seems to suggest that Scottish annual mortality rates have been used. Please clarify if this is

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the case and if so, please explain why English data have not been used. Please also clarify why mortality rates based on age bands have been used rather than age-specific life tables.

B16. **PRIORITY QUESTION.** CS, Section 3.3.5, page 127. The CS states *"The assumption made in the base case was that, except for those who stop treatment, patients in the nusinersen arm continue to improve, and therefore move to better health states, in line with improvements in CHOP INTEND observed over the period of trial follow-up. As motor function improvements seen in the clinical studies did not exhibit a plateau and, on the grounds of nusinersen's action on the underlying cause of disease, an expectation of continued improvement was supported by a panel of expert UK clinicians.(33)"*

(a) Please provide further detail about how these assumption were arrived at.
(b) Please clarify whether the expert UK clinicians believed that all patients receiving nusinersen would continue to improve, or whether on average, patients would continue to improve. Similarly, please clarify whether the UK clinicians believed that all patients receiving RWC would worsen, or whether on average they would continue to worsen.
(c) Please provide a figure similar to Figure 12 for the outcome of CHOP-INTEND

B17. CS, Section 3.3.5 page 128. The change in CHOP INTEND score observed in ENDEAR was an increase of [redacted] points for nusinersen and a decrease of [redacted] points for sham. CS Figure 13 (page 68, mean change based on HINE-2) suggests that the decrease in score for control is substantially lower in magnitude than the rate of improvement for nusinersen.

(a) Please provide a figure similar to Figure 13 for the outcome of CHOP-INTEND
(b) Please comment on the level of consistency between CHOP-INTEND and HINE-2

B18. CS, Section 3.3.5, page 127. Table 35 uses mean CHOP INTEND score for each health state, for each arm individually, and a scenario analysis for both arms combined. What is the logic behind using the mean for each arm separately? Is it expected that the mapping from CHOP INTEND to HINE-2 is dependent on treatment arm?

B19. CS, Section 3.3.5, page 129. The CS states that the model assumes that *"the probability of transitioning from the Walks with Assistance health state to the Stands/Walks Unaided health state is the same as the transition probability from the Stands with Assistance health state to the Walks with Assistance health state."* Why was this assumption made?

B20. **PRIORITY QUESTION.** Model, sheets "Markov Nusinersen T1" and "Markov Nusinersen T2". The ERG notes that the model appears to apply a relatively simple Markov approach, yet the formulae applied in the Markov trace are extremely complicated. Please explain:

(a) Why it was necessary to apply such complex formulae in the model

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(b) Why a conventional matrix-based implementation of the Markov model was not implemented
(c) Why the model does not separate out different health states for patients who are still on nusinersen and for those who have discontinued due to lack of efficacy or inability to receive the drug due to scoliosis surgery.
(d) Are tunnel states used to model outcomes for patients who discontinue nusinersen following scoliosis surgery?

B21. CS, Section 3.6.2, page 148. Please clarify the basis for the assumption that 20% patients will discontinue nusinersen following scoliosis surgery.

B22. Model, worksheets "Markov Nusinersen T1" and "Markov RWC T1", cells F20:N20, and "Markov Nusinersen T2" and and "Markov RWC T2", cells F20:N20. Please clarify why the initial distribution of patients is different between the intervention and comparator groups.

B23. CS, Section 3.4.2.2, page 131. The ERG notes that the caregiver utility for the "no milestones" health state is derived from utilities for the "Sits and rolls independently" and "Sits without support" health states. A similar approach is used for the "Sits without support", "Stands with assistance", "Walks with assistance" and "Stands/walks unaided" health states. Please explain the rationale for using patient utilities for other health states to determine the caregiver utility for the state under consideration.

B24. **PRIORITY QUESTION.** CS, Section 3.4.2.1, page 131. Please comment on the face validity of the patient utility scores applied in the model. In particular, please comment on the validity of assuming a utility score of [redacted] for patients who achieve no milestones and the relatively small difference between the best and worst health states (no milestones utility = [redacted], stands/walks unaided utility = [redacted]).

B25. CS, Section 3.4.2.1, page 131. Please comment on the appropriateness of using a mapping algorithm derived from a healthy cohort of schoolchildren aged 11-15 (Khan *et al*, *Pharmacoeconomics*, 2014) to determine EQ-5D scores for infant patients with SMA.

B26. CS, Section 3.4.2.2, page 133. Please comment on the validity of the assumption that caregivers' baseline utility (value=0.915) is assumed to remain constant over the entire time horizon.

B27. CS, Section 3.2.3, page 120. Please provide further details on the derivation of the discontinuation rule for nusinersen from the UK expert panel.

B28. CS, Section 3.5, page 137. Please explain why the costs of scoliosis surgery have not been included in the model.

B29. CS, Section 3.5.1, page 137. The text states *"The cost of nusinersen in the first year of treatment (6 doses consisting of 4 loading doses and 2 maintenance doses) is £450,000 for a full year. Annual costs thereafter for 4 maintenance doses are £300,000."* This wording

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suggests that maintenance doses of nusinersen would be given at 3-monthly intervals. Elsewhere (for example, pages 31, 37, 117 and 167), the CS indicates that maintenance doses would be given at 4-monthly intervals. Please clarify.

B30. CS, Section 3.5.1, page 140. The appendices of Bastida *et al* report the total annual costs presented in Table 46 (in Euros rather than pounds) for subgroups of patients with Type I, II and III SMA. Please clarify how the assumptions presented in Table 42 are used in the model.

B31. Model, Sheets “Markov Nusinersen T2” column IU and “Markov RWC T2” column GP. Why are end-of-life costs not included in the later onset SMA model?

B32. Model, sheet “Model selection”. The model received by the ERG is set to have a 60-year time horizon for the infant population, yet the CS states that the horizon is intended to be 40 years. The deterministic ICER presented in Table 50 reflects a 60-year time horizon. Please clarify the intended time horizon, and what time horizon has been used; please confirm the time horizon used for each of the results for the infant onset model presented in the CS and, if applicable, please provide corrected results.

Nusinersen for treating spinal muscular atrophy [ID1069]

Response to clarification questions

Submitted by Biogen Idec Ltd.

Single technology appraisal (STA)

National Institute of Health and Care Excellence

Submitted 27th April 2018

Table of Contents

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Table of Abbreviations

Abbreviation	Definition
AE	Adverse event
ALS	Amyotrophic lateral sclerosis
ASO	Antisense oligonucleotide
BiPAP	Bi-level airway positive pressure
BSC	Best supportive care
CGI	Clinical Global Impression
CHOP INTEND	Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders
CI	Confidence interval
CMAP	Compound muscle action potential
CSF	Cerebrospinal fluid
CSR	Clinical study report
CTA	Clinical Trial Authorisation
DMD	Duchenne muscular dystrophy
EC	Ethics Committee
EMA	European Medicines Agency
EQ-5D	European Quality of Life-5 Dimensions
ERG	Evidence Review Group
EFS	Event free survival
GT	Gastrostomy tube
HFMSE	Hammersmith Functional Motor Scale-Expanded
HINE-2	Module 2 of the Hammersmith Infant Neurological Examination
HRQoL	Health-related quality of life
HST3	Highly specialised technologies guidance
HTA	Health technology assessment
ICER	Incremental cost-effectiveness ratio
Inc.	Incremental
IPD	Individual patient data
ISSG	InterTASC Information Specialists' Sub-Group
ITT	Intention to treat
IQR	Interquartile range
K-M	Kaplan-Meier
LSM	Least squares mean
LYG	Life years gained
MI-E	Mechanical insufflation/exsufflation
MHRA	Medicines and Healthcare products Regulatory Agency
N/A	Not available
NG	Nasogastric
NICE	National Institute for Health and Care Excellence
NIV	Non-invasive ventilation
NRA	Non-invasive respiratory aid
OS	Overall survival
PedsQL	Paediatric Quality of Life Inventory
QALY	Quality-adjusted life year
RULM	Revised Upper Limb Module
RWC	Real world care
SAEs	Serious adverse events
SCC	International Standard of Care Committee

ScHARR	School of Health and Related Research
SD	Standard deviation
SE	Standard error
SLR	Systematic literature review
SMA	Spinal muscular atrophy
SMN	Survival of motor neuron
STA	Single technology appraisal
TV	Tracheostomy with ventilator
WHO	World Health Organization

1. Overview

This document contains Biogen's response to clarification questions from the Evidence Review Group (ERG), the School of Health and Related Research (ScHARR), and the technical team at the National Institute of Health and Care Excellence (NICE) that consulted with Biogen on 12th April 2018.

2. Response to clarification questions

Please find below responses by Biogen to each of the questions raised by the ERG, ScHARR, and the technical team at NICE.

Section A: Clarification on effectiveness data

A1. PRIORITY QUESTION. Company submission (CS), Section 2.1, page 25. The CS states that a systematic review of the clinical efficacy and safety of nusinersen was not undertaken because *"no relevant studies have been conducted outside of Biogen's clinical development programme."* Please clarify what steps were undertaken to ensure that no studies of nusinersen were missed.

A quarterly spinal muscular atrophy (SMA) bibliography is compiled by an external consultancy (Envision Pharma Group) on behalf of Biogen. PubMed and Web of Science are searched using the following search string: ((Spinal muscular atrophy) OR SMA) AND ((isis smn rx) OR Nusinersen OR (isis 396443) OR SMN1 OR SMN2 OR antisense OR (spinal injection) OR (intrathecal injection) OR (isis smn rx) OR Nusinersen OR (isis 396443) OR SMN1 OR SMN2 OR TC007 OR AAV9 OR RG3039 OR D156844 OR quinazoline OR IGHMBP2 OR Olesoxime OR ASO OR TRO19622 OR LMI070 OR RO6885247 OR Salbutamol OR albuterol OR Levetiracetam OR riluzole OR (Morpholin* oligomer*) OR (respiratory distress) OR SMARD1 OR (Werdnig-Hoffmann) OR (Kugelberg-Welander) or (Dubowitz disease) OR (*HFMS*) OR (Hammersmith Functional Motor Scale) OR (Hammersmith infant neurological exam)).

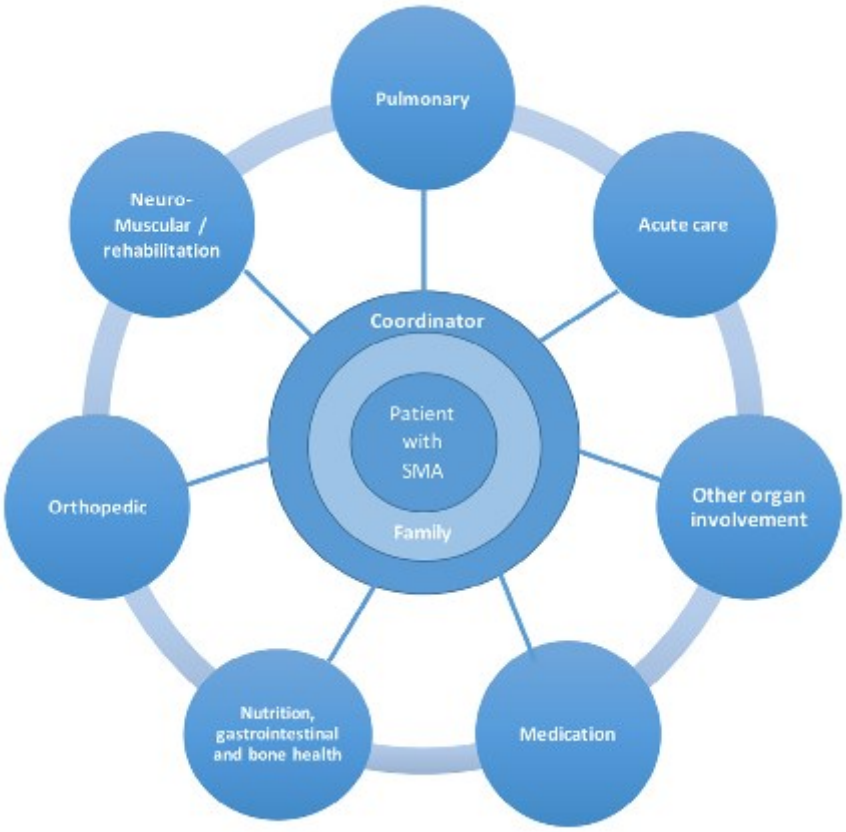
The Web of Science platform has a congress database and relevant published abstracts are included if they are identified by the search criteria. All Biogen and IONIS-sponsored abstracts that are listed in the companies' Datavision database as published in a particular quarter are also included. Using this strategy, no relevant studies have been identified that have been conducted outside of Biogen's clinical development programme for nusinersen.

A2. PRIORITY QUESTION. CS, Section 2.2, page 25. Please clarify why no searches or systematic review were undertaken to identify the comparator in the NICE scope, best supportive care.

CHERISH and ENDEAR were head-to-head trials versus sham in addition to best supportive care (BSC). The economic model therefore used clinical data versus the relevant as defined in the scope. In the economic model nusinersen was modelled as a first-line therapy, with symptomatic care applied according to patient health state (representing need) and compared to real world care (RWC) as is described in the ENDEAR and trials and according to the marketing authorisation. BSC or RWC, the term used in the economic model, was used as a comparator including respiratory, nutritional, gastrointestinal and orthopaedic interventions. This is consistent with the decision problem set out in the scope. Due to the availability of head-to-head data, it was considered unnecessary to a systematic literature review (SLR) to identify further comparator studies for an indirect comparison analysis. Furthermore, because supportive care may vary across regions, is multifactorial (

Figure 1) and must be tailored to meet the patients' physical status, any such indirect or mixed treatment comparison would not have been informative, and data from the head-to-head studies was considered preferable.

Figure 1. The multidisciplinary approach to SMA treatment



Source: Mercuri 2018(1)

[redacted]

The Consensus Statement was also used to define best supportive care in the nusinersen clinical trials. In December 2017, a two-part update to the Consensus Statement was published by the International Standard of Care Committee (SCC)(1,5). A thorough literature review was conducted to guide the discussions, during which all publications relevant to supportive care for SMA were identified. However, as changes in treatment patterns were guided by the published literature, they may not capture changing societal attitudes towards treatments such as the use of long-term ventilation. [redacted] Therefore, it is not clear how closely clinicians adhere to the Consensus Statement, making it difficult to define best supportive care in the UK.

A3. CS, Section 2.3.1, page 31. Both the ENDEAR and NURTURE studies include UK patients, however the CHERISH study does not. Please clarify the reasons for this.

[redacted]

[redacted]

A4. CS, Section 2.3.6, page 48. Please clarify how the 20 patients included the NURTURE study were identified and recruited?

Patients were enrolled in NURTURE if they were 6 weeks old or younger and pre-symptomatic at administration of the first dose, were genetically diagnosed with 5q SMA (homozygous gene deletion or mutation or compound heterozygous mutation), had 2 or 3 *SMN2* copies and an ulnar compound muscle action potential (CMAP) amplitude of ≥1 mV at baseline.(7) Please see Table 1 for the full eligibility criteria.

Table 1. NURTURE: Eligibility criteria

Inclusion criteria	Exclusion criteria
• Age ≤ 6 weeks at first dose • Genetic documentation of 5q SMA homozygous gene deletion or mutation or compound heterozygous mutation • Genetic documentation of 2 or 3 copies of *SMN2* • CMAP ≥1 mV at baseline • Gestational age of 37–42 weeks for singleton births; gestational age of 34–42 weeks for twins • Able to complete all study procedures, measurements and visits, and parent(s) or guardian(s)/subject has adequately supportive psychosocial circumstances in the opinion of the investigator	• Hypoxaemia (oxygen saturation <96% awake or asleep without any supplemental oxygen or respiratory support) • Any clinical signs or symptoms at screening or immediately prior to the first dosing (day 1) that are, in the opinion of the Investigator, strongly suggestive of SMA • Clinically significant abnormalities in haematology or clinical chemistry parameters • Treatment with an investigational drug given for the treatment of SMA biological agent, or device. Any history of gene therapy, prior ASO treatment, or cell transplantation • Presence of an untreated or inadequately treated active infection requiring systemic antiviral or antimicrobial therapy at any times during the screening period • History of brain or spinal cord disease that would have interfered with the lumbar puncture procedures, CSF circulation or safety assessments • Presence of an implanted shunt for the drainage of CSF or an implanted central nervous system catheter • History of bacterial meningitis or viral encephalitis • Diagnosis of neonatal respiratory distress syndrome requiring surfactant replacement therapy or invasive ventilator support • The subject's parent(s) or legal guardian(s) was unable to understand the nature, scope and possible consequences of the study or was unable to or did not agree to comply with the study requirements

Inclusion criteria	Exclusion criteria
	• Ongoing medical condition that, according to the investigator, would have interfered with the conduct and assessments of the study; an example is a medical disability that would have interfered with the assessment of safety or would have compromised the ability of the subject to undergo study procedures.

Abbreviations: ASO, antisense oligonucleotide; CSF, cerebrospinal fluid; CMAP, compound muscle action potential SMA, spinal muscular atrophy; SMN, survival of motor neuron
Source: NURTURE: Clinicaltrials.gov NCT02386553(8); NURTURE CSR(9)

As of 31 October 2016, 20 out of 25 screened infants had been enrolled. The 20 enrolled infants were identified through diagnosis of an affected sibling (n=15), a newborn screening program (n=3), prenatal testing (n=1) and known carrier status (n=1).(10)

Please note that Biogen now have data from an interim analysis with a data cut-off of 5th July 2017.(11,12) At this date, 25 out of 30 screened infants had been enrolled. The 25 enrolled infants were identified through diagnosis of an affected sibling (n=18), a new born screening program (n=3), prenatal testing (n=3) and known carrier status (n=1).(12) Please see Question A9 for further details of this interim analysis for NURTURE.

A5. PRIORITY QUESTION. CS, Section 2.3.2, page 37 and Section 2.3.4. Please clarify why the maintenance dosing was every 4 months in ENDEAR and every 6 months in CHERISH?

The clinical development plan evaluated a range of single and multiple doses of 1 mg to 12 mg of nusinersen. Several different loading dose regimens and two different maintenance dose regimens have also been evaluated across the clinical trials. Hence, ENDEAR evaluated a maintenance dosing of every 4 months, while CHERISH evaluated it every 6 months. This allowed the dosing regimen to be refined over time based upon emerging results from the clinical trials.

The licensed dosing is 4 loading doses on days 0, 14, 28 and 63, with a maintenance dose administered once every 4 months thereafter. In CHERISH, nusinersen was administered using 3 loading doses (on study days 1, 29 and 85), followed by maintenance dosing once every 6 months thereafter (on day 274). The recommended licensed dose of 12 mg was used in CHERISH. It is anticipated that the more intensive loading dose interval used in the licensed dosing vs CHERISH (i.e. 4 vs 3 loading doses and maintenance dose at every 4 months vs 6 months thereafter) would not lessen the efficacy of nusinersen in later onset SMA patients (if anything, it may increase the efficacy).(13)

The rationale for the licensed dosing came from results of ENDEAR, which validated the results of CS3A and demonstrated significant efficacy compared to control along with a favourable safety profile in subjects with infantile-onset SMA who received the proposed dosing regimen. Among the nusinersen-treated subjects in ENDEAR, response was observed as early as 2 months after the initiation of treatment, which lends support for the more intensive loading dose interval. Further support for the proposed dosing regimen derives from NURTURE, which demonstrated robust efficacy and a favourable safety profile in subjects with pre-symptomatic SMA.

In addition, an exposure-response analysis based on data from phase II study CS3A in infantile onset SMA patients demonstrated a clear relationship between increasing nusinersen exposure in the cerebrospinal fluid (CSF) and improvements in functional clinical outcomes, presumably resulting from increased SMN protein in the spinal cord and brain. Increased partial CSF area under the curve (AUC) values (0–3, 0–6, and 0–12 months) of nusinersen resulted in an increased probability of being a motor milestone responder at 6 and 12 months. In addition, higher partial CSF AUC values resulted in greater changes in Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders (CHOP INTEND) scores and CMAP amplitude at 6 or 12 months. Because SMN protein deficiency is apparent in all patients with 5q SMA and the mechanism of action of nusinersen is to increase SMN protein production, the results from the pharmacokinetic-pharmacodynamic (PK-PD) analysis apply to all patients with SMA.

Overall, in discussions with the European Medicines Agency (EMA), it was concluded that the more intensive loading dose interval (i.e. 4 loading doses on days 0, 14, 28 and 63 followed by 4 monthly maintenance dosing) is associated with increased efficacy with no additional safety signals, and therefore it was agreed that it should be the licensed dose.

A6. PRIORITY QUESTION. CS, Section 2.3.2, page 37 and Section 2.3.4. Please clarify whether or not sedation was used for both the administration of nusinersen and the sham procedure in ENDEAR and CHERISH?

Depending on institutional guidelines, anaesthesia or sedation could be used for the lumbar puncture procedure or the sham procedure in both ENDEAR and CHERISH.(14,15) In CHERISH, 43 (51%) of nusinersen treated patients and 24 (57%) of sham-control patients received inhalational anaesthesia and 72 (86%) and 34 (81%), respectively, received intravenous sedation. In ENDEAR, 6 (8%) of nusinersen treated patients and 2 (5%) of sham-control patients received inhalational anaesthesia and 2 (3%) and 0, respectively, received intravenous sedation.(16)

A7. CS, Section 2.3.5.4, page 48. In the CHERISH study, please clarify what the CGI scale measured.

The Clinical Global Impression (CGI) of change is a clinician reported outcome measuring patient's global functioning after initiating treatment.(17) It was applied to identify whether the patient's symptoms had improved based on the opinion of the clinician after initiating treatment (nusinersen or sham). The subject's caregiver also completed the assessment.

CGI of change was to be assessed at five visits post first dose on days 92, 169, 274, 365 and 456.(15) At each visit the investigator and the subject's caregiver each scored how the subject had changed compared to 'admission to the project'. The assessment is scored on a 7- point ordinal scale (1= "very much improved", 2 = "much improved", 3 = "minimally improved", 4= "no change", 5= "minimally worse", 6= "much worse", 7 = "very much worse").(18)

The CGI scale provides an overall clinician-determined summary measure that takes into account all available information, including knowledge of the patient's history, psychosocial circumstances, symptoms, behaviour, and the impact of the symptoms on the patient's ability to function.(17)

CGI is administered by an experienced clinician who is familiar with the disease under study and the likely progression of treatment.(17) The clinician makes a judgment about the total picture of the patient at each visit: the severity of illness, the patient's level of distress and other aspects of impairment, and the impact of the illness on functioning. The CGI is rated without regard to the clinician's belief that any clinical changes are or are not due to medication and without consideration of the aetiology of the symptoms.

A8. CS, Section 2.3.1, page 36. Please clarify what is meant by "pre-symptomatic". Is this referring to specific symptoms e.g. respiratory, sleep disturbance or feeding symptoms?

Please see Table 1 in Question A4 for the full eligibility criteria used in NURTURE. Patients with any clinical signs or symptoms at screening or immediately prior to the first dosing (day 1) that were, in the opinion of the investigator, strongly suggestive of SMA, were excluded; this was the main criteria to establish that the patient population was pre-symptomatic. In addition, they were 6 weeks of age or younger with a genetic documentation of 5q SMA homozygous gene deletion or mutation or compound heterozygous mutation. Additionally, these subjects were required to have a genetic documentation of 2 or 3 copies of the *SMN2* gene. The manifestation of SMA is nearly 100% in patients with this genetic background, which ensures that only pre-symptomatic infants with the greatest likelihood of developing type I or type II SMA, the most severe forms of the disease, both of which include a pre-symptomatic period, were included in the study. Of note, genetic diagnosis of SMA is straightforward and extremely accurate using blood or dried blood spots from a heel stick, and the test can be completed in 3–7 days. The majority of patients were identified due to having an affected sibling (please see the answer the Question A4 above).

A9. CS, Section 2.3.6, page 49. Have the results of the interim analysis (31 Oct 2016) of the NURTURE study been published?

The results of the interim analysis of the NURTURE study have not been published in a peer-reviewed journal. However, they have been presented at several conferences, most recently at the Muscular Dystrophy Association Clinical Conference 2018, which presented data from the most recent interim results from the July 5, 2017 data cut-off.(11,12)

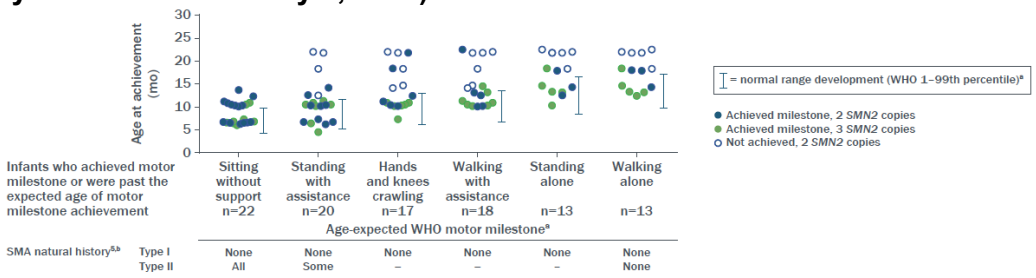
As of July 5, 2017, 25 infants (2 *SMN2* copies, n=15; 3 *SMN2* copies, n=10) were enrolled and received ≥1 dose of nusinersen (age at first dose: ≤14 days, n=9; >14 to ≤28 days, n=12; >28 days, n=4). The median (range) age at last visit was 14.7 (2.8–23.3) months and median (range) time on study was 16.1 (5.1–25.6) months.

As of July 5, 2017, all infants were alive and no infants required tracheostomy or permanent ventilation, which is inconsistent with the expected natural history of SMA type I.(19) Two of 15 (13%) infants with 2 *SMN2* copies required respiratory intervention for ≥6 hours/day continuously for ≥7 days during an acute, reversible viral infection, and thus met the primary endpoint. One additional infant with 2 *SMN2* copies (3/15; 20%) required respiratory support for ≥6 hours/day continuously for ≥1 day but less than 7 days.

The data as of July 5, 2017 continues to confirm that infants treated with nusinersen are achieving motor milestones (e.g., sitting, walking independently) beyond the natural history of SMA type I or II, as well as what was observed in their untreated siblings. Twenty-two of 22

(100%) infants achieved the World Health Organization (WHO) motor milestone sitting without support, and 8/13 (62%; 2 *SMN2* copies, n=3/8; 3 *SMN2* copies, n=5/5) achieved walking alone, among infants with enough observation time (Figure 2).

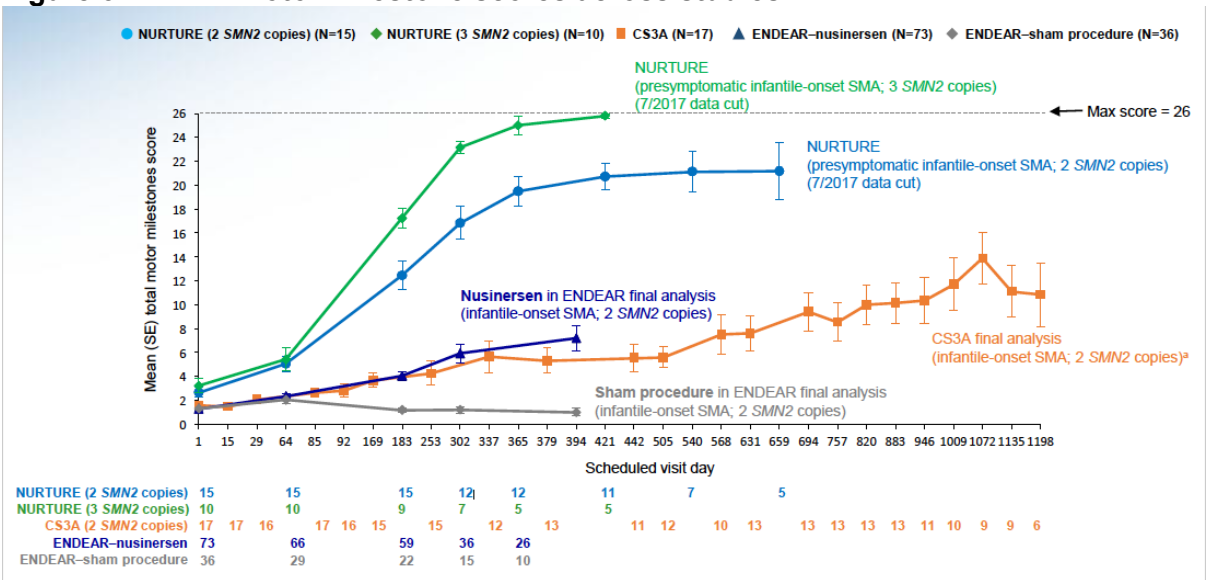
Figure 2. NURTURE: Achievement of age-expected WHO motor milestones[a] (interim analysis: data cutoff: July 5, 2017)



Abbreviations: SMA, spinal muscular atrophy; SMN, survival motor neuron; WHO, World Health Organization
NURTURE study interim analysis data cutoff date: July 5, 2017; – = natural history data not available
[a]Age-expected WHO motor milestones were determined based on the WHO Multicenter Growth Reference Study windows of achievement in healthy children;(20) for each motor milestone, infants who had not achieved the motor milestone but had not reached the age for the upper limit of achievement (i.e., WHO motor milestone 99th percentile) for the given motor milestone are not graphed
[b]Maximal motor function achieved based on classification of SMA phenotypeI(21)
Source: DeVivo 2018(11)

The data also continue to show that the greatest improvements in total Module 2 of the Hammersmith Infant Neurological Examination (HINE-2) motor milestones were observed in infants treated with nusinersen in the pre-symptomatic stage of SMA in NURTURE (Figure 3).

Figure 3. HINE-2 motor milestone scores across studies



Abbreviations: HINE-2, Module 2 of the Hammersmith Infant Neurological Examination; SE, standard error, SMA, spinal muscular atrophy; SMN, survival motor neuron
NURTURE study interim analysis data cut-off date: July 5, 2017. aCS3a end of study data for the cohort of infants with 2 *SMN2* copies.
Please note all patients in figure 3 have 2 copies of SMN2 except the green nurture line. This is for clarity of comparison
Source: Finkel 2018(12)

In summary, every infant continues to make progress throughout the duration of the study without sustained evidence of regression.(11,12) Infants are achieving motor milestones not ever acquired by infants with SMA type I (i.e., head control, sitting independently(21)) or type II (i.e., walking independently(21)) and are continuing to achieve normal motor milestones for their age. Early treatment of the pre-symptomatic infant prevents the onset of the SMA phenotype and allows for progressive gains in motor function and performance in the developing child. Nusinersen was well tolerated and no specific safety concerns were identified.

A10. CS, Section 2.10.5, page 94. Are any adverse event data from the post-marketing studies available?

[redacted]

A11. CS, Appendix D, Section 2.3. Please clarify which quality assessment checklists were used.

- The quality appraisal checklist for quantitative intervention studies, as specified by NICE (https://www.nice.org.uk/process/pmg4/chapter/appendix-f-quality-appraisal-checklist-quantitative-intervention-studies) was used to evaluate the quality of the ENDEAR and CHERISH clinical trials for nusinersen.

A12. CS, Appendix D, Section 2.2, Figure 2 and Figure 3. In the ENDEAR study, 2 patients withdrew from treatment. In the CHERISH study, 1 patient withdrew from treatment. Please state the reasons for treatment withdrawal.

In ENDEAR, 32 out of 80 subjects (40%) in the nusinersen group and 10 out of 41 subjects (24%) in the sham control group discontinued treatment due to early study closure. Thirteen out of 80 subjects (16%) in the nusinersen group and 16 out of 41 subjects (39%) in the sham control group discontinued due a severe adverse event leading to a fatal outcome. Two additional subjects in the nusinersen group and one additional subject in the sham control group withdrew voluntarily from the study. Reasons for voluntary withdrawal included hospitalisation for dyspnea and withdrawal of consent (n=1) and unknown (n=1) in the nusinersen group and poor health condition (n=1) in the sham control group.

In CHERISH, one subject discontinued study treatment as a result of early study termination. The subject received the day 1, 29, and 85 doses, but the dosing could not be completed on day 274 and the subject did not receive the fourth dose before the decision was made to terminate the study early.

A13. CS, Section 2.2, page 26. Are the interim analyses from the SHINE study available?

Data from an interim analysis (cut-off date June 30, 2017) of SHINE in infantile onset patients (i.e. not including data for later onset patients) has very recently been presented at the American Academy of Neurology (April 21-27, 2018), and as presented below.(22)

Summary of SHINE interim results (data-cut: 30th June 2017)

- Among patients who began nusinersen in ENDEAR and continued in SHINE, additional improvements in total and specific HINE-2 motor milestones, such as head control and sitting, along with general motor function as measured by CHOP INTEND occurred in SHINE. The median time to death or permanent ventilation was 73 weeks.
- Among patients who received sham control in ENDEAR and began nusinersen in SHINE, new improvements in total HINE-2 motor milestones and general motor function as measured by CHOP INTEND occurred in SHINE. Within ENDEAR, the median time to death or permanent ventilation was 22.6 weeks among patients who received sham control. Within SHINE, 58% of patients who were alive without permanent ventilation at baseline and began nusinersen in SHINE remained alive without permanent ventilation at the data cut-off.
- Among those who were protocol-defined responders at the last available assessment for motor milestones and general motor function, some of them were achieved as late as day 578 and 818, respectively. Supporting that some patients may take considerable time to respond to therapy.
- The safety findings were consistent with those previously reported for nusinersen.
- These interim data further support the favourable benefit-risk profile of nusinersen in patients with infantile-onset SMA, and demonstrate that improvements in motor milestones can be achieved regardless of age at treatment initiation, although the benefits are greatest with early treatment.
- Further analysis of SHINE data will provide additional information on the long-term safety/tolerability and efficacy of repeated nusinersen doses across multiple SMA populations.

A total of 89 patients transitioned from ENDEAR, 65/81 previously randomised to nusinersen and 24/41 to sham control. Baseline characteristics are shown in Table 2. Patients who received nusinersen for the first time in SHINE had 2 *SMN2* copies (except 1 patient), a median age of 18 months, and a lower mean CHOP INTEND score at baseline in SHINE compared with those treated with nusinersen in ENDEAR.

Table 2. SHINE: Baseline characteristics

Characteristic	Sham control in ENDEAR n=41	Sham control in ENDEAR and nusinersen treated in SHINE n=24	Nusinersen treated in ENDEAR and SHINE n=81[a]
Female, n (%)	24 (59)	15 (63)	44 (54)
Median (range) age at first dose, mo	6.7 (1-9)	17.8 (10-23)[b]	5.4 (2-15)
Median (range) age at symptom onset, mo	1.8 (0-5)	2.1 (1-5)[c]	1.6 (0-4)
SMN2 gene copies, n (%)			
2	40 (98)	23 (96)	81 (100)
3	1 (2)	1 (4)	0
Mean (SD) total HINE-2 motor milestone score	1.5 (1.29)	1.4 (1.28)	1.3 (1.08)
Mean (SD) CHOP INTEND score	28.4 (7.56)	17.3 (9.71)	26.7 (8.13)

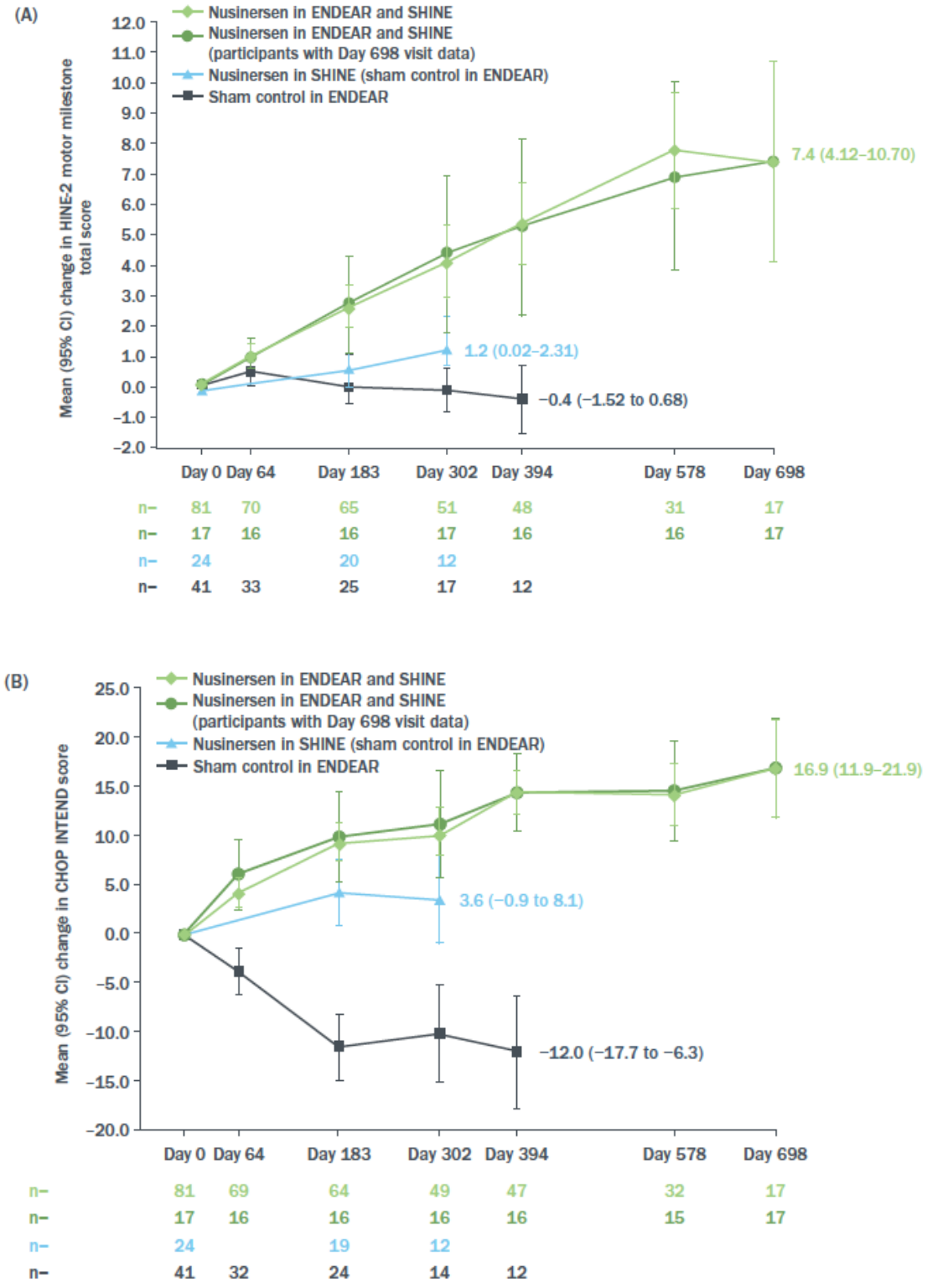
Abbreviations: CHOP INTEND, Children's Hospital of Philadelphia Infant Test for Neuromuscular Disorders; HINE-2, Hammersmith Infant Neurological Examination Section 2; SMN, survival motor neuron; SD, standard deviation;
[a]One infant randomised to receive nusinersen in ENDEAR was not dosed, but was dosed in SHINE
[b]Median in the 12 participants who were alive and without permanent ventilation at baseline in SHINE was 16.8 (range 10–23) months
[c]Median in the 12 participants who were alive and without permanent ventilation at baseline in SHINE was 2.2 (range 1–5) months
Source: Castro 2018(22)

Overall, among patients who began nusinersen in ENDEAR and continued in SHINE, additional improvements in total and specific HINE-2 motor milestones, such as head control and sitting, along with general motor function as measured by CHOP INTEND occurred in SHINE; in those who received sham control in ENDEAR and began nusinersen in SHINE, new improvements in total HINE-2 motor milestones and general motor function as measured by CHOP INTEND occurred in SHINE.

The mean (95% confidence interval [CI]) change from baseline in HINE-2 total score and CHOP INTEND score over time is shown in

Figure 4A and B. The mean (95% CI) change in HINE-2 total score from nusinersen initiation to last observed visit was 1.1 (0.20–1.90) for patients who received sham control in ENDEAR and nusinersen in SHINE (n=20/24) and 5.8 (4.58–7.04) for those who received nusinersen in ENDEAR and SHINE (n=74/81; pooled ENDEAR/SHINE data). NB, these data are based on the last observed visit available for each participant, including those who died or discontinued treatment.

Figure 4. Mean (95% CI) change in (A) HINE-2 total score and (B) CHOP INTEND score over time[a]



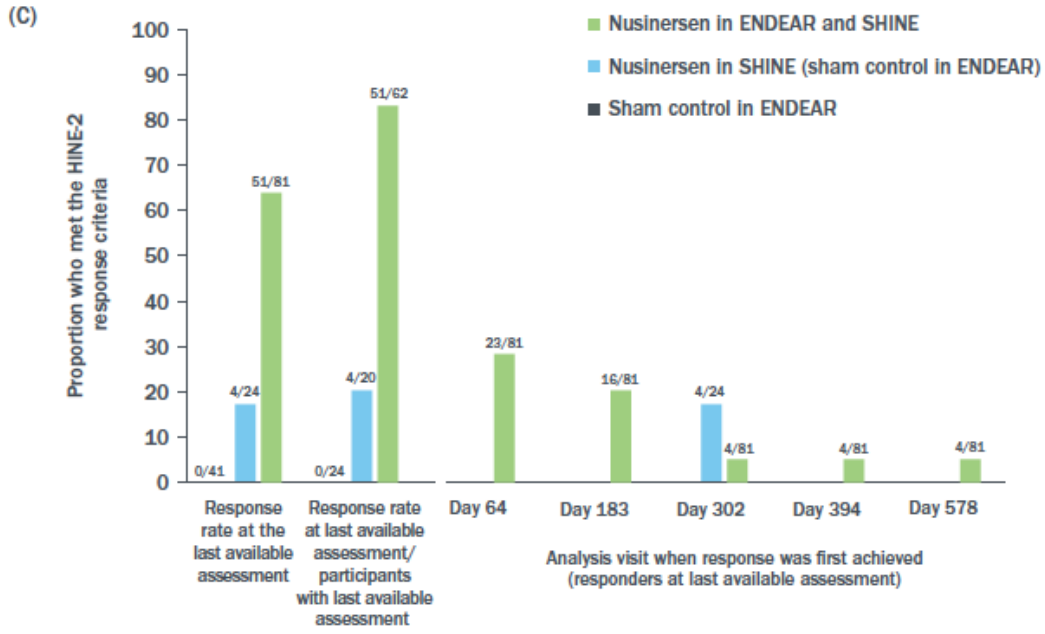
Abbreviations: CHOP INTEND, Children's Hospital of Philadelphia Infant Test for Neuromuscular Disorders; HINE-2, Hammersmith Infant Neurological Examination Section 2

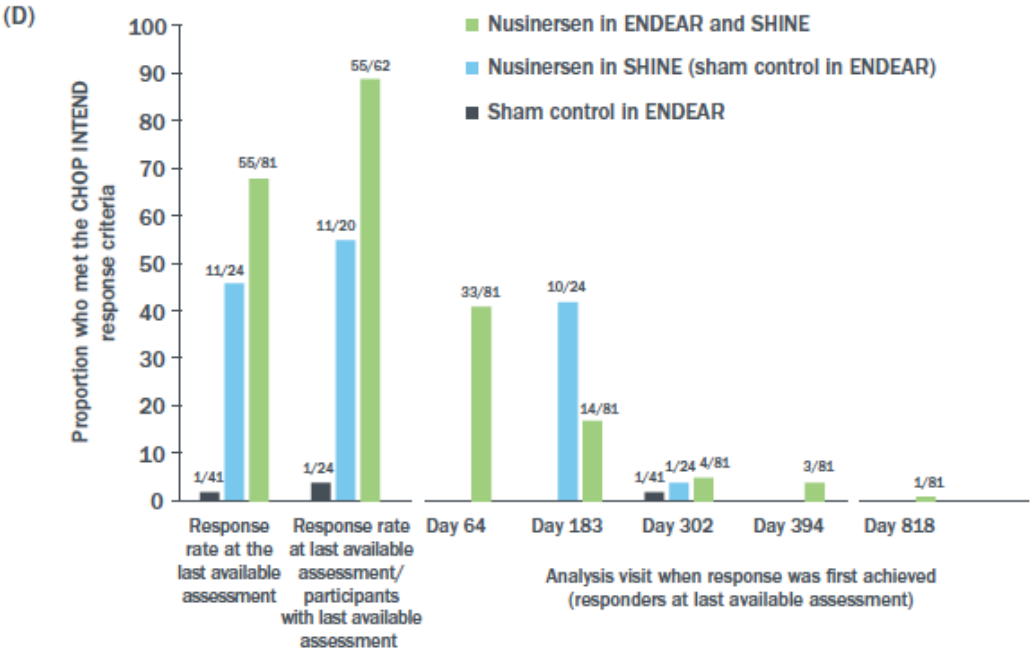
[a]Denominator is the number of participants with a value windowed to the analysis visit. Results displayed where n>10

Source: Castro 2018(22)

The proportions of patients achieving the HINE-2 or CHOP INTEND score (defined as ≥4-point improvement for CHOP-INTEND) response criteria at the last available assessment are shown in Figure 5. Among those who were protocol-defined responders at the last available assessment for motor milestones and general motor function, some of them were achieved as late as day 578 and 818, respectively.

Figure 5. Proportions of participants who met the (C) HINE-2b and (D) CHOP INTENDc score response criteria





Abbreviations: CHOP INTEND, Children's Hospital of Philadelphia Infant Test for Neuromuscular Disorders; HINE-2, Hammersmith Infant Neurological Examination Section 2

HINE-2 response defined as: ≥2-point increase or achievement of touching toes in ability to kick, or ≥1-point increase in other 6 categories excluding voluntary grasp; improvement in more categories than worsening, where worsening was defined as ≥2-point drop or decrease to no kicking in ability to kick, or ≥1-point decrease in the other 6 categories

CHOP INTEND response defined as a ≥4-point improvement; participants who died or who were withdrawn during the study were considered non-responders

Source: Castro 2018(22)

For patients who received nusinersen in ENDEAR and SHINE, 23/81 (28%) had achieved full head control and 12/81 (15%) independent sitting as their highest motor milestone (overall cohort; at the last available assessment); no patients had yet achieved standing unaided or walking independently, although patients were gaining HINE sub-milestones in both categories. The percentages of patients who received nusinersen in ENDEAR and SHINE and achieved full head control and independent sitting at different study visits (based on patients who attended those study visits only) are shown in Table 3.

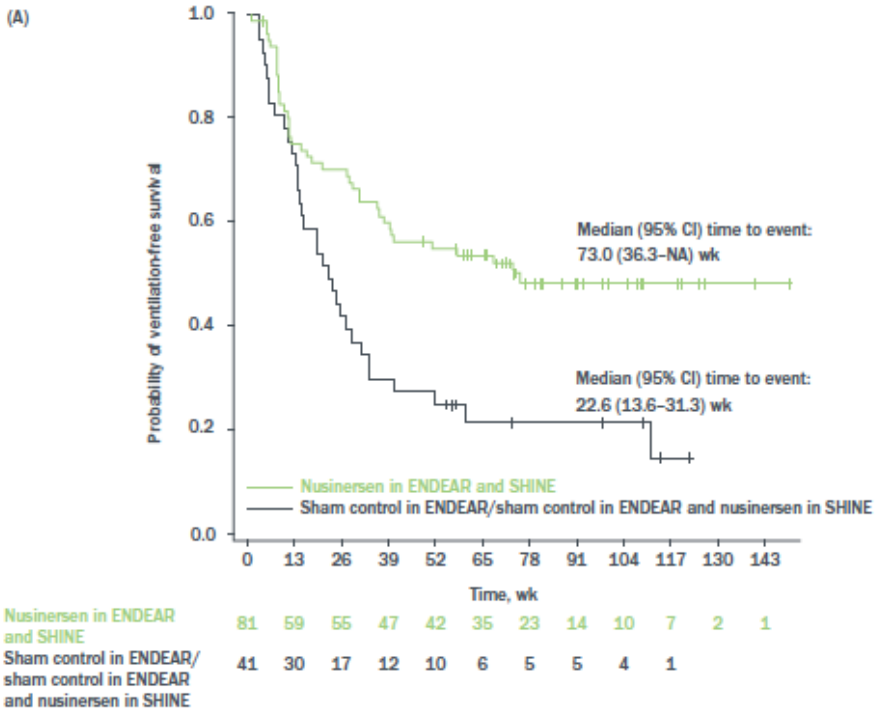
Table 3. Percentage of infants achieving full head control and independent sitting over time

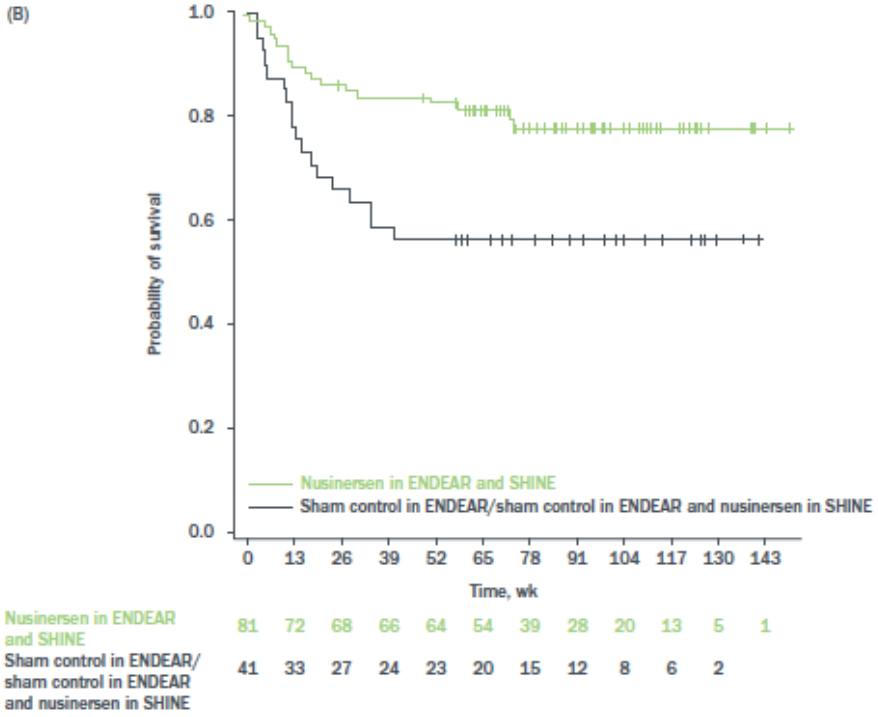
Study day	% achieving full head control[a]	% achieving independent sitting[a]
Baseline n=81	0	0
Day 64 n=70	7	1
Day 183 n=65	17	5
Day 302 n=51	25	10
Day 394 n=48	33	15
Day 578 n=31	45	29
Day 698 n=17	35	24

[a]The percentage is calculated based on the available data within each visit; participants who received nusinersen in ENDEAR and SHINE
Source: Castro 2018(22)

Time to death or permanent ventilation and time to death (starting from ENDEAR) are shown in Figure 6.The median time to death or permanent ventilation in patients treated with nusinersen in SHINE and ENDEAR was 73.0 (95% CI, 36.3–not available) weeks, and 22.6 (95% CI, 13.6–31.3) weeks in those who received either sham control in ENDEAR or sham control in ENDEAR and nusinersen in SHINE. Of the patients who received sham control in ENDEAR and nusinersen in SHINE (n=24), 12 were alive without permanent ventilation at baseline in the SHINE study. Of these 12 patients, 7 (58%) were alive and without permanent ventilation at the time of the data cut-off (median time on study in SHINE: 9.2 months).

Figure 6. SHINE (interim analysis: data-cut: 30th June 2017) (A) Time to death or permanent ventilation and (B) time to death





Abbreviation: N/A, not available

Please note on figure 6 ENDEAR Sham patients on these graphs initially did not have therapy until after 52 weeks of being on trial, at which point they transitioned to nusinersen therapy on SHINE. Data from ENDEAR and SHINE are displayed in figure 6.

Source: Castro 2018(22)

The safety findings were consistent with those previously reported for nusinersen.

In conclusion, these interim data further support the favourable benefit-risk profile of nusinersen in patients with infantile-onset SMA and demonstrate that improvements in motor milestones can be achieved regardless of age at treatment initiation, although the benefits are greatest with early treatment.

A14. CS, Section 2.2, page 26. Please provide the Clinical Study Report for the SHINE study if available.

The clinical study report (CSR) will not be available until late May 2018. Biogen will share this document as soon as it becomes available. Given the complexity of the analyses undertaken, Biogen propose a follow-up teleconference to provide an overview and address any queries when the SHINE CSR is available.

A15. CS, Section 2.2, page 27. Please clarify the inclusion criteria for the EMBRACE study. Why were patients ineligible for the ENDEAR and CHERISH studies?

Patients were included in EMBRACE if they had genetic documentation of 5q SMA (homozygous gene deletion or mutation or compound heterozygote) and:(23)

- Onset of SMA symptoms ≤6 months with 3 *SMN2* copies, or
- Onset of SMA symptoms ≤6 months and aged >7 months at screening with 2 *SMN2* copies, or
- Onset of SMA symptoms >6 months and aged ≤18 months at screening with 2 or 3 *SMN2* copies.

Patients were excluded if they had used a ventilator for 16 hours, or more, per day for more than 21 days at screening, or if they were hospitalised for surgery, a pulmonary event or for nutritional support 2 months before screening.(23)

These patients were ineligible for ENDEAR or CHERISH as they did not meet the inclusion criteria of:(23)

- Symptom onset ≤6 months and aged ≤7 months at screening with 2 *SMN2* copies (ENDEAR), or
- Symptom onset >6 months and aged 2–12 years at screening (CHERISH).

A16. CS, Section 2.5, page 62, "*ENDEAR and CHERISH were completed to the highest standard with adequate randomisation and blinding procedures (Table 19)*". Please clarify whether this statement relates to Table 18.

Yes, this statement applies to Table 18, not Table 19.

A17. Some of the tables in the CS are not fully labelled. The study that the table refers to is not explicitly stated in Table 11 (CS, p.50) and Table 22 (CS, p.82), and the time points of the data in the table are not explicitly stated in Tables 19 (CS, p.65), 20 (CS, p.76), 24 (CS, p.86), 25 (CS, p.88), 27 (CS, p.92) and 28 (CS, p.93). Please clarify.

Please find the additional labels for the above tables (Tables 4-11 in this document), with the changes highlighted in green, for the above tables

Table 4. Table 11 in the submission. ENDEAR: Baseline demographics of the ITT population

Characteristic	Nusinersen (N=80)	Sham control (N=41)
Female, n (%)	43 (54)	24 (59)
[redacted]	[redacted]	[redacted]
Mean (range) age at first dose, day	163 (52, 242)	181 (30, 262)
Mean (range) age at symptom onset, week	7.9 (2, 18)	9.6 (1, 20)
Mean (range) age at SMA diagnosis, week	12.6 (0, 29)	17.5 (2, 30)
Mean (range) disease duration at screening, week	13.2 (0, 25.9)	13.9 (0, 23.1)
[redacted]	[redacted]	[redacted]
SMA symptoms, n (%)		
Hypotonia	80 (100)	41 (100)
Developmental motor delay	71 (89)	39 (95)
Paradoxical breathing	71 (89)	27 (66)
Pneumonia or respiratory symptoms	28 (35)	9 (22)
Limb weakness	79 (99)	41 (100)
Swallowing or feeding difficulties	41 (51)	12 (29)
Other	20 (25)	14 (34)
Use of a ventilation support, n (%)	21 (26)	6 (15)
Use of a gastrointestinal tube, n (%)	7 (9)	5 (12)
Total HINE-2 score, mean (SD)	1.29±1.07	1.54±1.29
CHOP INTEND score at baseline, mean (SD)	26.63 (8.13)	28.43 (7.56)
CMAP amplitude, mV, mean (SD)		
Ulnar nerve	0.226 (0.19)	0.225 (0.12)
Peroneal nerve	0.371 (0.31)	0.317 (0.29)

Abbreviations: CHOP INTEND, Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders; CMAP, compound muscle action potential; ITT, intention to treat; SD, standard deviation; SMA, spinal muscular atrophy
Source: Finkel 2017a(24); *ENDEAR CSR(25)

Table 5. Table 22 in the submission. CHERISH: CGI assessment (investigator and caregiver) at month 15

	Investigator assessment		Caregiver assessment	
CGI assessment N (%)	[redacted]	[redacted]	[redacted]	[redacted]
Very much improved	[redacted]	[redacted]	[redacted]	[redacted]
Much improved	[redacted]	[redacted]	[redacted]	[redacted]
Minimally improved	[redacted]	[redacted]	[redacted]	[redacted]
No change	[redacted]	[redacted]	[redacted]	[redacted]
Minimally worse	[redacted]	[redacted]	[redacted]	[redacted]
Much worse	[redacted]	[redacted]	[redacted]	[redacted]
Very much worse	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: CGI = Clinical Global Impression
Source: CHERISH CSR(15)

Table 6. Table 19 in the submission. Summary of results from the interim (data-cut: 15th June 2016) and final analysis (data-cut: 21st November 2016) of ENDEAR

Efficacy parameter	Results	
	Nusinersen	Sham control
Interim analysis: primary endpoint of motor milestones (data-cut: 15th June 2016)		
Motor milestones [a]		
Proportion responders (HINE-2), n (%)	21 (41%)	0 (0%)
Difference (95% CI)	41.18 (18.16, 61.20)	
P value	P <0.001	
Final analysis (data-cut: 21st November 2016)		
Primary endpoints		
Motor milestones [b]		
Proportion responders (HINE-2), n (%) [c, d]	37 (51%)	0 (0%)
Difference (95% CI)	[redacted]	
P value	P <0.0001	
Proportion with improvement in total score	49 (67%)	49 (67%)
Proportion with worsening in total score	1 (1%)	1 (1%)
Event-free survival [e]		
Patients who died or received permanent ventilation, n (%)	31 (39%)	31 (39%)
Hazard ratio (95% CI)	0.53 (0.32, 0.89)	
P value	P=0.005	
Secondary endpoints		
CHOP INTEND [b]		
Proportion with ≥4-point improvement, n (%)	52 (71%)	52 (71%)
Difference (95% CI) *	[redacted]	
P value	P <0.001	
Proportion with any improvement, n (%)	53 (73%)	1 (3%)
Proportion with any worsening, n (%)	5 (7%)	18 (49%)
Overall survival rate[e]		
Dead, n (%)	13 (16%)	16 (39%)
Alive, n (%)	67 (84%)	25 (61%)
Hazard ratio (95% CI)	0.37 (0.18, 0.77)	
P value	P=0.004	
No use of permanent assisted ventilation [e], n (%)	62 (78%)	28 (68%)
Hazard ratio (95% CI)	0.66 (0.32–1.37)	
P value	P=0.13	
CMAP amplitude [b]		
CMAP responders, n (%)	26 (36%)	2 (5%)
Nominal P value	P=0.001	
Time to death or permanent ventilation in patients below median disease duration		
Hazard ratio (95% CI)	0.24 (0.10, 0.58)	
P value	P<0.001	
Time to death or permanent ventilation in patients above median disease duration		
Hazard ratio (95% CI)	0.84 (0.43, 1.67)	
P value	P=0.4	

Abbreviations: CHOP INTEND, Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders; CI, confidence interval; CMAP, compound muscle action potential; HINE-2, Module 2 of the Hammersmith Infant Neurological Examination

[a] Assessed in the Interim analysis set (nusinersen N=51; Sham control N=27)

[b] At the final analysis, CHOP INTEND, motor milestone and CMAP analyses were conducted using the efficacy set (nusinersen N=73; Sham control N=37)
[c] Assessed at the later of day 183, day 302, and day 394 Study Visit
[d] According to HINE-2: ≥2-point increase [or maximal score] in ability to kick, OR ≥1-point increase in the motor milestones of head control, rolling, sitting, crawling, standing or walking, AND improvement in more categories of motor milestones than worsening, defined as a responder for this primary analysis
[e] At the final analysis, event-free survival, overall survival and permanent ventilation were assessed using the intention to treat population (ITT nusinersen N=80; Sham control N=41)
Source: Finkel 2017(24); EPAR(26); SmPC(13); *ENDEAR CSR(25)

Table 7. Table 20 in the submission. Summary of primary and secondary results from the interim (data cut: 31st August 2016) and final (data cut: 3rd March 2017) analysis of CHERISH

Efficacy parameter	Results	
	Nusinersen (N=84)	Sham control (N=42)
Interim analysis: Primary endpoint (data cut: 31st August 2016)		
HFMSE score		
Change from baseline in HFMSE (95% CI)	4.0 (2.9, 5.1)	-1.9 (-3.8, 0.0)
LSM change difference (95% CI)	5.9 (3.7, 8.1)	
P value	P<0.001	
Final analysis (data cut: 3rd March 2017)		
Primary endpoint		
HFMSE score		
Change from baseline in HFMSE (95% CI)	3.9 (3.0, 4.9)	-1.0 (-2.5, 0.5)
LSM change difference (95% CI)	4.9 (3.1, 6.7)	
Nominal P value[a]	P=0.0000001	
Secondary endpoints		
Change in HFMSE score of ≥3 points		
Proportion of children with change in HFMSE score of ≥3 points, % (95% CI)	57 (46, 68)	26 (12, 40)
Odds ratio (95% CI)	6 (2, 15)	
P value	P=0<0.001	
Motor milestones at 15 months (WHO criteria)		
% who achieved ≥1 new motor milestone (95% CI)	20 (11, 31)	6 (1, 20)
Difference in proportions (95% CI)	14 (-7, 34)	
P value	P=0.08	
LSM number of new motor milestones achieved per child (95% CI)	0.2 (0.1, 0.3)	-0.2 (-0.4, 0.0)
LSM difference (95% CI)	0.4 (0.2, 0.7)	
Nominal P value[b]	P=0.0001	
% who achieved standing alone (95% CI)	2 (0, 8)	3 (0, 15)
Difference in proportions (95% CI)	-1 (-22, 19)	
Nominal P value[b]	P >0.9999	
% who achieved walking with assistance (95% CI)	2 (0., 8)	0 (0, 10.)
Difference in proportions (95% CI)	1.5 (-19.1, 22.0)	
Nominal P value[b]	P >0.9999	
RULM		
Change from baseline at 15 months (95% CI)	4.2 (3.4, 5.0)	0.5 (-0.6, 1.6)

Efficacy parameter	Results	
	Nusinersen (N=84)	Sham control (N=42)
LSM difference (95% CI) Nominal P value	3.7 (2.3, 5.0) P=0.0000001	

Abbreviations: CI, confidence interval; HFMSE, Hammersmith Functional Motor Scale Expanded; LSM, least squares mean; RULM, Revised Upper Limb Module; WHO, World Health Organization

[a]Because the P value for the primary endpoint was significant in the interim analysis, this endpoint was not formally tested for significance in the final analysis. The exploratory P value is not reported in the full publication and is from Mercuri et al. 2018(27)

[b]To control the overall type I error rate at 0.05 across the interim and final analyses for the testing of primary and secondary endpoints, a hierarchical strategy was used, in which significance of the primary endpoint was required before inferential conclusions could be drawn about the secondary endpoints. If an endpoint failed to reach significance, subsequent endpoints were not tested within the hierarchical analysis. Secondary endpoints are listed in hierarchical order. Because the P value for the second secondary endpoint was not significant,
all subsequent endpoints analysed in the hierarchical testing strategy were considered to be exploratory. The exploratory P values are not reported in the full publication and are from Mercuri et al. 2018(27)

Source: Mercuri 2018 (27)

Table 8. Table 24 in the submission. NURTURE: HINE motor milestone achievements (interim analysis: data-cut: 31 October 2016)

Motor function	Full head control	Independent sitting (stable sit, pivot [rotates])	Stands with support/stands unaided	Cruisinga /walking
Total infants achieving, n	15	12	9	6
Expected age of attainment, months	5	7	8	11
Infants achieving at expected age, n/N (%)	15/16 (94%)	10/12 (83%)	7/11 (64%)	5/9 (56%)

Abbreviation: HINE, Hammersmith Infant Neurological Examination

Data-cut: 31 October 2016 interim efficacy set

[a] Cruising = walks while holding on (e.g to furniture/baby walker)

Source: DeVivo 2017(28)

Table 9. Table 25 in the submission. NURTURE: WHO motor milestone achievement (interim analysis: data-cut: 31 October 2016)

WHO motor milestone	2 *SMN2* copies N=12	3 *SMN2* copies N=5	Total N=17
Sitting without support (sits up straight for ≥10 seconds), n (%)	7 (58)	5 (100)	12 (71)
Standing with assistance (stands with assistance for ≥10 seconds), n (%)	5 (42)	5 (100)	10 (59)
Hands and knees crawling (stomach does not touch surface during ≥3 continuous movements), n (%)	2 (17)	4 (80)	6 (35)
Walking with assistance (child takes ≥5 supported steps), n (%)	2 (17)	3 (60)	5 (29)
Standing alone (child stands alone for ≥10 seconds, n (%)	1 (8)	2 (40)	3 (18)
Walking alone	0	2 (40)	2 (12)

WHO motor milestone	2 *SMN2* copies N=12	3 *SMN2* copies N=5	Total N=17
(child takes ≥5 independent steps), n (%)			

Abbreviation: WHO, World Health Organization
Last observed visit: Data-cut: 31 October 2016 (interim efficacy set)
Source: Crawford 2017(10)

Table 10. Table 27 in the submission. Adverse event summary from integrated safety analysis of nusinersen

N (%)	Nusinersen-treated patients				Sham-control-treated patients
	Infantile onset SMA	Later onset SMA	Pre-symptomatic SMA	All nusinersen-treated patients	
	ENDEAR & CS3A (N=100)	CHERISH & CS1, 2, 10 & 12 (N=140)	NURTURE (N=20)	ENDEAR, CHERISH, NURTURE, CS1, 2, 3A, 10 & 12 (N=260)	ENDEAR & CHERISH (N=83)
Summary of AEs					
AEs leading to discontinuation [a]	16 (16)	0 (0)	0 (0)	16 (6)	16 (19)
Treatment-related AEs	0 (0)	1 (<1)	0 (0)	1 (<1)	0 (0)
Common AEs No. of events No. of patients	 1,627 97 (97)	 1,187 134 (96)	 141 16 (80)	 2,955 247 (95)	 909 82 (99)
AEs by preferred term, with an incidence of >10% in nusinersen-treated patients					
Pyrexia	59 (59)	49 (35)	5 (25)	113 (43)	39 (47)
Upper respiratory tract infection	36 (36)	50 (36)	8 (40)	94 (36)	25 (30)
Nasopharyngitis	21 (21)	33 (24)	4 (20)	58 (22)	15 (18)
Vomiting	22 (22)	33 (24)	0 (0)	55 (21)	8 (10)
Headache	0 (0)	51 (36)	0 (0)	52 (20)	0 (0)
Constipation	37 (37)	0 (0)	2 (10)	50 (19)	14 (17)
Back pain	0 (0)	44 (31)	0 (0)	45 (17)	0 (0)
Cough	15 (15)	26 (19)	3 (15)	44 (17)	17 (20)
Pneumonia	30 (30)	0 (0)	2 (10)	41 (16)	14 (17)
Respiratory distress	28 (28)	0 (0)	0 (0)	31 (12)	12 (14)
Scoliosis	11 (11)	18 (13)	0 (0)	29 (11)	0 (0)
Diarrhoea	16 (16)	0 (0)	0 (0)	27 (10)	7 (8)
Respiratory failure	26 (26)	0 (0)	0 (0)	27 (10)	16 (19)
Post-lumbar puncture syndrome	0 (0)	26 (19)	0 (0)	26 (10)	0 (0)

Abbreviations: AE, adverse event; SMA, spinal muscular atrophy
[a] All AEs leading to study discontinuation were events with fatal outcomes
The data are from the following data cuts: ENDEAR: final analysis (16th December 2016); CHERISH: interim analysis (30th April 2016) ; NURTURE: interim analysis (31st October 2016); CS3A: interim analysis (26th January 2016); CS1: final analysis (20th November 2012); CS2: final analysis (12 January 2015); CS10: final analysis (February 2014); CS12: interim analysis (07 April 2016)
Source: Mercuri et al. 2017(29)

Table 11. Table 28 in the submission. Serious adverse event and death summary from integrated safety analysis of nusinersen

N (%)	Nusinersen-treated patients				Sham-control-treated patients
	Infantile onset SMA	Later onset SMA	Pre-symptomatic SMA	All nusinersen-treated patients	
	ENDEAR & CS3A (N=100)	CHERISH & CS1, 2, 10 & 12 (N=140)	NURTURE (N=20)	ENDEAR, CHERISH, NURTURE, CS1, 2, 3A, 10 & 12 (N=260)	ENDEAR & CHERISH (N=83)
Patient death	17 (17)	0 (0)	0 (0)	17 (7)	16 (19)
Incidence of SAEs	77 (77)	19 (14)	6 (30)	102 (39)	50 (60)
SAEs					
Respiratory, thoracic, and mediastinal disorders	63 (63)	4 (3)	2 (10)	69 (27)	33 (40)
Infections and infestations	60 (60)	13 (9)	4 (20)	77 (30)	29 (35)
Cardiac disorders [a]	12 (12)	0 (0)	0 (0)	12 (5)	7 (8)
Metabolism and nutrition disorders [b]	10 (10)	0 (0)	2 (10)	12 (5)	7 (8)
Gastrointestinal disorders	7 (7)	1 (<1)	1 (5)	9 (3)	7 (8)
General disorders and administrative site conditions	7 (7)	1 (<1)	1 (5)	9 (3)	1 (1)
Injury, poisoning, and procedural complications [c]	3 (3)	3 (2)	0 (0)	6 (2)	3 (4)
Investigations [d]	3 (3)	0 (0)	0 (0)	3 (1)	3 (4)
Nervous system disorders	3 (3)	0 (0)	0 (0)	3 (1)	0 (0)
Vascular disorders	2 (2)	0 (0)	0 (0)	2 (<1)	0 (0)
Immune system disorders	0 (0)	1 (<1)	0 (0)	1 (<1)	-
Musculoskeletal and connective tissue disorders	1 (1)	0 (0)	0 (0)	1 (<1)	-
Skin and subcutaneous tissue disorders	1 (1)	0 (0)	0 (0)	1 (<1)	0 (0)

Abbreviations: SAE, serious adverse event; SMA, spinal muscular atrophy

[a] This class is partly based on anatomy (endocardial, myocardial and pericardial disorders, coronary artery disorders, and valve disorders) and partly on pathophysiology (neoplasia, arrhythmia, cardiac failure, congenital cardiac disorders, and cardiac signs and symptoms)

[b] Includes disorders in the handling of specific substances by the body (e.g., purine and pyrimidine metabolism disorders, inborn errors or metabolism, and lipid metabolism disorders), conditions associated with nutritional disorders in general (e.g., appetite and general nutritional disorders, vitamin-related disorders), and medical conditions that may not be associated with a specific metabolic or nutritional pathogenesis (e.g. acid-base disorders, electrolyte and fluid balance conditions)

[c] Covers cases where an injury, poisoning, procedural or device complication factor is significant in the medical event being reported, and includes: post-lumbar puncture syndrome; procedural pain, nausea, complication, headache, or site reaction; post-procedural swelling, complication of discomfort
[d] Includes clinical laboratory tests, radiological tests, physical examination parameters, and physiological tests
The data are from the following data cuts: ENDEAR: final analysis (16th December 2016); CHERISH: interim analysis (30th April 2016) ; NURTURE: interim analysis (31st October 2016); CS3A: interim analysis (26th January 2016); CS1: final analysis (20th November 2012); CS2: final analysis (12 January 2015); CS10: final analysis (February 2014); CS12: interim analysis (07 April 2016)
Source: Mercuri et al. 2017(29)

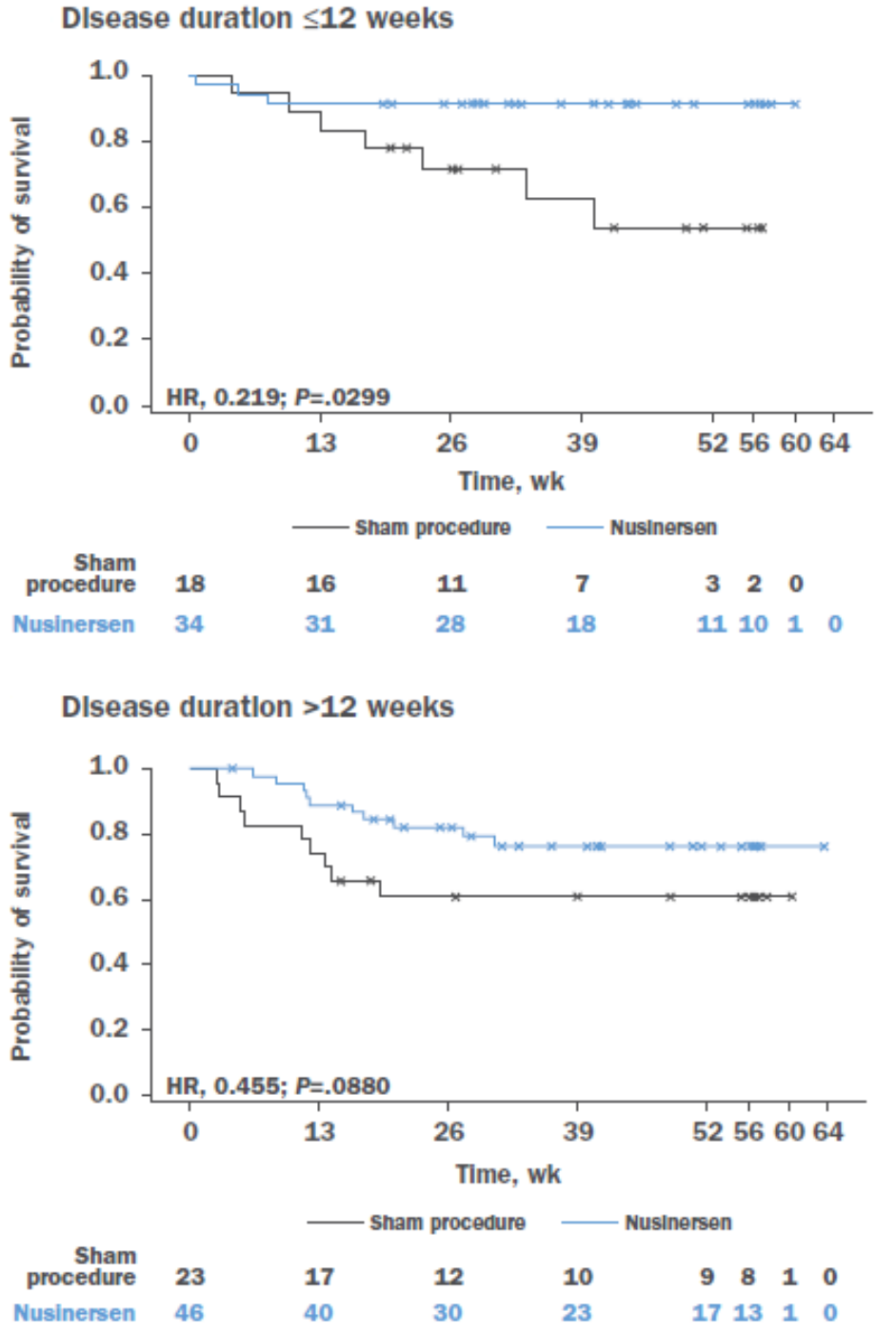
A18. Please provide the study start dates for ENDEAR and CHERISH.

- The start date for ENDEAR was 21st August 2014 when the first infant was treated.(24)
- The start date for CHERISH was 24th November 2014 when the first child underwent the first assigned procedure.(27)

A19. CS Section 2.6.3, page 70. Please provide separate Kaplan-Meier plots (with number at risk table, and number of events) for subgroups below and above study mean duration, for the outcome of OS for ENDEAR and CHERISH.

Please see the Kaplan-Meier plots below for overall survival (OS) in ENDEAR for the subgroups (as presented in Appendix E of the company submission) (Figure 7). However, no such analysis has been performed for CHERISH – OS was not an endpoint in CHERISH and no deaths were observed in either the nusinersen or sham arm.

Figure 7. Overall survival by disease duration



Abbreviations: HR = hazard ratio
Source: Servais et al 2017(30)

Section B: Clarification on cost-effectiveness data

Section B: Clarification on cost-effectiveness data

B1. CS, Appendix G. The ERG notes that a combined "economic" search was conducted to identify studies of cost-effectiveness, health-related quality of life (HRQoL) and resource use. Please confirm whether the search terms used to identify studies of each type were sourced from published and validated filters (providing details and citations where appropriate).

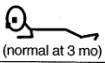
No validated filters were used in the economic SLR. Although there are filters for economic studies, none have been endorsed and there is no consensus on which ones should be used (i.e. statement on the InterTASC Information Specialists' Sub-Group [ISSG] website: "Inclusion of a search filter on this site is not an endorsement of its validity or a recommendation for its use by the editors of this site, by the InterTASC Information Specialists SubGroup or by the (UK) National Institute for Health and Care Excellence (NICE)")(31)

The search terms used in the economic SLR (Appendix G: Search terms) were developed in collaboration with information services specialists. Relevant search terms were identified by looking at the MESH terms of potential search terms within PubMed and also looking at the indexing of terms in the thesaurus of the database (e.g "Muscular Atrophy, Spinal"[MeSH] or hoffman diseases, werdnig[MeSH]). General terms and instrument specific terms were included as free text (i.e. different economic evaluation, cost and resource use, and utility instrument terms that were searched as Text Word or Title in the appendix). These terms were identified through consulting with internal economic experts and through searching relevant databases (e.g. PubMed and Embase). Relevant search terms were also identified from the NICE Guideline on Motor neurone disease: assessment and management (NG42) (Some of the common health economic and utility terms between NG42 and our review include "costs and cost analysis", "economics, hospital", "economics, medical", "economics, nursing", "economics, pharmaceutical", "fees and charges", "cost* ". "health utility* ", "eq 5d*", "quality-adjusted life years", "SF-6", "SF36", "quality of well-being").

B2. CS, Section 3.2.2.1 page 116. The ERG notes that the definition of the health states for the infant model are not exhaustively defined in the footnote to Figure 31. Please clarify:

Health states were based on section 2 (Developmental milestones) of the Hammersmith Infant Neurological Examination (HINE).

Figure 8. Overview of section 2, HINE

Score:	0	1	2	3	4	
Head control	unable to maintain head upright (normal < 3 mo)	wobbles (normal at 4 mo)	all the time maintained upright (normal at 5 mo)			
Sitting	cannot sit	sits with support at hips  (normal at 4 mo)	props  (normal at 6 mo)	stable sit  (normal at 7-8 mo)	pivots (rotates)  (normal at 9 mo)	Observed: Reported (age):
Voluntary grasp	no grasp	uses whole hand	index finger and thumb but immature grasp	pincer grasp		Observed: Reported (age):
Ability to kick (in supine)	no kicking	kicks horizontally legs do not lift	upward (vertically)  (normal at 3 mo)	touches leg  (normal at 4-5 mo)	touches toes  (normal at 5-6 mo)	Observed: Reported (age):
Rolling	no rolling	rolling to side (normal at 4 mo)	prone to supine (normal at mo)	supine to prone (normal at mo)		Observed: Reported (age):
Crawling	does not lift head	on elbow  (normal at 3 mo)	on outstretched hand  (normal at 4 mo)	crawling flat on abdomen  (normal at 8 mo)	crawling on hands and knees  (normal at 10 mo)	Observed: Reported (age):
Standing	does not support weight	supports weight (normal at 4 mo)	stands with support (normal at 7 mo)	stands unaided (normal at 12 mo)		Observed: Reported (age):
Walking		bouncing (normal at 6 mo)	cruising (walks holding on) (normal at 12 mo)	walking independently (normal at 15 mo)		Observed: Reported (age):

(a) What health state would a patient be in if they have a HINE-2 score of 1 for walking and a score of 0 for all other HINE-2 items?

Although this situation is highly unlikely and not observed in the ENDEAR trial (no patient in the ENDEAR trial had a score >0 in the walking item; for the 2 patients that gained the ability to walk in the CS3A trial, when the score for walking was ≥1, the score in at least 5 of the 6 remaining items was ≥ 1), according to the description in the footnote to Figure 31 in the submission, the patients could be assigned to the ***Moderate Milestones*** health state (i.e. the description of other health states state specific requirements in other milestones). The footnote to Figure 31 describing the state membership for the ***Moderate Milestones*** should have included the walking item as follows: "Moderate milestones: Patients have any of the following scores in at least one of the following items: Head control = 2; Sitting = 1; Ability to kick = 2 or 3; Rolling = 1 or 2; Crawling = 2; Standing = 1, Walking =1".

(b) With respect to the definition of the health state "Sits without support", why is a score of 4 for sitting not mentioned? Would a patient with a score of 4 for sitting put this patient in a different health state?

The description of the sitting health state should be updated as follows: *"**Sits Wthout Support**. Patients have a score of 2 or 3 or 4 in sitting ability and a score <2 in standing ability. Any score in other items except walking.*" This does not affect the state membership of any patient because as long as the sitting score is ≥ 2 and the standing score is <2, the patient will be assigned to the ***Sits without Support*** health state.

(c) Please clarify why the HINE-2 standing item has been included in determining whether a patient is in the "Sits without support" health state?

It was included to differentiate it from the patients that could also "Stand with assistance". [redacted]

B3.PRIORITY QUESTION. CS, Section 2.13.5, page 109. Based on the model predictions, mean survival in the modelled RWC group is greater than 2 years in both the infant and later onset cohorts (infant onset = 3.87 undiscounted life years gained [LYGs], later onset = 36.45 undiscounted LYGs). Please provide a rationale for why you consider that nusinersen should be considered as an end-of-life treatment in the infant onset population.

As far as we are aware, there are no published studies on the natural history of SMA in English (or UK) populations. Changes in standard of care over time, variable use of tracheostomy and invasive mechanical ventilation and small study populations lead to considerable differences in reported survival rates (Table 32 in the submission and added below for information). Death predominantly occurs as a result of respiratory compromise, and survival is highly dependent upon the nature and extent of supportive care, which may vary by country, institution and physician and patient preference.(32,33) Studies have shown that "proactive" supportive care can prolong survival, often due to dependence upon gastrostomy tube for nutritional support and non-invasive ventilation or tracheostomy/ventilator support (Table 32).(22,92,93,97) In Oskoui (2007), the median survival time was 8.5 months for patients born in 1980–1994 (with limited supportive care) and indeterminate for those born in 1995–2006 (when proactive supportive care was commonly provided).(38) The survival rate at 2 years was 30.8 vs 73.9%, respectively.

In the ENDEAR trial in infantile onset patients, which was used to inform the economic model in this patient population, patients were managed proactively with supportive care. Of the 121 subjects treated, 27 (22%) required ventilatory support at baseline, with a greater percentage of subjects in the nusinersen group requiring such support (26 vs. 15%).(24) [redacted]

[redacted]

In addition, a study looking at current care practice in 25 countries reported that in the UK only 3/83 SMA type I patients were invasively ventilated.(32)

More recent natural-history studies have focused on a combined survival endpoint of age at death or a surrogate of survival free of permanent ventilation, generally accepted as intubation or tracheostomy with mechanical ventilation or >16 hours/day non-invasive ventilation support for >14 consecutive days (16+/14+) in the absence of an acute reversible illness or following surgery. That is, the assumption is that the infant would have died without such support and a sufficient time period was allowed to ensure that the infant would not wean to <16 hours/day of non-invasive support.(35) This endpoint may be more relevant to the situation in England, where permanent ventilation may not be provided to patients; [redacted]

Please see Section 2.13.5 in the company submission for more information.

Table 32. Natural-history studies reporting survival in SMA type I

Study Years when data were collected Country	N	Supportive care provided	Survival	Age at death (months): Mean (M) and median (m) (range)
Oskoui, 2007(38) 1980-1994 1995-2006 Mainly USA	N = 143	1980–94: Limited (n = 65) Tracheostomy: 24.6% Ventilation (NIV and invasive): 30.8% Ventilation>16hr/d: 21.5% MI-E: 7.7% GT feeding: 40%	Death Median = 8.5 months Survival rate: 1 yr = 36.9% 2 yr = 30.8% 4 yr = 26.2% 10 yr = 24.6%	M = 19.1, m = 7.3 (1.0–193.5)
			Death or ventilation Median = 7.5 months Survival rate: 1 yr = 26.2% 2 yr = 18.5% 4 yr = 3.8% 10 yr = 10.8%	-
		1995–2006: Proactive (n = 78) Tracheostomy: 29.5% Ventilation (NIV and invasive): 82.1% Ventilation>16hr/d: 43.6% MI-E: 62.8% GT feeding: 78.2%	Median = indeterminate Survival rate: 1 yr = 79.3% 2 yr = 73.9% 4 yr = 65.1% 10 yr = 50.3%	M = 22.1, m = 10.0 m (2.5–112.0)
			Death or ventilation Median = 24 months Survival rate: 1 yr = 58.6% 2 yr = 47.0% 4 yr = 28.2% 10 yr = 15.7%	-

Study Years when data were collected Country	N	Supportive care provided	Survival	Age at death (months): Mean (M) and median (m) (range)
Finkel, 2014(19) 2005–09 enrolment USA	N = 34	Proactive: 76% with both GT and NIV/TV	Combined endpoint: Type IB, m = 11.9 Type IC, m = 13.6	Death (n = 9): m = 9 (2–14) Death or requiring >16 hours of BiPAP/day: 13.5 m (IQR: 8.1–22)
Other cohort studies				
Farrar, 2013(39) 1995–2010 Australia	N = 20	Minimal 5% with GT and NIV	Survival at 1 yr = 40% 2 yr = 25% 4 yr = 6% 10 yr = 0	95% died, m = 7.4 (3–56)
Petit, 2011(40) France	N = 45	Minimal None of the survivors >2 years had prior GT or NIV/TV support	9/34 (26%) survived to 2 yr	Mortality in 76%, M = 10.7 (10 days to 6.5 years)
Lemoine et al., 2012(41) 2002–09 USA	N = 49	2 groups: Proactive: NIV BiPAP at night and daytime sleep, and cough-assist device use at least twice daily Supportive: respiratory support, such as supplemental oxygen and suctioning	4-year survival: Proactive: 72% Supportive: 33%	Proactive care (n = 23; 6 deaths): m=7.6 (IQR 6.5,10.5) Supportive care (n = 26; 16 deaths), m = 8.8 (IQR 4.7, 23.7)
Rudnik-Schoneborn, 2009(42) 2000–05 diagnosis Germany	N = 66	Variable NIV/TV, strong NG/GT support	Alive at 2: Overall: 6%	Mortality in 57 (86.3%): All patients: M = 7.3 (few days to 34 months), m = 6.1
Mannaa, 2009(43) 1989–2005 USA	N = 13	Proactive: MI-E: 10 (77%) Mechanical ventilation: 10 (77%) Tracheostomy: 3 NIV: 7	53% survivors: 2 yr = 62% 4 yr = 62% 10 yr = 8%	Data not available

Study Years when data were collected Country	N	Supportive care provided	Survival	Age at death (months): Mean (M) and median (m) (range)
Cobben, 2008(44) 1996–99 Netherlands	N = 34	Minimal	26% survive to 1 yr	Entire group: M = 6 (CI: 5–7), m = 10
Gregoretti 2013(33) 1992 -2010 Italy	N = 194	Tracheostomy and invasive mechanical ventilation (N=42)	2 yr: 95%	-
		Non-invasive respiratory muscle aid (N=31)	2 yr: 68%	-
		No treatment "letting nature take its course" (N=121)	2 yr: 1.3%	-

Abbreviations: BiBAP, Bi-level airway positive pressure; GT, gastrostomy tube; IQR, interquartile range (25–75% percentile); M, mean (standard deviation); m, median (range, X–Y); MI-E, mechanical insufflation– exsufflation device; NG, nasogastric; NIV, non-invasive ventilation; TV, tracheostomy with ventilator; yr, year;
Proactive: both nutritional (NG tube or GT) and respiratory support (NIV or TV).

Furthermore, the NICE end-of-life criterion states that "the treatment is indicated for patients with a short life expectancy, normally less than 24 months". This could be interpreted as implying either that mean life expectancy is less than 2 years (compared with the mean undiscounted life years of 3.87 which the ERG quote) or that patients generally (>50%) live less than 2 years. In our model, the latter is approximately true as, from the start of the model (and treatment), 484 infantile onset patients out of an original cohort of 1000 have died by 22 months and 510 by 26 months under RWC. While more than 50% of patients have been alive for two years at month 18 of the model, life expectancy since birth is not relevant to the NICE criterion, otherwise all conditions experienced at later ages would be excluded from consideration.

B4. PRIORITY QUESTION. CS, Section 1.3.1, page 16. With respect to mortality in Type I SMA, the text states that *"patients rarely survive to their second birthday."* However, the infant onset model predicts that at 18-months following model entry (approximate cohort age = 2 years), around 54% of patients in the RWC group are still alive. The model also predicts that at 114 months following model entry (approximate cohort age = 10 years), around 13% of patients in the RWC group are still alive. Please comment on the validity of these predictions.

As the answer to question B3 illustrates, estimates of survival in infantile onset SMA can vary across studies and time periods. In this analysis, long-term survival is dependent on survival observed in the ENDEAR study (around 58% for RWC patients at the end of trial follow-up period of 13 months), the natural history data used to extrapolate beyond the end of trial follow-up and extrapolation beyond the natural history data using general population mortality. A number of studies were considered as the basis for extrapolation beyond the end of trial follow-up and the data from two of them (Zerres and Rudnik-Schöneborn, 1995 and Gregoretti et al., 2013) have been included in the model. The UK clinical advisory board was presented with a

number of survival extrapolations and agreed that the Gregoretti et al. (2013) data among patients receiving non-invasive respiratory aid (NRA) best reflected the UK population with standard of care. The Gregoretti et al. (2013) study gives conservative estimates of survival relative to those generated by Zerres and Rudnik-Schöneborn (1995). Survival at 48 months was 45% in NRA patients. Extrapolation of the exponential model fitted to the Gregoretti et al. (2013) NRA data based on the adjusted predictions from the Gompertz model fitted to the general population data gave survival of approximately 10% at 10 years. This compares with around 11% of the modelled cohort 10 years after the start of the model.

B5. CS, Section 3.3.1, page 121. The CS states *"A significantly greater percentage of patients achieving a motor milestone response as measured by HINE-2 (51 vs. 0%; difference of 50.68% [95% CI, 31.81–66.48%]; P <0.0001)."* In contrast, the model suggests that the proportion of surviving patients <u>not</u> in the "no motor milestones" state is 66%. Please comment on this apparent discrepancy.

The motor milestone response in the trial was defined as a change from baseline in the HINE score, while in the model we use an absolute measure. The following is the responder definition used in the trial:

- (i) subject demonstrates at least a 2-point increase in the motor milestones category of ability to kick or achievement of maximal score on that category (touching toes), or a 1-point increase in the motor milestones category of head control, rolling, sitting, crawling, standing, or walking, AND

- (ii) among the motor milestone categories with the exclusion of voluntary grasp, there are more categories where there is improvement as defined in (i) than worsening. Note: for the category of ability to kick, similar to the definition of improvement in (i) above, worsening is defined as at least a 2-point decrease or decrease to the lowest possible

Following discussions in the decision problem meeting regarding preferences to an absolute measure model, we updated the economic model. However, in the prior model version there was a response-based section combined with the later-onset health states (i.e. the ***No Milestones***, ***Mild Milestones***, and ***Moderate Milestones*** health states were changed for the ***Worsened***, ***Stabilisation of Baseline Function***, and ***Improvement*** health states). The health states were defined as follows:

- Improvement is defined in the HINE scale as at least a 2-point increase in the motor milestone category of ability to kick or achievement of the maximal score on that category (i.e., touching toes) or a 1-point increase in the motor milestones of head control, rolling, sitting, crawling, standing or walking AND, among the 7 motor milestone categories, the number of categories in which patients demonstrated improvement was greater than the number in which they worsened

- Worsening is defined as: at least a 2-point decrease or a decrease to the lowest possible score of no kicking; for the other 6 categories, worsening is defined as at least a 1-point decrease AND, among the 7 motor milestone categories (with the exclusion of voluntary grasp), the number of categories in which patients demonstrated improvement was greater than the number in which they worsened

- the number of the 7 motor milestone categories in which patients demonstrated improvement was greater than the number in which they worsened
- Later onset motor milestones defined as in the Absolute version of the model.

In the prior model, the proportion of patients surviving in the ***Improvement*** health state and the later onset motor milestones was 53.9% compared with the 51% in the trial. As the current ***Mild Milestones*** health state is a close approximation of the ***Stabilisation of Baseline Function*** health state in the previous scenario, most of the responders in the absolute version of the model will actually be located in the ***Moderate Milestones*** health state and the later onset health states which corresponds to 50% of patients.

B6. CS, Section 3.2.1, page 113. The CS states "*the infantile and later onset economic models include subgroups based on disease duration*" (less than or greater than 12 weeks). CS Section 3.9 (Subgroup Analysis, page 159) text states "*As the base case overall survival within the trial period was modelled using the flexible spline-based Weibull function with 1 knot fitted to the ITT Kaplan-Meier curve, the results of the subgroups are presented alongside the results for the ITT population using the Kaplan-Meier curve. However, it is also possible to use the ITT survival with the subgroup data.*" Please clarify how the two subgroups are handled in the model? If this did not involve fitting separate survival models to each subgroup, please comment on how the results would differ, had this approach been taken?

Subgroup analysis did not involve separate survival models for each subgroup, principally due to small patient numbers (Table 12). However, as overall survival is mainly driven by the long-term data used after trial follow-up, we don't expect major differences in the overall survival of the subgroups if parametric survival functions had been used. The impact is expected to be similar to the one observed for the ITT population (Table 13).

Table 12. Subgroup overall survival

Subgroup	Nusinersen	RWC
≤ 12 weeks disease duration		
N	34	18
Number of subjects who died	3 (9%)*	7 (39%)
> 12 weeks disease duration		
N	46	23
Number of subjects who died	10 (22%)	9 (39%)

*All deaths occurred before 3 months
Abbreviation: RWC, real world care

Table 13. ITT overall survival

Survival function	Nusinersen	RWC	Incremental	ICER
Flexible spline-based Weibull (1 knot)	11.04	2.84	8.20	407,605
Flexible spline-based Weibull (2 knot)	11.08	2.86	8.22	408,026
Weibull	10.79	2.68	8.10	403,348
Log-normal	10.61	2.80	7.80	414,819
K-M	11.15	2.85	8.30	405,825

Abbreviations: ICER, Incremental cost-effectiveness ratio; K-M, Kaplan-Meier; RWC, real world care

Separate analyses on only the trial data were performed for OS and event-free survival using Cox models:

I. Overall survival

OS = Treatment * age on onset (AGEONSET) + Treatment * disease duration (DISDURW)

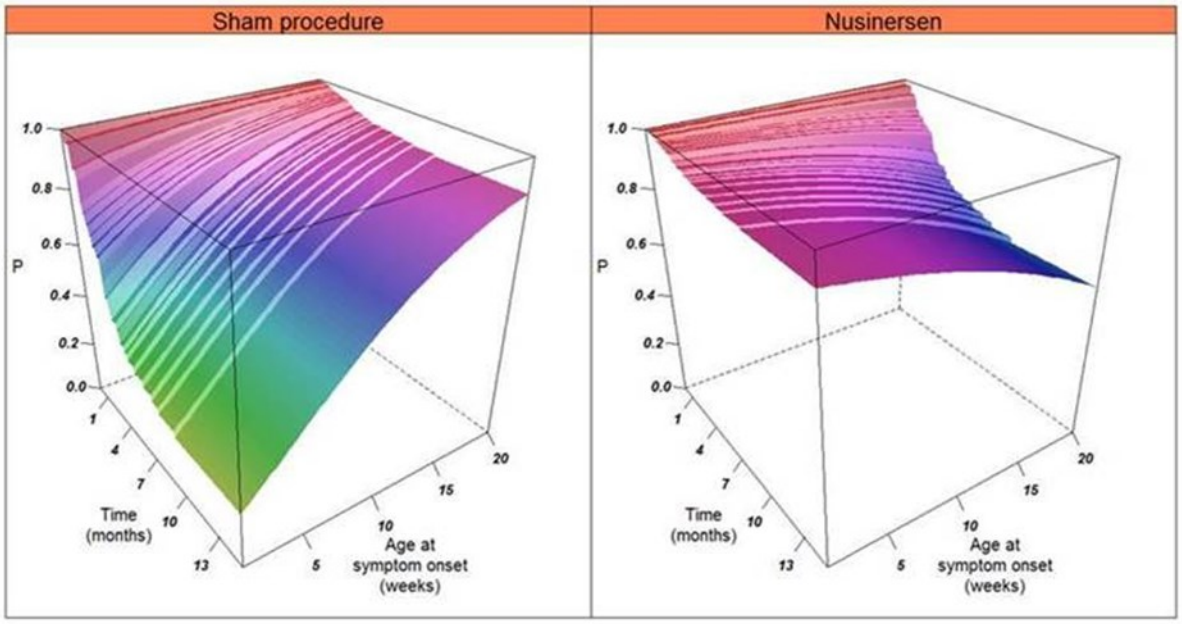
Wald Statistics Response: Surv(Months, Event)

Factor	Chi-Square	d.f.	P
Treatment (Factor+Higher Order Factors)	13.85	3	0.0031
All Interactions	6.56	2	0.0375
AGEONSET (Factor+Higher Order Factors)	6.60	2	0.0368
All Interactions	6.29	1	0.0122
DISDURW (Factor+Higher Order Factors)	1.51	2	0.4693
All Interactions	0.52	1	0.4704
Treatment * AGEONSET (Factor+Higher Order Factors)	6.29	1	0.0122
Treatment * DISDURW (Factor+Higher Order Factors)	0.52	1	0.4704
TOTAL INTERACTION	6.56	2	0.0375
TOTAL	15.15	5	0.0098

Abbreviation: d.f., degrees of freedom

Disease duration did not have a significant effect on overall survival, but age of onset did. Predictions are shown below for the effect of age of onset on overall survival.

Figure 9. Prediction in a Cox model for effect of age of onset on overall survival



P = probability of overall survival

From Figure 9, it appears that survival in the sham arm is poor if age of onset is less than around 10 or 12 weeks, whereas survival on nusinersen may not be affected by age of onset.

II. Event-free survival

EFS = Treatment * age on onset (AGEONSET) + Treatment * disease duration (DISDURW)

Wald Statistics Response: Surv(Months, Event)

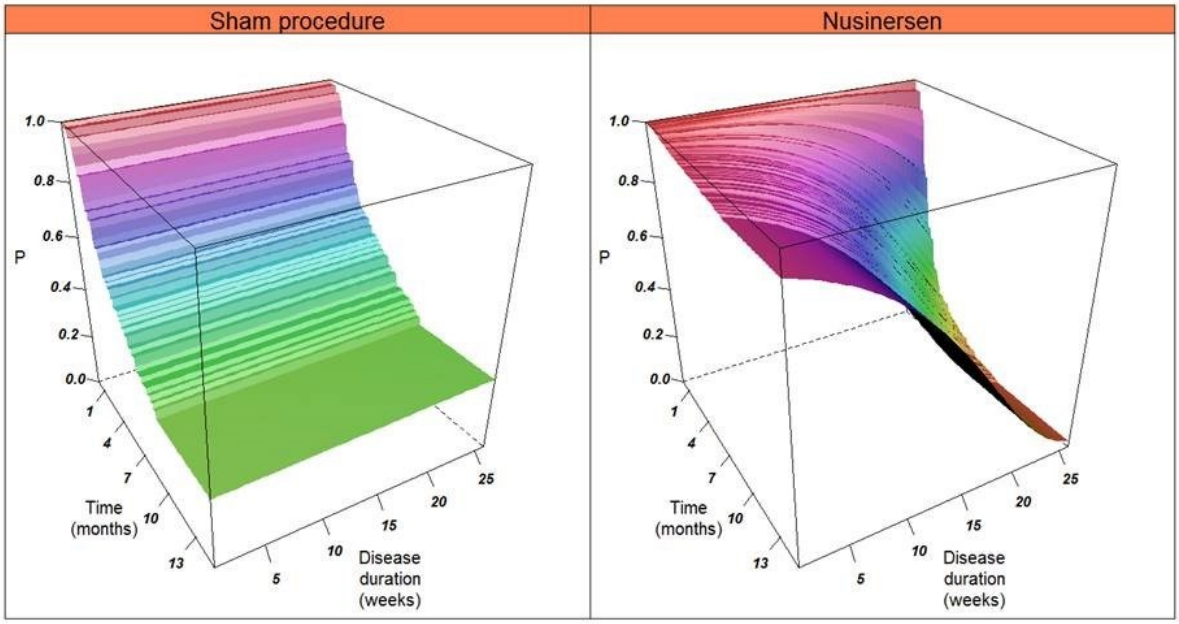
Factor	Chi-Square	d.f.	P
Treatment (Factor+Higher Order Factors)	18.75	3	0.0003
All Interactions	9.51	2	0.0086
AGEONSET (Factor+Higher Order Factors)	5.52	2	0.0633
All Interactions	0.01	1	0.9147
DISDURW (Factor+Higher Order Factors)	18.11	2	0.0001
All Interactions	9.51	1	0.0020
Treatment * AGEONSET (Factor+Higher Order Factors)	0.01	1	0.9147
Treatment * DISDURW (Factor+Higher Order Factors)	9.51	1	0.0020
TOTAL INTERACTION	9.51	2	0.0086
TOTAL	27.25	5	0.0001

Abbreviation: d.f., degrees of freedom

From the above, age of onset was seen to not be significant, but disease duration was.

Predictions are shown below in Figure 10 for the effect of disease duration on EFS.

Figure 10. Predictions for the effect of disease duration on EFS



P = probability of event-free survival

From Figure 10 it appears that event-free survival in the sham arm was unaffected by disease duration, whereas survival probability was greatly improved in the nusinersen arm if disease duration was less than 12 weeks.

It was not clear why disease duration should have such a noticeable effect on event-free survival in the nusinersen arm but show much less effect on overall survival.

It may have been at least partly down to correlation between these variables and small sample sizes (a good spread of patients across all variables would be needed), although there was little evidence of correlation in the actual data.

In summary, for age at onset <12 weeks, poor overall survival was observed in the sham arm, but survival in the nusinersen arm was unaffected.

When treated early (disease duration < 12 weeks), nusinersen was highly effective at reducing the probability of an event (i.e. permanent ventilation), although it had less impact on overall survival.

There is likely to have been confounding in both these analyses i.e. if age at onset young then more likely that disease duration was short.

B7. CS, Section 3.3.2, page 122. Please state the method used to fit survival models to the time-to-event data from ENDEAR (e.g. software, method for parameter estimation). The ERG notes that within the model, Sheet "KMT1" refers to "Least Squares".

All analyses for OS and EFS were conducted in R (R Foundation for Statistical Computing; Vienna, Austria). Exponential, Weibull, log-normal and log-logistic models were fitted using the eha package (Brostrom, 2012(45)) in R. Gompertz, generalized gamma and flexible spine-based Weibull models were fitted using the flexsurvreg package (Jackson, 2016(46)) in R.

Both procedures use the same default optimisation method (Broyden–Fletcher–Goldfarb–Shanno) (Nash 1990(47)) and use analytic derivatives of the likelihood with respect to the model parameters, if available, to improve the speed of convergence to the maximum. These derivatives are built-in for the exponential, Weibull, Gompertz, log-logistic, spline-based Weibull models.(48)

However, one of the scenario analyses in the "Costs" sheet allows the health state costs to be estimated based on major clinical events. One of the major clinical events included was permanent ventilation. In this scenario, the model fitted parametric functions to the permanent ventilation data using the "least square" method to estimate the proportion of patients receiving permanent ventilation. This method was only used for the major clinical events costing scenario.

B8. PRIORITY QUESTION. CS, Section 3.3.4.1, page 127. The CS states *"Drawing on clinical expert opinion(122) that infantile onset patients achieving later onset milestones could also experience later onset mortality, the adjustment factor was set to 0.9 in the base case where a factor of 0 applies the mortality of type I patients and a factor of 1 applies the mortality of type II patients."* The reference cited in the CS is an advisory workshop on SMA, the data from which are held as "Data on file." Please explain how this adjustment factor of 0.9 was derived or elicited. Please also explain why this adjustment factor is applied only in the nusinersen group of the model and whether there is any empirical evidence to support this.

There is currently no empirical evidence on long term survival in infantile onset patients who achieve motor milestones consistent with type II SMA. However, the UK clinical advisory group considered it possible that infantile onset patients who respond to nusinersen could effectively be converted into type II patients. It was thought that this would likely reflect an ideal world in which infantile onset patients are identified and treated early. This would imply that the survival curve with nusinersen will come to resemble the survival reported in Zerres et al. (1997)(49) among later onset patients. Given the uncertainty in this area, the model stops short of assuming that infantile onset patients achieving later onset motor milestones fully achieve the survival of type II patients. The best estimate to reflect this in the model's base case was judged to be an adjustment factor of 0.9, with the facility for users to conduct scenario analysis on this assumption.

The factor is applied to both arms in the model. However, patients in the RWC arm in the infantile-onset model do not reach the later onset milestones, and the adjusted probability of death is only applied to patients on those health states.

B9. CS, Section 3.3.3, page 123. Please justify why survival modelling has been used to estimate survival probabilities from ENDEAR given that the spline model is not used for extrapolation of outcomes following the trial follow-up period. Why was "clinical plausibility of the extrapolated portion" a criterion for model selection? Why was the Kaplan-Meier estimate of cumulative survival not used?

Survival curves were not mature. It is standard practice in health economics to use parametric models to extrapolate survival curves and not to rely on the Kaplan-Meier estimates of cumulative survival. NICE (2013)(50) states that "Clinical trial data generated to estimate treatment effects may not sufficiently quantify the risk of some health outcomes or events for

the population of interest or may not provide estimates over a sufficient duration for the economic analysis." Latimer (2013)(51) provides details of the use of parametric models for this reason. Use of Kaplan-Meier estimates with external data is also problematic. Simulated survival estimates are needed in a health economic model to take account of the error in the estimation. Bootstrapping can be used to create these estimates. However, this greatly slows down Excel because a loop is needed in the program code to go through all the bootstrap predictions. Any extrapolation is also dependent on where the steps occur in the Kaplan-Meier chart.

Clinical plausibility of the extrapolated portion is an important criterion as defined by Latimer (2013)(51) who states that "Statistical tests can be used to compare alternative models and their relative fit to the observed trial data. This is important, particularly when there is only a small amount of censoring in the dataset and thus the extrapolation required is minimal. However, it is of even greater importance to justify the plausibility of the extrapolated portion of the survival model chosen, as this is likely to have a very large influence on the estimated mean survival. This is difficult but may be achieved through the use of external data sources, biological plausibility, or clinical expert opinion."

NICE (2013)(50) also states that "The external validity of the extrapolation should be assessed by considering both clinical and biological plausibility of the inferred outcome as well as its coherence with external data sources such as historical cohort data sets or other relevant clinical trials."

Clinical plausibility was therefore considered to be an important criterion for model selection.

Parametric survival curves were fitted to the ENDEAR trial data. However, the Kaplan-Meier estimates flatten during the follow-up period. When parametric curves were fitted these either produced models that fitted the data well but produced biologically impossible extrapolations or fit the data poorly and some produced plausible predictions. The method described by Jackson et al. (2016)(46) was therefore used to utilise external data so that a model could be fitted to the ENDEAR trial data and produce plausible predictions. The rational for such a model is that hazard rates change over time making it unreasonable to fit a model to short-term data and expect such a model to make accurate long-term predictions. However, this also proved to be problematic because while several external data sources were found, these gave different shaped survival curves. Sensitivity analyses were therefore performed to model this uncertainty (**Error! Reference source not found.**).

B10. PRIORITY QUESTION. CS, Section 3.3.2, page 122. Type I SMA mortality is modelled using a piecewise approach using three different parametric functions (a spline model fitted to ENDEAR data, an exponential model fitted to adjusted Gregoretti data and a hazard ratio-adjusted Gompertz function fitted to general population mortality).

(a) Why was such a complex approach required and why were simpler standard models not applied for the entire time period?

See answer to B9. Also see paper by Jackson et al. (2016)(46) and Guyot et al. (2017)(52) for reasons why a single model may not be appropriate to make predictions for the life-time of patients. The authors argue against extrapolating beyond the data and instead show why long-term data are needed to make long-term predictions. Also see Davis et al. (2013)(53) who

show an example of changing hazard rates over time and the bias caused by relying on a single distribution, estimated from short-term data, to make long-term predictions. The model allows the exploration of scenarios where no long-term data is used. However, with no long-term data, only the Weibull function showed clinically plausible predictions for the RWC arm.

(b) What is being assumed about the underling hazard of death through the application of the models in a piecewise fashion?

Spline-based models allow the hazard rate to change over time. Jackson et al. (2016)(46) provide a rationale for this. There may be more than one survival distribution in the trial. Flexible spline-based models can often fit these data well in the short-term but may not give accurate long-term predictions. Trial data often provide evidence of decreasing hazard rates over time. If patients live long enough they are expected to show signs of exponentially increasing hazard rates with age. This cannot be derived from models fitted to short-term trial data alone.

B11. PRIORITY QUESTION. CS, Section 3.3.4, page 125, Figure 34. Please provide further details on the use of data from Gregoretti *et al*:

(a) How were the IPD reconstructed?

The method described by Guyot et al. (2012)(54) was used to re-construct patient level data.

(b) How were the reconstructed IPD "adjusted for mean age"?

Mean age of patients at the start of treatment in the ENDEAR trial was 5.56 months. The Gregoretti et al. (2013)(33) study presents data from birth. Therefore 5.56 months was subtracted from the re-constructed Gregoretti et al. (2013)(33) data and patients with negative times removed.

(c) How were the 95% confidence intervals constructed and do these incorporate uncertainty in the adjustment procedure?

Hazard rates were simulated from the model fitted to the trial data using the parameters and variance covariance matrix. At the end of follow-up simulated hazard rates were utilised from the model fitted to the Gregoretti et al. (2013)(33) data (minus 5.56 months). Since we know the mean age of the trial data and we know the age of patients in the Gregoretti et al. (2013)(33) data there is minimal error.

The model assumes that the Gregoretti et al. (2013)(33) data were comparable to the ENDEAR trial and that the main unknown factor was the length of the treatment effect after follow-up. This was investigated through sensitivity analyses using different times for the hazard ratio to taper to 1 for nusinersen compared to the sham procedure.

B12. CS Section 3.3.4.1 page 126 and CS Appendix P, page 212. Please provide further details on the use of data from Zerres *et al*:

(a) What is meant by "some uncertainty as to the number of risk" (a number of risk table was not provided in the paper)?

Re-constructing Individual Patient Data (IPD) is more reliable if the number at risk is known for different time points. If this is not provided, assumptions can made for when censoring occurs. Censoring information in the form of tick marks on Kaplan-Meier charts can be used to create the number at risk table. This type of chart was presented by Zerres and Rudnik-Schoneborn (1995) (55). However, the chart was of poor quality and a degree of judgement was required when there was more than one patient censored at the same time-point. Kaplan-Meier plots from the re-constructed data looked identical to the original charts so any bias should be minimal.

(b) How were the IPD reconstructed?

The method described by Guyot et al. (2012)(54) was used to re-construct patient level data.

(c) How do the characteristics of this population compare with that of ENDEAR? Was any adjustment to the original KM made (as with the Gregoretti data)?

Although the Zerres and Rudnik-Schoneborn (1995)(55) data appear suitable to use for long-term extrapolation, there is some uncertainty as to how comparable these data are because they are from German patients and the fit does not take into account any improvement in survival with time. Moreover, Zerres and Rudnik-Schoneborn (1995)(55) did not report the proportion of patients who received permanent ventilation.

The Gregoretti et al. (2013)(33) also presented patients from birth and so 5.56 months was subtracted from survival times and patients with negative values were removed. This study included more recently diagnosed patients and it was clear what treatment patients received. However, survival in the “continuous non-invasive respiratory muscle aid” arm appeared to be greater than that expected from the clinical advice we received for UK patients and the sample size was small. From this paper there is insufficient information to draw conclusions on why survival was higher in the Italian patient population compared to the UK patient population.

The results from separate models fitted to the external data sets were used in sensitivity analyses because we could not be sure how comparable these data sets were to the ENDEAR trial data.

B13. CS, Section 4.3.1, page 170. The CS states *“The hazard rate predicted from the flexible spline-based Weibull model with 2 knots fitted to the Zerres et al. (1997) data was estimated for the mean age at the end of follow-up of 53 years.”* Please explain how this was done, given that covariate information is not available for the reconstructed Zerres data.

Parametric models, that had proportional hazard properties, were fitted to the Zerres et al. (1997)(49) data and the general population data. Hazard rates were simulated from both models, using the variance covariance matrices. The follow-up of the Zerres et al. (1997)(49) study was 53 years. Hazard rates from the model fitted to the general population data were estimated for this time point. For each pair of simulated values, the hazard ratio between the two models was estimated and the hazard rates from the general population multiplied by this value so that the hazard rates from the general population data matched those from the Zerres

et al. (1997)(49) data. This assumes that hazard ratios remain constant over time. This is a conservative approach since we would expect hazard rates to get closer to those from the general population with time. However, the available data did not provide information on how the hazard ratio may change over time.

B14. CS Appendices 12.1.2.3. Page 186. Results are provided for a "Bayesian simultaneous model" for the combined ENDEAR trial data and external Gregoretti non-invasive respiratory aid (NRA), for event free survival (EFS). Was this conducted for OS as well, given that OS is needed for the model and the method provides a more consistent approach to extrapolation than the multi-stage procedure defined? Please provide the model and relevant OS data.

Models were run for OS. However, there are was too little information in the external data after the follow-up of the ENDEAR trial.

Table 14 below gives the Gregoretti et al. (2013)(33) data. The authors did not present a number at risk table, so the sample sizes may be an over-estimate.

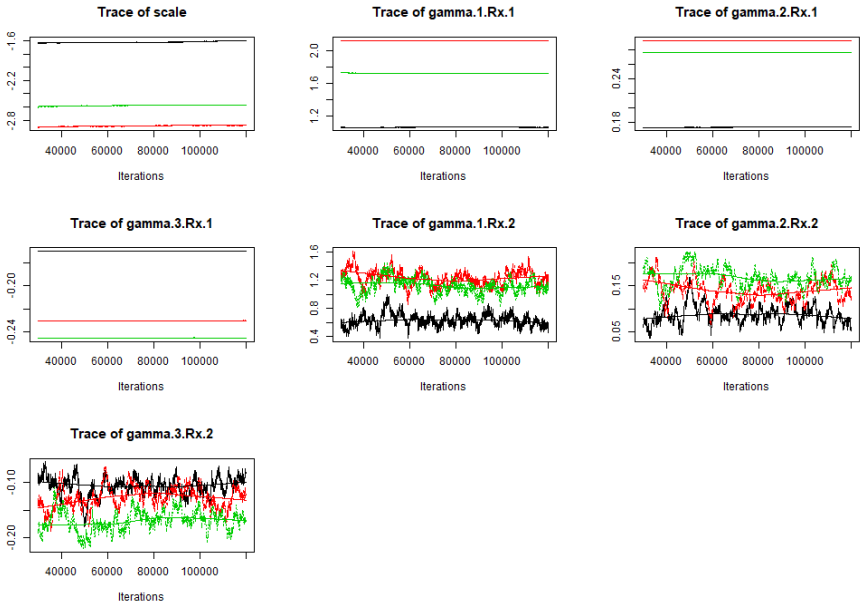
Table 14. Gregoretti data

Month	N at risk (numerator)	Alive at end of year (denominator)
24	21	16
36	16	12
48	12	12

The Bayesian model appeared to make little use of these data and was instead highly sensitive to the general population estimates. Guyot et al. (2017)(52) used survival estimates for a time point at which patients would all have expected to have died. This time point is unknown for the current standard of care and even with different estimates for this convergence could not be achieved.

Iteration plots are shown below. Iteration plots should just show random noise without any separation of the chains.

Figure 11. Iteration plots



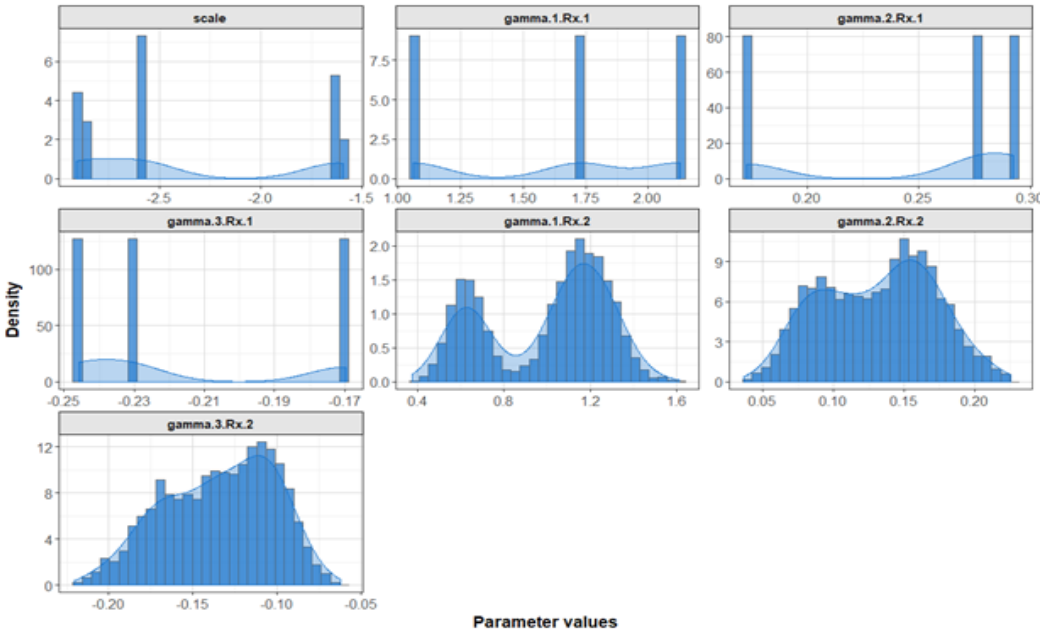
Gelman-Rubin diagnostics
Values should be close to one.

```
Potential scale reduction factors:

          Point est. Upper C.I.
beta[1]         5.33      10.28
beta[2]         3.16       5.88
beta[3]         3.09       5.70
deviance        3.94       7.31
gamma[1]      130.06     332.84
gamma[2]      625.13    1463.90
gamma[3]     1009.87    2317.24
gamma[4]      740.71    1466.21
```

Parameter distributions – should show normal distributions, instead shows clear differences for each chain.

Figure 12. Parameter distributions



Even if this model had shown good convergence diagnostics it would still be difficult to implement in a health economic model. Sensitivity analyses would be needed for the length of treatment effect after follow-up and for the time point where we assume all patients have died. Unlike the Jackson et al. (2016)(46) approach where these values can be entered into the health economic model, using the Bayesian models would mean a separate model would be needed for each scenario and it is therefore unlikely to offer a practical solution to this problem.

B15. Model, Worksheet Country Specific Sheet T1 cell I867. The text in the model cell seems to suggest that Scottish annual mortality rates have been used. Please clarify if this is the case and if so, please explain why English data have not been used. Please also clarify why mortality rates based on age bands have been used rather than age-specific life tables.

This is a typographical error. The mortality rates for England and Wales have been used. The model includes the option to enter mortality rates by age bands as it was designed to be adaptable to other countries. However, in our base case analysis the mortality rates by age band are not used. Instead, the Gompertz survival function fitted to yearly mortality data from the English life tables was applied. The "GP Mortality" sheet includes a dropdown that allows the user to select between the Gompertz function and the mortality by age band.

B16. PRIORITY QUESTION. CS, Section 3.3.5, page 127. The CS states *"The assumption made in the base case was that, except for those who stop treatment, patients in the nusinersen arm continue to improve, and therefore move to better health states, in line with improvements in CHOP INTEND observed over the period of trial follow-up. As motor function improvements seen in the clinical studies did not exhibit a plateau and, on the grounds of nusinersen's action on the underlying cause of disease, an expectation of continued improvement was supported by a panel of expert UK clinicians."*

(a) Please provide further detail about how these assumption were arrived at.

[redacted] the mean rate of improvement in CHOP INTEND was continued beyond the end of ENDEAR trial follow-up although, given the uncertainty around this parameter, a proportion of nusinersen patients can be assumed to reach a plateau or deteriorate. In the RWC arm, the base case assumes that the deterioration in CHOP INTEND observed in the ENDEAR trial continues beyond the end of trial follow-up. A lower rate of deterioration can be applied in the model by selecting the natural history study by Finkel et al. (2014) in infantile onset SMA or Kaufman et al. (2012) in later onset SMA.

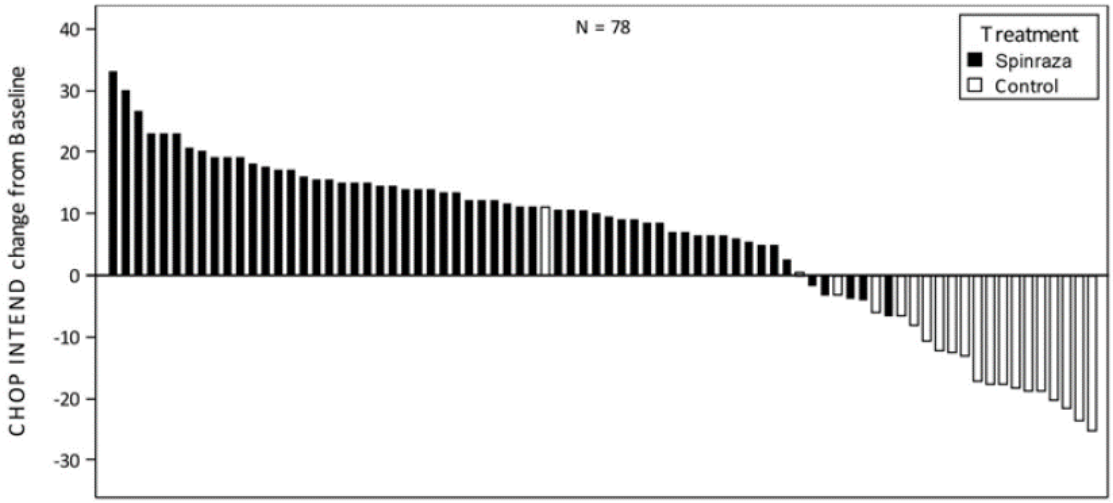
(b) Please clarify whether the expert UK clinicians believed that all patients receiving nusinersen would continue to improve, or whether on average, patients would continue to improve. Similarly, please clarify whether the UK clinicians believed that all patients receiving RWC would worsen, or whether on average they would continue to worsen.

[redacted]

(c) Please provide a figure similar to Figure 12 for the outcome of CHOP-INTEND

The figure below gives comparable results for CHOP INTEND to those for HINE-2 shown in Figure 12.(13) The waterfall plot below shows the change in CHOP-INTEND motor function scores at the end of the study compared with baseline.

Figure 13. ENDEAR: Change in CHOP INTEND from Baseline to Later of day 183, day 302, and day 394 study visit – (Efficacy Set, ES)



Note 1: Shortest bars at 0 line indicate 0 value.
Note 2: Out of the 110 patients in the efficacy set, 29 died (13 (18%) for Spinraza and 16 (43%) for Control) and 3 withdrew for reason other than death (2 (3%) for Spinraza and 1 (3%) for Control) and were therefore not included in this analysis of the ES.

Abbreviations: CHOP INTEND, Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders
Spinraza=nusinersen
Source: SmPC

B17. CS, Section 3.3.5 page 128. The change in CHOP INTEND score observed in ENDEAR was an increase of [redacted] points for nusinersen and a decrease of [redacted] points for sham. CS Figure 13 (page 68, mean change based on HINE-2) suggests that the decrease in score for control is substantially lower in magnitude than the rate of improvement for nusinersen.

(a) Please provide a figure similar to Figure 13 for the outcome of CHOP-INTEND

The figure below shows changes in CHOP INTEND score in nusinersen and control groups relative to baseline at each assessment point of the ENDEAR trial.

The rates of improvement and worsening in the nusinersen and sham arm used in the model were taken from table 146 in the ENDEAR CSR, using the weekly least squares mean of [redacted] and [redacted], respectively and adjusting them to a monthly rate. For clarity, the model uses results from the ENDEAR efficacy set.

To further clarify, figure 13 in the original company submission and figure 14 in this document refer to mean changes in HINE and CHOP-INTEND scales, respectively, whereas the model uses the least squares mean.

(b) Please comment on the level of consistency between CHOP-INTEND and HINE-2

The waterfall plots and the charts of changes from baseline in HINE-2 and CHOP INTEND scores are consistent in showing improvements in nusinersen patients and deterioration in sham procedure patients. There won't necessarily be a direct relationship between the changes on one measure and the changes in the other both because they are measuring different aspects of motor ability and because of the different properties of the two measurement scales. For example, considering patients' absolute scores, patients are closer to zero on the HINE-2 scale than on the CHOP INTEND scale at baseline, thus limiting the scope for further reductions in score over time with HINE-2.

B18. CS, Section 3.3.5, page 127. Table 35 uses mean CHOP INTEND score for each health state, for each arm individually, and a scenario analysis for both arms combined. What is the logic behind using the mean for each arm separately? Is it expected that the mapping from CHOP INTEND to HINE-2 is dependent on treatment arm?

The average CHOP INTEND scores for patients in the RWC arm were consistently lower to the scores for patients in the nusinersen arm in all health states and at each assessment day. In addition, while the average score for patients in the RWC arm decreased at each assessment, the average score for patients in the nusinersen arm increased. Therefore, in the base case analysis we considered that the score for each health state was dependent on treatment arm (i.e. patients receiving treatment with similar milestone achievement to patients without treatment showed better CHOP INTEND scores).

B19. CS, Section 3.3.5, page 129. The CS states that the model assumes that *"the probability of transitioning from the Walks with Assistance health state to the Stands/Walks Unaided health state is the same as the transition probability from the Stands with Assistance health state to the Walks with Assistance health state."* Why was this assumption made?

The CHOP INTEND score assigned to the ***Walks With Assistance*** health state was 63 points out of a maximum of 64 (CS, Section 3.3.5, page 127. Table 35). Therefore, the maximum score we could have assigned to the ***Walks/Stands Unaided*** health state would have been 64, which would translate into a probability of transitioning of 100% in one cycle. This would have overestimated the proportion of patients reaching the ***Walks/Stands Unaided*** health state. Hence, we used a more conservative approach and assigned the same probability of transitioning from the ***Stands with Assistance*** health state to the ***Walks with Assistance*** health state.

An example of the calculation of the transition probabilities based on the CHOP-INTEND score and rate of change is shown below.

$$transition\ probability_{standing\ to\ walking}$$
$$= Min\left(1, \left(\frac{Rate\ of\ CHI\ increase_{per\ month} \times Cycle\ length}{CHI_{walking} - CHI_{standing}}\right)\right)$$
$$= Min\left(1, \left([redacted]\right)\right)$$
$$= [redacted], transition\ probability_{standsing\ with\ assistance\ to\ walks\ with\ assistance}$$
$$= Min\left(1, \left(\frac{Rate\ of\ CHI\ increase_{per\ month} \times Cycle\ length}{CHI_{walks\ with\ assistance} - CHI_{stands\ with\ assistanceing}}\right)\right)$$
$$= Min\left(1, \left([redacted]\right)\right) = [redacted]$$ ¶

As the transition probability is also based on the cycle length, the infantile-onset model applied a different transition matrix at cycle 5 (month 14). The length of cycle 5 was set to one month so the cycles after trial follow-up matched the maintenance dose schedule after end of trial follow-up (i.e. trial follow-up was at 13 months where no maintenance dose was given, the next maintenance dose was at 14 months and every 4 months thereafter).

B20. PRIORITY QUESTION. Model, sheets "Markov Nusinersen T1" and "Markov Nusinersen T2". The ERG notes that the model appears to apply a relatively simple Markov approach, yet the formulae applied in the Markov trace are extremely complicated. Please explain:

- **(a) Why it was necessary to apply such complex formulae in the model**
- **(b) Why a conventional matrix-based implementation of the Markov model was not implemented**
- **(c) Why the model does not separate out different health states for patients who are still on nusinersen and for those who have discontinued due to lack of efficacy or inability to receive the drug due to scoliosis surgery.**
- **(d) Are tunnel states used to model outcomes for patients who discontinue nusinersen following scoliosis surgery?**

In response to parts (a), (b) and (c): The model had to be developed from scratch as no existing economic model exists for SMA. The model was developed as an iterative process over a number of months and although starting out as a seemingly simple Markov process becoming more complex as elements such as scoliosis surgery and different model extrapolation approaches were considered. We acknowledge that the formulae are more complicated than they should be, but the model builders found it easier to build upon the existing structure, as changes were made, rather than separate out the different patient groups as suggested.

In response to part (d): For patients who discontinue nusinersen following scoliosis surgery tunnel states are used to model outcomes. This is done to ensure the number of new discontinuations are separate from the patients that have previously discontinued due to scoliosis surgery.

B21. CS, Section 3.6.2, page 148. Please clarify the basis for the assumption that 20% patients will discontinue nusinersen following scoliosis surgery.

The proportions of patients discontinuing nusinersen following scoliosis surgery are assumptions. Varying these assumptions did not have a large impact on the incremental cost-effectiveness ratio (ICER), as illustrated below.

Table 15. Scoliosis scenarios infantile onset

Scoliosis scenarios	Infantile-onset model ICER (£/QALY gained)
Base case (1% of patients reaching later onset milestones have scoliosis surgery; 20% of patients having scoliosis surgery discontinue)	407,605
Scenario 1: 1% of patients reaching later onset milestones have scoliosis surgery; 0% of patients having scoliosis surgery discontinue)	409,837
Scenario 2: 1% of patients reaching later onset milestones have scoliosis surgery; 100% of patients having scoliosis surgery discontinue)	400,979
Scenario 3: 100% of patients reaching later onset milestones have scoliosis surgery; 20% of patients having scoliosis surgery discontinue)	398,939
Scenario 4: 100% of patients reaching later onset milestones have scoliosis surgery; 100% of patients having scoliosis surgery discontinue)	400,918

Abbreviations: ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year;

Table 16. Scoliosis scenarios later onset

Scoliosis scenarios	Later-onset model (£/QALY gained)
Base case (43% of patients have scoliosis surgery; 20% of patients having scoliosis surgery discontinue)	1,252,991
Scenario 1: 43% of patients have scoliosis surgery; 0% of patients having scoliosis surgery discontinue)	1,344,681
Scenario 2: 43% of patients have scoliosis surgery; 100% of patients having scoliosis surgery discontinue)	1,199,079

Scenario 3: 100% of patients have scoliosis surgery; 20% of patients having scoliosis surgery discontinue)	1,250,979
Scenario 4: 100% of patients have scoliosis surgery; 100% of patients having scoliosis surgery discontinue)	1,195,971

Abbreviation: QALY, quality-adjusted life year;

B22. Model, worksheets "Markov Nusinersen T1" and "Markov RWC T1", cells F20:N20, and "Markov Nusinersen T2" and and "Markov RWC T2", cells F20:N20. Please clarify why the initial distribution of patients is different between the intervention and comparator groups.

The initial distribution of patients between the health states in the model is based on the distribution of patients seen in the pivotal trials ENDEAR and CHERISH for infantile and later onset SMA, respectively. This was to ensure that the model followed the trial data more accurately. Altering the starting patient distribution in the model to be the same for both the sham and nusinersen arms has very little effect on the results. The table below shows the revised results using a common distribution of patients, based on the initial patient distribution seen in the nusinersen and sham arms, respectively, for infantile onset. Similar small effect in the economic results is seen for later onset SMA. (not shown).

Table 17. Base case results Initial Patient Distribution Scenarios – infantile onset SMA, patient QALYs

Technology	Total costs (£)	Total LYG	Total QALYs	Inc. costs (£)	Inc. LYG	Inc. QALYs	ICER vs. base-line (£/QALY)	ICER inc. (£/QALY)
RWC	71,540	3.39	2.49					
Nusinersen	2,258,852	9.34	7.86	2,187,311	5.95	5.37	407,605	407,605
Base case results using the nusinersen arm initial patient distribution								
RWC	71,485	3.39	2.49					
Nusinersen	2,258,852	9.34	7.86	2,187,367	5.95	5.37	407,642	407,642
Base case results using the Sham arm initial patient distribution								
RWC	71,540	3.39	2.49					
Nusinersen	2,274,987	9.39	7.91	2,203,447	6.00	5.41	406,971	406,971

Abbreviations: ICER, incremental cost-effectiveness ratio; inc., incremental; LYG, life years gained; QALY, quality-adjusted life year

B23. CS, Section 3.4.2.2, page 131. The ERG notes that the caregiver utility for the "no milestones" health state is derived from utilities for the "Sits and rolls independently" and "Sits without support" health states. A similar approach is used for the "Sits without support", "Stands with assistance", "Walks with assistance" and "Stands/walks unaided" health states. Please explain the rationale for using patient utilities for other health states to determine the caregiver utility for the state under consideration.

Given a lack of data on carer utilities by health state for the SMA model, we assumed, for the base case analysis, that patient and carer utilities were positively correlated so that health states with a higher patient utility also had a higher carer utility and those with a lower patient utility would also have a lower carer utility. Taking the reference point of ***Mild Milestones*** in

infantile onset patients and assuming that the carer's utility from Bastida et al. (2016)(56) refers to this state, it was assumed that a carer's utility for a given state deviated from this reference point by the same amount as the patient utility for that state deviated from the patient's utility for ***Mild Milestones***. A similar approach was adopted in later onset patients. Scenario analyses explored different approaches to utility values.

The caregiver utility estimate is based on the caregiver utility derived from the Bastida et al., 2016 study.(56) The study reported values of [redacted] and [redacted] from the self-reported EQ-5D 5L for caregivers of patients with infant-onset SMA and later-onset SMA, respectively. No caregiver utilities were available that differentiate by SMA disease severity. Thus, the assumption the model makes is to use the difference seen in patients' health-related quality of life (HRQoL) utility values by health state and apply this to the caregiver HRQoL to obtain differential caregiver utilities. The assumption is that the more severe the SMA patient is the lower the caregiver's HRQoL as more care is required.

B24. PRIORITY QUESTION. CS, Section 3.4.2.1, page 131. Please comment on the face validity of the patient utility scores applied in the model. In particular, please comment on the validity of assuming a utility score of [redacted] for patients who achieve no milestones and the relatively small difference between the best and worst health states (no milestones utility = [redacted], stands/walks unaided utility = [redacted]).

A lack of HRQoL measurements in SMA was identified in the economic systematic literature review. As the Paediatric Quality of Life Inventory (PedsQL) was a measurement undertaken as part of the CHERISH trial for patients with later-onset SMA, it would have been remiss not to include this data source in the modelling. The resulting utility values do appear to be higher than would be expected for this severe condition. Also, the difference between the most severe health state (***No Milestones Achieved***) and the best health state (***Stands/Walks Unaided***) is small ([redacted]). We suggest that using the PedsQL data was a very conservative assumption.

Following discussions with the Swedish health technology assessment (HTA) body, the Tandvårds- och läkemedelsförmånsverket (TLV), it was suggested that surrogate HRQoL utility values from the disease of amyotrophic lateral sclerosis (ALS) may be more appropriate for later-onset SMA. The utility values as suggested by the TLV were derived from the publication by Green et al., 2003. The utility values for the four severity levels of ALS are described in the table below. The assumption was that the mild ALS health state was similar to ***Walks Unaided*** and ***Stands Unaided*** SMA health states, the moderate ALS health state reflected the ***Stands/Walks with Assistance*** SMA health state, the severe ALS health state reflected the ***Sits and Rolls Independently*** and ***Sits and Crawls with Hands and Knees*** SMA health states and the terminal ALS health state reflects the ***Sits without Support but does not Roll*** health state.

Table 18. The ALS health state scale (ALS/HSS)

Level	Description	EQ-5D Value
1: Mild	Recently diagnosed; mild deficit only in one region (i.e. speech, arm, or leg); and functionally independent in speech	0.63
2: Moderate	Mild deficit in all three regions, or moderate to severe deficit in one region, while the other two regions are normal	0.56
3: Severe	Needs assistance in two or three regions; speech is dysarthric and/or patient needs assistance to walk and/or needs	0.27
4: Terminal	Non-functional use of at least two regions and moderate or non-functional use of the third region	-0.01

Abbreviations: ALS Amyotrophic lateral sclerosis; EQ-5D, European Quality of Life-5 Dimensions

The results using the surrogate ALS utility values, as described above, are shown in the table below. This results in an ICER for the later-onset SMA patients treated with nusinersen of £467,531, which is more than 60% less than the current base case.

Table 19. Base case results using ALS utility values scenario – later onset SMA, patient QALYs

Technology	Total costs (£)	Total LYG	Total QALYs	Inc. costs (£)	Inc. LYG	Inc. QALYs	ICER inc. (£/QALY)
RWC	184,312	19.61	14.52				
Nusinersen	3,148,754	20.99	16.88	2,964,442	1.38	2.37	1,252,991
Base case results using ALS utility values							
RWC	184,312	19.61	0.99				
Nusinersen	3,148,754	20.99	7.33	2,964,442	1.38	6.34	467,531

Abbreviations: ALS Amyotrophic lateral sclerosis; EQ-5D, European Quality of Life-5 Dimensions; ICER, incremental cost-effectiveness ratio; inc., incremental; LYG, life years gained; QALY, quality-adjusted life year

B25. CS, Section 3.4.2.1, page 131. Please comment on the appropriateness of using a mapping algorithm derived from a healthy cohort of schoolchildren aged 11-15 (Khan *et al*, *Pharmacoeconomics*, 2014) to determine EQ-5D scores for infant patients with SMA.

The mapping algorithm reported by Khan et al., 2014(57) is currently the only algorithm that mapped the PedsQL to a utility score such as the EQ-5D. We agree that the mapping algorithm is not ideal. However, as the PedsQL was the only HRQoL questionnaire administered in either clinical trial it was felt that the mapping should be undertaken.

B26. CS, Section 3.4.2.2, page 133. Please comment on the validity of the assumption that caregivers' baseline utility (value=0.915) is assumed to remain constant over the entire time horizon.

Our base case assumption was that the caregiver disutility was constant over time. In the scenario which applies an age dependent general population utility, the model applies a utility decrement based on a fixed percentage applied to the varying general population utility. For example, the caregiver utility for the ***Sits without Support*** health state was [redacted] and the general population utility was 0.915 at baseline. We estimated the "% decrease" as [redacted] That "% decrease" was then applied to the varying general population utility, which translated into a decreasing disutility over time. However, there is no data to support a decreasing caregiver disutility over time; it could also increase. Therefore, we

considered that applying a fixed disutility over time would add less uncertainty by not assuming a specific behaviour of the disutility over time.

In addition, we consider that our approach was conservative in nature, as a patient potentially has more than one caregiver and, in our model, we only applied the QALY gains of one caregiver. In the highly specialised technologies guidance (HST3) submission for Duchenne muscular dystrophy (DMD), the model applied caregiver disutilities for 2 caregivers (original submission included 3, but the ERG suggested 2). Our model also included caregiver mortality. However, after the primary caregiver (i.e. parent) is unable to provide care (or dies), there is no reason to believe that another caregiver (i.e. close family member) would not take their place. Hence, it is possible we are underestimating QALY gains associated with caregivers in our base case analysis.

Table 20. Caregiver utility scenarios

Caregiver utility scenario	Infantile-onset model ICER (including caregivers -£/QALY gained)	Later-onset model (including caregivers - £/QALY gained)
Base case	402,361	898,164
Age dependent general population utility	402,171	916,045
No mortality for caregivers (i.e. age at death set to large number)	402,171	887,927
2 caregivers (x2 disutility)	397,867	699,981

Abbreviations: ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year

B27. CS, Section 3.2.3, page 120. Please provide further details on the derivation of the discontinuation rule for nusinersen from the UK expert panel.

[redacted] In the base case, discontinuation of treatment is dependent on health state and/or scoliosis surgery. The health states from which patients discontinue are ***No Milestones*** in infantile onset SMA and ***Sits without Support but does not Roll*** in later onset SMA. In scenario analysis, the health states can be altered to ***No Milestones*** and ***Mild Milestones*** in infantile onset SMA. In both infantile and later onset SMA, discontinuation can be made independent of health state, with a proportion discontinuing from each health state.

B28. CS, Section 3.5, page 137. Please explain why the costs of scoliosis surgery have not been included in the model.

The health state costs in the base case analysis were based on the total annual costs by SMA type reported by Bastida (2016).(56) Although this study does not make specific reference to scoliosis surgery, it does mention that surgical procedures were included. Therefore, it was assumed that the costs associated with scoliosis surgery would have been captured in the annual costs by SMA type.

The annual costs by SMA type estimated by Klug et al. (2016)(58) can be used in a scenario analysis. In the cross-sectional study by Klug et al. (2016) 22% and 8% of SMA type II and

SMA type III patients, respectively, had scoliosis surgery. Hence, we assumed that the annual cost of SMA type II and SMA type III captured scoliosis surgery.

Alternatively, the model included a scenario where the health state costs are based on the costs of major clinical events, including scoliosis surgery. ICERS obtained in scenario analyses for infantile and later onset patients are reported below.

Table 21. Scenarios including major clinical events

	Base Case	Scenario	ICER (£QALY)
SMA type II			
Scenarios for health state costs	From published sources	Cost major clinical events only	442,838
Cost source	Bastida et al. 2016(56)	Klug et al. 2016(58)	405,194
SMA type II			
Scenarios for health state costs	From published sources	Cost major clinical events only	1,276,308
Cost source	Bastida et al. 2016(56)	Klug et al. 2016(58)	1,258,136

Abbreviation: SMA, spinal muscular atrophy

B29. CS, Section 3.5.1, page 137. The text states *"The cost of nusinersen in the first year of treatment (6 doses consisting of 4 loading doses and 2 maintenance doses) is £450,000 for a full year. Annual costs thereafter for 4 maintenance doses are £300,000."* This wording suggests that maintenance doses of nusinersen would be given at 3-monthly intervals. Elsewhere (for example, pages 31, 37, 117 and 167), the CS indicates that maintenance doses would be given at 4-monthly intervals. Please clarify.

Annual costs in year 2 and subsequent years should be for three maintenance doses (a 4-monthly dosing schedule), giving a cost of £225,000. In the first year of treatment, four loading doses are administered in the first 2 months (infantile onset) or 3 months (later onset), followed by two maintenance doses. The first year cost of £450,000 is therefore correct.

B30. CS, Section 3.5.1, page 140. The appendices of Bastida *et al* report the total annual costs presented in Table 46 (in Euros rather than pounds) for subgroups of patients with Type I, II and III SMA. Please clarify how the assumptions presented in Table 42 are used in the model.

Table 42 was constructed using clinical opinion and assumptions. In this table each of the cost items was distributed among four categories (respiratory care, gastrointestinal care, nutritional care, and orthopaedic care). For example, for the "Medical visits" item, we asked a clinical expert which proportion of the costs would be associated with each category [redacted]. The model then uses the proportions in Table 42 to calculate the total costs for each category.

The type I cost for "Medical visits" was [redacted] (Table 41 [2016 costs]). The costs distributed across the four categories would be: respiratory care [redacted] (i.e. [redacted]); gastrointestinal care [redacted]; nutritional care [redacted]; orthopaedic care [redacted]. The same procedure was applied to all cost items and then added up to estimate the total cost per category.

B31. Model, Sheets "Markov Nusinersen T2" column IU and "Markov RWC T2" column GP. Why are end-of-life costs not included in the later onset SMA model?

The mortality rate for later onset SMA patients is far lower than that seen in the infantile-onset SMA patients, with later-onset SMA patients having a life expectancy closer to the general population than the infantile onset patients. Thus, on average the end-of-life costs for the later-onset patients in the model would be heavily discounted and thus have a very small effect on the resulting ICER. However, a scenario where the end-of-life costs have been included for later-onset SMA patients is shown in the table below.

The table below shows that including end-of-life costs for the later-onset SMA patients has a marginal effect on the ICER.

Table 22. Base case results applying end-of-life costs scenarios – late onset SMA, patient QALYs

Technology	Total costs (£)	Total LYG	Total QALYs	Inc. costs (£)	Inc. LYG	Inc. QALYs	ICER vs. RWC (£/QALY)
RWC	184,312	19.61	14.52				
Nusinersen	3,148,754	20.99	16.88	2,964,442	1.38	2.37	1,252,991
Base case results applying the end-of- life costs							
RWC	188,309	19.61	14.52				
Nusinersen	3,152,192	20.99	16.88	2,963,883	1.38	2.37	1,252,755

Abbreviations: ICER, incremental cost-effectiveness ratio; inc., incremental; LYG, life years gained; QALY, quality-adjusted life year; RWC, real world care; SMA, spinal muscular atrophy

B32. Model, sheet "Model selection". The model received by the ERG is set to have a 60-year time horizon for the infant population, yet the CS states that the horizon is intended to be 40 years. The deterministic ICER presented in Table 50 reflects a 60-year time horizon. Please clarify the intended time horizon, and what time horizon has been used; please confirm the time horizon used for each of the results for the infant onset model presented in the CS and, if applicable, please provide corrected results.

The intended and modelled time horizon for infantile onset SMA is 60 years in the base case. The results therefore stand but the stated time horizon of 40 years should be corrected to 60 years.

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Sent by email 11 May 2018

Single technology appraisal

Nusinersen for treating spinal muscular atrophy [ID1069]

Dear Michael and Jonathan

Thank you for your clarification response. The Evidence Review Group (ERG) have some additional follow up questions. Please could you clarify the following five queries and upload your response to NICE Docs using this link: https://appraisals.nice.org.uk/request/49197

- The company's response to clarification question B12 relates to Zerres and Rudnik-Schoneborn (1995) rather than Zerres (1997). Can the company look at this again?
- We are struggling to replicate the subgroup results presented in CS Table 57 - how do we set the model to produce these?
- What time horizon do the company intend for the early onset model? The CS says it should be 40 years but all results presented relate to 60 years, the original model was set to 60 years but the later model was set to 40 years and the clarification response says its 60 years

- In the model "Default data T1" matrix for Month 13, there are only [redacted] patients including those who died, whilst there were [redacted] alive and at risk at the beginning. Why are the other [redacted] patients not accounted for?
- When patients discontinue nusinersen due to scoliosis surgery, is the model applying the sham transition matrix?

We would be most grateful if you are able to answer these queries by 5:00pm Tuesday 8 May to allow the ERG to continue their review.

Kind regards

Jo Ekeledo, Project Manager - Technology Appraisals & HST

Nusinersen for treating spinal muscular atrophy [ID1069]

Response to further clarification questions

Submitted by Biogen Idec Ltd.

Single technology appraisal (STA)

National Institute of Health and Care Excellence

Submitted 8th May 2018

Table of Contents

List of Tables

Table of Abbreviations

Abbreviation	Definition
ARR	Absolute risk reduction
CI	Confidence interval
ERG	Evidence Review Group
IPD	Individual patient data
ITT	Intention to treat
LOCF	Last observation carried forward
NICE	National Institute for Health and Care Excellence
OR	Odds ratio
RR	Relative risk
ScHARR	School of Health and Related Research
SD	Standard deviation
SE	Standard error

1. Overview

This document contains Biogen's response to five further clarification questions from the Evidence Review Group (ERG), the School of Health and Related Research (ScHARR), and the technical team at the National Institute of Health and Care Excellence (NICE) that consulted with Biogen on 4th of May 2018.

2. Response to clarification questions

Please find below responses by Biogen to each of the questions raised by the ERG, ScHARR, and the technical team at NICE.

The company's response to clarification question B12 relates to Zerres and Rudnik-Schoneborn (1995) rather than Zerres (1997). Can the company look at this again?
We have amended the responses below to ensure it incorporates Zerres et al. (1997).

B12: CS Section 3.3.4.1 page 126 and CS Appendix P, page 212. Please provide further details on the use of data from Zerres *et al*:

(a) What is meant by "some uncertainty as to the number of risk" (a number of risk table was not provided in the paper)?

Re-constructing Individual Patient Data (IPD) is more reliable if the number at risk is known for different time points. If this is not provided, assumptions can made for when censoring occurs. Censoring information in the form of tick marks on Kaplan-Meier charts can be used to create the number at risk table. This type of chart was presented by both Zerres and Rudnik-Schoneborn (1995)(1) and Zerres et al. (1997)(2). However, the charts were of poor quality and a degree of judgement was required when there was more than one patient censored at the same time-point. Kaplan-Meier plots from the re-constructed data looked identical to the original charts so any bias should be minimal.

(b) How were the IPD reconstructed?

The method described by Guyot et al. (2012)(3) was used to re-construct patient level data.

(c) How do the characteristics of this population compare with that of ENDEAR? Was any adjustment to the original KM made (as with the Gregoretti data)?

Zerres and Rudnik-Schoneborn (1995)(1) was used to model survival of patients with infantile onset. Although the Zerres and Rudnik-Schoneborn (1995)(1) data appear suitable to use for long-term extrapolation, there is some uncertainty as to how comparable these data are because they are from German patients and the fit does not take into account any improvement in survival with time. Moreover, Zerres and Rudnik-Schoneborn (1995)(1) did not report the proportion of patients who received permanent ventilation.

The population in Zerres et al. (1997) were all German and Polish patients who had achieved the ability to sit unaided. We used Zerres et al. (1997) to model survival of patients achieving motor milestones characteristic of later-onset patients. No adjustments were made to the original Kaplan-Meier data from either study. It was assumed that time was from birth for both studies.

The Gregoretti et al. (2013)(4) also presented patients from birth and so 5.56 months was subtracted from survival times and patients with negative values were removed. This study included more recently diagnosed patients and it was clear what treatment patients received. However, survival in the "continuous non-invasive respiratory muscle aid" arm appeared to be greater than that expected from the clinical advice we received for UK patients and the sample size was small. From this paper there is insufficient information to draw conclusions on why survival was higher in the Italian patient population compared to the UK patient population.

The results from separate models fitted to the external data sets were used in sensitivity analyses because we could not be sure how comparable these data sets were to the ENDEAR trial data.

We are struggling to replicate the subgroup results presented in CS Table 57 - how do we set the model to produce these?

Subgroup results in Table 57 were not updated correctly and have been adjusted below in Table 1. Because overall survival for the subgroups was based on the Kaplan-Meier curves, we also added the comparison to the ITT population using the Kaplan-Meier curve to model OS.

The following settings in the model should lead to the results below. Please ensure to return to the base case settings of the model for each step. In case the model is set to a 40 year time horizon by default, please change this on sheet 'model selection' and set the time horizon for the infantile onset population to 60 years.

For the Intention To Treat (ITT) population – ITT each arm (to use the Kaplan-Meier instead of the flexible spline based Weibull function with 1 knot, update the dropdown in row 20)

- No steps required

For the ITT population – ITT both arms (to use the Kaplan-Meier instead of the flexible spline based Weibull function with 1 knot, update the dropdown in row 20)

- On sheet 'Efficacy T1', please set "*Please select one of the scenarios to define the mean CHOP INTEND score per health state"* to "*ITT population: all measurements during trial follow up – both arms combined."*

For the ≤12 weeks disease duration – ≤ 12 weeks each arm

- On sheet 'Efficacy T1', under 'Population' please set "*Please select the population"* to "*≤12 weeks disease duration."*

- On sheet 'Efficacy T1', please set the dropdown in row 20 "*Please choose from the following parametric survival functions*:" to the Kaplan-Meier function. This enables a user input cell in J23. Please set it to 1 to use the subgroup KM overall survival.

- On sheet 'Efficacy T1', under 'Treatment Effects and Disease Progression Probabilities After the End of Trial Follow-Up' please set "*Please select one of the scenarios to define the mean CHOP INTEND score per health state"* to "*Subgroup ≤12 weeks disease duration: all measurements during trial follow up – each arm."*

- When the scenario analyses in the dropdown on row 79 on sheet 'Efficacy T1' (OS treatment effect scenarios) are set to "Apply in trial HR indefinitely" or "Taper the HR over a defined period", please set "*Select the subgroup HR"* to "*Disease duration ≤ 12 weeks."* under 'Treatment Effects and Disease Progression Probabilities After the End of Trial Follow-Up' section

For the ≤12 weeks disease duration – ≤ 12 weeks both arms

- On sheet 'Efficacy T1', under 'Population' please set "*Please select the population"* to "*≤12 weeks disease duration."*

- On sheet 'Efficacy T1', please set the dropdown in row 20 "*Please choose from the following parametric survival functions*:" to the Kaplan-Meier function. This enables a user input cell in J23. Please set it to 1 to use the subgroup KM overall survival.

- On sheet 'Efficacy T1', under 'Treatment Effects and Disease Progression Probabilities After the End of Trial Follow-Up' please set "*Please select one of the scenarios to define the mean CHOP INTEND score per health state"* to "*Subgroup ≤12 weeks disease duration: all measurements during trial follow up – both arms combined."*

- When the scenario analyses in the dropdown on row 79 on sheet 'Efficacy T1' (OS treatment effect scenarios) are set to "Apply in trial HR indefinitely" or "Taper the HR over a defined period", please set "*Select the subgroup HR"* to "*Disease duration ≤ 12 weeks."* under 'Treatment Effects and Disease Progression Probabilities After the End of Trial Follow-Up' section

For the >12 weeks disease duration – >12 weeks each arm

- On sheet 'Efficacy T1', under 'Population' please set "*Please select the population"* to "*> 12 weeks disease duration."*

- On sheet 'Efficacy T1', please set the dropdown in row 20 "*Please choose from the following parametric survival functions*:" to the Kaplan-Meier function. This enables a user input cell in J23. Please set it to 1 to use the subgroup KM overall survival.

- On sheet 'Efficacy T1', under 'Treatment Effects and Disease Progression Probabilities After the End of Trial Follow-Up' please set "*Please select one of the scenarios to define the mean CHOP INTEND score per health state"* to "*Subgroup > 12 weeks disease duration: all measurements during trial follow up – each arm."*

- When the scenario analyses in the dropdown on row 79 on sheet 'Efficacy T1' (OS treatment effect scenarios) are set to "Apply in trial HR indefinitely" or "Taper the HR over a defined period", please set "*Select the subgroup HR"* to "*Disease duration > 12 weeks."* under 'Treatment Effects and Disease Progression Probabilities After the End of Trial Follow-Up' section

For the >12 weeks disease duration – >12 weeks both arms

- On sheet 'Efficacy T1', under 'Population' please set "*Please select the population"* to "*> 12 weeks disease duration."*

- On sheet 'Efficacy T1', please set the dropdown in row 20 "*Please choose from the following parametric survival functions*:" to the Kaplan-Meier function. This enables a user input cell in J23. Please set it to 1 to use the subgroup KM overall survival.

- On sheet 'Efficacy T1', under 'Treatment Effects and Disease Progression Probabilities After the End of Trial Follow-Up' please set "*Please select one of the scenarios to define the mean CHOP INTEND score per health state"* to "*Subgroup > 12 weeks disease duration: all measurements during trial follow up – both arms combined."*

- When the scenario analyses in the dropdown on row 79 on sheet 'Efficacy T1' (OS treatment effect scenarios) are set to "Apply in trial HR indefinitely" or "Taper the HR over a defined period", please set "*Select the subgroup HR"* to "*Disease duration > 12 weeks."* under 'Treatment Effects and Disease Progression Probabilities After the End of Trial Follow-Up' section

Table 1. Table 57 of the CS - updated

Population	Mean monthly rate of CHOP INTEND increase/decrease	Mean CHOP INTEND score per health state	Incremental cost (£)	Incremental QALY*	ICER (£/QALY gained)*
ITT population (flexible spline Weibull with 1 knot)	Nusinersen: [redacted] / RWC: [redacted]	ITT each arm	2,187,311	5.37 5.44	407,605 402,361
		ITT both arms	2,175,081	5.31 5.38	409,235 404,015
ITT population (Kaplan-Meier)	Nusinersen: [redacted] / RWC: [redacted]	ITT each arm	2,206,203	5.44 5.51	405,825 400,716
		ITT both arms	2,193,837	5.38 5.45	407,434 402,352
≤12 weeks disease duration	Nusinersen: [redacted] / RWC: [redacted]	≤ 12 weeks each arm	2,896,474	7.72 7.81	375,237 370,915
		≤ 12 weeks both arms	2,889,196	7.69 7.78	375,775 371,458
>12 weeks disease duration	Nusinersen: [redacted] / RWC: [redacted]	> 12 weeks each arm	1,826,521	3.77 3.86	484,614 473,247
		> 12 weeks both arms	1,821,951	3.75 3.84	485,766 474,355

*Patient perspective (upper), combined patient and carer perspective (lower)
Source: ENDEAR CSR(5)

What time horizon do the company intend for the early onset model? The CS says it should be 40 years but all results presented relate to 60 years, the original model was set to 60 years but the later model was set to 40 years and the clarification response says its 60 years

The time horizon for the infantile onset model should be set to 60 years as there is still benefit accruing at 40 years. By setting it to 60 years, the entire survival distribution is captured.

In the model "Default data T1" matrix for Month 13, there are only [redacted] patients including those who died, whilst there were [redacted] alive and at risk at the beginning. Why are the other [redacted] patients not accounted for?

We did not use any imputation for missing visits due to study closure (all ongoing subjects were transitioned to SHINE). The main analyses in the trial were based on subjects in the Efficacy Set, which includes subjects who have the opportunity for at least day 183 assessment; therefore, no imputation was used in the efficacy set for missing visits due to study closure.

Table 2, Table 3 and Table 4 show the score change from baseline for the ITT population assuming Last Observation Carried Forward (LOCF) for missing assessments. Results show that motor milestone response and CHOP-INTEND response are still clinically meaningful and highly statistical significant.

The attached excel file includes the patient counts at each assessment for the ITT population assuming LOCF for missing assessments. When using these patient counts to calculate the transition matrices, the ICER increased by £4,106 per QALY gained (Table 5). However, as motor function increases over time for nusinersen treated patients and decreases over time for the sham patients, the LOCF approach provides a conservative estimate of the treatment effect. Also, with the LOCF assumption the deaths in the sham arm could be underestimated.

Table 2. [redacted]

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

[redacted]

Table 3. [redacted]

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

[redacted]

Table 4. [redacted]

[redacted]

Table 5. Base case results LOCF

	Incremental cost (£)	Incremental QALY*	ICER (£/QALY gained)*
Base case (no imputation for missing assessments)	2,187,311	5.37 5.44	407,605 402,361
Base case assuming LOCF for missing assessments	2,198,661	5.34 5.41	411,711 406,434

*Patient perspective (upper), combined patient and carer perspective (lower)

When patients discontinue nusinersen due to scoliosis surgery, is the model applying the sham transition matrix?

Yes. The model applies the sham transition matrix to patients discontinuing due to scoliosis surgery.

Reference list

1. Zerres K, Rudnik-Schöneborn S. Natural history in proximal spinal muscular atrophy. Clinical analysis of 445 patients and suggestions for a modification of existing classifications. Arch Neurol. 1995;52:518–23.

2. Zerres K, Rudnik-Schöneborn S, Forrest E, Lusakowska A, Borkowska J, Hausmanowa-Petrusewicz I. A collaborative study on the natural history of childhood and juvenile onset proximal spinal muscular atrophy (type II and III SMA): 569 patients. J Neurol Sci. 1997;146(1):67–72.

3. Guyot P, Ades AE, Ouwens MJNM, Welton NJ. Enhanced secondary analysis of survival data: reconstructing the data from published Kaplan-Meier survival curves. BMC Med Res Methodol. 2012;12(1):9.

4. Gregoretti C, Ottonello G, Chiarini M, Mastella C, Ravà L, Bignamini E, et al. Survival of Patients With Spinal Muscular Atrophy Type 1. Pediatrics. 2013;131(5):1509–14.

5. Biogen and IONIS Pharmaceuticals data on file. CS3B (ENDEAR). A phase 3, randomized, double-blind, sham-procedure controlled study to assess the clinical efficacy and safety of ISIS 396443 administered intrathecally in patients with infantile-onset spinal muscular atrophy. Clinical study report. Study. 2017.

NICE National Institute for Health and Care Excellence

Patient organisation submission

Nusinersen for treating spinal muscular atrophy [ID1069]

Thank you for agreeing to give us your organisation's views on this technology and its possible use in the NHS.

You can provide a unique perspective on conditions and their treatment that is not typically available from other sources.

To help you give your views, please use this questionnaire with our guide for patient submissions.

You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type.

Information on completing this submission

- Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable
- We are committed to meeting the requirements of copyright legislation. If you intend to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Your response should not be longer than 10 pages.

About you	
1.Your name	[redacted]

2. Name of organisation	Muscular Dystrophy UK
3. Job title or position	[redacted]
4a. Brief description of the organisation (including who funds it). How many members does it have?	Muscular Dystrophy UK (previously known as the Muscular Dystrophy Campaign) is the charity bringing individuals, families and professionals together to beat muscle-wasting conditions. Founded in 1959, we have been leading the fight against muscle-wasting conditions ever since. We bring together more than 60 rare and very rare progressive muscle-weakening and wasting conditions, affecting around 70,000 children and adults in the UK. We fund research, provide vital information, advice, resources and support for people with these conditions, their families and the professionals who work with them. We are also a member of NHS England's Paediatric Neurosciences and Adults Clinical Reference Groups. Our funding comes from donations, gifts, grants and trusts. We have received funds from 11 pharmaceutical companies, including the manufacturers of nusinersen. These were educational grants and one grant for mitochondrial disease research. The funds equate to 0.1% of our overall income. We don't receive any government funding.
4b. Do you have any direct or indirect links with, or funding from, the tobacco industry?	No.
5. How did you gather information about the experiences of patients and carers to include in your submission?	Information has been gathered by: • Disease impact statements from people affected by spinal muscular atrophy (SMA) • Published evidence on disease burden • Media case studies and reports • A survey conducted by SMA Support UK.

Living with the condition	
6. What is it like to live with the condition? What do carers experience when caring for someone with the condition?	SMA is a complex, rare inherited neuromuscular condition that affects the lower motor-neurons in the spinal cord. It leads to the gradual loss of the ability to walk, crawl, move, breathe and swallow. It is a condition that requires complex medical support and is the leading genetic cause of death in infants. Type 1, the most severe and also most common, leads to 80% of affected children dying before the age of 2. Type 2 and 3 still result in significant muscle weakness and disability: Type 2 patients never walk and many Type 3 patients will lose the ability to walk. **A parent of a child with Type 2 said:** "The major impact for our son is in his physical ability to move. He cannot crawl, stand or walk, and has very restricted movement and strength in his body. Additionally, his breathing is affected as he has little strength in his torso, which directly affects his lung capacity. His breathing can be shallow and quick." **A teenager with SMA Type 2 said:** "Every new day is a new challenge for me and my family. Every breath is a challenge, every dress up is a challenge. We are trying to keep the motivation, but is very difficult when we see how is getting worse my condition. Do you know how is when you cannot scratch your head when is itchy? Do you know how it is when you are hungry or thirsty and you cannot even hold a mug in your hand?" Types 1, 2 and 3 are all childhood-onset forms of SMA. Improvements in standards of care mean that people with Types 2 and 3 of SMA are now living into adulthood with the progressive effects of the condition and the associated care needs that come with this. **An adult with Type 2 commented:** "My strength is getting less and less. I used to be able to crawl and sit. Now holding my own neck up and swallowing food is becoming problematic. I rely on help to do things I want/used to be able to do easily. For example, I can't roll in bed anymore and need so much help that it disturbs my sleep…My bladder is getting weaker too- emotionally this bothers me. My life is great but for the SMA. I feel like a burden and I can't stop myself getting weaker…I live in fear I will get a chest infection and die like my younger brother did (who also had type 2 SMA)." Children require help with washing, dressing, toileting, transferring, eating / drinking. Chest weakness and lung underdevelopment can result in serious respiratory symptoms, such as infections, a weak cough and sleeping problems due hyperventilation. These respiratory issues necessitate constant vigilance and care due to the

	increased risk of aspiration which can be life threatening. Night care is needed for many people with SMA and parents provide almost all unpaid care. Paid care packages to help parents and families for children range from 0 to 40 hours / week and for adults, from 0 to 70 – 90 hours / week. However, finding and coordinating good paid carers is extremely challenging. The financial impact on affected families is considerable due to expenditure on specialised equipment, adaptations and support. There are also some psychological effects of living with SMA, as identified by patients and carers. These include; confronting premature death, difficult treatment choices, fear at loss of function abilities and coming to terms with lost expectations. **A Mum of a child with Type 2 commented:** "Keeping our son well throughout the winter proves challenging. The slightest cough, sniffle has me on pins for fear it leads to pneumonia or a collapsed lung. The emotional battle is pure torture and my anxiety is ridiculous. I live in constant fear that his body may one day be too weak to recover and that thought tears through my heart. My physical health is poor due to lifting, not sleeping or eating enough." **Another Mum of a 2 year old girl with SMA Type 2 said:** "It is frustrating for both parents and children. I watch my daughter and realise it is frustrating for her. I can see how she gets upset each time she tries to do something, and when she is unable to, she loudly cries "I can't, I can't". She is 2 years old and she likes to be independent and explore but her condition limits her dramatically…I can see, is that she knows something is not right with her, I can see her sad face each time she stares at others kids while they are jumping and running around…As both mother and carer it is really difficult, tiring, debilitating, depressing, stressful and expensive to deal with this disability."
Current treatment of the condition in the NHS	
7. What do patients or carers think of current treatments and care available on the NHS?	Current treatments focus on the management of symptoms, rather than addressing their underlying genetic cause. There are no other medicines currently available to help patients with SMA. Although there is currently no cure for SMA, this does not mean that nothing can be done. There are a range of options aimed at managing symptoms, reducing complications of muscle weakness and maintaining the best quality of life. Other treatments are typically non-drug treatments. People with SMA would require the input of a multidisciplinary healthcare team including specialists in physiotherapy, palliative care, respiratory medicine and speech and language therapy. These are outlined in the internationally agreed Standards of Care for SMA.

Management interventions include:

- Respiratory support, including chest physiotherapy, oral suctioning, medication to reduce secretions, cough assist and invasive and non-invasive ventilation;
- Feeding support;
- Help with managing constipation;
- Physiotherapy and occupational therapy;
- Treatment for spinal scoliosis, including a lycra suit, spinal brace or jacket and surgery.

An adult with Type 1 said: "Pain and fatigue make most days unbearable, I have recently started to experience increasing issues with swallowing…This severely limits the options available for pain control (timed-release mechanisms, for example). The fatigue and eating has recently begun to impact upon my food intake, and I am losing weight sporadically less and less. I am going to have a PEG tube fitted soon, which is going to be very difficult to place due to a very severe scoliosis/kyphosis …. I am concerned that many medications that I need, for instance, esomeprazole, do not come in a form that can go through a feeding tube about completely negating the delivery mechanism."

The mother of a 3 year old with Type 2 said: "My son has been admitted into Intensive Care with lung collapses and consequently been intubated 7 times and he is only 4 years old… When he is not in hospital we are petrified of him becoming ill again and try to live life to its fullest whilst protecting him from numerous bugs…The care we provide for him is intense yet does not mean that he will not become ill again....we live in fear. We do not function as a 'normal' family would."

An adult with Type 3 said: "As the SMA deteriorates it becomes more expensive to buy the equipment that makes living with the condition easier. I have had to take ill health retirement a couple of years ago which has resulted in a significant reduction in income. I have been using my savings to install a stair lift, to adapt a Motability vehicle, buy a rolator and to pay for some physiotherapy. There will come a point when these savings will run out. I feel that my life is slowly shutting down as the level of pain increases and what I can do decreases."

Families, especially those with children with Type 1 or 2, spend a considerable amount of time on daily exercises to help with contractures and pain. Interventions for those with Type 2 to manage choking, swallowing, fatigue with feeding, digestion, constipation and managing weight, may include tube feeding, gastrostomy, medication and dietary management. A major management tool, however, is vigilance and time on the part of carers.

	The number of health and social care professionals involved with each person can be as many as 7 for adults and 10 for children. Most children require hospital appointments (2 – 6 / month). Attending these and generally managing to coordinate care and support depends on the complexity of the individual's condition and can be very time consuming (2 – 80 hours / month).
8. Is there an unmet need for patients with this condition?	Nusinersen is the first and only treatment for SMA to receive marketing authorisation from the European Medicines Agency. This means there is a serious unmet need for patients in the UK living with SMA. All the interventions mentioned are useful and often essential in helping to alleviate the most serious complications of SMA. However, in most cases they do not deliver long-term improvement and are just ways of keeping patients as comfortable and mobile as possible while their condition continues to decline. In addition, many of the interventions necessitate constant management and increasing amounts of care, further impacting parents and others responsible for delivering that care. **One mother listed all of the unmet needs of her daughter, who has SMA Type 2:** "Daily physiotherapy, hydrotherapy, horse riding therapy, electric wheelchairs, lightweight manual wheel chairs, occupational therapy, carer's assistance, medical knowledge of SMA inside the NHS, etc." **As the Dad of a 2 year old girl with SMA Type 2 said:** "When she was diagnosed with SMA Type 2, our world began to fall apart. All the hopes and dreams we had for our little girl began to fade away. When we heard that NICE was starting a review for Spinraza, our spirits were immediately lifted. We know it's not a cure, but it could give her the chance to do the simple things that other children take for granted, like dressing up and playing on her bed. This would be the biggest blessing for my daughter."
Advantages of the technology	
9. What do patients or carers think are the advantages of the technology?	Nusinersen is the first treatment that improves outcomes for patients with 5q SMA and has the potential to save the lives of babies with Type 1. Many regard the treatment as a bridge to a longer-term potential cure for future children. For most children receiving Nusinersen it is arresting the progress of the condition. **A parent of a child who had received 5-7 nusinersen injections said:** "After years of deterioration and hearing that everything is getting worse at every review, this year for the first time our daughter heard that she's doing better, both at spirometry and CHOP. This gave her hope that her life can improve, the trouble of stretching and physio is worth it, and there is a future for

	her. Her biggest joy is being able to cough better, and deal with mucus plugs without so much chest physio and cough assist. Also, previously every illness (respiratory or gastric) meant non-reversible deterioration, and now she bounces back almost to the same level as before the illness." Clinical trials showed significant improvement in children's motor function, allowing them to achieve, or maintain, physical milestones that they would never reach without treatment, and to survive longer than expected considering the typical course of the condition. Some children who would never have sat independently have been able to and some have been able to crawl or even walk. Research suggests that the earlier the intervention, the stronger the chance of positive treatment outcomes. However, there is also evidence that nusinersen could benefit patients with other types of SMA, including adults, such as slowing down or stopping the conditions progress. **As one adult with Type 2 SMA said:** "I'm desperate to try this drug. Even a bit of strength or slowing down the atrophy process would make a huge difference to my life and my family (who help me day to day)." The progressive nature of SMA means that, for many, stabilisation is as valuable as improvement. Changes don't have to be dramatic to make a big difference to peoples' lives if they enable people to live more independently. **A Mum of a young boy with Type 2 SMA commented that:** "If my son were to receive Spinraza, he may be able to stand up or even take a step. This would be life changing. However, if this were never to happen, Spinraza could still massively enhance his quality of life by enabling him to do many day to day tasks which we all take for granted. Such as: Manual dexterity/strength - Taking off a pen top, opening a birthday or Christmas present, opening an envelope, opening a packet of crisps or sweets, pushing a straw into a carton, opening a bottle or jar" Caring for someone with SMA can be demanding and affect all aspects of life. It puts considerable stress on carers and families emotionally, financially, physically and practically. Any improvement in the patient's health would therefore potentially have a very positive impact on the family and carers. **A parent of a child on nusinersen said:** "This has completely turned our lives around…We were told to enjoy our time left with our child at point of diagnosis and before treatment had become available which was simply heart-breaking. Life as we knew it stopped. Numb with pain and filled with fear we were unable to work/sleep/deal with normal day to day life. However now I'm witnessing first-hand the benefits of nusinersen I'm simply filled with hope for my child's future. This has had such a positive turnaround for our family, myself, my husband, siblings, grandparents. I feel like I'm no longer waiting on a ticking time bomb, but now look forward to my child's future."

	The Mum of a 2 year old with Type 1 SMA said: "Every baby born in this country should be given equal opportunity to fulfil his or her potential and the new medicines that are being developed to treat and improve the lives with those born with a disadvantage should be available. The gains are not always apparent, but small improvements are huge but may seem insignificant to some. A baby, child or an adult with a rare condition such as Spinal Muscular Atrophy must fight their way through life, they shouldn't have to fight for the correct care and treatment." Although not a cure, the potential to slow down or stop progress would have an immense impact on both those with the condition and their unpaid carers, reducing dependency and freeing up time that might allow more sleep, less social isolation and more opportunities to live, work and enjoy leisure time in ways they choose. **As one parent of a child on nusinersen said:** "(It) is giving me hope. It makes me strong, because I know I do have more time with my child."
Disadvantages of the technology	
10. What do patients or carers think are the disadvantages of the technology?	We know that whilst the treatment has been highly effective in most treated children, there are some who have not responded to the treatment. There are also some patients who are too weak, due to their condition, to receive the intrathecal injection via a lumbar puncture or found the procedure to be too traumatic. **As one parent of a child described:** "Physically: It did not affect him significantly giving him the injection. He did not reach any milestones. He developed the ability to move his forearms for short periods against gravity and in his legs small movements, but not against gravity. We have since learnt that this may not have been a reflection of the benefits of Nusinersen as our Neurologist explained that babies become relatively stronger as they grow. Emotionally: Caused him to cry for a matter of minutes to administer the drug." However, despite any concerns, **102 of 119 respondents to SMA Support UK's survey said that they would want the treatment for themselves as person with SMA/their relative with SMA.** Although some people might chose not to have the treatment they should at least be given the opportunity and then they can make an informed decision.

Patient population	
11. Are there any groups of patients who might benefit more or less from the technology than others? If so, please describe them and explain why.	Data suggests that the earlier the intervention, the stronger the chance of positive treatment outcomes. **However, as one parent of a child with Type 2 said:** "From research that we have read, the more earlier you have access to the treatment is of greater benefit however from other people's personal experiences, even with older children and young adults it has helped them to achieve more muscle strength and maintain their skills and make them less fatigued which can make life more fulfilling if you are not tired all the time." **138 of 151 respondents (91%) to SMA Support UK's survey said that they believed that if it is clinically safe for someone with 5q SMA to be treated with nusinersen, they should be given the opportunity to do so.** **A parent of a 2 year old on nusinersen said:** "We feel this treatment would be a life saver for people with SMA & with the improvements we have seen in our child we feel this treatment should be considered for all types. To see milestones being reached that were never possible before is an incredible achievement for our children. Even to have the ability to sit up, feed yourself, lift & play with toys gives our children so much more opportunity to enjoy life than they would have without this treatment."
Equality	
12. Are there any potential equality issues that should be taken into account when considering this condition and the technology?	There is currently a 'postcode lottery' of access to the expanded access programme for Nusinersen. It is vital that patients are able to access treatment locally due to the frequency of treatment and complex means of administration. Making people travel incurs financial and emotional costs. It can also impact on people's health as many patients would be physically fragile making travelling challenging and unsafe.

Other issues	
13. Are there any other issues that you would like the committee to consider?	

Key messages

15. In up to 5 bullet points, please summarise the key messages of your submission:

- SMA is a serious and progressive muscle-wasting condition and managing it is physically, emotionally and practically demanding for both the person with the condition and their family/carers.
- Nusinersen is the first and currently only treatment for people with SMA and has been shown to have positive, potentially life-changing and life-saving results, as well as representing a bridge to emerging treatments for people with SMA.
- Evidence shows that treated individuals have lived longer than clinicians would have expected and are achieving and maintaining physical milestones they would never have reached without treatment.
- Although not a cure, the potential to slow down or stop progress of the condition would have an immense impact on the lives of all people affected by SMA, enabling greater independence.
- If it is clinically safe for someone with 5q SMA to be treated with Nusinersen then they should be given the opportunity to access the treatment.

NICE National Institute for Health and Care Excellence

Patient organisation submission

Nusinersen for treating spinal muscular atrophy [ID1069]

Thank you for agreeing to give us your organisation's views on this technology and its possible use in the NHS.

You can provide a unique perspective on conditions and their treatment that is not typically available from other sources.

To help you give your views, please use this questionnaire with our guide for patient submissions.

You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type.

Information on completing this submission

- Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable
- We are committed to meeting the requirements of copyright legislation. If you intend to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Your response should not be longer than 10 pages.

About you	
1.Your name	[redacted]

2. Name of organisation	The SMA Trust
3. Job title or position	[redacted]
4a. Brief description of the organisation (including who funds it). How many members does it have?	The SMA Trust was founded in 2003 as the only UK charity solely focussed on research into a cure and treatments for spinal muscular atrophy. Recent advances in the drug development pipeline have led to the expansion of our remit into advocating/campaigning on behalf of patients, with the aim of accelerating access to treatments. Vision: a world where SMA is curable and treatable Mission: to radically improve the lives of people affected by SMA by funding world-class research and accelerating progress towards treatments and a cure We do not receive funding from the pharmaceutical industry and rely entirely on voluntary donations to fund our work. We are not a membership organisation but work closely with many individuals and families affected by SMA in a number of ways, such as fundraising, awareness-building and campaigning. Many of these have formed their own voluntary regional networks ('teams'), usually named after someone who is either living with SMA or who has died. Communication with these groups is via newsletters, email and social media.
4b. Do you have any direct or indirect links with, or funding from, the tobacco industry?	No
5. How did you gather information about the experiences of patients and	Information has been gathered from a variety of sources, including a bespoke UK survey, a similar Scottish survey recently conducted for the Scottish Medicines Consortium (both conducted by SMA Support UK) and previous international patient surveys in which we have been involved through our membership of SMA Europe and close working relationship with the US patient organisation, Cure SMA.

carers to include in your submission?	The UK survey generated 136 responses and was conducted between Jan and Feb 2018. SMA Support UK collated the results and have given permission for all of us to refer to them as part of our submissions. Please see SMA Support UK's submission for full survey details. The European Patient Survey (August 2015) generated 822 responses from many different European countries. It included patients and carers/parents affected by Types II and III SMA. (Please see Appendices) A Qualitative Project to Obtain Information from Spinal Muscular Atrophy Patients, Caregivers, and Clinicians (US 2015) canvassed the experiences of 91 patients and carers across all SMA types. Methodology involved 16 focus groups and 37 interviews. (Please see Appendices) The Voice of the Patient (US April 2017) was published as part of the FDA's Patient-Focused Drug Development Programme. 98 of meeting attendees either had SMA or were parents/carers of a child with SMA. A further 160 attended via webcast. The meeting focused on the burden of disease and unmet needs in people with SMA and their families, as well as exploring perspectives on current/future treatments, including treatment benefits they considered clinically meaningful. (Please see Appendices) For the purposes of this submission, we have concentrated on the UK survey as it has more direct relevance, but it is worth pointing out that the main conclusions were very similar to the recent Scottish and international studies and therefore provide extra reassurance as to accuracy.
Living with the condition	
6. What is it like to live with the condition? What do carers experience when caring for someone with the condition?	SMA is a complex, progressive neuromuscular condition, currently the leading genetic cause of death in infants. It causes muscle weakness, affecting crawling and walking, arm, hand and neck movement, breathing and swallowing. For a full description of the condition, and to avoid duplication, please see the SMA Support UK submission, with which we fully concur. Although the way in which SMA affects people can vary according to Type and age, there are nevertheless many symptoms and effects which are common across different Types and age groups. These can be grouped into broad categories as follows: **1. Physical/health**

People living with SMA experience many health problems. The recent UK survey highlighted the main health impacts reported by patients/carers. Top mentions were contractures, pain, scoliosis and eating difficulties, all mentioned by over 50% of the sample (n=128). In the Scottish survey, breathing difficulties and constipation were also mentioned by over half the respondents (n=19).

The nature of SMA means that one of the main effects is severely compromised mobility, progressively worsening over time, resulting in patients' reliance on a range of interventions and equipment. In the UK survey 83% (n128)) of total respondents used a powered wheelchair, with more than 60% (n=128) of the sample also mentioning the following: home adaptations (especially bathroom/toilet), wheelchair accessible vehicles, specialist beds and fixed/mobile hoists.

2. Self-care

Progressive loss of strength in legs, arms and hands means that SMA patients experience many difficulties with daily living and self-care. The UK survey showed that the majority of respondents required full support in a number of key areas: problems with dressing, transfers, toileting, meal preparation and washing were all mentioned by over 70% (n=128) of respondents. These numbers were even higher in the more severely affected sub-groups.

Night-time care is also a major factor for many SMA patients, with many not able to turn themselves, whilst others need other help, eg relating to breathing equipment and suction. Within the total UK sample, 66% (n=128) require night-time care, with 48% needing it 3 – 6 times per night. In Scotland, 77% (n19) required night-time care.

'The biggest challenges are: lack of sleep (I wake up 8-10 times a night, every night, to turn my son); emotional distress at seeing my son's strength deteriorate in front of my eyes, despite everything we do to keep him as strong and as well as possible…'
Type 2, age 3-4 years, mother

3. Usual Activities

SMA does not affect cognitive ability and patients' desire to live as active and fulfilling a life as possible is therefore very strong.

'Like most people with SMA I'm intelligent and keen to participate in work and with friends but staying healthy is like running the wrong way on an escalator because it's a battle that you can't win'
Type 2, age 26-35 years, adult

This presents considerable challenges and isn't possible without significant interventions and support. In the UK survey respondents (patients and carers) were asked whether the interventions and support they receive are enough for the patient to manage certain aspects of daily living. Over 50% (n=132) answered *'no/not really'* to the

following descriptors: getting out and about, keeping physically well, emotionally well, socially connected, getting enough sleep and working/studying the hours you wish.

Another limiting factor is the amount of time spent by SMA patients/carers attending hospital and other associated appointments. In the UK survey 57% (n128) of respondents had seen between 6 and 20 health/social care professionals in the last 12 months.

Fatigue can be another major limitation for many SMA patients, often preventing them from having similar work patterns and social lives to their peers. In the US 72% (n=66) of Type 2/3 patients/carers mentioned fatigue as one of the four symptoms that have most impact on their lives.

4. Anxiety/Depression

In the US, 10 psychosocial effects of living with SMA were identified by patients and carers:

- Confronting premature death
- Difficult treatment choices
- Fear at loss of function abilities
- Coming to terms with lost expectations
- Loss of sleep and increased stress
- Social discomfort and stigma
- Limitations on social activities
- Struggle to achieve independence
- Uncertainty and helplessness
- Financial pressure

Financial pressure has a double impact, coming partly from ***additional expenses*** not funded by the NHS (eg wheelchairs, car seats, wheelchair accessible vehicles, home adaptations etc) and partly from ***reduced income***, as parents/unpaid carers have to give up their jobs or reduce their working hours in order to provide care. In the UK survey, out of 146 unpaid carers, 39% (57) had given up work completely and 25% (36) had gone down to part-time. In Scotland the total was even higher at 83% (n=12).

	Anxiety and depression can become more acute as patients/carers have to live with the day to day knowledge of the progressive nature of this condition and the patients' gradual loss of independence. *'I am … finding it increasingly difficult to participate in daily activities. I used to be able to do everything without help and enjoyed dog walking with a mobility scooter, driving, swimming, gardening and part time work. However, my condition has recently deteriorated rapidly so I am no longer able to do any of those things without help. I also now need help with personal care, which I find embarrassing and upsetting. I am fearful of the future and depressed about my situation most of the time.'* ***Type 3, age 56-65 years, adult***
7. What do patients or carers think of current treatments and care available on the NHS?	There is currently no SMA treatment available in the UK so Nusinersen is the first and only option. It is currently available for Type I babies under a compassionate use programme (EAP). However, this is only a temporary solution and Biogen has made it clear that it will be kept under regular review. In the absence of specific SMA treatments, various other ways of managing the condition and alleviating symptoms have been developed over the years: **Respiratory Support** Particularly relevant for Type I patients, but also for Type II patients, options currently include the following: chest physio, suction machines, cough-assist machines and non-invasive ventilation. **Feeding Support** Many patients have difficulty chewing and swallowing and eventually require external feeding e.g. via NG tube, NJ tube or Gastrostomy (PEG) **Constipation** This is a common side-effect and medication can be prescribed to reduce discomfort and avoid other complications. **Physiotherapy and occupational therapy** Play a large part in the ongoing management of SMA patients, not just to enable them to improve strength and movement but importantly also to slow decline. **Scoliosis** Many patients develop scoliosis (spine curvature) which needs to be closely monitored and managed. Early interventions can include a lycra suit or spinal brace/jacket. Those more severely affected will require spinal surgery to insert growing rods or fusion rods, depending on how badly a patient's breathing/comfort is compromised.

	Whilst useful and often essential in helping to alleviate the most serious complications of SMA, in most cases these care interventions do not deliver long-term improvement and are just ways of keeping patients as comfortable and mobile as possible while their condition continues to decline. Many of the interventions also necessitate constant management and increasing amounts of care, further impacting parents and others responsible for delivering that care. For patients too, it's extremely hard becoming more dependent just at a time in their life when they should be more independent. *"Needing assistance is THE WORST part of my type of disability. I am an independent 24-year old – I want to live my life exactly as I want and the biggest thing stopping me is my physical dependence on others."* ***Type 2, age 24*** The involvement of increasing numbers of health professionals and hospital visits also put more logistical, emotional and financial strain on parents/carers. **Importantly, with the exception of those babies on the Nusinersen Expanded Access Programme, none of the care interventions have any effect on the patient's spinal muscular atrophy.**
8. Is there an unmet need for patients with this condition?	Nusinersen is the first SMA-specific treatment and has the potential to address an enormous unmet need. As described above, all existing treatments are based on symptom relief, whereas Nusinersen has been shown to boost SMN protein in patients, thereby directly addressing the main problem of SMA. What is more, the need is urgent. Whilst the needs of Type 1 babies are temporarily being addressed through the EAP, this is not a permanent solution and there are many people with Type 2/3 who are finding it increasingly frustrating that they can't have Nusinersen, especially when clinical trial evidence shows that any benefits increase significantly the earlier the drug is administered.

Advantages of the technology	
9. What do patients or carers think are the advantages of the technology?	Nusinersen, the first SMA treatment, has the potential, not only to save the lives of Type 1 babies, but to dramatically improve/maintain the quality of life of all SMA patients. Positive results have been seen in clinical trials and it will be for NICE to assess the data presented. It is also important to consider Nusinersen, not just in terms of saving lives, but bringing improvements which, even though relatively small, have the potential to make big differences to peoples' quality of life and independence. The progressive nature of SMA also means that, for many, stabilisation is as valuable as improvement. In the SMA Europe survey, 97% (n=822) thought that a medicine that could stabilise the current clinical state would represent progress. *'I am not worried about never being able to walk or having weak arms. I have accepted those things. What I really worry about is that eventually I will have no function left and will not be able to work … I can handle the loss I've experienced so far, all I want is a chance at maintaining my current levels of function.'* ***Type 2, age 26-35 years, adult*** In the UK survey, 65% of the 20 open comments saw the main advantage as hope, whilst 40% thought they would feel happier/more positive and 20% commented on the decreased care that would be needed. Now that the EAP for Type 1 babies has been in place for several months, it is possible to include patient/carer perceptions of the treatment. In order to increase the numbers, the results of the UK survey were combined with those from the Scottish survey. In addition to the physical/muscle improvements observed by 95% (n=20) of respondents (parents/carers), 35% also mentioned respiratory improvement, 20% mentioned general health improvement and 40% mentioned the baby seeming happier. In terms of the impact on the whole family, 65% (n=20) wrote open comments saying Nusinersen had given them hope, with 20% reporting a decrease in the amount of care needed. *'Physically he has gained so much strength in comparison to how he was when he started…He can now move his legs, grip better, lift his arms …, play with toys, hold his head with minimal support…He can tolerate sitting up for hours without any respiratory support. I can cuddle him!'* ***Type 1, treatment started <7mths, 11+ injections***

Disadvantages of the technology	
10. What do patients or carers think are the disadvantages of the technology?	The main disadvantage of Nusinersen is that it has to be administered as an intrathecal injection and therefore necessitates admission to a specialist hospital. It is also a multi-dose treatment requiring several loading doses in the first year, followed by regular top up injections. This inevitably has an impact on the patient and the carer, necessitating the time/expense of hospital visits and a certain degree of stress related to the procedure itself due to its invasive nature compared with tablets, medicines or normal injections. A few parents of Type 1 babies have taken the decision not to register on the EAP, either because they are too sick or because they are worried that the child might still live with a significant disability, but they are a small minority. Reports from some adults, especially those with milder Type 3, show that not all would wish to access Nusinersen on the basis of the inconvenience to their lives for what they perceive as a possibility of marginal benefit. Anecdotal evidence of improvement in other countries is, however, growing. The vast majority, therefore, would want to have Nusinersen, even if it only resulted in stabilisation/small improvements as this alone would have a dramatic effect on their quality of life. Despite any concerns, 86% of UK respondents (n=128) said they would want the treatment.
Patient population	
11. Are there any groups of patients who might benefit more or less from the technology than others? If so, please describe them and explain why.	Clinical trial evidence suggests that the treatment effect is better in patients treated soon after symptoms appear. It will therefore be important to diagnose and treat patients as quickly as possible, as they may be likely to show the greatest benefit. Much of the clinical trial data centres around children under 12, with an emphasis on Types 1 and 2. It is therefore difficult to arrive at a true comparison between benefits in different Types and age groups. Nevertheless, as already mentioned, a significant improvement to Type 3 patients' lives could be achieved from achievement/retention of relatively small physical benefits (eg strength in finger/thumb to control wheelchair joystick), enabling them to live as independently as possible.

Equality	
12. Are there any potential equality issues that should be taken into account when considering this condition and the technology?	There are some groups of patients for whom it might be difficult to administer Nusinersen, mainly those with severe scoliosis or who have already had spinal surgery. The only other limiting factor might be proximity to a centre experienced in Nusinersen administration, although the EAP experience has shown that this is possible in far more centres than originally envisaged, provided appropriate training is given.
Other issues	
13. Are there any other issues that you would like the committee to consider?	It cannot be stated strongly enough that Nusinersen represents a 'step change' in life expectancy and treatment for people living with SMA. There is currently no treatment and the drug uses an innovative antisense oligonucleotide technology to re-engineer a 'back-up gene' to increase production of SMN protein, vital for healthy motor neurone/muscle connections. For many patients (estimated around 1,300 in the UK), it could provide the hope of significant improvements in motor function and quality of life. For those with Type 1 SMA, (80% of whom would normally die before 2 years), Nusinersen should therefore also be considered as an end of life drug, providing dramatic improvements in life expectancy. In the ENDEAR clinical study, all babies achieved the primary endpoint of still being alive. SMA has proved a fruitful arena for new drug developments in recent years, with several other potential treatments showing promise in clinical trials. The most advanced of these is the Avexis gene therapy which has shown dramatic results in Type 1 babies in US trials and is now expanding its programme into Europe and other SMA types. The treatment involves complete gene replacement and trials so far have been based on a one-off dose. Nusinersen's huge value is that it is currently the **only** treatment but the likelihood is that other, less-invasive drugs may well emerge in years to come. As such, it could be viewed as a vital 'bridging treatment'.

Key messages

15. In up to 5 bullet points, please summarise the key messages of your submission:

- There is currently no treatment for SMA. Nusinersen is an innovative treatment that addresses a totally unmet need and has the potential to deliver life-saving and life-changing benefits to patients.
- SMA has a huge impact on patients, their unpaid carers and entire families in every aspect of life, exacerbated by its progressive nature.
- The indirect benefits of Nusinersen are equally as important as the direct health benefits, dramatically improving patients' ability to participate in education, work and lead as independent a life as possible.
- There are significant differences between different SMA types, as well as within types and age groups. Whilst this makes it difficult to extrapolate the clinical trial data, it is clear that there are potential benefits for all groups included on the licence, with evidence showing that stabilisation can be just as important as improvement.
- It is important to view Nusinersen in the context of an overall care package, ie it doesn't negate the need for other forms of supportive care but should be used in conjunction with them in order to optimise patient benefit and with the aim of reducing long-term health and social care costs.

Thank you for your time.

Please log in to your NICE Docs account to upload your completed submission.

NICE National Institute for Health and Care Excellence

Patient organisation submission

Nusinersen for treating spinal muscular atrophy [ID1069]

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- Your response should not be longer than 10 pages.

About you	
1.Your name	[redacted]

2. Name of organisation	Spinal Muscular Atrophy Support UK
3. Job title or position	[redacted]
4a. Brief description of the organisation (including who funds it). How many members does it have?	We are a charitable organisation that started work 32 years ago providing free information and support to anyone affected by any form of SMA in the UK. We provide a phone, email and home visiting service, and also a 'Shared Experiences' Service. In 2017, we supported 357 adults/families with children living with SMA and are in contact with some 900, including those who are bereaved. We are accredited to the Information Standard and our information sheets are signposted by NHS Choices. Our Research Correspondents have reported on the development of this treatment since trials were initiated. We have contact with clinicians delivering the treatment and had contact with NHS England as it addressed the management of the administrative costs of the SMA Type 1 Expanded Access Programme (EAP), as well as with families wanting access. Our funding comes predominantly from Trusts, the SMA Community and some corporates. This financial year, 2018/19, we received funds from five pharmaceutical companies, including the manufacturers of nusinersen. This was for our core 'outreach' services (6% of overall income) and to cover the costs of our bi-annual information, support and social weekend for families and individuals to be held in April 2018 (9.4% of overall income). We don't receive any government funding.
4b. Do you have any direct or indirect links with, or funding from, the tobacco industry?	No
5. How did you gather information about the experiences of patients and	We invited people to complete our on-line surveys via: a direct email to 605 English households related to people living with SMA / bereaved by SMA; our, other SMA charities and the campaign group TreatSMA's social media channels. We received:

carers to include in your submission?	• 128 returns describing **the health-related impacts of SMA** for 128 people living with SMA Types 1-3. 61% from the adult / young person, 51% from the main unpaid carer. 52% were about people with SMA age 0 – 17 years; 48% about those age 18+ years. • returns describing **the health-related impacts of SMA** for 3 people living with SMA Type 4 • 5 returns from people bereaved by SMA We also sought **people's views on the impact of SMA on their day to day lives and the treatment nusinersen**. We heard from: 56 with the condition; 55 main unpaid carers; 21 other relatives; 5 bereaved by SMA; 26 parents of children treated with nusinersen. In the same way, we sought **the experiences of parents whose children had been treated by nusinersen**. We received 22 replies and added to this replies from our recent Scottish survey – 4 from England, 3 from Scotland. Based on the prevalence of SMA of 1 – 2 in every 100,000, **we estimate we have gathered the experiences of some 14-28 % of those diagnosed with the condition in England.** The full survey results are provided as **appendices 1 - 10.** The numbers and % referred to in this submission relate to these. The picture of the impact of SMA that they paint is confirmed by our Support Services team and our information sheets for families. We speculated that those with stronger views about wanting to access nusinersen may have been more likely to have responded to our survey. We therefore contacted the convenor of what is called the SMA Support UK/SMA Trust 'Adult Insight Group' who is an adult with Type 2. On our behalf, he asked the 35 members if they would want to access nusinersen if it were available. Group members are adults aged 25 – 55 affected by Type 2 or 3 who are interested in having a voice about SMA / disability-related issues. 19 (54%) replied.

Living with the condition	
6. What is it like to live with the condition? What do carers experience when caring for someone with the condition?	SMA is a complex, neuromuscular condition causing progressive muscular weakness and loss of movement. **Types 1, 2 and 3 are childhood-onset forms.** **Type 1** is the most severe - babies are unable to sit without support. Without intervention, most rarely survive beyond two years of age, usually due to breathing difficulties. Some children with **Type 2** sit independently, others require support. Though life expectancy may be shortened, improvements in care standards mean that the majority can live a long life. Children with **Type 3** can stand and walk, although this becomes more difficult and they need support with this over time. Life expectancy is normal. As Types are not rigid categories and there is too much detailed information to present in this summary, the following descriptions of the impact of the condition describe the overall findings from the survey. Clearly some aspects, such as the impact on mobility, will vary according to the severity of the condition and the person's age. This detail can be seen in the full survey results. Our 128 respondents, affected by Types 1, 1/2 and 2 (62%) and Type 2/3 and 3 (38%), with the person with SMA ranging in age from < 2 years to 66+ years, vividly describe their day to day experiences in many pages of responses to the question 'what are the biggest challenges of living with SMA?' It is impossible to do justice to the time and effort they have taken to tell us, a few representative quotes will have to suffice: "The hardest part of SMA for me is the regression….to watch your child lose his greatly achieved milestone it's heart-breaking, you can't explain to him why he can't do that thing he was doing two months ago." **Age 0-2 years, Type 2, father** "My grandson is unable to walk or stand and can sit only with support. He is susceptible to serious respiratory problems….this leads to frequent emergency admissions to PHDU and PICU for up to 5 weeks at a time - the stress placed both on the child and probably more so on the parents in these dangerous situations is immeasurable." **Age 3-4 years, Type 2, grandparent**

	In terms of mobility, 83% use powered wheelchairs, 68% use manual wheelchairs and 21% use wizzybugs – designed for children age 18 months - 3 years who are unable to walk. "As he gets older and bigger the strain of moving and carrying him means more adaptations are needed in the home and less places are accessible. Joining in at school is becoming more difficult. Not being able to go to friends and family's homes. Needing to be turned in the night. Struggling with weight gain. Watching him become less balanced, not being able to sit unaided. Everything getting weaker." **Age 5-12 years, Type 2, aunt/uncle** "My grandson is now unable to walk unaided and uses a wheelchair all the time. He is also slowly losing the strength in his arms. Until the age of 15 he was at least able to walk albeit slowly so you can imagine how frightening it is for the whole family to see how quickly he is deteriorating. It affects us all emotionally, and my grandson physically and practically. He has days when he just can't come to terms with what is happening to him." **Age 13 – 17 years, Type 3, grandparent** Full support – more than would be expected considering the age of the person - is needed for people to go to the toilet (78%), wash (74%), dress (81%), transfer (80%), eat and drink (31%) and, for those who require this, to prepare meals (75%). Between 10 – 42% of others require some support with these tasks. 66% require night care as they are unable to turn over at night or are, for example, needing night time invasive ventilation (29%). For 64% of these, this care is needed between 3 – 6+ times each night. "I cannot do the simplest things on my own: lift my hand to my face, pick up a cup with water, keep my head upright….I cannot go to meet my friends on my own, I cannot go to their houses (not accessible), I cannot hang out with them without having everything pre-arranged so a carer is present." **Age 13-17 years, Type 2, young person** "My son …has become more isolated, doesn't want his friends to see that he can't hold his head up if it falls forward so avoids putting himself in a position where he might need to ask for help and has slowly been pulling away from going out." **Age 13-17 years, Type 2, mother**

	This support is needed because of people's muscle weakness and the other health impacts of the condition: contractures (84%), pain (62%), scoliosis (60%), fatigue with oral feeding (50%), constipation (45%), bone weakness (41%), breathing difficulties (40%) and other health problems. "Physically, I am unable to do anything for myself as all my muscles are that weak now; I cannot walk, stand, transfer, change position independently, hold a pen to write, cannot move or turn over a piece of paper, send a text, use a cash point, clean my teeth, blow my nose, brush my hair, shake your hand, put make up on, scratch an itch, wipe my bottom, feed myself, hold a cup, cuddle my son….." **Age 46-55, Type 2 / 3 years, adult** 48% have no paid support, 25% have between 1 – 10 hours each 24-hour period and 27% have between 11- 24 hours. Respondents described unpaid support for the 128 people with SMA coming from a range of 146 different people with 75% of respondents receiving support from parents. These unpaid carers have other caring responsibilities as well. 51% care for other children, 32% for ageing relatives. Additionally, 39% of the 146 carers had had to give up work completely due to their caring responsibilities, 25% had dropped to part-time. "I am a qualified professional and would love to return to work full time….I am unable to sleep at night as I have to roll my daughter frequently…..All the hospital appointments, treatments, surgeries, etc take up a lot of our time…..I have to do all of the household chores….while my kids are at school, because as soon as my disabled daughter is home she needs my help with everything (bathing, toileting, physio, getting dressed, doing homework, etc). My able-bodied daughter often feels neglected….and I am constantly torn and feel guilty…..SMA has had a huge negative impact on the whole family in every area of our lives - financial, emotional, marital, personal, self-fulfilment and physical health". **Age 5-12 years, Type 2, mother** All those affected by and living with the condition and their carers are describing in their different ways the emotional impact of the condition – the 'chronic sorrow' associated with their ongoing living loss. Symptoms of **SMA Type 4** begin in adulthood and include mild to moderate muscle weakness in the arms and legs and some difficulty walking. This loss of function and the adaptations people who have, until then, often had no physical limitations, is distressing.

Current treatment of the condition in the NHS	
7. What do patients or carers think of current treatments and care available on the NHS?	**Management interventions**, particularly for infants with Type 1, focus on **correct positioning** and ameliorating **breathing difficulties**. These include: chest physiotherapy; oral suctioning; medication to reduce secretions; cough assist; non-invasive ventilation. This is very time-consuming for parents and can be distressing for both them and their child. **Spinal scoliosis**, with its physical and emotional impact, is often managed initially with a lycra suit, spinal brace or jacket but surgery may be recommended if it is contributing to breathing difficulties, preventing comfortable sitting or the curvature has progressed beyond a certain point. 20% of respondents have / have had spinal orthotics; 35% have spinal rods / spinal fusion (54% of those with Type 1-2 aged 18+ years). **Physiotherapy** helps manage contractures and pain, chest physiotherapy (43%) helps manage breathing difficulties. Interventions, particularly for those with Type 2, to manage choking, swallowing, fatigue with feeding, digestion, constipation and managing weight, may include **tube feeding, gastrostomy, medication** and **dietary management**. A major management tool, however, is vigilance and time on the part of carers. To manage the impact of their condition, the children, young people and adults who responded to the survey are having to use **powered wheelchairs** (83%), **manual wheelchairs** (68%), **wheelchair accessible vehicles** (66%), **specialist beds** (63%), **hoists** (60%), **orthotics** (54%), **specialist seating** (50%), **assisted cough machines** (38%), **nebulisers** (31%) and **assistive technology** (30%) as well as other equipment. They require **adaptations to toilet and bathroom facilities** (73%) as well as **other home adaptations** (69%). “Practically our house is full of medical devices and equipment. If we want to go on a trip overnight there is an assisted cough machine and a nebuliser to take, as well as a sleep aid and maybe a specialised chair. Our ‘normal’ is very different from most peoples’.” **Age 0-2 years, Type 2, father** Many described the frustrations they experience in their efforts to secure the support they need in their day to day lives:

	"Being on a wheelchair referral waiting list for so long. Waiting for possible adaptions to house, ground floor bedroom for son as stairs a hazard. As a parent the emotional stress of watching my son's strength quickly deteriorating is unbearable." **Age 5-12 years, Type 3, mother** For 57%, **the number of health and social care professionals** involved range from 6 - 20. Attending appointments and generally managing to coordinate care and support depends on the complexity of the individual's condition and can be very time consuming. Many of the interventions / equipment to manage the condition are **not funded by the NHS** and, although funding may be secured via other statutory sources, many are invariably secured privately or via charitable funding, creating significant financial pressure on families. For example, for these respondents, the NHS is not funding 50% of their powered wheelchairs, 27% of hoists, 36% of toilet and bathroom adaptations, 52% of other home adaptations. Children under the age of 3 years cannot access NHS funded powered chairs so 71% of families find funding for their 'wizzybugs'.
8. Is there an unmet need for patients with this condition?	This is the first drug treatment for SMA. Despite the management interventions that focus on positioning and breathing difficulties, infants with SMA Type 1 rarely survive longer than 2 years. **Spinal surgery** with 'growth rods' means earlier and potentially more effective surgical procedures than previously, but remains daunting for a young child and, as with any surgery, not without risk. Though it results in significant physical and emotional improvements, ongoing vigilance is needed when transferring. Families, especially those with children with Type 1 or 2, spend a considerable amount of time on **daily exercises** to help with contractures and pain and in an effort to maintain mobility. Many comments referred to the **stress of carers** trying to ensure enough is done. Also, despite these management interventions, the stress of trying to avoid chest infections and frequent life-threatening emergency hospital admissions is always there.

Advantages of the technology

9. What do patients or carers think are the advantages of the technology?

We heard from 29 parents, 27 of whom have children still being treated, 2 of whom are now bereaved:

Doses/injections	Nos.	%
0-4 'loading' year 1	10	34.5
5 - 7	18	62.0
11+	1	3.5

SMA Type	Nos.	%
Type 1	17	59
Type 1 - 2	11	38
Type 3	1	3

Nine parents did not provide any commentary about the impact of the treatment on their child or their family. In their open comments, the other twenty reported already seeing the following advantages for their child:

Total of 20 respondents making 'open' comments	Nos.	%
Physical / muscle improvements	19	95
Much happier	8	40
Respiratory gains	7	35
General improvement in health	4	20
Increased vocalisation	2	10
Tolerates procedure well	2	10
No physical / muscle improvement	1	5
No respiratory gain	1	5
Improved swallow	1	5
Improved quality of life	1	5

"Before treatment he could not even grasp - now he can use both hands to play with toys… he is beginning to hold his head up and can move his legs a little. He has been managing colds all through winter at home whereas before he was in intensive care on life support for every cold he got. He is a happy boy who can now start to explore his

surroundings, he is also beginning to talk … and can sing and clap." **Type 1, treatment started < 7 months, 5-7 injections**

"She has gained skills whereas before treatment she was just losing skills. She has gained head control, more movement in arms and legs. She is able to roll forward which was something she could never do. It has given us all hope. She has stayed off respiratory support and feeding support." **Type 1 / 2, treatment started age 13 - 24 months, 0-4 injections**

"He doesn't fall/collapse as he did before treatment. He fell at least twice a day & some days multiple times. He can now walk faster/further, his gait has improved & is less waddling….He has improved in other motor functions, he's stronger/has more stamina/doesn't fatigue as he did before. He can cycle on the exercise bike and getting better/faster with every treatment. …He can now independently rise from the floor. Emotionally: He is becoming increasingly able and independent which is positively affecting his attitude to life. He has a thirst for knowledge and life. He is exceptional in all subjects at school. He wants to study law and become a lawyer…" **Type 3, treatment started overseas age 12 years, 5-7 injections (See Appendix 11, 1 minute 35 second film clip of before and after treatment)**

This level of ability and drive is something we see frequently in young adults and adults with SMA. How much more could this potential with its positive economic impact be unleashed for them and today's children with treatment?

In their open comments, the following advantages were reported for the parents/family:

Total of 20 respondents made comments	**Nos.**	**%**
Given hope	13	65
Emotionally positive / happier	8	40
Decrease in care needed	4	20
More inclusive family time	1	5
More relaxed	1	5

"This has completely turned our lives around…We were told to enjoy our time left with our child at point of diagnosis and before treatment had become available which was simply heart-breaking. Life as we knew it stopped. Numb with pain and filled with fear we were unable to work/sleep/deal with normal day to day life. However, now I'm witnessing first-hand the benefits of nusinersen I'm simply filled with hope for my child's future. This has had such a positive turnaround for our family, myself, my husband, siblings, grandparents. I feel like I'm no longer waiting on a ticking time bomb, but now look forward to my child's future." **Type 1, treatment started age 13-24 months, 5-7 injections**

When those who have not had treatment and their relatives were asked what they thought the treatment would bring to them / their relative with SMA, 132 responded. The following felt it would bring these advantages:

Total of 132 respondents	**Nos.**	**%**
Will maintain muscle strength	101	77
Will improve muscle strength	96	73
Will extend the life expectation associated with this type of SMA	63	48

44% of them regard themselves as well informed about the treatment, 16% not well informed and 40% 'know a bit'.

"Anything that can increase muscle strength will be life changing for children with SMA, and potentially life-saving if it keeps the respiratory muscles a bit stronger." **Age 5-12 years, Type 2, parent**

"Even if Nusinersen does not provide the desirable results for all patients, clinicians can learn from the results. it will help to develop better drugs that work on wider across SMA spectrum and improve drug delivery mechanisms." **Age 5 - 12 years, Type 2, father**

"The costs associated with having a disabled child are extremely high. With treatment this would be dramatically reduced. Money would be saved on hospital stays, equipment and care. It could also help the economy as it would stop parents / carers having to take time off work /stop working." **Age 5 - 12 years, Type 2, mother**

Disadvantages of the technology

10. What do patients or carers think are the disadvantages of the technology?

Though the description of the impact of the treatment for 95% of the 20 parents responding is very positive, one had not yet seen respiratory gain and one bereaved parent reported no physical / muscle improvement and also said:

"We experienced great distress as a result of conflicting expectations of the likely impact of the drug set by teams in two hospitals. One told us that the drug would slow or even halt the decline. Whereas the other told us that it could reverse the process which would allow him to reach milestones and that he would sit up and possibly even walk. This gave us hope, joy and relief, but later grief when these milestones failed to materialise." **Type 1, bereaved parent**

One parent (5%) commented on the emotional distress caused to their child by the treatment, and two parents (10%) commented on the stress it caused them:

"It is stressful attending the treatment because as a parent you do not want to put your child through a painful procedure but I feel the benefits far outweigh this." **Type 1, treatment started age 8 - 12 months, 5-7 injections**

When asked what impact they thought nuisnersen would have on them / their relative, 9 of the 132 respondents (7%) felt 'it was unlikely to change the natural course of their condition'.

When those who had not been treated / whose relative had not been treated were asked for open comments about any concerns they had heard or read about the treatment, 74 responded as follows:

Open comments from 74 respondents	Nos.	%
No/not really	38	51
Lumbar puncture process / safety / discomfort	13	18
Headaches / nausea	6	8
Price	6	8
Scoliosis / spinal fusion may prevent treatment	5	7

Risk of respiratory issues / chest infection	4	5
Side effects	4	5
Unknown long-term outcomes	4	5
No guarantee it will work	2	3
Frequency of treatment / scheduling	2	3

One mother said:

"A lady with a daughter posts details on Facebook of her child's treatment so this is where I have read most details of how it is administered. The injections into the spine put my son off and frightened him. But if he could take nusinersen orally or through his peg he says he might give it a go but I'm not sure if someone so weak like my child would really benefit. When his quality of life is already good he does not want the interruption of keeping going to hospitals for treatment. Now he is older we only have 3 visits a year.' **Age 5- 12 years, Type 2, Mother**

Our understanding from clinicians and families whose children have been treated is that though a lumbar puncture and the need for ongoing delivery isn't the ideal way for treatment to be administered, it is being done successfully and, for many, the procedure is short and straightforward.

As another mother said:

"Every medical procedure carries risk and I would not put our son through these lightly. However, if this were to improve his respiratory and overall muscle function meaning less PICU admissions then we would grab at the chance." **Age 5 – 15 years, Type 2, Mother**

Despite these concerns, 102 of 119 respondents (86%) said they would want the treatment for themselves as a person with SMA / their relative with SMA.

Of the 19 respondents from the adult insight group, 10 (52.6%) would want treatment, 6 (31.6%) wouldn't and 3 (15.8%) would want to see more evidence first:

	"Spinraza - I'd want some really concrete evidence of significant benefit in adults with type 2 before letting them put a needle in my spine. The risk vs benefit is too high for me with the evidence available at the moment. I'd gladly have more or preserved strength and reduced risk of chest infections, but am not convinced Spinraza can do that for me. Lumbar punctures have a risk attached, and where it needs repeated lumbar punctures this increase the risk." **Adult Insight Group member** That said, none of the respondents would want to deny others who wish for the opportunity to access this treatment and interest in other future possible treatments is high.
Patient population	
11. Are there any groups of patients who might benefit more or less from the technology than others? If so, please describe them and explain why.	**138 of 151 respondents (91%) said that they believed that if it is clinically safe for someone with 5q SMA to be treated with nusinersen, they should be given the opportunity to do so.** Asked if they considered any groups might benefit more from treatment (and able to choose more than one option), between 43 - 59% specified the different Types 1 – 3, 32% said Type 4. In terms of those selecting an age group, 52% suggested age 0 – 35 months with a gradual reduction to 35% for age 26 years +. These results must be treated with caution in view of the mix of ages and types represented by respondents. One of the difficulties with judging which groups might benefit more is the lack of clinical trial evidence of the treatment which is thus far only with children aged 0 – 12 years and Types 1 – 3. The evidence of the success of treatment provided to us by the mother of a young person who is now age 13 years and has Type 3 does though highlight the great potential of the treatment to change lives outside this trial group. Many respondents also referred to the positive outcomes that are being reported via social media – particularly from the USA. Clearly there are concerns from people who have a scoliosis and / or have had spinal surgery. We understand, however, from Biogen's community update (21st February 2018) that work is taking place to try to address these challenges.

Equality	
12. Are there any potential equality issues that should be taken into account when considering this condition and the technology?	Local access is very important. Due to the need for regular treatments and the fragility of some, travelling can be very difficult and unsafe. The experience of the slow and uneven geographical roll-out of the EAP and the initial 'postcode lottery' was devastating for many families. The travelling, and the overnight stays needed for some receiving treatment, impacted significantly on those without the financial means / transport. One child and parent we know had to travel huge distances in an ambulance with the other parent following by car while siblings were cared for by relatives. Older children and adults without wheelchair accessible transport of their own will require assistance.
Other issues	
13. Are there any other issues that you would like the committee to consider?	For infants with Type 1, this clearly meets NICE's criteria as an 'end of life' treatment with supportive clinical evidence of its efficacy. Many are seeing this as a potential 'bridge to a cure' with the possibility of future combination therapies. However, in the light of the experience of the bereaved parent, it is vital that information about possible outcomes is clear and expectations are carefully managed. **Emotional and psychological support** is essential. Nusinersen must be supported by **palliative care**, an active approach to care aiming to support the physical, emotional and practical needs of a child and family with a life-threatening condition. Guided by the **International Standards of Care for SMA**, it includes symptom management and reducing complications of muscle weakness. As one parent whose child is being treated said, "It's not a cure… we follow all protocol; we are very strict with bipap, chest physio and general physio which is incredibly important.. it needs to be led by hospitals with amazing respiratory departments." It also needs to be supported by the **swift provision of equipment and housing adaptations**, particularly for some children with Type 1 who may, at least initially as they grow, need lie flat car seats and larger buggies that are not easy to obtain and to date are not NHS funded. Those that are stronger will need access to mobility aids such as the

	'wizzy bug' and appropriate powerchairs – again rarely funded by the NHS to those under age 3 years, despite most children with SMA Type 2 being quite capable of managing these essential aids that enable them to gain independence, access and join in with the world around them. **Starting and stopping criteria** for treatment have been established **for Type 1**, and are used by Centres delivering treatment via the EAP (NHS England's interim policy updated March 2018). We understand that these criteria are discussed with parents before treatment starts so that there is a shared and agreed understanding. Even with this, it can be difficult for medical teams to manage these difficult discussions. The collegial support of the UK-wide NorthStar clinical group is very helpful. Equally, families seeking to make their case for access or faced with treatment being stopped need appropriate support. With further resourcing it should be practically quite possible to roll out the treatment programme to a wider group of children / young people and monitor outcomes through routine clinic visits. The **SMA REACH project,** which already monitors disease progression for 305 children with Type 2 or 3 and the 66 who are receiving nusinersen treatment via the EAP, is an ideal if not essential tool for gathering this data and for further study of the effectiveness of treatment. **For adults,** we suggest outcome goals clearly tied to meaningful day-to-day tasks, as well as more traditional clinical measuring tools would need to be individually agreed between the person and their clinical team. We don't know how 'ready' adult clinicians are to embrace the delivery of this treatment but we imagine many will be keen to offer it to those that wish to access the opportunity. **We suggest treatment should continue unless there is a measurable deterioration.** **Not everyone wants treatment** and this must be respected. We know families with babies with Type 1 who have decided this is not a path they wish to follow. The clinical trial results are good but, as the bereaved parent quoted above shows, they are not guaranteed. Parents may hear that their child could become 'a strong Type 2' but for some, the thought of their child having a lifetime of lumber puncture treatments and living with uncertainty and potentially a very challenging disability (as described), is not a life they feel is right for them or that they could manage for their child or their family.

	The inability to access nusinersen has created huge emotional distress in the SMA community. We sincerely hope this will change: "Small improvements in muscle strength have a disproportionately huge impact on quality of life. So, going from not being able to pick up a drink to being able to do this, for example, is a really big deal. Anything that can increase muscle strength will be life changing for children with SMA, and potentially life-saving if it keeps the respiratory muscles a bit stronger. Watching some of the younger SMA children in the USA hitting milestones and achieving mobility having been treated with Spinraza is really emotional. I wish we could have done that for our son when he was little." **Age 5-12 years, Type 2, Parent**

Key messages

15. In up to 5 bullet points, please summarise the key messages of your submission:

- Day-to-day management of this progressive condition is physically, emotionally and practically hugely demanding for both the person with SMA and their unpaid carers
- Health and social care costs associated with SMA are very high and often not at a level that is sufficient for the person and their unpaid carer(s) to keep physically and emotionally well, get enough sleep, keep socially connected, manage financially and work / study for the hours they wish
- Nusinersen treatment is leading to life-saving and life-changing results for children with Type 1, but it is vital that information about possible outcomes is clear and expectations are carefully managed
- For those with other types of 5q SMA, the small improvements in muscle strength that nusinersen could bring would have a hugely positive impact on their quality of life and health and independence, with a resultant reduction in health and social care costs
- The option of treatment should be supported by symptom management as outlined in the International Standards of Care for SMA, along with ongoing emotional and psychological support for both those with the condition and their carers, and the swift provision of any equipment, home adaptations and care / support packages that are needed to maintain a good quality of life

NICE National Institute for Health and Care Excellence

Patient organisation submission

Nusinersen for treating spinal muscular atrophy [ID1069]

Thank you for agreeing to give us your organisation's views on this technology and its possible use in the NHS.

You can provide a unique perspective on conditions and their treatment that is not typically available from other sources.

To help you give your views, please use this questionnaire with our guide for patient submissions.

You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type.

Information on completing this submission

- Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable
- We are committed to meeting the requirements of copyright legislation. If you intend to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Your response should not be longer than 10 pages.

About you	
1.Your name	[redacted]
2. Name of organisation	**TreatSMA**
3. Job title or position	[redacted]

4a. Brief description of the organisation (including who funds it). How many members does it have?	TreatSMA is independent organisation founded by families affected by spinal muscular atrophy to advocate on behalf of other families. We are involved in a number of projects within the patient and clinical communities. We played a key role in bringing about nusinersen Expanded Access Programme to the UK. Currently, TreatSMA has 15 active members (Board Members) and several hundred associated families.
4b. Do you have any direct or indirect links with, or funding from, the tobacco industry?	No
5. How did you gather information about the experiences of patients and carers to include in your submission?	We ourselves are a group made up of adults with SMA and parents of children and young people with SMA. Within our membership we have adults as well as parents of children with all functional abilities and SMA "types". We are therefore in the unique position of having first-hand experience of many of the issues discussed in this submission. To gather experiences of the wider SMA community we asked that parents and carers of type 1 children receiving treatment via the nusinersen Expanded Access Programme provide us with a written testimony that included experiences and perceptions of treatment in addition to photos and videos showing to what extent, if at all, their child's abilities and health had changed since receiving treatment. We also received written accounts from parents and carers of children as well as adults who have not received treatment (SMA type 2, 3 and 4) to understand the everyday impact of SMA on their lives and the extent of care needs. In total we received 23 accounts from parents and carers of children with type 1 SMA on the Expanded Access Programme and 27 accounts from the adults and the parents of children not receiving treatment.
Living with the condition	
6. What is it like to live with the condition? What do carers experience when caring for someone with the condition?	Spinal muscular atrophy (SMA) is a genetic disease that causes **muscle weakness** and **progressive loss of movement**. It is caused by deterioration of motor neurones connecting the brain and spinal cord to the body's muscles. As the link between the nerves and muscles breaks down, the muscles used for activities such as crawling, walking, sitting up, moving the head and even swallowing, become progressively weaker and shrink (atrophy). In time, all voluntary muscles, as well as muscles responsible for breathing, get significantly weaker. As a result, respiratory complications occur frequently. These can be and often are life threatening. SMA is a **progressive** disorder **and everyone affected by it experiences deterioration in mobility**

and health over time. Mental abilities are unaffected in SMA, however mental health in patients and a care is an issue. For children affected by the most severe forms of SMA the condition can be extremely life limiting.

For many, the impact of SMA is vast, it affects so many areas of life; mobility, health, family life, mental health, independence, access to school, to work, to travel, to social interaction. For some, especially those with the most severe forms of the disease, it affects the ability to breathe, to eat, *to live*.

> *SMA permeates into every aspect of [her] life* (parent of a 3 year old child with type 3)
>
> *Having SMA affects my life every minute of every day. It affects me physically, mentally and emotionally. Throughout my life, I have had to constantly adapt and adjust to accommodate the changes and deterioration I have experienced through having SMA. This has been incredibly difficult and isolating at times.* (Adult with SMA type 2)

The aspects of SMA most commonly reported by people with SMA/ parents of children with SMA as most difficult are two-fold.

1. **The progressive loss of mobility, and deterioration in many aspects of physical strength and health, associated with the condition is generally considered to be the most difficult part of SMA.**

   [She] was losing strength, literally before our eyes. As first time parents, to watch something so precious to us deteriorate, so quickly was heart breaking, we could not even began to explain the complete heart ache and constant feeling of dread – we would not wish it on our worst enemy. (parents of a 1 year old child with SMA type 1)

   Due to the progression of [his] SMA he has over time lost abilities such as being able to bare weight through his legs, crawl, stand with support, feed himself, lift his hands above his head, open his own Christmas presents. [He] has struggled to understand why he can no longer do the things he once could and often asks if he will one day not be able to some of the things he can do now. (parent of a 5 year old child with SMA type 2)

   Over the years I have slowly lost the ability to walk, to stand, to raise my arms to my head, which means I have also lost the ability to cook as I want to, shop as I want to, take care of myself as I want to. Not to mention the effect I FEEL it has for my children & grandchildren and my husband as I cannot take a full part in their lives as I want to. I don't have days out with my sisters, or daughters like other normal people, I MISS OUT ON NORMAL LIFE. (adult with SMA 3)

2. **Alongside this, the potentially life-limiting implications of respiratory difficulties associated with SMA are another aspect of the condition that parents/carers as well as adults with SMA find especially difficult and terrifying.** Such difficulties include a weak cough, causing an inability to clear mucus, which can result in illnesses as simple as a common cold becoming life threatening. Many parents provided details of hospital admissions where their

child was battling extremely serious, often life threatening respiratory complications. For many families, especially those with ineffective coughs, this has become a regular occurrence.

The one huge weakness that we couldn't hide from was the huge decline in his respiratory health, his cough was pretty non-existent meaning every tiny cold was a collapsed lung. We'd started the very common cycle of PICU, getting better then straight back again. We've been in the situation where we were told to expect the worst in PICU. We lived in constant fear, we lived in the moment and we never thought about the future; we knew in the back of our minds that one time he wouldn't come home from hospital. (parent 3 year old type 1)

My biggest fear, and that of my family, is the risk of respiratory infection. We do everything we can to avoid my catching a cold because managing it is so traumatic. (Adult with SMA type 2)

Many children and adults with SMA require a degree of ventilation support either through non-invasive ventilation such as Bi-level positive airway pressure (BiPAP) or a tracheostomy. For some, the need for ventilation is constant, for others it may only be used nocturnally or during periods of illness. A cough assist machine is often required to help clear secretions from the lungs. Depending on the ability to manage secretions, regular suctioning is also needed.

Difficulties with feeding, swallowing and maintaining weight are commonly experienced, often necessitating feeding support in the form of an NG or PEG. Joints can become stiff and range of movement reduces as contractures develop. Scoliosis is a condition very often experienced by people with SMA.

I developed scoliosis and had the rods put in when I was around 12 years old I seemed to lose my head control once that was done, I now have to be fed by a button in my stomach as I'm frightened to swallow in case I choke. I can't open my mouth as far as I used to so I think people have difficulty in understanding me sometimes. I also have to use a bipap every night and if the dreaded chest infection gets hold I use it all day as well. I also now have to be suctioned as I make too much and very thick saliva and it needs done every 10 mins. (Adult with SMA type 2)

Repeated hospitalisations as a result of complications arising from SMA can be extremely traumatic, especially for young children. In fact, accounts were provided of how significant time spent in hospital caring for a loved one with SMA could impact on the whole family, especially other siblings.

His increased awareness of treatments with each admission is heart breaking and hearing him shout 'please no more' whilst sobbing uncontrollably desperately trying to writhe away from having suction catheters pushed far down his nose and throat making him gag and sometimes vomit is something that no child should have to experience. We as parents have to help hold him down and he looks at us with pleading eyes. Every fibre in your body aches for him and wishes there were an easier way for the secretions to come up. Then after two weeks his little body is exhausted and an x ray shows a complete left lung collapse. We as parents have to tell him that once again will have to go to sleep and have 'the tube' in his nose to help make him better and ease his breathing. (Parent 4 year old type 2)

> *We were also in hospital for [older son's] 15th birthday so meant that we had not had a proper celebration. Each time we were admitted it meant that my mum came to live in our house to care for [older son] who was a young teenager and [we] lived on the hospital site...Our family was ripped apart with every admission (*Parent of a 4 year old child with SMA type 2)

There is a great deal of anxiety associated with the condition. Parents worry daily for their child's health. They live in a constant state of fear of their child catching a simple childhood illness that could have serious consequences and be potentially life threatening. The anxiety parents feel can have a detrimental impact on their health and relationships.

> *I have been on a permanent state of high alert since February 2017. The anxiety of what was happening caused me night sweats and then regular day sweats until someone finally told us what the cause was. The pressure on my wonderful husband and I has been huge as we both deal with the pain of watching our little girl struggle and deteriorate in different ways.* (parent 2 year old child type 2/3)

The need to avoid illness can also have an extremely isolating impact:

> *We made a conscious decision not to send him to nursery because we were so worried about him falling sick. It has been difficult keeping him busy and entertained at home, but it has kept him well* (parent 3 year old type 2)

> *Christmas used to be a lovely big family affair but it was downscaled significantly due to our fear of [him] coming into contact with any other germs*.(parent 4 year old type 2)

Some adults with SMA also explained that they suffered anxiety as a result of their condition, sometimes around the impact of their care needs on their family or even the aging of a relative who had had significant involvement in their care and what would happen in the future as their main care givers became older (for instance, where care was provided by elderly parents).

> *Being a teenager was not nice, I had awful anxiety over my disability, in-fact the anxiety was pretty prominent in my life right into my 40s, and still remains to a lesser degree today...I have been extremely lucky though to of married and have 3 healthy unaffected children, who now have families of their own. Bringing up the children was not without its difficulties, they missed out on things which brought the 'Partner of anxiety, Guilt' along .*

> *Guilt is with me every single day! Because I feel that I am a burden to my family.* (type 3 adult)

It was also mentioned in the case of both children and adults with SMA that the sense of being unable to move independently or finding themselves reliant on others can make them feel vulnerable.

> *One underlying concern we always have for [him] is the physiological effect that having SMA and all that comes with it has on [him]. [He] gets very anxious in situations of potential danger for example Bonfire Night, Halloween, unfamiliar*

	loud sounds in the house. His fear of not being able to independently move away from danger is becoming more apparent. This condition is all consuming. (parent 8 year old type 2) Knowing there is treatment but that it is currently out of reach is a cause of much anxiety and distress for people with SMA and their families. Even parents of young children reported their child questioning why they are not receiving treatment that could help them. *After many heart wrenching conversations with [him] he is fully aware that there is a treatment out there and he has seen videos of children making tremendous progress. He asks when he is allowed the 'special medicine'.* (parent 5 year old type 2) *He is being emotionally tortured (as are his close family) knowing that there sitting on the shelf of a large pharmaceutical company is a treatment, not a cure but nonetheless a treatment which could make a huge difference to [him] and those close to him* (parent 17 year old type 3) Across all severities of SMA parents reported that the lack of age appropriate motor milestones in children who were cognitively aware and often very bright was a cause of much frustration to the child. *Although [he] is now nearing two and a half years of age, [his] routine has and would appear going forward to be very much the same, it's very much caring for our baby. Unable to fully roll over, unable to fully lift his legs into the air whilst lay on his back, he is dependent on a full time carer* (parent 2 year old type 2) Despite many children with SMA enjoying learning, fatigue, potential exposure to illness and time away from school due to the high number of medical appointment and lengthy periods of illness can limit access to education *The physical barriers of SMA have stunted his mental development, his speech has been delayed, and this kills both parents to acknowledge this. We embrace attending pre-school for [him] to learn, and grow. But on every day he has attended, he has more often than not returned home with some cold, or illness in the making. His weak cough doesn't keep at bay what others expose him to.* (parent 2.5 year old child, type 2) *His daily school life is becoming more challenging as SMA causes extreme fatigue and just getting out of the house, walking to class and then sitting down on the chair exhausts him. This is all before he has started his lessons* (parent 11 year old type 2 child) For parents it is painful to see their child want to achieve things that SMA may make more difficult or even impossible.

> *[He] is 6 years of age, he is telling us how he wants to be a policeman; how do you explain to your son he will never become a policeman? How do you explain he will never be able to play football with his mates? You can't* (parent, 6 year old child, type 2)

There is also a concern for many parents as to how the condition will impact their children's ability to follow chosen career paths of pursue areas where they show promise and talent

> *[He] already shows an interest in technology, in engineering, in transport, in games, in videos, in software. At the age of two and a half he already has a better grasp of navigating a tablet and the use of applications that his mum and dad combined. He deserves an opportunity to pay-back through pursuing a career of his own.* (parent 2 year old child, type 2)

SMA often has a detrimental impact on work arrangements. Many parents become their child's carer and so experience a loss of employment and earnings.

> *An educated professional I provided a service for many a year to the local authority….. I'm more than likely going to be [his] carer from here on. So that cost to replace, to train, and to back fill will now be at the County's door. At a cost to the local and central government. Without earning, my tax contributions will diminish. Therefore a straight cost comparison for sourcing and administering a drug is unfair.* (parent 2 year old child, type 2)

Both adults with SMA and parents/ carers of children with SMA mentioned self-care as an area where the condition causes difficulties and frustrations.

> *Approximately 12 months ago [he] was able to comb his hair and brush his own teeth, but SMA slowly robbed him of this also. Watching your own child deteriorate before your eyes is absolutely soul destroying.(*parent 5 year old type 2)

> *As I got older I lost the ability to wash myself, wipe myself, dress parts of myself, weight bare, wash my hair, put my hair up, play musical instruments, lift and grip things and cook. I am unable to feed, bathe, dress or toilet myself. I can't even scratch my own head. I have very limited movement and need assistance in every aspect of my life*. (Adult with SMA type 2)

Inability to turn during the night means the need to have frequent help with repositioning and a great deal of night time waking for people with SMA and their carers.

> *One of the biggest challenges of [his] progressive loss of strength has been night time waking. [He] no longer has the strength to reposition himself at night, so he calls out to us to turn him. On average we wake up 10-12 times a night to turn him. Luckily this does not seem to have impacted the quality of [his] sleep, but it has left myself and my husband permanently exhausted.* (parent 3 year old type 2)

	This list of quotes and examples can go on and on and testimonials are all available.
Current treatment of the condition in the NHS	
7. What do patients or carers think of current treatments and care available on the NHS?	**The current system offers a symptomatic treatment and palliative care only. This often means that weaker children pass away and stronger children become weaker. Therefore as we see it, currently there is no treatment available for Spinal Muscular Atrophy on the NHS; there are approaches to manage certain symptoms and aspects of the condition, but no treatment. Whatever available is not always accessible and depends on where you live and often MUST be supplemented with private care which costs significant amount of money.** *In the year and a half since diagnosis, it's been merely supportive care and means to starve off his loss of limited function. We take [him] swimming every week as a form of hydrotherapy. We undertake daily physio therapy, stretches, special forms of play, to target grip, reach and torso and head turning. But there simply has been no form of medical intervention. No treatment available.* (parent 2 year old type 2) Especially for type 1 children, prior to treatment being an option, families often report being told that there was not much that could be done and their child had a very limited life expectancy. *Following on from diagnosis we were told that there was no available treatment for this condition other than palliative care and ventilation support, but basically were advised to enjoy the time we have with him as it was highly unlikely our son would live past the age of two*. (parent 2 year old type 1). *On the day of diagnosis we were told take her home, love her, but do not get used to her*. (parent 2 year old type 1) Despite this, across all types of SMA, certain approaches have been regularly used to address specific aspects of the condition: • BiPAP, cough assist and suction are considered some of the vital tools in maintaining respiratory health by many parents and adults with SMA. Sleep studies are often conducted to assess nocturnal breathing and determine the level of respiratory support required. *we welcomed the best bit of kit we have home, bipap! This was a game changer, like with physio we embraced our new routine and saw great benefits in sleep, stamina, energy and volume* (parent 3 year old type1) *The Cough Assist machine we have has been a key part of this – we use it every morning and every night, even when [he] is not sick, and it has really helped to keep his chest clear.* (parent 3 year old type 2)

- Oral feeding becomes a complex procedure and more often then not involves installation of PEG. Whilst speech and language therapist supervises the development, it is constant fear of chocking that influences daily routines. Furthermore, the dietician have no clue about what is good for SMA person and just fall back on passive views.

  Seeing your child choke, tears welling up and face turning red/purple leaves us in a state of fear for weeks. We are unable to eat as a family as one of us needs to feed the child. We are the lucky ones, because our child can still eat orally. (parent 2 year old type 1)

- Orthoses such as splints (AFOS), spinal braces (TLSOs), knee, ankle, foots orthoses (KAFOs) are used to stabilise joints, reduce contractures and hold off scoliosis. However there is growing body of evidence that this is not enough.
- A range of medication is used – including laxatives to address constipation, prophylactic antibiotics, salbutamol, medication to address reflux, supplementary vitamins.
- Frequent physiotherapy, hydrotherapy and even hippotherapy. Whilst some of this is available on the NHS, the level of physiotherapy input required and lack of availability of hydrotherapy pools often mean that families find themselves supplementing their child's physiotherapy care by using a private practitioner, often at a high and on going cost to the family.
- Provision of a range of specialist mobility and care equipment. Whilst these are often supported by the physiotherapy and occupational therapy teams involved in care, there are certain pieces of equipment that are frequently self-funded such as powerchairs. Again this is a large cost to families £5,000-£25,000 depending on levels required.

The degree of care needed by someone with SMA to some extent varies according to the severity of the condition. During periods of acute illness care needs can increase dramatically.

> *We have a plan that we follow as soon as [he] shows the first signs of a cold: every 3 hours during the day we do chest physio, followed by postural drainage, followed by 3 rounds of his Cough Assist machine and suction to clear out any secretions in his chest. We supplement this with an inhaler to keep his airways clear, and immediately stop all exercise to enable him to conserve as much strength as possible to fight the illness*.(parent 3 year old type 2)

One issue that is often encountered is inconsistency in the care and approaches taken to managing SMA depending on the hospital. Knowledge and awareness of best practice approaches vary widely and this can impact the care received.

> *Very soon after diagnosis we came to learn that bipap can be helpful in SMA to aid the development of the lungs and chest wall and expressed that we would like to have proactive use of bipap (especially as bipap is not available at our local hospital), but we were told this would not be offered. We were also told, after asking, that it would not be appropriate to offer [her] cough assist at that time either. Due to our disagreements over the respiratory management [she] was receiving we transferred [her] care and after transfer [she] was immediately fitted for AFOs and TLSO at 18*

	months old and a year after diagnosis we were finally given our own bipap, cough assist, sats monitor and suction machine. (parent 3 year old type 1)
8. Is there an unmet need for patients with this condition?	**Absolutely YES. There is currently no existing treatment available on the NHS that is shown to have an impact on preventing the progressive loss of physical strength/ abilities and deterioration in health associated with SMA. It is preventing this deterioration in health and mobility and prolonging life expectancy that people most want from treatment.** *First and foremost, a means to safeguard what we have. The thought of losing [him] fills us with dread. It doesn't matter if we don't make "gains". Anything else is a plus. We just need to safe guard him.* (parent 2 year old type 2)
Advantages of the technology	
9. What do patients or carers think are the advantages of the technology?	<u>CHILDREN RECEIVING TREARMENT ON THE NUSINERSEN EXPANDED ACCESS PROGRAM</u> **For families of children receiving treatment through the EAP, stability in their child's condition was a key motivator to starting treatment. Given the progressive nature of SMA, achieving stability and stopping the condition progressing would be a successful outcome.** *I feel it's vital to note how important even "just" stability is when living with SMA and how even what might be perceived as a small improvement in physical strength can have a profound effect. It can be the difference between not being able to draw and being able to make a mark for the first time, being a bit clearer to understand when speaking, being able to fight off the next cold a little bit quicker, being able to move very slightly to maintain comfort in bed, being able to put food to your own mouth*. (parent 3 year old type 1) However, **many parents of children being treated with Nusinersen through the EAP reported outcomes beyond stability, with significant gains in strength and physical abilities and regaining of lost motor abilities.** *[she] was almost completely immobile by the time of treatment, she had minimal movement in terms of gross motor function..[she] is now on her fifth dose, and have regained arm strength and movement, she is improving constantly with her legs. She can hold them vertically for about 10-15 seconds – she has not done this since about 2-3 months old. She can roll from side to back, she is able to lie on her side comfortably, she can use supportive seating and wheelchairs comfortably. She continues to strengthen respiratory wise as her body strengthens, her neck and head control are retaining, she can sit up aided for a few minutes – we believe she will be able to sit unaided within the next year. This we thought would never be possible.(*parent 1 year old type 1)

*Since starting nusinersen [he] can sit with minimal support, his head control is fantastic, he works so hard during his physio and can move his legs and feet, he sits straight in his wheelchair pushing himself away from the backrest as he doesn't need to depend on this. He can lift lots more toys and his tablet....Everyone comments on his new strength....He's much stronger now than at his strongest before the rapid decline of SMA started.(*parent 3 year old type 1)

Before Nusinersen she could hardly move her legs, upper arms and she had no head control. Now she had great head control and she can move her arms and legs. She can now move and her trunk control is so much better. She can also sit unassisted for a couple of seconds. Her breathing is so much better now... She can play with her sister her speech is getting so much better and clearer. (parent 2 year old type 1)

In some cases gains in physical abilities were of such an extent that children treated on the EAP were meeting milestones traditionally never expected for a type 1 child. This was even the case for children who had commenced treatment not in early infancy.

Just before her 6th dose [she] gained the ability, for the first time, to sit totally unsupported. She can now also roll her top half if given minimal assistance with her legs and has regained the ability to pick up her left elbow from the ground when lying in a supine position. (parent 3 year old type 1)

Families commonly reported they felt their child's respiratory health had improved, reporting a reduction in the need for bipap (both the amount of time used and the pressures needed) as well as a more effective cough. Given that it is often respiratory complications that cause loss of life amongst people with SMA, it is not surprising that **this improvement in respiratory strength was considered as the most significant gain by many**. While treated children still require regular hospital appointments and involvement from specialists in monitoring their condition, many families felt that an improvement in respiratory health since starting treatment has meant a **reduction in critical/ acute illness and hospital admissions** (This is supported in an independent study and will be discussed by clinicians seperatly).

She got her trach and vent...She was vented 24/7 from then on. Since she's been on nusinersen her vent settings have been dropped and she can come off her vent for up to 3 hours when well.(parent 2 year old type 1)

he [now] has an effective cough that can bring the mucous from his throat into his mouth-thus resulting in [him] being admission free from hospital for a year (parent 3 year old type 1)

The improvements that we see ...include better lung function, the pressures on his bi-pap machine have been lowered and the "belly breathing" typical of an SMA baby has become more "normal" indicating he is breathing more effectively. His cough has developed from being very weak given him the ability to move secretions from his lungs to reduce the

amount of gruelling chest physio and suctioning. Sleep studies indicate no deterioration and ability to expel carbon dioxide. There have been no hospital admissions due to SMA since the start of treatment. (parent 2 year old type 1)

Parents also reported an improvement in their child's swallow and speech.

[He] continues to enjoy a well-balanced diet eating orally, his speech and language therapist believes without treatment he would have needed the help of an ng tube or "peg" to maintain his dietary requirements and weight gain. [His] conversational development is fantastic, talking, singing and learning new words. His voice has got louder since starting treatment also. (parent 2 year old type 1)

Her feeding consultant also feels that her oral feeding has improved and has suggested if she continues to improve she may soon be able to start eating some soft chew foods rather than just the pureed and bite and dissolve foods she currently eats. (parent 3 year old type 1)

One family demonstrated how their child's increase in strength had allowed them to then have a procedure to more effectively manage their condition:

[*She] recently had a PEG inserted for feeding. This procedure was initially refused as her consultant felt she was too weak to undergo surgery, however since treatment commenced and [she] improved it was reconsidered. She coped amazingly with the operation and the PEG has been far better for her and us as caregivers.* (parent 1 year old type 1)

It was commonly mentioned that treatment has led to notable improvement in quality of life due to children being able to do everyday activities that they could not previously

He can play and join in at nursery much more, can use crayons and pencils that he's never been strong enough for. His last half term's attendance was over 90%, due to appointments rather than illness. Before Nusinersen he couldn't manage a week never mind a whole half term.(parent 3 year old type 1)

We've also been able to consider a manual wheelchair for her now as she has gained just enough strength needed to self propel. (parent 3 year old type 1)

This drug has improved her quality of life and her ability to access more with her peers at school. She is desperate to be independent and this is making the little things much easier for her.

Emotional wellbeing for the whole family was seen to have greatly improved due to a new sense of hope for the future.

It has improved not only [her] life, but our family life too. We have improved emotional and physical health, we no longer live in fear, we live in hope of what the future holds. (parent 3 year old type 1)

Nusinersen means that the historical progression of the disease is now unwritten. There is hope beyond hope, there are possibilities (parent 1 year old type 1)

A number of Type 1 children receiving Nusinersen have gained physical abilities which are now great than those of older children with Type 2 who are not receiving the treatment, clearly indicating that treatment is working. Furthermore, whilst clinical trials suggest that the treatment is most effective in presymptomatic children, EAP clearly shows that even administration of the treatment at later stages can have massive impact on the individual health.

She started treatment when she was nearly two years old… by her 6th injection she almost saturated CHOP and in practical terms gained enough strength to play with toys whilst sitting without any support, albeit for short periods of time.

HOPES OF THOSE NOT YET RECEIVING TREATMENT

There is no direct data for patients with type 2-4 in the UK, however the evidence from other EU countries and USA clearly indicates the benefits of Nusinersen throughout the whole spectrum of patients. For many people not yet receiving treatment, their hopes are slowing or stopping deterioration. Stability of health and no more loss of ability were seen as huge benefits to people living with a condition that if untreated would inevitably lead to progressive loss of strength and a deterioration in health.

We as a family fully understand that Nusinersen is not a cure but a treatment, the ONLY treatment proving to work. I believe that these amazing children deserve the choice of access to Nusinersen, it gives us hope for the future that we can watch our children grow up. We would be grateful if it meant [his] condition became stable and not have to watch him lose any more of his abilities. We would no longer dread the appointments where they measure the degeneration of his condition. If Nusinersen could help [him] to manage a slight cold and prevent him from spending another Christmas in hospital would be life changing for us all. (parent 5 year old type 2 child)

The prospect of Nusinersen halting any further progression is truly amazing. It would make care and planning so much easier if my abilities were stable and not liable to decline. Each year I attend my annual sleep study with dread that there has been further deterioration in my breathing, and what this means for my health; every time I ask someone to lift my arm on to the joystick of my wheelchair, I try not to think that I could do this small task myself just 3 years ago (adult type 2 SMA)

Parents of children with SMA and adults with SMA both explained that what may appear to some as small gains could actually be hugely significant to independence and quality of life.

	what I do want, or I would like, is more use of my arms and hands, so that I can be more independent. Scratch an itch when I have one, hold my grandchild, stroke the dog, or even be able to drive again... And hug! (adult with type 2 SMA) *The prospect of small functional gains is even more priceless: The idea that my breathing and strength could be what it was five years ago, before I needed night ventilation or my fork pushed into food to skewer it, or to be fed my food in a restaurant when I am tired, would completely change my life. The idea that I might even be able to lift my own drink to my mouth again would increase my independence and quality of life immensely. While the difference between the ability to do or not do these seemingly little things might appear small, for someone who gradually loses these abilities, it is truly transformational to know you can keep them or may even get them back.* (Adult with type 2 SMA) *Whilst being fully independent would be a dream, my hopes for now are more realistic: being able to brush my teeth without assistance, brushing my hair and styling it how I would like, and eating without feeling fatigue.I would love to be able to turn myself in bed at night to avoid pressure sores…*
Disadvantages of the technology	
10. What do patients or carers think are the disadvantages of the technology?	In many cases, there were no perceived disadvantages of the treatment. Method of administration (the fact that the treatment is given via lumbar puncture) and necessitates a hospital visit were raised by some– although both of these considerations were seen as minor issues in that accessing the treatment was considered to far outweigh these concerns. *We have not experienced any negative side effects of the drug, but the administration by lumbar puncture is a worry, as I do not want to put my daughter through a painful procedure. However, the injection is very quick and does not seem to cause [her] much stress, and at this moment the benefit seems to far outweigh this small negative.* (parent 1 year old type 1) *The only disadvantage is that the drug has to be administered in a hospital environment, this is totally unavoidable, and frankly – the risk of infection is worth it. We are very mindful and take the necessary precautions to ensure our hospital visits are as 'risk free' as possible.* (parent of a 1 year old with type 1) *Intrathecal injection can be worrying procedure for children, as they can't see what happens behind their backs. Fortunately, [she] never suffered any side effect of the injections and recently mentioned that she prefers Nusinersen to Zoledronate infusion, as spinal injection is less uncomfortable than cannula.* (parent 10 year old type 1)

Patient population	
11. Are there any groups of patients who might benefit more or less from the technology than others? If so, please describe them and explain why.	Since SMA is a spectrum condition, inevitably some will benefit more than others. Furthermore, some would not even wish to change their on-going lifestyle for personal reasons. However, we must be careful defining benefit as this is a non-quantifiable variable and almost always personal. The truth is – treatment should be available to ALL those who want it and only withdrawn in cases where decline continue to be observed.

Equality	
12. Are there any potential equality issues that should be taken into account when considering this condition and the technology?	**Age at diagnosis is not a reliable or equitable proxy for disease severity or type** as this is largely dependent on the awareness of the medical team the child presents to, and so can vary greatly by area, hospital, consultant. Within the community we know of many families where symptoms were noticed by parents early in a child's life but parent concerns were dismissed by medical professionals (with children being passed off by professionals as lazy babies or parents flagging delays but these being attributed to other more minor conditions) and the process of getting a formal diagnosis taking many months. *I went to the health visitor expressing my concerns where she made a referral to a physiotherapist. Once going to the appointment we got told [he] was hyper-mobile. I never felt happy with this I could not see how a child who is basically 'double jointed' could be so clumsy and walk so badly. I asked for a second opinion and was told there was no issue, I pushed and pushed.....finally she admitted there wasn't something quite right! To me this was more of a relief! Someone finally listened to me as a mum.*(Parent of 6 year old type 3 child) **SMN2 copy number is also not a definitive measure** of predicting disease severity. For instance, whilst many type 1 infants have 1 or 2 copies, there are also a sizeable number with three copies and some type 2 children have two copies. The prevalence of type 1 children with 3 copies is unknown however data from various studies suggest it is a notable proportion. "In the severe form, one or two SMN2 copies (59% of patients) were most frequently seen, but three copies of the gene (41%) were also quite frequent." *Phenotype modifiers of spinal muscular atrophy: the number of SMN2 gene copies, deletion in the NAIP gene and probably gender influence the course of the disease* M. Jędrzejowska *et al*. The prognosis for type 1 children even with three copies is still presented as poor without treatment. This is just one example to show that it has been well established that copy number alone does not determine SMA type/ severity and that there are other less understood genes that are also influential as modifiers. For a number of years there have been **discrepancies in classification of the condition**. Even expert clinicians agree that SMA types have significant overlap and for example strong type 1 can be classified as a weak type 2 and vice versa. This means that if the treatment is approved for type 1 there will be a number of patients discriminated against because of the person who is their consultant.

Other issues	
13. Are there any other issues that you would like the committee to consider?	**The direct and indirect cost of the condition to the family has never been fully understood**, but at least one parent becomes a full time caregiver thus halving the family income, whilst the expenses dramatically increase. Mental health and wellbeing of the family is severely affected and not understood. This is not about the price of a drug, but about the price of people's lives.

Key messages

15. In up to 5 bullet points, please summarise the key messages of your submission:

- There is a clear unmet medical need in the case of SMA with fatalities and ongoing deterioration of health in affected individuals that could be immediately addressed through treatment with nusinersen, a treatment that can stop deterioration and bring about stability. Improved respiratory health/preventing the life threatening impact of relatively minor illnesses are the main hopes for treatment.
- Parents of children on the nusinersen Expanded Access Programme frequently mention notable gains in strength and abilities, with a number of children achieving major motor milestones such as independent sitting as an effect of treatment. Many children gained back the motor abilities they had lost. Some gained abilities that they had never achieved – even at their strongest – before treatment. Improvements were noted in respiratory strength (and as a result a better ability to cope with illness/ reduction in necessity of emergency hospital admissions), swallow and speech.
- Significant improvements have been reported in children who fall outside of the initial criteria of SMA 1 clinical trial (for instance in older type 1 children).
- Some improvements in older or stronger populations may appear to outside observers to be less significant but in reality they can be life changing – especially in terms of skills that allow more independence with self-care.
- Even amongst stronger types SMA can be life threatening and life limiting; many parents of type 2 children for instance talked of frequent hospital admissions with serious illness.

Thank you for your time.

Please log in to your NICE Docs account to upload your completed submission.

NICE National Institute for Health and Care Excellence

Professional organisation submission

Nusinersen for treating spinal muscular atrophy [ID1069]

Thank you for agreeing to give us your organisation's views on this technology and its possible use in the NHS.

You can provide a unique perspective on the technology in the context of current clinical practice that is not typically available from the published literature.

To help you give your views, please use this questionnaire. You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type.

Information on completing this submission

- Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable
- We are committed to meeting the requirements of copyright legislation. If you intend to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Your response should not be longer than 13 pages.

About you	
1. Your name	[redacted]
2. Name of organisation	Association of British Neurologists

3. Job title or position	[redacted]
4. Are you (please tick all that apply):	☒ an employee or representative of a healthcare professional organisation that represents clinicians? ☐ a specialist in the treatment of people with this condition? ☐ a specialist in the clinical evidence base for this condition or technology? ☐ other (please specify):
5a. Brief description of the organisation (including who funds it).	The Association of British Neurologists' mission is to improve the health and well-being of people with neurological disorders by advancing the knowledge and practice of neurology in the British Isles. Its 1400 members comprise predominantly UK trainee and consultant neurologists but also includes neurologists from Ireland and abroad. The ABN is funded predominantly from members' subscriptions; with additional sponsorship from the pharmaceutical industry.
5b. Do you have any direct or indirect links with, or funding from, the tobacco industry?	No
The aim of treatment for this condition	
6. What is the main aim of treatment? (For example, to stop progression, to improve mobility, to cure the condition,	To stop progression and improve function in individuals with type 1 and 2 Spinal Muscular Atrophy.

or prevent progression or disability.)	
7. What do you consider a clinically significant treatment response? (For example, a reduction in tumour size by x cm, or a reduction in disease activity by a certain amount.)	Stopping disease progression would be a hugely significant treatment response, as reported by patients, their families and their doctors (McGraw et al. BMC Neurology (2017) 17:68; doi: 10.1186/s12883-017-0853-y).
8. In your view, is there an unmet need for patients and healthcare professionals in this condition?	Yes. Prior to nusinersen, the treatment of patients with SMA was purely supportive: there was no pharmacological intervention that would impact on the natural history of the condition. The condition was inevitably fatal in childhood.
What is the expected place of the technology in current practice?	
9. How is the condition currently treated in the NHS?	

• Are any clinical guidelines used in the treatment of the condition, and if so, which?	Consensus statement for standard of care in spinal muscular atrophy. Wang CH, Finkel RS, Bertini ES, Schroth M, Simonds A, Wong B, Aloysius A, Morrison L, Main M, Crawford TO, Trela A; Participants of the International Conference on SMA Standard of Care. J Child Neurol. 2007 Aug;22(8):1027-49.
• Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please state if your experience is from outside England.)	Emphasis is predominantly on pulmonary care, with progressively increasing support leading up to non-invasive ventilation (NIV). The pathway, which is provided by respiratory physicians working closely with paediatric neurologists, is well defined. Pathways of care for Type 1 and Type 2 SMA are through paediatric neurology centres and are highly variable across the UK. Multidisciplinary care is essential and although pulmonary management is central to the more distressing deterioration in the natural history, mobility and therapy issues are crucial to day to day management. As patients become older then transition to adult services will define other pathways of care, probably through Neuromuscular Complex Care Centres such as at the National Hospital for Neuorology.
• What impact would the technology have on the current pathway of care?	By preventing or reducing disease progression, the technology would significantly delay the need for active pulmonary interventions, including NIV. Mortality would be reduced or stopped. Transition to adult care and more normal adult functioning may be possible.
10. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice?	
• How does healthcare resource use differ	There are currently no disease-modifying treatments in SMA and children are not given repeated lumbar punctures. This treatment is provided to children with SMA through repeated intrathecal injections.

between the technology and current care?	
• In what clinical setting should the technology be used? (For example, primary or secondary care, specialist clinics.)	The treatment is only suitable for delivery in a tertiary care setting. By virtue of its invasive nature and novelty, it is likely that in practice it will only be provided by specialist paediatric neurology services with high dependency/PICU facilities.
• What investment is needed to introduce the technology? (For example, for facilities, equipment, or training.)	Facilities, bed and staff would need to be identified to allow the treatment to be administered safely. This would usually be in the form of a high dependency unit or paediatric intensive care unit admission. Children will probably need overnight stay as they may have to travel far and are very weak
11. Do you expect the technology to provide clinically meaningful benefits compared with current care?	
• Do you expect the technology to increase length of life more than current care?	Yes, with supportive care all infants with type 1 SMA are deceased by 18 months and most by 12 months of age. Among infants with spinal muscular atrophy, those who received nusinersen were more likely to be alive and have improvements in motor function than those in the control group. Early treatment may be necessary to maximize the benefit of the drug. (2017: Finkel R et al N Engl J Med 2017; 377:1723-1732)
• Do you expect the technology to increase health-related quality of	Yes. The treatment improves not just longevity but also motor function, including respiratory function.

life more than current care?	
12. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	The currently available evidence suggests that the technology is particularly useful at the earliest stages. This would make it more appropriate to prioritise treatment in the following patient groups: Children at diagnosis - the younger the better Presymptomatic children
The use of the technology	
13. Will the technology be easier or more difficult to use for patients or healthcare professionals than current care? Are there any practical implications for its use (for example, any concomitant treatments needed, additional clinical requirements, factors affecting patient acceptability	The treatment will be more difficult to deliver for patients and healthcare professionals alike. The treatment is only suitable for delivery in a tertiary care setting. By virtue of its invasive nature and novelty, it is likely that in practice it will only be provided by specialist paediatric neurology services. Patients will require day case or overnight stay on a high dependency unit or paediatric intensive care unit for the procedure.

or ease of use or additional tests or monitoring needed.)	
14. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	It would be appropriate to consider withdrawing treatment in children who have not demonstrated a clinically meaningful response.
15. Do you consider that the use of the technology will result in any substantial health-related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation?	The effect of Nusinersen is of such a magnitude that I would expect this to be reflected in the QALY calculation.
16. Do you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related	

benefits and how might it improve the way that current need is met?	
• Is the technology a 'step-change' in the management of the condition?	Yes: this is the first and currently only disease-modifying treatment available in SMA.
• Does the use of the technology address any particular unmet need of the patient population?	The technology has been shown to be transformative in patients with SMA, improving lung and motor function and life expectancy beyond recognition. The results of the treatment trials were so clearcut that it was considered unethical to complete the work and they had to be discontinued prematurely.
17. How do any side effects or adverse effects of the technology affect the management of the condition and the patient's quality of life?	The commonest reported side effects of the treatment are post-lumbar puncture headache, respiratory tract infections and constipation. A proportion of children developed meningitis. A small number of children developed a low blood platelet count and renal toxicity. The serious side effects are infrequent. In the context of inexorably progressive neuromuscular paralysis, which is prevented by the drug, these side effects are likely to have a major adverse effect on the management of the condition or the patient's quality of life.
Sources of evidence	

18. Do the clinical trials on the technology reflect current UK clinical practice?	
• If not, how could the results be extrapolated to the UK setting?	At present, the drug is not available to patients in the UK, (except on Nusinersen Extended Acess Programme for children with SMA type 1.).
• What, in your view, are the most important outcomes, and were they measured in the trials?	The most important outcomes of reduced disease progression, reduced time to ventilator support, increased proportion of children walking; increased life expectancy were all measured in the trials.
• If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes?	Not applicable.
• Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	None of which I am aware.
19. Are you aware of any relevant evidence that might	No

not be found by a systematic review of the trial evidence?	
21. How do data on real-world experience compare with the trial data?	This treatment is uniquely effective in preventing disease progression and prolonging life expectancy that are evident in a real-world setting.
Equality	
22a. Are there any potential equality issues that should be taken into account when considering this treatment?	None.
22b. Consider whether these issues are different from issues with current care and why.	None.
Key messages	

24. In up to 5 bullet points, please summarise the key messages of your submission.

- Transformative treatment
- Stops the progression of SMA
- Radically improves mobility in affected children.
- Radically increases life expectancy of affected children.
-

Thank you for your time.

Please log in to your NICE Docs account to upload your completed submission.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal (STA)

Nusinersen for treating spinal muscular atrophy [ID1069]

Thank you for agreeing to give us your views on the technology and the way it should be used in the NHS.

The Department of Health and the Welsh Government provide a unique perspective on the technology, which is not typically available from the published literature. NICE believes it is important to involve NHS organisations that are responsible for commissioning and delivering care in the NHS in the process of making decisions about how technologies should be used in the NHS.

To help you give your views, we have provided a template. The questions are there as prompts to guide you. You do not have to answer every question. Short, focused answers, giving a Department of Health and Welsh Government perspective on the issues you think the committee needs to consider, are what we need.

About you

Your name: [redacted]

Name of your organisation British Paediatric Neurology Association. Based at Robert Jones and Agnes Hunt hospital, Oswestry.

Please indicate your position in the organisation:

- Department of Health or Welsh Government in general?
- commissioning services for the Department of Health or Welsh Government specific to the condition for which NICE is considering this technology?
- responsible for quality of service delivery in the CCG (e.g. medical director, public health director, director of nursing)?
- **a specialist in the treatment of people with the condition for which NICE is considering this technology?**
- a specialist in the clinical evidence base that is to support the technology (e.g. participation in clinical trials for the technology)?
- other (please specify)

Links with, or funding from the tobacco industry - please declare any direct or indirect links to, and receipt of funding from the tobacco industry:

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal (STA)

Nusinersen for treating spinal muscular atrophy [ID1069]

Nil

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal (STA)

Nusinersen for treating spinal muscular atrophy [ID1069]

What is the expected place of the technology in current practice?

How is the condition currently treated in the NHS? Is there significant geographical variation in current practice? Are there differences in opinion between professionals as to what current practice should be? What are the current alternatives (if any) to the technology, and what are their respective advantages and disadvantages?

The current technology is being used within the NHS via an Expanded Access Programme, and over the last 12 months, specialist neuromuscular centres have been working with local services to enable children and babies with SMA type 1 to receive the drug in a safe and appropriate fashion. The ability to achieve this initially varied depending on geographical location, due to organising services, management teams and the set-up of the service, however all neuromuscular centres can now offer this.
As a group of specialists, we are part of the Northstar/SMARTNET organisation and have been, with the SMA reach coordinator reviewing the process in the UK to address numbers treated and any problems encountered during the administration of this new technology. There have been in-depth discussions to look at appropriate tools to monitor the effect of this new technology and safety data.
We have discussed as a group the need for a patient registry for these babies and children receiving Nusinersen, that captures this data and can be used as an audit tool against previous best practice and outcomes.

The alternatives for this technology is to follow the standards of care documents;

Consensus Statement for Standard of Care in Spinal Muscular Atrophy
Ching H. Wang, MD, PhD Richard S. Finkel, MD Enrico S. Bertini, MD Mary Schroth, MD Anita Simonds, MD Brenda Wong, MD Annie Aloysius, MRCSLT, HPC Leslie Morrison, MD Marion Main, MCSP, MA Thomas O. Crawford, MD Anthony Trela, BSParticipants of the International Conference on SMA Standard of Care
Journal of Child Neurology, vol. 22, 8: pp. 1027-1049., First Published Aug 1, 2007.

These have recently been revised in 2017/2018, however vast majority (95%) of children with SMA type 1 will die before 18 months of age.

Eugenio Mercuri, et al., Diagnosis and management of spinal muscular atrophy: Part 1: Recommendations for diagnosis, rehabilitation, orthopedic and nutritional care, Neuromuscular Disorders (2017), doi: 10.1016/j.nmd.2017.11.005

Richard S. Finkel, et al., Diagnosis and management of spinal muscular atrophy: Part 2: Pulmonary and acute care; medications, supplements and immunizations; other organ systems; and ethics, Neuromuscular Disorders (2017), doi: 10.1016/j.nmd.2017.11.004

There is no other treatment available apart from supportive measures; ventilation, feeding via nasogastric or PEG feeding, medication to control bowels, saliva and secretion management, postural management with seating and sleep systems, physio therapy and orthotics to treat contractures and scoliosis (no surgery

previously had been done in general on these babies for scoliosis) and palliative care.

Following the standards of care these babies would be seen frequently and have lengthy hospital stays, often in PICU, until they were transferred fully to palliative care – this is both difficult for parents as well as professionals and there is significant investment in these babies to enable these babies to have the best quality of life in their short lives. The introduction of Nusinersen has meant that these babies can have an extended life with potential to improve in motor milestones and require less intervention and hospital stays; it does mean that they have more outpatient appointments and day case admissions for assessments and delivery of the drug.

To what extent and in which population(s) is the technology being used in your local health economy?

- is there variation in how it is being used in your local health economy?
- is it always used within its licensed indications? If not, under what circumstances does this occur?
- what is the impact of the current use of the technology on resources?
- what is the outcome of any evaluations or audits of the use of the technology?
- what is your opinion on the appropriate use of the technology?

All children within the West Midlands who are eligible are being treated with Nusinersen. This is a total of 4 babies (after an estimate of 5-7 per year based on genetic studies in SMA type 1). It is always used within its licensed indications and is administered within a specialised unit which undertakes regular intrathecal injections via an oncology anaesthetic list and a respiratory unit and PICU if required for those children who are less stable or require ventilation.

Currently we are funded by NHS England for the administration costs of the drug and as small numbers there is only a small impact of these children being added to a lumbar puncture list, however this will become more problematic as numbers increase year on year and new cases added to the list.

At present there is no UK registry for recording outcome measures and assessments, although this is being developed, and as a neuromuscular group we are collecting data and doing the same assessments on these babies which are being reviewed. Within our cohort in the West Midlands there has been no complications and in all cases there have been improvements with assessments in all domains; CHOP Intend scores and also time spent out of hospital and PICU. These are all important outcomes as well as no deaths.

The earlier these babies are identified and treated the better the outcome.

Servais et al, Nusinersen demonstrates greater efficacy in Infants with Shorter Disease Duration: Final Results From the ENDEAR Study in Infants With Spinal Muscular Atrophy (SMA), P-381, The 22nd International Annual Congress of the World Muscle Society, 3-7 October 2017, Saint Malo, France

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal (STA)

Nusinersen for treating spinal muscular atrophy [ID1069]

Finkel RS, Mercuri E, Darras BT et al. Nusinersen versus Sham Control in Infantile-Onset Spinal Muscular Atrophy. The New England Journal of Medicine 2017; 377: 1723-1732 DOI: 10.1056/NEJMoa1702752

Potential impact on the NHS if NICE recommends the technology

What impact would the guidance have on the delivery of care for patients with this condition?

With all new treatments and delivery of drugs; approval by NICE and adoption by NHS England would allow appropriate planning of the services with funding to support such services. If recommended by NICE, we are assured it has been through a vigorous review and serves as a 'gold standard' in order to compare against.

In what setting should/could the technology be used – for example, primary or secondary care, specialist clinics? Would there be any requirements for additional resources (for example, staff, support services, facilities or equipment)?

These babies need to be in specialist clinics for appropriate staff to carry out the assessments, and as outlined below the administration of the treatment would require specialist intervention with provision of staff and services to enable the treatment to be delivered, assessments completed and data collected to enable audit and outcome management.

Can you estimate the likely budget impact? If this is not possible, please comment on what factors should be considered (for example, costs, and epidemiological and clinical assumptions).

The factors needed to be considered here is that there needs to be infrastructure that is able to cope with the numbers of children eligible for this treatment, which would increase year on year and therefore a robust service needed in order to deliver this should be in place.
At present many neuromuscular centres, either administer the drug themselves on top of their usual demands or enlist the help of other teams; such as oncology, who add on a child to their list to inject. This will not be feasible in the long term and a dedicated SMA team per neuromuscular centre or region is more appropriate.

This team would need to consist of a specialist, possibly a specialist nurse appropriately trained to deliver IT injections and anaesthetic input for airway maintenance and potential problems.
The team would need to be supported by dedicated theatre/sterile treatment list provision, as these children need timely injections, particularly when receiving the loading doses.
Within the neuromuscular services; additional time for clinic assessments and physiotherapists trained in the outcome measures should also be addressed; investment to ensure delivery of the assessments and recording of these outcomes

in a timely fashion and data collection may require additional funding for data clerks or admin.

Would implementing this technology have resource implications for other services (for example, the trade-off between using funds to buy more diabetes nurses versus more insulin pumps, or the loss of funds to other programmes)?

This is difficult to comment on.

Would there be any need for education and training of NHS staff?

As a continued service to these children I would envisage that numbers requiring IT injections would continue to increase year on year; in the West Midlands we would expect 5-7 new patients per year, however within 5 years we would therefore be treating potentially 25-35 patients arranging 4 monthly IT injections.
We would therefore envisage that a specialist team to administer the injection would be the best proposal; possibly a specialist nurse with training and anaesthetic input to manage the intrathecal list.
As numbers increase we would foresee that further training of physiotherapists with awareness of SMA as well community teams would be foreseeable and important in the management of these children.

Equality

NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Please let us know if you think that this appraisal:

- could exclude from full consideration any people protected by the equality legislation who fall within the patient population for which [the treatment(s)] is/are/will be licensed;

At present we are currently treating patients with SMA type 1, however this drug is potentially beneficial to both Type 2 and type 3 SMA patients, however evidence not as robust as for type 1 SMA due to numbers studied, this therefore could be seen as excluding other patient groups.

- could lead to recommendations that have a different impact on people protected by the equality legislation than on the wider population, e.g. by making it more difficult in practice for a specific group to access the technology;
- could lead to recommendations that have any adverse impact on people with a particular disability or disabilities.

Please tell us what evidence should be obtained to enable the Committee to identify and consider such impacts.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal (STA)

Nusinersen for treating spinal muscular atrophy [ID1069]

Other Issues

Please include here any other issues you would like the Appraisal Committee to consider when appraising this technology?

NICE National Institute for Health and Care Excellence

Professional organisation submission

Nusinersen for treating spinal muscular atrophy [ID1069]

Thank you for agreeing to give us your organisation's views on this technology and its possible use in the NHS.

You can provide a unique perspective on the technology in the context of current clinical practice that is not typically available from the published literature.

To help you give your views, please use this questionnaire. You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type.

Information on completing this submission

- Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable
- We are committed to meeting the requirements of copyright legislation. If you intend to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Your response should not be longer than 13 pages.

About you	
1. Your name	[redacted]
2. Name of organisation	**SMA-REACH UK**

3. Job title or position	[redacted], **Dubowitz Neuromuscular Centre, UCL Great Ormond Street Institute of Child Health and Great Ormond Street Hospital for Children Foundation Trust**
4. Are you (please tick all that apply):	☐ an employee or representative of a healthcare professional organisation that represents clinicians? ☒ a specialist in the treatment of people with this condition? ☒ a specialist in the clinical evidence base for this condition or technology? ☒ other (please specify): I am the Principal Investigator of a Clinical Network- SMA REACH UK, which is involved in a funded Natural History study for SMA, definition of outcome measures and in translational research in SMA
5a. Brief description of the organisation (including who funds it).	SMA Reach is a network of the paediatric clinical sites involved in the delivery of care and in translational research in Spinal Muscular Atrophy. The network is funded by the Charities SMA Trust and Muscular Dystrophy UK (http://www.musculardystrophyuk.org/information-for-professionals/health-professionals/community-physiotherapy-working-group/sma-reach-uk/). Main aims of this multidisciplinary network are: the optimisation of outcome measures for SMA; longitudinal data collection of functional outcome measures of children with all SMA subtypes; training of physiotherapists; organisation of annual meetings to discuss developments and standards of care, in close partnership with advocacy groups. As 2 of the centres which are part of SMA REACH were involved in the original Nusinersen clinical trial for SMA1 (London GOSH and Newcastle); the SMA REACH network has taken an active role in facilitating the Biogen-initiated Nusinersen EAP in the UK, with: consensus documents submitted to NHSE; policy commissioning input especially in relation to inclusion / exclusion criteria and discontinuation criteria for Nusinersen. The network is currently collecting the collaborative efficacy data of all SMA1 children currently receiving Nusinersen in the UK(>70). Finally and for full disclosure, Muntoni is the Chief Investigator of the trial studying Nusinersen in SMA1 in the UK and has participated in 2 Biogen organised SABs on SMA in 2017, and received speaker honorarium for participation in a symposium on SMA in 2017 and one in 2018. In addition, SMA REACFH UK has established a collaborative link with 2 International Networks (one in Italy, Italian Telethon; and one in the US, PNCRN) for optimisation of outcome measures for all SMA subtypes. This network has been approached by Biogen for the possibility to organise post-marketing surveillance of Nusinersen in the UK. This model could be a model not dissimilar from the postmarketing surveillance model that our Duchenne network (the North Star network) has

	established in collaboration with MDUK and with NHSE and NICE for ataluren for children with DMD and eligible mutations
5b. Do you have any direct or indirect links with, or funding from, the tobacco industry?	**No**
The aim of treatment for this condition	
6. What is the main aim of treatment? (For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability.)	Data from well conducted randomised placebo controlled (RPCT) studies published in the New England Journal of Medicine in 2017 and 2018 (N Engl J Med. 2017 Nov 2;377(18):1723-1732; N Engl J Med. 2018 Feb 15;378(7):625-635.) and previous open label studies (Lancet. 2016 Dec 17;388(10063):3017-3026) have met the endpoint of improving function in patients with type 1 SMA and in the non-ambulant type 2 and type 3 SMA. There is an ongoing study, called Nurture, involving pre-symtpomatic children expected to have type 1 or 2 SMA based on previous family history and on SMN2 copy number; interim results have been presented in 2017 at the World Muscle Society meeting (October 2017). In answer to the specific question of what is the main aim of the treatment, the published data clearly indicate that improvement in functional outcomes (as measured by disease specific outcome measures) was achieved in the RPCT studies with acquisition of meaningful milestones (i.e. rolling for example in type 1 SMA; or sitting) in a percentage of patients; these milestones are never achieved in untreated patients. Reduction of respiratory co-morbidities was also demonstrated in the infant study (NEJM2017) with increased ventilator free survival and age at death. The efficacy of the restoration of SMN protein expression appears strongly related to the duration of the symptomatic phase of the disease, especially for type 1 SMA. This is a condition that affects motorneurons progressively, so that where there is very advanced and chronic pathology (see for example figure 1 in Finkel et al, N Engl J Med. 2017 Nov 2;377(18):1723-1732 with a clear difference for the children who were symptomatic for less than 12 weeks compared to those symptomatic longer than 12 week) . At the other end of the spectrum, treatment in the early phases of the disease as for example the pre-symptomatic Nurture study demonstrated striking clinical efficacy, with the majority of children treated since the first month of life, having achieved the normal motor milestones at the age of 1 year including sitting and standing unaided. While the long term efficacy of the treatment in

	all these forms still needs to be established, there is no doubt that earlier intervention is associated with much better outcomes, to the point that the majority of children treated in the presymptomatic study were phenotypically normal at the age of 1 year. Considering the progressive nature of the condition, one can therefore expect stabilisation but not necessarily improvement for children with very advanced stage of disease and severe weakness; improvement of function as measured by functional scales and acquisition of meaningful novel milestones in children treated in the symptomatic, but not too advanced, phase of the disease; and a significantly better outcome in children treated pre-symptomatically.
7. What do you consider a clinically significant treatment response? (For example, a reduction in tumour size by x cm, or a reduction in disease activity by a certain amount.)	The results of the published studies in the NEJM are certainly clinically meaningful: in the symptomatic type 1 SMA study (NEJM 2017), in the nusinersen group, 22% of the infants achieved full head control, 10% were able to roll over, 8% were able to sit independently, and 1% were able to stand; in the control group, no infants achieved these milestones. Regarding respiratory function, the risk of death or the use of permanent assisted ventilation was 47% lower in the nusinersen group than in the control group Regarding the SMA2 and non-ambulant type 3 study (NEJM2018), there was an increase of 4.9 points in the Hammersmith Scale, which is highly superior to the minimal clinical significant difference for this scale. . On the other hand untreated children had a nearly 2 points decrease in function.
8. In your view, is there an unmet need for patients and healthcare professionals in this condition?	Absolutely Yes, however it varies with a degree of severity. There are different degrees of severity for SMA, each associated with a different level of burden for families and patients. Infants with type 1 SMA have no autonomy nor motor acquisition and are completely dependent on their parents and carers for any activity of daily living. In addition, as disease progresses, the medical care escalates. Assisted feeding via gastrostromy feeding is now increasingly common, as is non-invasive ventilation and cough assistance offered as a palliative measure. These interventions however not only decrease symptoms but increase disease duration to several years. Patients with type 2I SMA never acquire the ability to walk., Whilst mean survival of affected individuals is now well into the 5th decade of life, the severity of the muscle weakness is such that scoliosis requiring surgical intervention is invariable and gastrostomy and non invasive ventilation are essentially invariably needed at some point.. The severe weakness of the axial muscles means that individuals need to be turned in bed often, up to 6-8 times per night (as in SMA1). This has tremendous impact on the families of these affected children who essentially become full time carers for these severely affected children.

	Type 3 SMA is divided into 2 subtypes based on age of onset. In the 3A, onset is by the age of 3 years. These children have a 90% probability of losing their ability to walk by the late teens. Children with later onset and adults with the condition can usually maintain some degree of independent mobility into later adulthood but with increasing difficulties in walking long distances, going upstairs and getting up from the floor.
What is the expected place of the technology in current practice?	
9. How is the condition currently treated in the NHS?	Symptomatically with extensive multidisciplinary team involvement that in type 1 involves paediatrician; neuromuscular specialist; physiotherapist; occupational therapist; respiratory paediatrician ; speech and language therapist; dietician; orthopaedic surgeon; palliative care paediatrician; community children's specialist nurse; orthotics; just to mention the most consulted specialists. Gastrostomy, ventilation and cough assistance are commonly used, although children at the very severe end of the spectrum usually are channelled towards early palliative care and may die in the first few months of life, without having the opportunity to be exposed to these symptomatic interventions. For children with type 2 SMA the MDT support needed is much the same, with the exceptions that palliative care is less commonly needed, but additionally spinal surgery is essentially invariable. Regular physiotherapy to reduce the burden of the progressive contractures is the norm. For children with type 3 SMA, there is no usually need for involvement of the respiratory team and feeding is not an issue. Regular physiotherapy is needed for all, and for children who lose the ability to walk in the first decade of life, surgical correction of progressive scoliosis is commonly required
• Are any clinical guidelines used in the treatment of the condition, and if so, which?	There have been very recently published guidelines (2018) following a ENMC international workshop and a DELPHI technique effort to obtain international consensus: Finkel RS et al Diagnosis and management of spinal muscular atrophy: Part 2: Pulmonary and acute care; medications, supplements and immunizations; other organ systems; and ethics. Neuromuscul Disord. 2017 Nov 23. pii: S0960-8966(17)31290-7. doi: 10.1016/j.nmd.2017.11.004. PMID: 29305137 Mercuri E, Finkel RS, Muntoni F et al Diagnosis and management of spinal muscular atrophy: Part 1: Recommendations for diagnosis, rehabilitation, orthopedic and nutritional care. Neuromuscul Disord. 2018 Feb;28(2):103-115. doi: 10.1016/j.nmd.2017.11.005. These update and replace previously published SOC document (J. Child Neurology 2007)

• Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please state if your experience is from outside England.)	The pathway of care for type 2 and type 3 is pretty uniform across the NHS although there is inequality to the access to wheelchair services; cough assistance and expert physiotherapy. As for type 1 SMA, this is an area in which there is more divergence between different centres as this is an area in rapid evolution. Especially regarding the provision of cough assistance and non-invasive ventilation. There is ongoing effort to work toward equity of access and agreed care pathways promoted by SMA REACH UK in collaboration with the UK networks
• What impact would the technology have on the current pathway of care?	To some extent the answer to this question depends on the timely diagnosis and initiation of therapeutic intervention as discussed above. As a newborn screening program is currently not available for SMA, we will continue to treat symptomatic children although it is hoped that with time if the drug was available the newly diagnosed patients will start treatment earlier than even the children in the clinical trials. Assuming however the mean age at recruitment to be similar as in the published data, for type 1 SMA there will be delayed in the requirement for ventilator support, more arm independence and longer survival; for type II SMA improved function with longer maintenance of higher level of motor function and delay in the need for respiratory intervention (note this has not been demonstrated in the relative short study but it is reasonable to assume based on the impact in the more severe SMA1 children).
10. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice?	The administration of Nusinersen requires intrathecal injections. For type 1 SMA this require a centre with expertise in the management of these children and availability on site of respiratory physicians, anaesthetists and specialist nurses with expertise in this condition. . These children will probably not need a general anaesthetic for the procedures, at least in infancy, but need these available safety measures In children with type 2 and type 3 SMA a brief general anaesthetic to reduce distress of the procedure is likely to be needed; type 2 children will require competent management during and after GA A special issue is the intrathecal access for children who have had a previous spinal fusion. This might require discussion with the surgeons/ neurosurgeons.
• How does healthcare resource use differ between the technology and current care?	The main difference will be the requirement for safe and comfortable repeated intrathecal drug administration. Trial results point to decreased morbidity resulting from respiratory infections, lower number of hospitalisations and better functional outcomes, all of which, over time, are expected to result in significantly decreased use of healthcare resources compared to the current situation.
• In what clinical setting should the technology be	Hospitals with specialist paediatric Neuromuscular clinics

used? (For example, primary or secondary care, specialist clinics.)	
• What investment is needed to introduce the technology? (For example, for facilities, equipment, or training.)	Dedicated Time of physicians; nurses; respiratory team and anaesthetist to deliver the drug. Expert physiotherapy to monitor outcomes. Psychology services to support the child and family. Hospital procedure / theatre space and bed allocation. Maintenance of intrathecal drug administration competency register. In rare technically challenging cases, radiology and neurosurgery might become necessary
11. Do you expect the technology to provide clinically meaningful benefits compared with current care?	Absolutely yes especially if initiated early
• Do you expect the technology to increase length of life more than current care?	Absolutely yes for type 1; possibly for type 2. Not relevant for type 3 (as life expectancy for SMA3 normal)
• Do you expect the technology to increase health-related quality of life more than current care?	QOL and burden of disease for affected people and their carers should be positively affected in responding patients
12. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	As indicated before, the very chronic and weak patients might not respond with the same degree as early symptomatic patients. The risk benefit for very weak type 1 children needs to be carefully considered. At the other end of the spectrum, the efficacy in the milder patients group, say adults with mild forms of SMA3 and only very slowly progressive disease is currently not known.

The use of the technology	
13. Will the technology be easier or more difficult to use for patients or healthcare professionals than current care? Are there any practical implications for its use (for example, any concomitant treatments needed, additional clinical requirements, factors affecting patient acceptability or ease of use or additional tests or monitoring needed.)	Following the administration of the treatment (which requires lumbar puncture, a mode of administration that is available in most of the largest specialist neuromuscular centres), the continuing specialist neuromuscular care of the patient is not essentially different, and the recently published International Care guidelines should be followed. The exception is that there will be a larger population of surviving type 1 children who will reach milestones and functional achievements that will require assessment and monitoring by physiotherapists and surgeons currently only very rarely involved in the delivery of care for these patients
14. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	The SMA REACH has already elaborated rules / suggestion for starting and stopping medication for SMA1 children involved in the EAP. As for the chronic SMA types, the recent NEJM publication (2018) provided a rational framework to monitor and benchmark response. SMA REACH could certainly be involved in providing an opinion on the start-stop criteria for SMA2 and 3.
15. Do you consider that the use of the technology will result in any substantial health-related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation?	QALY for infants in the first year of life are not really relevant There is incomplete understanding from health care professionals of the immense burden of disease and for the implication for parents and carers of children with these diseases. Mothers (more often than fathers) will need to turn their child in bed 6-8 times per night, every single night of the year. This leads to consequences in terms of mental and personal health, employment, and wellbeing of the wider family that we do not feel are well captured by the QALY calculations. Whilst the most immediate family affected the most, the issue will affect pretty much everybody who is in contact with the family and has a very wide overall impact.
16. Do you consider the technology to be innovative in	Yes especially if administered early. Type 2 patients can already be active members of society (for example a Baroness in the House of Lords has type 2 SMA).). However the health-related complications and lack of

its potential to make a significant and substantial impact on health-related benefits and how might it improve the way that current need is met?	independent mobility limits the possibility of such achievements for most, and that achieved by rare fortunate individuals could be attained by more if affected patients were stronger
• Is the technology a 'step-change' in the management of the condition?	Absolutely yes. We have seen advances in symptomatic support treatments, particularly the introduction of non-invasive ventilation for neuromuscular disorders. This, however, is the first specific disease treatment to have such an impact; it is hard to underestimate its importance.,
• Does the use of the technology address any particular unmet need of the patient population?	Muscle weakness is the primary issue affecting patients with SMA. This is addressed by this drug
17. How do any side effects or adverse effects of the technology affect the management of the condition and the patient's quality of life?	
Sources of evidence	
18. Do the clinical trials on the technology reflect current UK clinical practice?	Largely yes and indeed the trial for SMA1 was done in the UK; the trial in type 2 (not done in the UK) used as outcome measure the Hammersmith Motor Functional Scale originally developed in the UK and currently in use in clinics around the country.
• If not, how could the results be extrapolated to the UK setting?	

• What, in your view, are the most important outcomes, and were they measured in the trials?	Improved function (yes measured both for SMA1 and SMA2 and 3) Reduced respiratory morbidity (measures in SMA1 trial; duration of trial for the more chronic form not adequate for a respiratory endpoint, so was not an outcome) Improved survival (clearly demonstrated in the SMA1 study)
• If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes?	
• Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	The main side effects are related to the mode of administration of the drug (back pain, cerebrospinal fluid leakage, headache, nausea, the post–lumbar puncture syndrome, procedural pain, procedural nausea, procedural headache, and vomiting). There were no clinically relevant changes related to nusinersen in clinical laboratory test results
19. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	No
21. How do data on real-world experience compare with the trial data?	We recently reported (SMA Europe meeting, 2018) the experience in administering this drug under the EAP in 16 specialised centres in UK and Ireland. From March 2017 to October 2017, 63 patients (25 males, 38 females) were treated with nusinersen; the intrathecal injections were performed using topical anaesthetic cream in most cases, few patients older than 12 months required general anaesthetic. The mean CHOP-intend total score at baseline was 25/64 (range 5- 52), and 36/64 (range 9- 51) at the 5th injection. Most patients improved the CHOP-intend total score (1-17 points); few remained stable, while only one dropped from 52 at baseline to 46 at the 5th injection due to limited mobility secondary to a bone fracture, but scored 58 after the 4th injection. HINE-2 scores were available in 16 patients at baseline and at 5th injection; an improvement of at least 2 points was observed in 8 patients with no cases of motor regression. At baseline 33/63 patients were receiving non-invasive ventilation (NIV), fourteen of them for

	>16 hours/day; none had tracheostomy. In 5 patients a reduction of the hours on NIV was noted; four additional patients needed to start NIV while on treatment.
Equality	
22a. Are there any potential equality issues that should be taken into account when considering this treatment?	The original difficulties for many centres to be authorised to initiate the EAP for type 1 SMA has given an insight of how devastating inequality of access for the drug is for families and has had wide publicity in the national press. Ensuring there is an appropriate plan to allow patients with SMA to access the drug in several centres distributed nationwide will be important as the burden of delivering the treatment is considerable hence not only a very small number of centres can manage the national demand. At the same time administration of the drug especially to fragile infants requires a level of expertise that is not present in every general paediatric hospital. The specification of the centre eligibility need to be considered
22b. Consider whether these issues are different from issues with current care and why.	The main issue is the need to increase capacity for administering the drug. However a second and important point to consider is that a consequence of treating children with type 1 SMA will be that there will be an increasingly large population of children originally with SMA1 who will survive longer and who will remain symptomatic with a protracted, milder form. As we do not have a newborn screening programme for SMA, these children will be symptomatic at the time of starting therapy and hence their rescue incomplete.
Key messages	

24. In up to 5 bullet points, please summarise the key messages of your submission.

- This is a highly effective novel therapy for a group of patients in whom the unmet need is grossly underestimated
- Earlier treatment leads to considerably better outcome
- The treatment requires knowledge of the disease and its complications to be administered safely and effectively, and to monitor response to therapy.
- As chronic and very weak patients might not respond as effectively as patients with short disease duration, criteria for start- stop treatment need to be agreed and implemented
- While there is concern regarding how the price band of this drug could make its availability to patients complicated; we equally do not consider the QUALY instrument a completely appropriate instrument to assess efficacy and cost benefit for a rare condition with a vast unmet need that affects most people from birth or infancy and for the rest of their life, often shortened as a result of the weakness

Thank you for your time.

Please log in to your NICE Docs account to upload your completed submission.

NICE National Institute for Health and Care Excellence

Clinical expert statement

Nusinersen for treating spinal muscular atrophy [ID1069]

Thank you for agreeing to give us your views on this technology and its possible use in the NHS.

You can provide a unique perspective on the technology in the context of current clinical practice that is not typically available from the published literature.

To help you give your views, please use this questionnaire. You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type.

Information on completing this expert statement

- Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable
- We are committed to meeting the requirements of copyright legislation. If you intend to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Your response should not be longer than 13 pages.

About you	
1. Your name	[redacted]
2. Name of organisation	**Great Ormond Street Hospital –** [redacted]

3. Job title or position	[redacted]
4. Are you (please tick all that apply):	☐ an employee or representative of a healthcare professional organisation that represents clinicians? ☐**X** a specialist in the treatment of people with this condition? ☐ a specialist in the clinical evidence base for this condition or technology? ☐ **X** other (please specify): full-time consultant clinician treating children with paediatric neuromuscular disorders and spinal muscular atrophies, including intrathecal administration of nusinersen to SMA1 children participating in the extended access program at Great Ormond Street Hospital to
5. If you wrote the organisation submission and/ or do not have anything to add, tick here. (If you tick this box, the rest of this form will be deleted after submission.)	☐ yes
The aim of treatment for this condition	
6. What is the main aim of treatment? (For example, to stop progression, to improve mobility, to cure the condition,	To stop progression, and to gain functional benefit for mobility, muscle strength, respiratory and bulbar muscle function. In the longer term, prevent and treat disability, improve function, Survival and quality of life

or prevent progression or disability.)	
7. What do you consider a clinically significant treatment response? (For example, a reduction in tumour size by x cm, or a reduction in disease activity by a certain amount.)	Achievement of stability of motor function together with, improvement in posture, mobility, arm function, hand function respiratory function, swallowing, survival and quality of life
8. In your view, is there an unmet need for patients and healthcare professionals in this condition?	There is a major unmet need for patients is by muscle atrophy.
What is the expected place of the technology in current practice?	
9. How is the condition currently treated in the NHS?	Current treatment is symptom based, together with interventions like nasogastric tube placement, gastrostomy, Noninvasive Nasal Mask Ventilation, and spinal surgery. Some children are treated with Salbutmol (not very effective) Children with SMA one currently can get nusinersen under the extended access program with the drug is being provided free by the manufacturer and the administration costs are borne by the NHS
• Are any clinical guidelines used in the	The recently published standards of care by Mercuri and Finkel et al. 2018

treatment of the condition, and if so, which?	
• Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please state if your experience is from outside England.)	The pathway of care is reasonably well defined, but the resources and expertise for management varies across the various centres of NHS England
• What impact would the technology have on the current pathway of care?	Increased frequency of hospital appointments, with the need for making arrangements for lumbar punctures and intrathecal and mistress of nusinersen. In the longer term, if the treatment is beneficial, then there will be a benefit in lower costs for ventilatory support / mobility aids.
10. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice?	The nusinersen therapy will become a complement to the present symptom based management. This treatment will stay in place till a more effective treatment becomes available. There may be a potential role for complementation with different novel treatments.
• How does healthcare resource use differ between the technology and current care?	The current care is symptom based. The nusinersen technology is an entirely different plan of treatment, aiming at increasing the amount of the deficient survival motor neuron protein. The parhway for ongoing assessment, implementation and monitoring, with longer-term survival of SMA one infants, will have an impact on health resource development.

• In what clinical setting should the technology be used? (For example, primary or secondary care, specialist clinics.)	SMA specialist clinics with MDT care facilities, together with facilities for non-toxic intrathecal drug administration. This will need to be implemented in paediatric and adult neurology/neuromuscular centres, primarily secondary and tertiary care.
• What investment is needed to introduce the technology? (For example, for facilities, equipment, or training.)	Clinic for intrathecal nusinersen administration and maintenance of non-toxic intrathecal prescription and administration register. MDT care including neurology paediatrics respiratory medicine physiotherapy and occupational therapy anaesthetist and symptom get teams clinical physiotherapists in the relevant SMA specific assessments
11. Do you expect the technology to provide clinically meaningful benefits compared with current care?	Definitively. This has now been published in peer-reviewed journals for SMA1. Studies for SMA2 are in progress
• Do you expect the technology to increase length of life more than current care?	Yes, definitively, especially for SMA1
• Do you expect the technology to increase health-related quality of life more than current care?	Yes

12. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	Infants with SMA1, and especially the presymptomatic ones, would have the highest improvement in survival. Young infants with a SMA2 would be anticipated to have better stability Young children with SMA3, who are at risk of loss of independent walking, no potentially maintain the ability to walk. The benefit may be less pronounced in individuals with long duration disease with is being maintained on intensive respiratory support like tracheostomy. How are, this observation is theoretical, and practical experience needs to be accrued.
The use of the technology	
13. Will the technology be easier or more difficult to use for patients or healthcare professionals than current care? Are there any practical implications for its use (for example, any concomitant treatments needed, additional clinical requirements, factors affecting patient acceptability or ease of use or additional tests or monitoring needed.)	The technology is more difficult to implement as compared to the current standards of care. This is mainly because of the need for lumbar puncture in children with respiratory compromise and spinal deformities.

14. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	Complete lack of benefit and continuing deterioration after one year of treatment, with parental or patient wish not to undergo further lumbar punctures, may be reason to stop.
15. Do you consider that the use of the technology will result in any substantial health-related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation?	I'm not fully familiar with these calculations to answer correctly.
16. Do you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits and how might it	Yes, nusinersen technology is both innovative and has huge potential. The current data on improvement in survival and motor function, in SMA1, is compelling.

improve the way that current need is met?	
• Is the technology a 'step-change' in the management of the condition?	Yes
• Does the use of the technology address any particular unmet need of the patient population?	Yes, there is no other treatment available as of now which has anywhere similar benefit
17. How do any side effects or adverse effects of the technology affect the management of the condition and the patient's quality of life?	Apart from the inconvenience of lumbar punctures required long-term for intrathecal nusinersen restriction, there have been no major adverse effects reported.
Sources of evidence	
18. Do the clinical trials on the technology reflect current UK clinical practice?	Yes, the population samples used in the clinical trials reflect the UK SMA1 population accurately. Similar trials for SMA2 are also valid

• If not, how could the results be extrapolated to the UK setting?	
• What, in your view, are the most important outcomes, and were they measured in the trials?	Survival improvement in motor function, respiratory outcomes yesterday were measured for the SMA1 study
• If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes?	Motor function and respiratory outcomes are important surrogate measures and reflect the clinical outcome
• Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	I'm not aware of the of these
19. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	No Most data from clinical practice is been reported in scientific meetings, at least as abstracts.

20. How do data on real-world experience compare with the trial data?	Very similar
Equality	
21a. Are there any potential equality issues that should be taken into account when considering this treatment?	The cost of this treatment should not be defective which denies the availability of this treatment to the patient's
21b. Consider whether these issues are different from issues with current care and why.	The needs to be a step change in the way NHS fast tracks and authorises use of innovative medication as a part of translational research application
Key messages	

22. In up to 5 bullet points, please summarise the key messages of your statement.

- Nusinersen was effective in clinical trials of SMA1, achieve preset efficacy endpoints, and had to be discontinued
- Nusinersen is the only current available treatment we should radically alter is the natural history of SMA1, and the favour of the patient and family
- The outcome is shown in the clinical trial, are the clinical outcomes which are desirable in clinical practice
- The use of nusinersen for SMA2 and SMA3 needs to be considered carefully and has potential benefits for the patients
- Resource allocation will need to be made to enable implementation of nusinersen treatment

Thank you for your time.

Please log in to your NICE Docs account to upload your completed statement, declaration of interest form and consent form.

NICE National Institute for Health and Care Excellence

Patient expert statement

Nusinersen for treating spinal muscular atrophy [ID1069]

Thank you for agreeing to give us your views on this technology and its possible use in the NHS.

You can provide a unique perspective on conditions and their treatment that is not typically available from other sources.

To help you give your views, please use this questionnaire with our guide for patient submissions.

You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type.

Information on completing this expert statement

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- Your response should not be longer than 10 pages.

About you	
1.Your name	[redacted]
2. Are you (please tick all that apply):	☐ a patient with the condition? ☒ a carer of a patient with the condition? ☐ a patient organisation employee or volunteer?

	☐ other (please specify):
3. Name of your nominating organisation	SMA TRUST
4. Did your nominating organisation submit a submission?	☒ yes, they did ☐ no, they didn't ☐ I don't know
5. Do you wish to agree with your nominating organisation's submission? (We would encourage you to complete this form even if you agree with your nominating organisation's submission)	☒ yes, I agree with it ☐ no, I disagree with it ☐ I agree with some of it, but disagree with some of it ☐ other (they didn't submit one, I don't know if they submitted one etc.)

6. If you wrote the organisation submission and/ or do not have anything to add, tick here. (If you tick this box, the rest of this form will be deleted after submission.)	☐ I have more to add.
7. How did you gather the information included in your statement? (please tick all that apply)	☒ I have personal experience of the condition ☐ I have personal experience of the technology being appraised ☐ I have other relevant personal experience. Please specify what other experience: ☐ I am drawing on others' experiences. Please specify how this information was gathered:
Living with the condition	
8. What is it like to live with the condition? What do carers experience when caring for someone with the condition?	One of our twin sons, [redacted], has SMA type 2. He is an extremely bright and popular 7-year-old who has a great sense of humour. He attends mainstream school where he is exceeding age related expectations academically. [redacted] has a lot of potential and has great aspirations for his future. Despite being born seemingly healthy, [redacted] was diagnosed with SMA at eleven months. He was diagnosed as having SMA 'type 2' because at diagnosis he could maintain a sitting position when positioned in one. **What is it like to live with the condition?** [redacted] is a full-time wheelchair user. Without help, he cannot even sit up. He has never been able to bear any weight on his legs so he cannot stand or walk independently. He has weak arm and neck muscles and has an ineffective cough. [redacted] also has mild scoliosis, which despite targeted exercises

	and wearing a rigid back brace, could worsen over time. As [redacted] grows, his muscles will struggle to support his increasing weight. [redacted] works incredibly hard to maintain as much of his muscle strength as possible, regularly taking part in sessions of hydrotherapy, physiotherapy and riding for the disabled. Despite all of [redacted]'s hard work and effort, he will slowly lose strength, skill and ability. This is both frustrating and disheartening. When [redacted] wakes up in the morning he cannot sit up, he cannot get out of bed. He relies on us to lift / hoist him in and out of bed, transfer him on and off the toilet, deal with all his personal care, dress and undress him. [redacted] has no physical independence until he is transferred into his powered wheelchair which gives him his much-loved freedom. Both during and after school, [redacted] is transferred in a supportive standing positive, with the help of orthotic aids, and a standing frame. This can avoid painful muscles contractures, aids digestion and can increase bone strength. At the moment [redacted] has enough arm strength to feed himself. However, if [redacted]'s arm muscles weaken further, he will no longer have the strength to lift a fork or cup to his mouth and will need to be fed. This would mean [redacted] would require more care and would lose more independence. If the muscles that help [redacted] swallow weaken, doctors have also discussed the potential need for a gastrostomy. [redacted] travels to school independently in his powerchair which he drives with great precision and control. He requires 1:1 support at school for his physical needs only. [redacted] can currently write and use a computer both competently and independently. [redacted] is a skilled artist both on paper and on screen. If [redacted]'s muscles continue to weaken he could struggle to continue to grip a pen effectively and may not have the strength to operate a computer mouse and keyboard. Losing abilities like this is a real fear for [redacted] and it could have an extremely negative impact on him both practically, psychologically and emotionally. It could also affect his future employability and therefore his ability to contribute to society. [redacted] and others with SMA can suffer from fatigue. If [redacted] didn't have to work his muscles so hard to support his body and head, he may have more energy and strength to fulfil other tasks, like take the lid off a pen to write, or peel a banana. The inability to cough and blow his nose effectively is a huge problem for [redacted]. It makes SMA a threat to his life. We live in fear that a simple cold could progress into a serious infection requiring

hospital admission. Throughout the winter months, [redacted] takes prophylactic antibiotics, has daily chest physio and the prophylactic use of a cough assist machine (a form of non-invasive ventilation).

The winter can be a very isolating time for someone with SMA, affecting them socially and emotionally as well as physically.

What do carers experience when caring for someone with the condition?

Caring for a child with SMA has a huge impact **physically**, **emotionally** and **financially** on the whole family. This is exacerbated by its progressive nature.

Physical effects

Caring for a child with SMA is exhausting, both physically and emotionally.

The lifting and transferring is physically exhausting. During the period when we were raising the funds to adapt our house to facilitate installation of equipment to assist us lifting [redacted], my husband injured his back while manually lifting [redacted]. This meant my husband needed regular physiotherapy and resulted in him needing steroid injections in his back under general anaesthetic.

[redacted] also needs care during the night. He may need to be re-positioned, or if he gets too hot he doesn't have the strength to adjust his bedding. When poorly, [redacted] requires cough assist and chest physio throughout the night. All of this contributes to sleepless nights for our family. The emotional stress and worry also leads to a lack of sleep. The resulting tiredness and the anxiety caused by the fear of further decline in [redacted], has resulted in my own mental and physical health suffering.

Emotional affects

Caring for a child with SMA results in **constant** worry. We worry every time [redacted] is exposed to a cough. Will this result in a hospital admission?

Another huge emotional strain is watching the loss of function. **Despite continuous and tireless efforts by the patient and their caregivers, SMA will progress**. This loss of strength is extremely hard to watch, particularly in [redacted]'s case: we have to watch him decline in parallel to his twin who continues to gain skills every day.

How will this affect [redacted]'s future physically and emotionally? How does he feel watching his twin improve physically whilst he declines? How would he cope if he lost the ability to feed himself? What would happen if he lost the ability to write and operate a computer. How employable would he be?

Medical professionals have advised us to keep [redacted] in the best possible shape until treatment becomes available. We continuously and tirelessly do this yet fear that we are not doing enough. Time is not on our side. In the last 12 months [redacted]'s spine has gone from having a 0-degree curve to a 35-degree curve. We're terrified it's going to worsen despite our constant efforts to prevent it. A curved spine could restrict the lungs and cause further problems to a child with an already compromised respiratory system. This could increase the likelihood of hospital admissions and the future need for invasive spinal surgery.

Since the existence of Nusinersen, our emotional stress and anxiety has increased. It has been proven that the earlier a SMA patient is given Nusinersen, then the more effective it will be. It's now much harder to watch [redacted] decline and lose function, knowing that a drug now exists which could prevent this.

[redacted]'s siblings, in particular his twin brother, experience a lot of emotional stress and anxiety. His twin brother presents some very challenging and exhausting behaviour due to jealously of the extra attention and time we need to provide [redacted]. This is very difficult to deal with.

SMA can also be socially isolating for the whole family. Inaccessibility is a real problem.

Financial effects

Caring for a child with SMA has put a financial strain on our family.

I have had to reduce my work hours significantly to enable me to care for [redacted] effectively. This was also a necessity due to physical and emotional exhaustion. I regularly needed to take time off due to [redacted]'s appointments under numerous different teams. During the winter months, when [redacted] is susceptible to hospital admissions due to his ineffective cough, I have been unable to work. This has been either due to an unexpected hospital admission, or due to sheer exhaustion of trying to avoid a hospital admission by regularly administering chest physio, cough assist and sometimes suctioning throughout the night.

This has had a financial impact on our family due to reduced income. Fortunately, I can rely on family to assist us in care giving so I am still able to work part time. Even so, I am not eligible for carers allowance.

	We have also had to raise money to contribute significantly to the majority of all of [redacted]'s equipment, including a five-figure power chair, other specialist equipment, extensive house adaptations and also a wheelchair accessible vehicle.
Current treatment of the condition in the NHS	
9. What do patients or carers think of current treatments and care available on the NHS?	There is currently no treatment for SMA available for [redacted]. Whilst [redacted] is seen by numerous different health professionals, all care provided is purely aimed at managing his condition and attempting to slow down its progression. Problems that arise from having SMA are managed, whereas SMA itself isn't. For example, constipation is managed by Movicol, muscle contractures are hopefully prevented by the use of orthotics, scoliosis is potentially slowed by wearing a spinal jacket, [redacted]'s ineffective cough is helped by chest physio and the use of a cough assist machine. There is no care or treatment available to either improve, or completely stabilise his condition.
10. Is there an unmet need for patients with this condition?	Yes. Current care interventions available solely help to [redacted] remain comfortable and mobile whilst his muscle function continues to decline.
Advantages of the technology	
11. What do patients or carers think are the advantages of the technology?	If Nusinersen could **stop the progression of SMA, stabilise [redacted] and prevent further decline**, this would be incredibly beneficial for him, both physically and emotionally. It would stop the worry about losing his current skills and function. He would still be able to lift a fork and a cup to his mouth, to write and to operate his powerchair, to use a computer. The loss of further independence, and the need for increased care and expensive equipment could all be avoided. If the curvature of the spine could be stabilised then invasive spinal surgery could also be avoided. **A small gain in strength might seem insignificant, but for someone with SMA it could be both life changing and life-saving.** The evidence from trials demonstrated less respiratory related hospital admissions. If Nusinersen could **increase respiratory strength** this could be life saving for [redacted]. It

	would also reduce the emotional stress, anxiety and physically exhaustion of care givers. Having the strength to cough and blow his nose effectively could stop lengthy hospital admissions with the reliance of machines to assist him. This would stop SMA being a threat to his life. Increased arm strength would enable [redacted] to gain new skills. Having enough arm strength to manage his own personal care e.g. self-clean would provide more independence, have huge emotional and psychological gains with less reliance on carers. Increased arm strength could also enable [redacted] to unscrew a lid from a bottle, open food packets and prepare his own food. Something taken for granted by many. If [redacted] had slightly more muscle strength he would not tire so easily and therefore accomplish more. Even holding his head up towards to end of a school day requires a lot of effort. Imagine if Nusinersen could increase [redacted]'s arm strength enough to assist with transfers? Or bear weight on his legs, if only for 30 seconds, while being transferred to the toilet? This would not only dramatically increase [redacted]'s independence, but would put less physical and financial strain on the carer. I have seen footage of Type 2 children of a similar age and ability to [redacted] who have recently started receiving Nusinersen. Already there is evidence of them gaining new skills and ability. These skills might seem small, but for someone with SMA, they are life changing and could open many new opportunities.
Disadvantages of the technology	
12. What do patients or carers think are the disadvantages of the technology?	The administration could be seen as a problem by some; however, people with SMA and their carers are used to frequent hospital appointments, admissions, needles and invasive investigations. I believe the benefits of Nusinersen proven in trials outweigh the invasive nature of its administration. It could also prevent future invasive surgeries at great cost to the NHS. The technology may be expensive but it would significantly reduce care costs long term. Small increases in strength would mean less hospital admissions, less care requirements and less expensive equipment.

Patient population	
13. Are there any groups of patients who might benefit more or less from the technology than others? If so, please describe them and explain why.	**It has been proven that the earlier a SMA patient is given Nusinersen, then the more effective it will be.** With SMA, time is not on your side. Despite continuous and tireless efforts by the patient and their caregivers, SMA will progress. Without treatment, more care will be needed, more medical intervention, more equipment. Treatment needs to be given **now** for the physical, emotional and psychological needs of the patients and their families. It's incredibly hard to experience decline, especially when technology now exists which could prevent this. **The 'type' of SMA should NOT determine whether or not a patient should be eligible to receive treatment.** SMA is sub divided by its severity into types. However, there is such a broad spectrum across each type and the boundaries between types can be blurred. E.g. Is there enough difference between a strong type 1 and a weak type 2 to justify excluding a type? Some stronger type 1s currently accessing Nusinersen on the EAP are now sitting. This now clinically makes them a type 2!
Equality	
14. Are there any potential equality issues that should be taken into account when considering this condition and the technology?	**No one should be denied treatment.** If an effective treatment is available, we believe it should be available to all those who chose to have it, and are able to have it, as soon as possible.
Other issues	
15. Are there any other issues that you would like the committee to consider?	SMA is progressive. Every day matters. Although various other drugs are in currently in trials, Nusinersen is the first and only treatment available for SMA. It is more effective the earlier it's given. Pausing the progression of SMA would be life changing for many.

	As a parent, it is incredible hard to watch your child decline, despite working tirelessly to try and prevent this. Knowing that technology that has proven to help exists, yet isn't available for your child, is an extremely difficult and frustrating situation to be in.

Key messages

16. In up to 5 bullet points, please summarise the key messages of your statement:

- **A small gain in strength might seem insignificant, but for someone with SMA it could be both life changing and life-saving**. Having enough arm strength to manage their own personal care e.g. transfer themselves on/off toilet, self-clean, open food packets etc. would provide more independence and have huge emotional and psychological gains with less reliance on carers. Having the strength to cough and blow their nose effectively would stop lengthy hospital admissions with the reliance of machines to assist them. This would stop SMA being a threat to life.
- **With SMA, time is not on your side.** Despite continuous and tireless efforts by the patient and their care givers, SMA will progress. More care will be needed, more medical intervention will take place, more equipment will be required. Treatment needs to be given **now** for the physical, emotional and psychological needs of the patients and their families.
- **Children with SMA have huge potential** with at least average intellectual abilities. With the correct support and treatment, they will lead fulfilling lives, and contribute to society through successful careers. Knowing their SMA wouldn't progress any further e.g. not losing the strength to operate a computer keyboard or mouse, would offer huge practical and emotional gains for them.
- **Treatment should not be limited by 'type' of SMA.** There is such a broad spectrum across each type. E.g. Is there enough difference between a strong type 1 and a weak type 2 to justify excluding a type?
- **Drug may be expensive but would significantly reduce care costs long term**. Small increases in strength would mean less hospital admissions, less care requirements, less expensive equipment and most importantly, more independence for the SMA patient.

Thank you for your time.

Please log in to your NICE Docs account to upload your completed statement, declaration of interest form and consent form.

NICE National Institute for Health and Care Excellence

NHS commissioning expert statement

Nusinersen for treating spinal muscular atrophy [ID1069]

Thank you for agreeing to give us your views on this technology and its possible use in the NHS.

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- Your response should not be longer than 10 pages.

About you	
1. Your name	[redacted]
2. Name of organisation	**NHS England**

3. Job title or position	[redacted]
4. Are you (please tick all that apply):	☐ commissioning services for a CCG or NHS England in general? ☒ commissioning services for a CCG or NHS England for the condition for which NICE is considering this technology? ☐ responsible for quality of service delivery in a CCG (for example, medical director, public health director, director of nursing)? ☐ an expert in treating the condition for which NICE is considering this technology? ☐ an expert in the clinical evidence base supporting the technology (for example, an investigator in clinical trials for the technology)? ☐ other (please specify):
Current treatment of the condition in the NHS	
5. Are any clinical guidelines used in the treatment of the condition, and if so, which?	It is understood that treatment follows guidelines from the International Standards of Care Committee for Spinal Muscular Atrophy.
6. Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please state if your	It is understood that the pathway of care is well defined and consistent and that there are about 12 centres treating children in England; this is through an Expanded Access Programme where Biogen are funding the drug on a commercial-in-confidence scheme and NHS England are funding the administration costs.

experience is from outside England.)	
7. What impact would the technology have on the current pathway of care?	For some patients with Type 1 SMA, there is an Expanded Access Programme in place whereby Biogen are funding the drug on a commercial-in-confidence scheme and NHS England are funding the administration costs; there would be no impact on the current pathway of care for these patients. Patients with Types 2 and 3 SMA will mostly be cared for at the 12 paediatric neuroscience centres but, as care is supportive, some will have been discharged to local supportive care.
The use of the technology	
8. To what extent and in which population(s) is the technology being used in your local health economy?	The technology is being used (through an Expanded Access Programme) for patients with Type 1 SMA who meet the criteria set out in the NHS England commissioning policy statement: https://www.england.nhs.uk/publication/clinical-commissioning-policy-statement-nusinersen-for-genetically-confirmed-spinal-muscular-atrophy-sma-type-1-for-eligible-patients-under-the-expanded-access-programme-eap/
9. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice?	As there are no other active treatments, the current pathway of care involves multi-disciplinary supportive care including respiratory, gastroenterology, and orthopaedic care, as well as nutritional support, physiotherapy, assistive technologies, occupational therapy and social care. The care of patients receiving nusinersen would be overseen by one of the 12 centres.

• How does healthcare resource use differ between the technology and current care?	For those Type 1 SMA patients who meet the criteria set out in the NHS England commissioning policy statement, there is an Expanded Access Programme in place whereby Biogen are funding the drug on a commercial-in-confidence scheme and NHS England are funding the administration costs. For new patients, as there are no other active treatments, the pathway of care involves multi-disciplinary supportive care including respiratory, gastroenterology, and orthopaedic care, as well as nutritional support, physiotherapy, assistive technologies, occupational therapy and social care.
• In what clinical setting should the technology be used? (For example, primary or secondary care, specialist clinics.)	The technology should only be initiated in a small number of expert centres that have expertise in looking after patients with Type 1 SMA and in delivering intrathecal treatments.
• What investment is needed to introduce the technology? (For example, for facilities, equipment, or training.)	No specific investment is required to introduce the technology in terms of facilities, equipment or training for Type 1 SMA (excluding the drug costs). If the drug was supported for Type 2 and 3 SMA, investment would be required both in terms of the drug costs and administration.
• If there are any rules (informal or formal) for starting and stopping treatment with the technology, does this include any additional testing?	The rules for patients with Type 1 SMA are set out in the NHS England commissioning policy statement: https://www.england.nhs.uk/publication/clinical-commissioning-policy-statement-nusinersen-for-genetically-confirmed-spinal-muscular-atrophy-sma-type-1-for-eligible-patients-under-the-expanded-access-programme-eap/

10. What is the outcome of any evaluations or audits of the use of the technology?	These are not yet available.
Equality	
11a. Are there any potential equality issues that should be taken into account when considering this treatment?	No
11b. Consider whether these issues are different from issues with current care and why.	Not applicable
Key messages	

12. In up to 5 bullet points, please summarise the key messages of your statement.

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-
-
-
-

Thank you for your time.

Please log in to your NICE Docs account to upload your completed statement, declaration of interest form and consent form.

BIOGEN

Draft Managed Access Agreement – Data collection outline

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Nusinersen for the treatment of 5q spinal muscular atrophy

1. Purpose of this document

1.1 The purpose of this draft agreement is to outline a set of auditable measures that can be used to address potential sources of uncertainty within the evidence package for nusinersen as reviewed by the National Institute for Health and Care Excellence (NICE; TA 1069).

1.2 This outline approach to a managed access agreement (MAA) has been drawn up by Biogen following discussions with the National Health Service (NHS) England and NICE and is to be considered by the NICE committee at the meeting on 27th June 2018. As discussed with NICE, a more detailed proposal including a statistical analysis plan and commercial aspects will be provided following the appraisal committee meeting.

1.3 Details of patient eligibility, start and stop criteria are also still to be discussed relevant stakeholders including clinical experts and patient advisory groups although potential considerations are provided in later sections.

1.4 For the avoidance of doubt, this document represents an initial proposal for discussion on potential procedures for data collection to address sources of uncertainty. It should not be seen by either party as legally binding.

2. Background

2.1 SMA is a rare, genetic, neuromuscular disease, characterised by spinal motor neuron loss, muscle atrophy and motor impairment. SMA is debilitating for all patients and fatal for the worst affected; patients and their families can experience extremely high levels of burden.

2.2 Nusinersen is the first and only disease-modifying treatment for 5q SMA and was granted a marketing authorisation from the European Medicines Agency (EMA) on 30 May 2017.

2.3 NICE are in the process of considering all evidence relating to the use of nusinersen in SMA.

2.4 Biogen would like to initiate discussions with NICE and other stakeholders in relation to potential uncertainties relating to the use of nusinersen in SMA and how best to acknowledge and address these in the form of a potential MAA.

3. Scope and timelines for MAA

3.1 If required and agreed by all parties, it is envisaged that the MAA outlined by this document would commence following the final appraisal determination of the ongoing NICE technology appraisal.

3.2 In order to gather sufficient data, given the limited rate of events within the nusinersen clinical trials programme and need for longer term data collection, it is envisaged that the MAA would run initially for a period of five (5) years with the option to terminate earlier if sufficient evidence is generated.

3.3 Data generated by this MAA will also be used to fill uncertainties in the current data and modelling.

4. Patient eligibility

4.1 Nusinersen's full marketing authorisation includes the treatment of all patients with 5q SMA. The submission and this draft MAA focuses on a subset of the authorised population, specifically patients with infantile onset (those who have or are most likely to develop type I) or later onset (those who have or are most likely to develop types II and III) SMA. The proposed population is narrower than the marketing authorisation (all patients with 5q SMA) because the evidence base on nusinersen is limited to patients with pre-symptomatic and symptomatic infantile onset and later onset SMA.

4.2 In order to be considered eligible for treatment within this draft MAA, patients should fulfil all criteria of the marketing authorisation (including consideration of special warnings); specifically, patients should be excluded if:

4.2.1 Administration via lumbar puncture is contraindicated or of specific risk for any reason (including patients with significant scoliosis);

4.2.2 A patient has significant renal impairment as this population has not been studied in the clinical trial programme (however, the nusinersen clinical trial programme gives no reason to believe that nusinersen worsens renal function).

4.3 Patients should fulfil all starting criteria, which have been differentiated by maximum motor milestone achieved (non-sitters; sitters; ambulatory) in order to avoid inequity in access based on age at symptom onset:

4.3.1 Non-sitters

- Homozygous gene deletion or homozygous mutation or compound heterozygous mutation detected in 5q-related SMA

- *SMN2* copy number ≥2
- <18 years of age at diagnosis

4.3.2 Sitters

- Homozygous gene deletion or homozygous mutation or compound heterozygous mutation detected in 5q-related SMA
- *SMN2* copy number ≥2
- <18 years of age at diagnosis

4.3.3 Ambulatory

- Homozygous gene deletion or homozygous mutation or compound heterozygous mutation detected in 5q-related SMA
- *SMN2* copy number ≥ 2
- <18 years of age at diagnosis

4.4 Patients currently treated using nusinersen under other access mechanisms (e.g. expanded access programme) are eligible for treatment providing all other criteria are met, however distinction should be made between patients who are naïve to treatment and patients who have been on treatment or those who become the commissioning responsibility of NHS England.

4.5 Patients could stop treatment under the MAA on potential criteria as outlined in the Section 5 below or where patients become non-compliant. Such patients may be eligible for continued treatment under different mechanisms outside this agreement.

5. Data collection

5.1 Data should be collected on all patients starting nusinersen therapy at initiation and/or at every subsequent planned clinic visit.

5.2 Data should be collect on all patients who discontinue nusinersen for any reason to allow for the assessment of disease trajectory in such patients

5.3 To conform to standard clinical practice and align to existing data, evaluation of response should be made: 14 months after initiation of therapy (equivalent to 4 loading and 3 maintenance doses) with further assessments every 12 months thereafter.

5.4 Given an absence of appropriate active, disease modifying alternative therapies, no comparative data will be collected prospectively.

5.5 Adverse event (AE) collection is not mandated as part of this MAA as Biogen are committed to post-marketing authorisation data collection/pharmacovigilance studies (including periodic safety update reports [PSURs] with the EMA to collect AEs via other mechanisms).

5.6 Endpoints to be evaluated will be determined by patient motor milestones at initiation of therapy (non-sitters; sitters; ambulatory) but will conform to a standard set of top-line variables according to the following hierarchy:

- SURVIVAL
- VENTILATION / RESPIRATORY EVENTS (E.G. INFECTIONS)
- MOTOR FUNCTION
- QUALITY OF LIFE

5.7 It is envisaged that data will be collected using the established SMART NET registry with modifications required.

ENDPOINT	PROPOSED ASSESSMENT	STOPPING CRITERIA FOR CONSIDERATION*
SURVIVAL	Patients, regardless of initially diagnosed motor milestone state, will be assessed for mortality with any cause and for mortality linked to SMA by ICD-10 coding relating to SMA in either death certificate PART I (including a, b and c) (immediate cause of death) or PART II (significant conditions contributing to death) of death certificate	All patients stop due to mortality
VENTILATION / RESPIRATORY EVENTS (E.G. INFECTIONS)	Patients, regardless of SMA type, will be tracked for incidence, length and type of ventilation Rates of pneumonia and pneumonia-like illness including severity and duration together with all LRTI will be collected	Invasive ventilation e.g. tracheostomy
MOTOR FUNCTION	For SMA patients that are initially diagnosed as non-sitters, achievement of motor milestones will be tracked using standard measures: HINE in infants; CHOP INTEND; HFMSE; 6MWT + RULM For SMA patients initially diagnosed as sitters or ambulatory, maintained motor function according to HFMSE, 6MWT + RULM will be tracked	Patients with SMA, two (2) consecutive measures of decline (in the absence of alternate explanations e.g. infection) of: - >4 points on the CHOP INTEND scale - >3 points on the HFMSE scale - 30m drop in distance walked in the 6MWT which corresponds to a greater than the MCID decline on any scale

QUALITY OF LIFE	Patients between the ages of 8 and 12 years old PedsQL 3.0 Neuromuscular Module and PedsQL 4.0 Generic Core Scales will be administered either in concert with administration of nusinersen or at a separate clinical evaluation. Administration where possible will be conducted directly but, where impractical, proxy assessment by carers will be captured. However, further discussion is required on which quality of life instrument would be most appropriate. For older patients, EQ-5D-5L will be administered either in concert with administration of nusinersen or at a separate clinical evaluation In addition, carer quality of life will be captured using EQ-5D-5L at each clinical evaluation of the patient	N/A

* Please note considerations for stopping criteria will require further validation with clinical community and relevant stakeholders but are based on early discussions and the clinical data available.

Abbreviations: CHOP INTEND, Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders; EQ-5D-5L, European Quality of Life-5 Dimensions 5-level scale; HFMSE, Hammersmith Functional Motor Scale-Expanded; HINE, Hammersmith Infant Neurological Exam; ICD-10, International Statistical Classification of Diseases and Related Health Problems 10th Revision; LRTI, lower respiratory tract infection; MCID, minimal clinically important difference; PedsQL, Paediatric Quality of Life Inventory; RULM, revised upper limb module; SMA spinal muscular atrophy; 6MWT, six minute walk test;

6. Glossary

Abbreviation	Definition
6MWT	Six minute walk test
AE	Adverse event
CHOP-INTEND	Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders
EAP	Expanded Access Programme
EMA	European Medicines Agency
EQ-5D-5L	European Quality of Life-5 Dimensions 5-level scale
HINE	Hammersmith Infant Neurological Exam
HFMSE	Hammersmith Functional Motor Scale-Expanded
ICD-10	International Statistical Classification of Diseases and Related Health Problems 10th Revision
LRTI	Lower respiratory tract infection
MAA	Managed access agreement
MCID	Minimal clinically important difference
NICE	National Institute for Health and Care Excellence
NHS	National Health Service
PSUR	Periodic safety update reports
PedsQL	Paediatric Quality of Life Inventory
RULM	Revised upper limb module
SAP	Statistical analysis plan
SMA	Spinal muscular atrophy

Nusinersen for treating spinal muscular atrophy: A Single Technology Appraisal

Produced by	School of Health and Related Research (ScHARR), The University of Sheffield
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Declared competing interests of the authors

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Rider on responsibility for report

The views expressed in this report are those of the authors and not necessarily those of the NIHR HTA Programme. Any errors are the responsibility of the authors.

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Contributions of authors

Eva Kaltenthaler and Emma Hock summarised and critiqued the clinical effectiveness evidence reported within the company's submission. Paul Tappenden and Andrew Rawdin critiqued the health economic analyses submitted by the company and undertook the ERG's exploratory analyses. Jean Hamilton critiqued the statistical analyses presented in the company's submission. Clara Mukuria provided advice on the mapping analysis used to value health states. Mark Clowes critiqued the company's search strategy. Anne-Marie Childs and Anita Simonds provided clinical input to the ERG. All authors were involved in drafting and commenting on the final report.

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Abbreviations

ACEND	Assessment of Caregiver Experience with Neuromuscular Disease
ADL	Activities of daily living
AE	Adverse event
AFT	Accelerated failure time
AIC	Akaike Information Criterion
ASO	Antisense oligonucleotide
BIC	Bayesian Information Criterion
BiPAP	Bi-level positive airway pressure
CADTH	Canadian Agency for Drugs and Technologies in Health
CEAC	Cost-effectiveness acceptability curve
CGI-I	Clinical Global Impression of Improvement
CHOP INTEND	Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders
CI	Confidence interval
CMAP	Compound Muscle Action Potential
CPAP	Continuous positive airway pressure
CRD	Centre for Reviews and Dissemination
CS	Company's submission
CSR	Clinical study report
DSA	Deterministic sensitivity analysis
EFS	Event-free survival
EMA	European Medicines Agency
EQ-5D	Euroqol 5-Dimensions
EQ-5D-5L	Euroqol 5-Dimensions 5-Level
EQ-5D-Y	Euroqol 5-Dimensions Youth
ERG	Evidence Review Group
FDA	Food and Drug Administration
GP	General practitioner
HFMSE	Hammersmith Functional Motor Scale-Expanded
HINE-2	Hammersmith Infant Neurological Examination (Module 2)
HR	Hazard ratio
HRQoL	Health-related quality of life
IBS	Integrated Brier Score
ICER	Incremental cost-effectiveness ratio
IPD	Individual patient-level data
ITT	Intention-to-treat
KM	Kaplan-Meier
LSM	Least squares mean
mg	Milligram
MI-E	Mechanical insufflation-exsufflation
mRNA	Messenger ribonucleic acid
MUNE	Motor Unit Number Estimation
mV	Megavolt
N/A	Not applicable
NG	Nasogastric
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
NIV	Noninvasive ventilation
NJ	Nasojejunal
NR	Not reported
NRA	Non-invasive respiratory aid
OLS	Ordinary least squares
ONS	Office for National Statistics

OS	Overall survival
OT	Occupational therapy
PedsQL	Paediatric Quality of Life Inventory
PedsQL NMM	Paediatric Quality of Life Inventory Neuromuscular Module
PH	Proportional hazards
pre-mRNA	Pre-messenger ribonucleic acid
PSA	Probabilistic sensitivity analysis
PSS	Personal Social Services
PT	Physiotherapy
QALY	Quality-adjusted life year
RCT	Randomised controlled trial
RULM	Revised Upper Limb Module
RWC	Real world care
SAE	Serious adverse event
SCC	International Standard of Care Committee
SMA	Spinal muscular atrophy
SMN	Survival motor neuron
SmPC	Summary of Product Characteristics
STA	Single Technology Appraisal
UK	United Kingdom
WHO	World Health Organization
WTP	Willingness-to-pay

1. SUMMARY

1.1 Critique of the decision problem in the company's submission

The company's submission (CS) assesses the clinical effectiveness and cost-effectiveness of nusinersen (Spinraza®) within its licensed indication for the treatment of 5q spinal muscular atrophy (SMA). The CS notes that nusinersen is the first and only approved disease-modifying treatment for SMA. The company's description of SMA and its management is generally appropriate. The decision problem addressed by the CS is partly in line with the final scope issued by the National Institute for Health and Care Excellence (NICE). The evidence presented within the CS relates to a narrower population than that defined in both the NICE scope and the marketing authorisation for nusinersen; specifically, the available evidence is limited to patients with pre-symptomatic and symptomatic early (infantile) onset and later onset SMA. No evidence is presented on the clinical effectiveness or cost-effectiveness of nusinersen in people with Type 0 or Type IV SMA. Despite the limited scope of the available evidence, the CS states that the anticipated place of nusinersen in therapy is as a first-line treatment for all SMA patients as soon as possible after diagnosis (in combination with usual symptomatic care).

The final NICE scope defines the comparator as best supportive care (BSC). The comparator within the randomised controlled trials (RCTs) of nusinersen is a sham procedure. The comparator considered within the company's health economic analysis is "real world care" (usual care), including respiratory, gastrointestinal, nutritional and orthopaedic care. The CS highlights that the differential use of life-extending symptomatic care, including permanent respiratory support, means that real world survival may not reflect that seen in clinical trials. The CS argues that nusinersen meets NICE's end-of-life criteria in the early onset (Type I) SMA population, but not the later onset (Types II and III) SMA population. The Evidence Review Group (ERG) notes that the company's model suggests that the mean predicted survival for patients with early onset SMA receiving usual care is 3.87 years.

1.2 Summary of clinical effectiveness evidence submitted by the company

The CS did not contain a systematic review of clinical effectiveness evidence; this is a requirement of the NICE Single Technology Appraisal (STA) process. Two key studies were presented in the CS: (i) the ENDEAR study, which recruited infantile onset SMA patients, and (ii) the CHERISH study, which recruited later onset SMA patients. Both studies were RCTs comparing nusinersen against a sham procedure control group. ENDEAR (n=122) was undertaken in 31 secondary care centres worldwide. CHERISH (n=126) was undertaken in 24 secondary care centres worldwide.

In the ENDEAR study, 80 participants received nusinersen, administered as a single intrathecal lumbar puncture injection with a scaled 12mg loading dose on study days 1, 15, 29 and 64 and maintenance dosing every 4 months (days 183 and 302), while 41 patients received the sham procedure. Overall, the

baseline characteristics of the two groups were similar, although patients in the nusinersen group were on average younger than those in the control group and had an earlier age of symptom onset. Primary outcomes were: proportion of motor milestone responders (measured using Module 2 of the Hammersmith Infant Neurological Examination [HINE-2]) and event-free survival (EFS, defined as time to death or permanent ventilation). ENDEAR included three analysis sets: (i) an interim analysis set; (ii) a final efficacy set and (iii) a final intention-to-treat (ITT) set. With regard to HINE-2, a significantly greater percentage of patients in the nusinersen group achieved motor milestone responses than the control group (41% vs 0% in the interim analysis and 51% vs 0% in the final efficacy set), although many patients in the nusinersen group could not be classified as responders (49% of patients in the final efficacy set). There was a statistically significant increase in EFS for the nusinersen group compared with the sham control group (ITT analysis set, p=0.005). ENDEAR was rated as being at low risk of bias in the CS; the ERG consider this study to be at moderate risk of bias due to concerns regarding the preservation of blinding, an imbalance in dropouts between groups, and the potential for incomplete reporting of outcomes.

The CHERISH study included 84 patients who received nusinersen administered as single intrathecal lumbar puncture injection, at single dose level of 12mg delivered in 4 doses over 9 months using a loading regimen (days 1, 29, 85) with a maintenance dose at 6 months (day 274). The control group was comprised of 42 patients who received the sham control. Overall, the two groups were similar, although there were imbalances between groups with respect to the proportions of patients who had ever achieved a motor milestone and in the median time from disease onset to study enrolment, with a longer delay in receiving therapy in the nusinersen group compared with the sham group. The nusinersen group had a slightly higher Hammersmith Functional Motor Scale-Expanded (HFMSE) total score at baseline. The CHERISH study included three analysis sets: (i) an interim analysis set; (ii) an efficacy set and (iii) an ITT set. The primary outcome measure in CHERISH was motor function as measured by the HFMSE instrument. The change in HFMSE from baseline was significant in both the interim analysis (least squares mean [LSM] change difference: 5.9; 95% confidence interval [CI] 3.7 to 8.1; p<0.001) and the final efficacy set analysis (LSM change difference: 4.9; 95% CI 3.1 to 6.7; p=0.0000001) for the nusinersen group compared with the control group. CHERISH was rated as being at low risk of bias in the CS; the ERG consider this study to be at moderate risk of bias due to concerns regarding the preservation of blinding and the potential for incomplete reporting of outcomes.

In the ENDEAR study, treatment effects for key outcome measures were evaluated for two pre-specified subgroups: disease duration at screening (≤12 weeks, >12 weeks) and age at symptom onset (≤12 weeks, >12 weeks). Overall, nusinersen demonstrated a benefit in all subgroups, except for the analysis of overall survival (OS) in the subgroup with age at onset of symptoms >12 weeks; however, the number of patients in this subgroup was small. For all outcomes, more pronounced treatment effects were

observed for infants with a disease duration ≤12 weeks at screening; however, statistical tests for a difference between subgroups were not provided.

An integrated safety analysis with data from eight completed or ongoing studies including a total of 260 patients was presented in the CS. In the integrated safety analysis, both nusinersen-treated patients and control group patients experienced adverse events (AEs). The most commonly reported AEs were those expected in patients with SMA or after lumbar puncture, such as headache, vomiting, back pain and post-lumbar puncture syndrome. Overall, there were fewer deaths in the nusinersen-treated patients than the control patients (19% vs 7%) and fewer serious adverse events (SAEs) in the nusinersen-treated patients compared with the control patients (39% vs 60%).

1.3 Summary of the ERG's critique of clinical effectiveness evidence submitted

Although no systematic review was presented in the CS, the ERG is confident that no relevant studies of nusinersen for SMA were missed. However, a systematic review of studies related to the BSC comparator was not presented. The quality assessment tools used to appraise the included studies was considered appropriate by the ERG. Most outcomes listed in the NICE scope were presented, with the exception of complications of SMA and stamina and fatigue.

1.4 Summary of cost effectiveness submitted evidence by the company

The company submitted two *de novo* model-based health economic evaluations of nusinersen: the first model relates to patients with early onset (Type I) SMA, whilst the second relates to patients with later onset (Type II/III) SMA.

Early onset model

The company's early onset model assesses the cost-effectiveness of nusinersen versus usual care for the treatment of patients with early onset SMA (initial age = 5.58 months), based on the ENDEAR trial. The incremental health gains, costs and cost-effectiveness of nusinersen are evaluated over a 60-year time horizon from the perspective of the NHS and Personal Social Services (PSS). The company's early onset model adopts a state transition approach, with health states defined by motor function milestones based on the HINE-2 instrument. The model parameters were largely informed by: HINE-2 and Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders (CHOP INTEND) outcomes collected within ENDEAR; mortality outcomes from ENDEAR and other observational data (Gregoretti *et al*, Zerres *et al* and general population life tables); a mapping exercise to translate Paediatric Quality of Life Inventory (PedsQL) outcomes collected in the CHERISH trial to the Euroqol 5-Dimensions (EQ-5D); a cross-sectional study of the costs and caregiver health-related quality of life (HRQoL) impacts of SMA and standard costing sources. The model assumes that treatment using nusinersen will be discontinued for patients who do not achieve any milestones after 13 months, and

for patients undergoing scoliosis surgery who cannot subsequently receive nusinersen administration via lumbar puncture. The company's early onset model employs two key assumptions: (i) after month 13, nusinersen-treated patients who reach health states consistent with Type II/III SMA milestones gain an additional survival advantage, and (ii) after month 13, the motor function of nusinersen-treated patients cannot deteriorate, whilst the motor function of patients receiving usual care cannot improve.

Based on a re-run of the probabilistic version of the company's early onset model by the ERG, nusinersen is expected to generate an additional 5.29 quality-adjusted life years (QALYs) at an additional cost of £2,160,048 per patient; the corresponding incremental cost-effectiveness ratio (ICER) for nusinersen versus usual care is £408,712 per QALY gained. The inclusion of caregiver QALY losses leads to a slightly lower probabilistic ICER of £404,270 per QALY gained. The probability that nusinersen produces more net benefit than usual care at willingness-to-pay (WTP) thresholds below £337,000 per QALY gained is approximately zero. The company's subgroup analyses suggest that the cost-effectiveness profile for nusinersen may be improved in early onset SMA patients with shorter disease duration (≤12 weeks subgroup ICER≈£375,000 per QALY gained, ICER includes patient health gains only).

Later onset model

The company's later onset model assesses the cost-effectiveness of nusinersen versus usual care for the treatment of patients with later onset SMA (initial age = 43.71 months), based on the CHERISH trial. The incremental health gains, costs and cost-effectiveness of nusinersen are evaluated over an 80-year time horizon from the perspective of the NHS and PSS. The company's later onset model adopts a state transition approach, with health states defined by motor function milestones based on the HFMSE instrument and WHO criteria. The model parameters were largely informed by: HFMSE outcomes collected within CHERISH; mortality outcomes from CHERISH and other observational data (Zerres *et al* and general population life tables); and the same cost and HRQoL sources as those used in the early onset model (see above). The company's model assumes that treatment using nusinersen will be discontinued for patients who do not achieve milestones beyond the Sits without support but does not roll state after 15 months, and for patients undergoing scoliosis surgery who cannot subsequently receive nusinersen administration via lumbar puncture. The later onset model includes two key assumptions: (i) after month 15, patients in either treatment group who reach health states consistent with Type III SMA milestones gain an additional survival advantage, and (ii) after month 15, the motor function of nusinersen-treated patients cannot deteriorate, whilst the motor function of patients receiving usual care cannot improve.

Based on a re-run of the probabilistic version of the company's later onset model by the ERG, nusinersen is expected to generate an additional 2.28 QALYs at an additional cost of £2,938,441 per

patient: the corresponding ICER for nusinersen versus usual care is £1,286,149 per QALY gained. The inclusion of caregiver QALY losses leads to a markedly lower probabilistic ICER of £933,088 per QALY gained. The probability that nusinersen produces more net benefit than usual care is approximately zero even at WTP thresholds of £500,000 per QALY gained. The company's subgroup analyses are inconclusive with respect to whether the cost-effectiveness profile for nusinersen is improved for later onset SMA patients with shorter disease duration (<25 months).

1.5 Summary of the ERG's critique of cost effectiveness evidence submitted

The ERG critically appraised the company's economic analyses of early and later onset SMA and double-programmed: (a) simplified versions of the Markov traces from the company's models and (b) the remainder of the model structures based on the company's Markov traces. The ERG's critical appraisal identified a number of issues relating to the company's economic analyses and the evidence used to inform them. The most pertinent of these include: (i) the absence of economic evidence relating to Type 0 and Type IV SMA; (ii) the unnecessary complexity of the company's implemented models; (iii) highly favourable assumptions regarding the expected trajectory of nusinersen-treated patients through modelled motor milestone health states; (iv) highly favourable assumptions regarding the expected survival of nusinersen-treated patients; (v) poor face validity of patient utilities used in the models, and (vi) arbitrary calculations underpinning the caregiver disutilities used in the models.

1.6 ERG commentary on the robustness of evidence submitted by the company

1.6.1 Strengths

The two key RCTs of nusinersen were included in the CS; these studies included early onset and later onset SMA patients. The included studies were considered to be of moderate quality and included most outcomes of relevance for this appraisal.

The clinical advisors to the ERG considered that the structures of the company's health economic models were broadly appropriate and reflected some of the key outcomes associated with SMA.

Despite the unnecessary complexity of the company's models, the ERG's model verification exercise did not identify any significant programming errors.

1.6.2 Weaknesses and areas of uncertainty

The limitations of the clinical evidence review mainly concern the absence of a systematic review and the absence of a systematic review of studies relating to BSC, the comparator of interest in the NICE decision problem.

The long-term probabilities of achieving, maintaining and losing motor function for nusinersen-treated patients, the long-term survival advantage of nusinersen and the relationship between motor function milestones and HRQoL are all highly uncertain. The ERG notes that the use of less optimistic assumptions regarding the extrapolation of motor function and survival outcomes has the propensity to markedly increase the ICERs for nusinersen. However, the ERG also notes that given the acquisition cost of nusinersen, the level of decision uncertainty with respect to NICE's usual thresholds for cost-effectiveness is low.

1.7 Summary of exploratory and sensitivity analyses undertaken by the ERG

The ERG undertook eight sets of exploratory analyses using the deterministic version of the company's early onset and later onset models. The ERG's preferred analysis includes: (i) the use of a common initial distribution across health states for both treatment groups; (ii) the inclusion of end-of-life costs for the later onset population; (iii) the use of patient utilities from the vignette study (Lloyd *et al*) and (iv) the application of caregiver utilities by SMA type (from Bastida *et al*) to states relating to SMA milestones. Importantly, this analysis does not address the ERG's concerns regarding the lack of plausibility surrounding the company's modelled survival and motor function trajectories; as such, the ERG's "preferred" ICERs are very likely to be underestimated in both SMA populations. In order to address this uncertainty, additional sensitivity analyses were undertaken to explore the use of alternative patient utilities, the exclusion of mortality adjustments for better health states and the use of alternative long-term (post-trial) transition probabilities.

Early onset model

The ERG's preferred ICER for nusinersen versus usual care in the early onset population is estimated to be £421,303 per QALY gained (including patient health gains only). The inclusion of caregiver QALY losses increases the ICER to £631,583 per QALY gained. The ERG's additional exploratory analyses lead to ICERs ranging from £366,289 per QALY gained to dominated (the ERG notes that the upper limit of the ICER range reflects a particularly pessimistic scenario).

Later onset model

The ERG's preferred ICER for nusinersen versus usual care in the later onset population is estimated to be £408,769 per QALY gained (including patient health gains only). The inclusion of caregiver QALY losses increases the ICER to £632,850 per QALY gained. The ERG's additional exploratory analyses lead to ICERs ranging from £432,191 per QALY gained to in excess of £18.4million per QALY gained (again, the upper limit of the ICER range reflects a particularly pessimistic scenario).

2. BACKGROUND

This report provides a review of the evidence submitted by Biogen in support of nusinersen for the treatment of spinal muscular atrophy (SMA). It considers both the company's submission[1] (CS) received on 20th March 2018 and the subsequent responses to clarification questions supplied by the company.[2, 3]

2.1 Critique of company's description of the underlying health problem

The CS[1] (pages 15-17) provides a reasonable description of the underlying health problem; this is summarised briefly below.

SMA is a progressive neuromuscular disease which results from mutations in chromosome 5q in the *SMN1* gene. The disease causes muscle weakness and progressive loss of movement and physical disability. As well as affecting patients' musculoskeletal system, SMA also impacts upon their respiratory and gastrointestinal systems.[1] SMA is rare and is recognised as an orphan disease by the European Medicines Agency (EMA).[4] SMA is recognised as the most common genetic cause of death in infants.[5]

SMA affects the motor neurons (the nerves from the brain and spinal cord that control muscle movements). Patients with SMA lack a protein called "survival motor neuron" (*SMN*) which is made by the *SMN1* and *SMN2* genes; this protein is essential for the normal functioning and survival of motor neurons. In the absence of this protein, the motor neurons deteriorate and eventually die, leading to muscle disuse, atrophy and weakness.[6]

SMA presents across a spectrum of subtypes (Types 0-IV) which are related to the age of onset (see Table 1). Younger age of onset is associated with greater severity of disease and poorer prognosis. The CS[1] defines Type I as early (infantile) onset SMA and Type II and III as later onset SMA, based on the age of onset and the level of motor function achieved. With the exception of Type 0 SMA, the disease usually involves a pre-symptomatic period followed by rapidly progressive functional loss and a later relatively static phase with slow progression.[7] Diagnosis of Type I SMA and more severe Type II SMA usually occurs during the first year of life. Most patients with Type II SMA are diagnosed in their second year of life, whilst Type III SMA is typically diagnosed at age 2-3 years, but may be later.

Table 1: Classification and subtypes of SMA (adapted from CS Table 3, based on Farrah *et al*[8])

SMA type	Age of onset	Maximal motor milestone	Motor ability and additional features	Prognosis‡
SMA Type 0	Before birth	None	Severe hypotonia; unable to sit and roll*	Respiratory insufficiency at birth: death within weeks
SMA Type I	2 weeks (Ia) 3 months (Ib) 6 months (Ic)	None	Severe hypotonia; unable to sit and roll†	Death/ventilation by 2 years
SMA Type II	6–18 months	Sitting	Proximal weakness: unable to walk independently	Survival into adulthood (typically >25 years)
SMA Type III	<3 years (IIIa) >3 years (IIIb) >12 years (IIIc)	Walking	May lose ability to walk	Normal life span
SMA Type IV	>30 years or 10–30 years	Normal	Mild motor Impairment	Normal life span

SMA - spinal muscular atrophy
** Need for respiratory support at birth; contractures at birth, reduced foetal movements*
† Ia joint contractures present at birth; Ic may achieve head control
‡ Prognosis varies with phenotype and supportive care interventions

Type I SMA (early onset)

Type I SMA has been reported to be the most common and severe form of the disease (accounting for approximately 45% of all cases of SMA), with an estimated incidence of 5.83 per 100,000 live births.[1, 9] Type I SMA is associated with a particularly poor prognosis and early mortality; most patients do not survive to their second birthday unless they receive ventilatory support.[8] Symptoms appear early (before 6 months) and include severe hypotonia (decreased muscle tone), inability to lift head/poor head control, and poor feeding.[1, 7] By definition, patients with Type I SMA never develop the ability to sit independently.[7] Patients suffer from a range of severe problems including pulmonary, nutritional and gastrointestinal complications. Despite these symptoms, cognitive ability is normal.

Type II/III SMA (later onset)

Type II and Type III SMA (accounting for around 50% of all cases of SMA) are less severe forms of the disease compared with Type I SMA. The incidence of Type II and Type III SMA is reported to be 2.66 and 1.20 per 100,000 live births, respectively.[1, 9] The age of onset is usually between 6 and 18 months for Type II SMA, and between 18 months and adulthood for Type III SMA.[7] Both Type II and Type III SMA are associated with a loss of motor function over time and numerous secondary complications. The severity of motor function impairment is highly variable between patients, with some patients with Type III SMA developing the ability to walk without assistance and others with Type II SMA being unable to sit without support.[1] Scoliosis is universally present in patients with Type II disease. Patients have an increased risk of respiratory disease and muscle weaknesses in the upper

chest make breathing and coughing more difficult, thereby leading to ineffective secretion clearance and an increased risk of chest infections.[1] Survival of patients with Type II SMA is typically greater than 25 years, and many patients live considerably longer as a consequence of more aggressive supportive care.[7] Survival of patients with Type III SMA is believed to be normal. As with more severe types of SMA, cognitive ability in these patients is normal.

The CS highlights the impact of the disease on patients' health-related quality of life (HRQoL), particularly with respect to physical disability, the inability to live independently, the high incidence of chronic pain, and the psychological burden associated with the progressive decline in health, including fear of losing independence, difficulties feeding and impaired breathing.[1] The CS also highlights the considerable economic and emotional burden affecting parents/caregivers as a consequence of giving up work to provide care, attending frequent hospital appointments and undertaking other SMA-related tasks.[1] Additional information relating to the impact of SMA on patients and caregivers is available within the submissions to NICE from clinical and patient groups.

2.2 Critique of company's overview of current service provision

The CS presents a useful overview of the current management of SMA. This is briefly described below.

There is no standard of care pathway for SMA and no guidance has been published by the National Institute for Health and Care Excellence (NICE). The CS notes that, excluding nusinersen, there is currently no effective disease-modifying therapy for SMA. Treatment requires a multidisciplinary approach and is focussed principally on respiratory and nutritional support, but also includes neuromuscular and orthopaedic care.

The CS refers to an SMA consensus statement released by the International Standard of Care Committee (SCC), which reports recommendations on the management of SMA according to physical functioning (non-sitters, sitters and walkers) rather than SMA type (Types 0 to IV).[10, 11] Non-sitters include patients who currently are not able to sit independently (i.e. the infantile Type I SMA patients). Sitters include those patients who can sit independently but cannot walk independently. Walkers can walk independently.[1] The guidelines from the SCC (summarised by the company) are reproduced in Table 2. Clinical advisors to the Evidence Review Group (ERG) noted that there has been a shift towards proactive/anticipatory respiratory care which is unlikely to be reflected within historical SMA natural history studies.

The CS highlights that for early onset patients (non-sitters), survival is very poor. [redacted].The ERG notes that the number of

patients, the disease subtype and the extent of ventilatory support provided is not clear within this survey sample. Whilst gastrostomy and ventilation can extend patient survival for early onset patients, these interventions do not impact upon motor function decline and their use in clinical practice is variable. With respect to later onset patients (sitters and walkers), symptoms may be highly variable between patients and the requirement for intensive nutritional and respiratory support may be less than for patients with early onset SMA. Later onset patients who are classed as sitters are more likely to develop scoliosis and subsequently require surgery, bracing and physical therapy.

Table 2: Clinical management recommendations from the consensus statement by the SCC for SMA (reproduced from CS, Table 4)

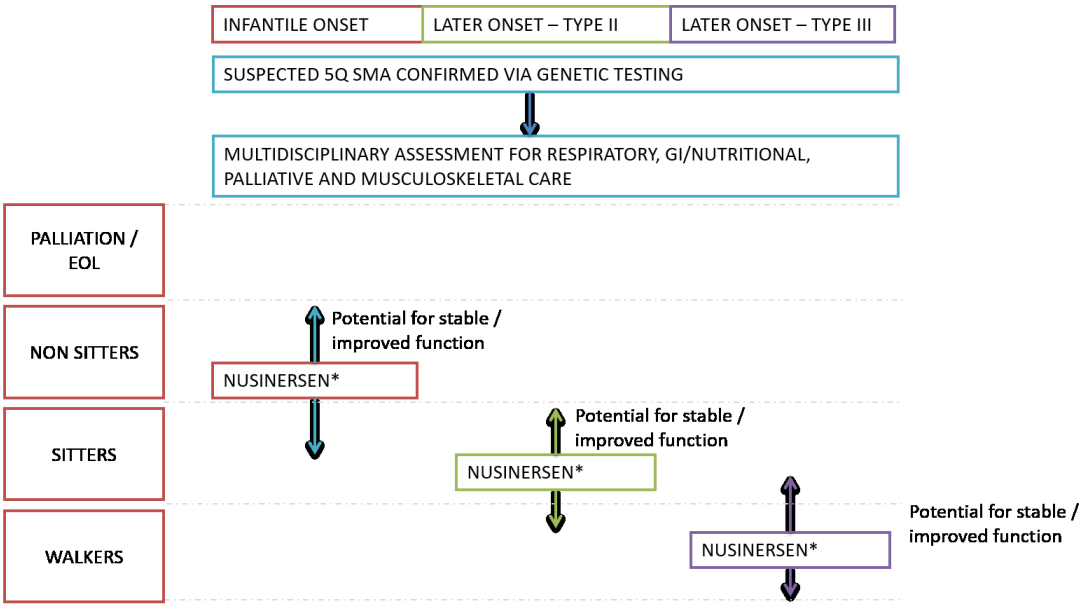
<table>
<tr><th>Type of care</th><th>NON-SITTERS</th><th>SITTERS</th><th>WALKERS</th></tr>
<tr><td colspan="4">Pulmonary care</td></tr>
<tr><td>Anticipatory respiratory care</td><td colspan="3">• Understanding the child's baseline, deviations from his/her baseline, hypoventilation and intervention
• Acute illness management including rapid access to specialty medical care providers
• Nutrition and hydration
• A low threshold to start antibiotics
• Routine immunisations</td></tr>
<tr><td rowspan="3">Chronic respiratory management</td><td colspan="3">Airway clearance:
• Assisted cough (MI-E or manual)
• Secretion mobilisation techniques (chest physiotherapy, postural drainage)
• Oximetry to guide therapy
Respiratory support:
• NIV
CPAP (goal to transition to BiPAP)</td></tr>
<tr><td>• Option: Care without ventilation support
• Palliative care
• Tracheotomy</td><td>Airway clearance/ respiratory support, as needed</td><td rowspan="2">Airway clearance/ respiratory support not likely to be required until late into the disease course</td></tr>
<tr><td colspan="2">NIV with high span BiPAP, even for short daytime periods</td></tr>
<tr><td rowspan="2">Acute care management</td><td colspan="3">Airway clearance:
• Assisted cough (MI-E or manual), oral or airway suctioning
• Oximetry
• Chest physiotherapy
• Postural drainage
Respiratory support:
• Acute use of NIV
• Oxygen therapy</td></tr>
<tr><td colspan="2">Respiratory support:
• Daytime NIV with airway clearance
• Intubation and mechanical ventilation
• Palliative care</td><td>Respiratory support:
• NIV for home use</td></tr>
<tr><td colspan="4">Gastrointestinal and nutritional care</td></tr>
<tr><td>Feeding and swallowing difficulties</td><td colspan="3">• Changing food consistency
• Positioning and seating alterations and orthotic devices
• Nutritional supplementation through NG or NJ feeding
• Gastrostomy tube feeding</td></tr>
</table>

Type of care	NON-SITTERS	SITTERS	WALKERS
Gastrointestinal dysfunction	Management of gastroesophageal reflux: • Short term use of acid neutralisers and/or inhibitors of acid secretion • Prokinetic agents • Probiotics • Laparoscopic anti-reflux Nissen fundoplication		
Growth and under or over nutrition problems	• Monitoring of growth velocity (growth charts) • Dietician assessment of nutritional intake • Appropriate intake of calcium and vitamin D • Monitor pre-albumin levels		
Management of nutrition in acutely sick SMA patients	• Avoid prolonged fasting due to high risk of hypoglycaemia • Enteral and/or parenteral feeding to meet caloric needs within 4-6 hours of acute illness admission • Post-operative caloric supplementation		
Neuromuscular and musculoskeletal evaluation			
Managing musculoskeletal system problems and related functional impairments	• Assessments of strength and range of joint motion, relevant motor functional scales and timed tests to monitor those aspect of function that reflect activities of daily living		
Orthopaedic care and rehabilitation			
Managing problems caused by muscle weakness	• Wheelchair mobility • Environmental controls and home modifications		
	• Nutritional support • Posture management with supportive seating • Contracture management by splinting • Pain management • Therapy for ADL and assistive equipment • Limb orthotics	• Contracture management by stretching, bracing, serial casting, orthotics and supports/ slings • Regular exercise and standing with appropriate assistive devices and orthotics • Spine orthotics and surgery	• Contracture management and education • PT and OT • Regular exercise and walking with appropriate assistive devices and orthotics • Spine/limb orthotics and surgery
Orthopaedic surgery	Non-sitters do not benefit from surgery	• Hip subluxation and contractures • Scoliosis surgery	
Other care			
Perioperative care	Due to high risk for post-anaesthesia complications, respiratory status needs to be optimised and orthotic interventions need to be adjusted before surgery. After surgery, close monitoring, aggressive respiratory management, and rapid mobilisation, may be required.		

ADL - activities of daily living; BiPAP - bi-level positive airway pressure; CPAP - continuous positive airway pressure; NIV - non-invasive ventilation; NG - nasogastric; NJ - nasojejunal; MI-E - mechanical insufflation/exsufflation; PT - physiotherapy; OT - occupational therapy; SCC - International Standard of Care Committee; SMA - spinal muscular atrophy

The CS states that nusinersen is the first disease-modifying treatment for SMA. The anticipated place of nusinersen in therapy is as a first-line treatment for all SMA patients as soon as possible after diagnosis, in addition to existing symptomatic care (see Figure 1).[1] Nusinersen is currently available in England for patients with Type 1 SMA (subject to eligibility criteria) through an Expanded Access Programme; under this programme, the acquisition costs of nusinersen are reimbursed by NHS England.

Figure 1: Clinical care pathway with nusinersen (reproduced from CS, Figure 2)



**With symptomatic care according to clinical need*

3. CRITIQUE OF COMPANY'S DEFINITION OF THE DECISION PROBLEM

This chapter presents a summary and critique of the decision problem addressed by the CS.[1] A summary of the decision problem as outlined in the final NICE scope[12] and addressed in the CS[1] is presented in Table 3.

Table 3: Company's statement of the decision problem (reproduced from CS Table 1)

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
Population	People with 5q SMA	Pre-symptomatic and symptomatic people with 5q SMA who have infantile onset (those who have or are most likely to develop type I) or later onset (those who have or are most likely to develop types II and III) SMA	The proposed population is narrower than the marketing authorisation (which includes all patients with 5q SMA) because the evidence base on nusinersen is limited to patients with pre-symptomatic and symptomatic infantile onset and later onset SMA
Intervention	Nusinersen	Nusinersen	N/A
Comparator(s)	Best supportive care	Sham procedure and standard of care treatment	Biogen consider that the most appropriate comparator is sham procedure (administered by lumbar puncture prick), as no disease-modifying therapies (other than nusinersen) are approved or routinely used in SMA
Outcomes	The outcome measures to be considered include: • Motor function (including, where applicable, age appropriate motor milestones) • Respiratory function • Complications of SMA (including, for example, scoliosis and muscle contractures) • Need for non-invasive or invasive ventilation • Stamina and fatigue • Mortality • Adverse effects of treatment • HRQoL	The outcome measures to be considered include: • Motor function (including, where applicable, age appropriate motor milestones) • Event-free survival (time to death or permanent assisted ventilation) and overall survival • Respiratory function • Need for non-invasive or invasive ventilation • Mortality • Adverse effects of treatment • HRQoL	Complications of SMA (including, for example, scoliosis and muscle contractures), and stamina and fatigue, are not included as these outcomes were not collected in the pivotal clinical trials

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
Economic analysis	The reference case stipulates that the cost effectiveness of treatments should be expressed in terms of incremental cost per QALY. The reference case stipulates that the time horizon for estimating clinical and cost effectiveness should be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared. Costs will be considered from an NHS and personal social services perspective.	The economic analysis considers 2 *de novo* models to assess the cost-effectiveness of nusinersen using motor milestones health states – 1 relating to infantile onset SMA and the other to later onset SMA. The pre-symptomatic health state is being developed but could not be modelled in time for submission.	N/A
Subgroups to be considered	Consideration will be given to subgroups based on severity of disease (including considerations such as age of SMA onset, SMA type and genotype [including *SMN2* copy number]). Guidance will only be issued in accordance with the marketing authorisation. Where the wording of the therapeutic indication does not include specific treatment combinations, guidance will be issued only in the context of the evidence that has underpinned the marketing authorisation granted by the regulator.	The pivotal trials in infantile onset (ENDEAR) and later onset SMA (CHERISH) included pre-specified subgroups based on disease duration and age at symptom onset. For infantile onset SMA patients the economic analysis has evaluated the subgroups based on age at onset of SMA symptoms and disease duration (>12 weeks and ≤12 weeks) from the ENDEAR trial For later onset SMA patients, subgroup analysis has not been conducted in the economic analysis due to the small subgroup sample sizes within	N/A
Special considerations including issues related to equity or equality	NR	N/A	N/A

SMA - spinal muscular atrophy; HRQoL - health-related quality of life; QALY - quality-adjusted life year; SMN2 - survival motor neuron 2; N/A - not applicable; NR - not reported

3.1 Population

The population defined in the NICE scope[12] relates to people with 5q SMA. This is consistent with the marketing authorisation for nusinersen.[4] The evidence presented within the CS[1] relates to a population which is narrower than that defined in both the final NICE scope and the marketing authorisation for nusinersen. The available evidence for nusinersen is limited to patients with pre-symptomatic and symptomatic infantile onset and later onset SMA; no evidence is presented on the clinical effectiveness or cost-effectiveness of nusinersen in people with Type 0 or Type IV SMA.

3.2 Intervention

The intervention under appraisal is nusinersen (Spinraza®). Nusinersen is an antisense oligonucleotide (ASO) which increases the proportion of exon 7 inclusion in survival motor neuron 2 (*SMN2*) messenger ribonucleic acid (mRNA) transcripts by binding to an intronic splice silencing site (ISS-N1) found in intron 7 of the *SMN2* pre-messenger ribonucleic acid (pre-mRNA). By binding, the ASO displaces splicing factors, which normally suppress splicing. Displacement of these factors leads to retention of exon 7 in the *SMN2* mRNA and hence when *SMN2* mRNA is produced, it can be translated into the functional full length *SMN* protein.[4] The CS[1] states that the anticipated place of nusinersen in therapy is as a first-line treatment for all SMA patients as soon as possible after diagnosis (in combination with usual symptomatic care).

Nusinersen is available as a single vial containing 12mg of nusinersen solution. The current list price for a single vial of nusinersen is £75,000.[13]

The Summary of Product Characteristics[4] (SmPC) recommends that nusinersen treatment should be initiated as early as possible after diagnosis of SMA with four loading doses on days 0, 14, 28 and 63. A maintenance dose should be administered once every four months thereafter. This corresponds to an acquisition cost of £450,000 per patient in the first year of treatment, and £225,000 per patient for each subsequent year of treatment. It should be noted that this dosing regimen reflects the treatment schedule adopted within the ENDEAR study[14] (infant onset); however, a different treatment schedule was used in the CHERISH study[15] (later onset). The SmPC notes that there is no evidence relating to the long-term efficacy of nusinersen and that the need for continuation of nusinersen treatment should be reviewed regularly and considered on an individual basis depending on the patient's clinical presentation and response to the therapy.[4]

The SmPC[4] states that nusinersen has not been studied in patients with renal or hepatic impairment and there are no or limited data from the use of nusinersen in pregnant women. The SmPC also highlights a risk of adverse reactions occurring as part of the lumbar puncture procedure, which may be a problem particularly for very young children and those with scoliosis. According to the SmPC,

thrombocytopenia and coagulation abnormalities (including acute severe thrombocytopenia) and renal toxicity have been observed after the administration of other subcutaneously and intravenously administered ASOs.[4] The available data on adverse events (AEs) from the clinical study programme and post-marketing studies of nusinersen are presented in Chapter 3 of this report (see Section 3.2.7).

Contraindications to nusinersen include hypersensitivity to the active substance or to any of the excipients listed in the SmPC.[4]

3.3 Comparators

The final NICE scope[12] defines the comparator as best supportive care (BSC). The comparator within the randomised controlled trials (RCTs) of nusinersen is a sham procedure. The comparator considered within the company's health economic analyses is defined as "real-world care", including respiratory, gastrointestinal, nutritional and orthopaedic care. As noted in the CS,[1] the differential use of life-extending symptomatic care, including permanent respiratory support, means that real world survival may not reflect that seen in clinical trials.

3.4 Outcomes

The final NICE scope[12] lists the following outcomes:

- Motor function (including, where applicable, age appropriate motor milestones)
- Respiratory function
- Complications of SMA (including, for example, scoliosis and muscle contractures)
- Need for non-invasive or invasive ventilation
- Stamina and fatigue
- Mortality
- Adverse effects of treatment
- HRQoL.

The CS[1] includes evidence relating to all of these outcomes except for: (i) stamina and fatigue, and (ii) complications of SMA. These outcomes were excluded from the CS as these endpoints were not included in the pivotal clinical trials (ENDEAR[14] and CHERISH[15]). Clinical advisors to the ERG commented that measuring stamina and fatigue in younger children involves subjectivity and that there are no useful questionnaires available, hence this omission may be reasonable. However, one advisor noted that it is possible to record specific outcomes such as the length of time for which a particular motor skill can be maintained. The advisors also commented that scoliosis is an important marker for disease progression, particularly in older children. However, the advisors also noted that complications of SMA are long-term problems that would be difficult to measure in short-term trials.

3.5 Economic analysis

The CS[1] reports the methods and results of two *de novo* model-based health economic analyses to assess the incremental cost-effectiveness of nusinersen versus usual care for the treatment of patients with early onset (Type I) SMA and later onset (Types II and III) SMA. The company's health economic analyses are detailed and critiqued in Chapter 5.

3.6 Subgroups

The pivotal trials included in the CS (ENDEAR[14] and CHERISH[15]) included pre-specified subgroups based on disease duration and age at symptom onset. Clinical data relating to these subgroups are summarised in Section 4.2.6.

The company's health economic analysis includes subgroup analyses based on duration of disease (≤12 weeks, >12 weeks).[1] CS Table 1 states that subgroup analysis was also undertaken according to age of onset, however no results are presented in the CS for these subgroups. Table 1 of the CS states that subgroup analysis was not conducted for the later onset population due to the small subgroup sample sizes; however, this statement is inaccurate as CS Table 77 reports the results of subgroup analyses based on duration of disease (<25 months, ≥25 months). No subgroup analysis is presented for age of onset within the later onset economic analysis.

3.7 Special considerations

Table 1 of the CS[1] states that there are no equality issues relating to the use of nusinersen for the treatment of SMA. CS Section 1.4 notes that although the available RCT evidence relates specifically to infants and children, older patients may also benefit from nusinersen treatment. Despite the absence of evidence for older patients, the CS argues that it is important that all age groups and patient disabilities are considered regarding access to treatment.

The CS[1] argues that NICE's end-of-life criteria apply to the early onset SMA population, but not the later onset population. The evidence supporting this argument is presented and critiqued in Chapter 6.

4. CLINICAL EFFECTIVENESS

This chapter presents a summary and critique of the clinical evidence contained within the CS[1] for nusinersen for the treatment of SMA. Section 4.1 presents a critique of the methods used to identify and select evidence for inclusion in the CS. Section 4.2 presents a critique of the key studies included in the CS. Section 4.3 presents the conclusions relating to the clinical effectiveness evidence.

4.1 Critique of the methods of review(s)

The CS[1] did not include a systematic review of the clinical effectiveness evidence for nusinersen. No searches were reported, hence it is unclear whether all relevant studies of nusinersen were identified. However the ERG is confident that all relevant studies have been included in the CS. No searches were undertaken for studies of BSC, the comparator listed in the final NICE scope.[12] In response to a request for clarification regarding the absence of systematic review from the CS (see clarification response,[2] question A1), the company stated that a quarterly SMA bibliography is compiled by an external consultancy firm on behalf of Biogen to ensure that no relevant studies were overlooked. The company also stated in their clarification response that *"due to the availability of head-to head data, it was considered unnecessary to perform a systematic literature review to identify further comparator studies for an indirect comparison analysis"* (Company's clarification response,[2] question A2).

As part of the NICE Single Technology Appraisal (STA) process, it is a requirement for the company to present a systematic review of the clinical effectiveness evidence. The review should have addressed the decision problem set out in the NICE scope (see Table 3).

4.2 Critique of studies of nusinersen for treating SMA

4.2.1 Studies included in the submission

The company states that there are 10 studies in the nusinersen development programme. These studies are shown in Table 4, and include four patient groups: (i) pre-symptomatic; (ii) infantile onset; (iii) later onset and (iv) both infantile and later onset. Of the studies listed in Table 4, ENDEAR (CS3B), in infantile onset patients and CHERISH (CS4), in later onset patients, are the two studies presented as the key evidence in the CS.[1] The CS presents results for these two key studies together with additional results from the NURTURE study (pre-symptomatic patients), which is stated to be a supporting study.

Table 4: Nusinersen studies identified in the CS (adapted from CS, Figure 3)

Pre-symptomatic patients	Infantile onset	Both infantile and later onset	Later onset (Type I and Type II)
CS5 **NURTURE**: Phase II, open-label, target enrolment n=25	CS3B **ENDEAR**: Phase III, RCT n=122	CS7 **EMBRACE** Phase II, open-label, n=21 enrolled	CS4 **CHERISH**: Phase III RCT n=126
	CS3A: Phase II, open-label , n=21 enrolled	CS11 **SHINE:** Phase III, extension for CS3B, CS4 and CS12, open-label, target enrolment n=274	CS1: open-label, dose escalation, n=28
			CS10: extension for CS1, open-label, n=18
			CS2: open-label, dose-escalation, n=34
			CS12: extension for CS2 and CS10, n=47

RCT - randomised controlled trial; n - number

4.2.1 Critique of quality assessment

The CS[1] included quality appraisals of the ENDEAR, CHERISH and NURTURE studies. The company used the Centre for Reviews and Dissemination (CRD) checklist[16] to assess the study quality of ENDEAR and CHERISH; this checklist is appropriate for the assessment of RCTs and is recommended in the NICE guide for preparing company submissions.[17] In addition, a quality assessment checklist for quantitative intervention studies taken from the Methods for the Development of NICE Public Health Guidance[18] was provided in CS Appendix D. The ERG have not considered this checklist as the NICE guide for company submissions[17] recommends the use of the CRD checklist.[16] Quality assessment of NURTURE was undertaken using only the quality appraisal checklist for quantitative intervention studies[18] in the CS. The ERG has used the Newcastle-Ottawa Scale[19] for assessing the quality of NURTURE, as it is an appropriate and validated quality assessment tool for non-randomised studies. The CS does not provide details regarding the number of reviewers who undertook the quality assessments, nor does it state whether, if more than one reviewer was involved, they undertook quality appraisal independently from one another.

4.2.2 Early onset studies

The ENDEAR study is the main source of evidence for patients with infantile onset SMA. The key study characteristics of ENDEAR are presented in Table 5.

Table 5: ENDEAR study characteristics (adapted from CS, Table 5 and Table 7)

Study	Location (sites)	Design	Population	Interventions	Comparator	Primary outcome measure	Secondary outcome measures	Duration
ENDEAR	31 secondary care settings in Austria, Belgium, Canada, France, Germany, Italy, Japan, Korea, Spain, Sweden, Turkey, UK, USA	Phase III, randomised, double blind	Symptomatic infantile onset SMA,(n=122); those who have or are most likely to develop SMA Type 1	Nusinersen (n=80); administered as a single intrathecal lumbar puncture injection with a scaled 12mg loading dose on study days 1, 15, 29 and 64. Maintenance dosing every 4 months (days 183 and 302)	Sham procedure control (n=41)	Proportion of motor milestone responders (HINE-2) Event-free survival (EFS): Time to death or permanent ventilation	CHOP INTEND responders Proportion of CMAP responders Survival rate Participants not requiring permanent ventilation Time to death or permanent ventilation by disease duration subgroup	Unclear, study terminated early when at least 80 infants had been enrolled for at least 6 months, 27 months from date of first treatment to last patient visit[14]

CHOP INTEND - Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders; CMAP - compound muscle action potential; HINE-2 - Module 2 of the Hammersmith Infant Neurological Examination

Patients

Patients in the ENDEAR study were infants with symptomatic infantile onset SMA. Infants enrolled in the study had:

- Signed informed consent of parent(s) or guardian(s)
- A genetic diagnosis of 5q-linked SMA due to homozygous gene deletion or compound heterozygote deletion/mutation of *SMN1*
- Two copies of the *SMN2* gene; younger than 6 months of age (180 days) at SMA symptom onset
- Younger than 7 months of age (210 days) at screening;
- Receiving adequate nutrition and hydration (with or without gastrostomy) in the opinion of the site investigator at the time of study entry
- Measuring to at least the third percentile in body weight using country-specific guidelines
- Adherence to the consensus statement for standard of care in SMA for medical care guidelines
- Gestational age of 37–42 weeks
- Live within a 9-hour ground travel time from a study centre
- Ability to complete all study procedures and parent/guardian has adequate psychosocial support.[1]

Exclusion criteria for the ENDEAR study can be found in Appendix 1. Table 6 presents the baseline characteristics of patients enrolled into the ENDEAR study.

Table 6: ENDEAR baseline demographics of the ITT population (adapted from CS, Table 11)

Characteristic	**Nusinersen (N=80)**	**Sham control (N=41)**
Female, n (%)	43 (54)	24 (59)
[redacted]	[redacted]	[redacted]
Mean (range) age at first dose, day	163 (52, 242)	181 (30, 262)
Mean (range) age at symptom onset, week	7.9 (2, 18)	9.6 (1, 20)
Mean (range) age at SMA diagnosis, week	12.6 (0, 29)	17.5 (2, 30)
Mean (range) disease duration at screening, week	13.2 (0, 25.9)	13.9 (0, 23.1)
[redacted]	[redacted]	[redacted]
SMA symptoms, n (%) Hypotonia Developmental motor delay Paradoxical breathing Pneumonia or respiratory symptoms Limb weakness Swallowing or feeding difficulties Other	 80 (100) 71 (89) 71 (89) 28 (35) 79 (99) 41 (51) 20 (25)	 41 (100) 39 (95) 27 (66) 9 (22) 41 (100) 12 (29) 14 (34)

Characteristic	Nusinersen (N=80)	Sham control (N=41)
Use of a ventilation support, n (%)	21 (26)	6 (15)
Use of a gastrointestinal tube, n (%)	7 (9)	5 (12)
Total HINE-2 score, mean (SD)	1.29±1.07	1.54±1.29
CHOP INTEND score at baseline, mean (SD)	26.63 (8.13)	28.43 (7.56)
CMAP amplitude, mV, mean (SD) Ulnar nerve Peroneal nerve	 0.226 (0.19) 0.371 (0.31)	 0.225 (0.12) 0.317 (0.29)

CHOP INTEND - Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders; CMAP - compound muscle action potential; ITT – intention-to-treat; HINE-2 - Module 2 of the Hammersmith Infant Neurological Examination; SD - standard deviation; SMA - spinal muscular atrophy; SMN – survival of motor neuron. Source: Finkel 2017[20]; ENDEAR CSR[14]

Overall, demographic and baseline disease characteristics and SMA history of the intention-to-treat (ITT) population in the ENDEAR study are consistent with a population highly likely to develop Type I SMA.[4] The groups were similar, although patients in the nusinersen group were on average younger than those in the control group and had an earlier age of symptom onset. Information on subgroups relating to age of onset of symptoms is provided in Section 4.2.7. There was an apparent imbalance with regard to SMA symptoms, with more infants in the nusinersen group (n=80) than the control group (n=41) having the following: history of paradoxical breathing (89% vs 66%), pneumonia or respiratory symptoms (35% vs 22%), ventilator support (26% vs 15%) and more swallowing or feeding difficulties than the control group (51% vs 29%), (see Table 6). The difference in symptoms implies a worse prognosis for the nusinersen group. The ERG's clinical advisors suggested that patients in ENDEAR had a lower use of ventilation and tubes than would be expected in this patient population.

Intervention and comparator

Nusinersen was administered in the ENDEAR study as a single intrathecal lumbar puncture injection on study days 1, 15, 29 and 64 followed by maintenance dosing once every four months (days 183 and 302). Dosage was adjusted for age in order to be equivalent to a 12mg dose in a person two years of age or older. The sham procedure was a small needle prick to the skin over the lumbar spine covered with a bandage. In response to a clarification request from the ERG regarding the use of sedation in the ENDEAR study, the company stated that *"in ENDEAR 6 (8%) of nusinersen treated patients and 2 (5%) of sham control patients received inhalation anaesthesia and 2 (3%) and 0 respectively received intravenous sedation"* (Company's clarification response,[2] question A6).

Quality assessment for ENDEAR

Table 7 compares the quality assessments of the ENDEAR study undertaken by the company and the ERG.

Table 7: Company and ERG quality assessment for ENDEAR (adapted from CS, Table 18)

Quality assessment question	Company's quality assessment	ERG's quality assessment
Was randomisation carried out appropriately?	Yes	Yes: performed using an interactive voice/web response system.[4, 21]
Was the concealment of treatment allocation adequate?	Yes	Yes: performed using an interactive voice/web response system.[4, 21]
Were the groups similar at the outset of the study in terms of prognostic factors?	Partly: Baseline demography was balanced between the nusinersen and control groups. Patients enrolled in the nusinersen treatment group showed greater disease severity compared with the sham-control group.	Unclear: It appears that patients randomised to receive nusinersen had earlier symptom onset and greater burden of disease than patients randomised to the control group.
Were the care providers, participants and outcome assessors blind to treatment allocation?	Yes	Partly: Very few participants received sedation (see clarification response,[2] question A6), although participants' age may negate this. Outcome assessors may have been able to determine which participants received a lumbar puncture due to related AEs.
Were there any unexpected imbalances in drop-outs between groups?	No	Yes: A disproportionately high proportion of participants in the control group dropped out (17/41 - 41%) compared with the nusinersen group (15/80 - 19%), according to data on clinicaltrials.gov[22] and the clinical study report (CSR).[21] In most cases (16/41 and 13/80, respectively[21]), this was due to an AE.
Is there any evidence to suggest that the authors measured more outcomes than they reported?	No	Unclear: In the protocol registered on clinicaltrials.gov, secondary outcome measures 8, 9, 10, 11 and 12 relating to specific types of AEs do not appear to be reported in the Finkel *et al* paper,[20] although these outcomes are reported on clinicaltrials.gov.[22]
Did the analysis include an ITT analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	Yes	Yes: Participants who died or withdrew were counted as non-responders.[4]
Summary rating	**Low risk of bias**	**Moderate risk of bias**

AEs - adverse events; ITT – intention-to-treat

Overall, the CS[1] rated ENDEAR as a good quality study, with a low risk of bias. The ERG agrees with this in terms of randomisation, allocation concealment, and ITT analysis. The quality assessments undertaken by both the company and the ERG agree that there are differences between the nusinersen and control groups on some key variables at baseline. The CS and ERG differ in terms of ratings of:

- *Blinding:* The CS rated this item as "yes" (low risk of bias), however the ERG rated it as "partly" (moderate risk of bias) and noted that very few patients were sedated or received inhalational anaesthesia. However, due to patients' age, it is unlikely that patients would have been aware of which treatment they were receiving. Outcome assessors, however, may have been able to determine which participants had received a lumbar puncture according to which participants experienced AEs associated with lumbar puncture.
- *Unexpected imbalances in drop-outs between groups:* The CS rated this item as "no" (low risk of bias). However, the ERG noted an imbalance (as reported on the clinicaltrials.gov study record[22]), in that there were twice as many drop-outs in the control group compared with the nusinersen group (41% versus 19%, respectively); drop-outs were counted as non-responders, although it was not clear whether they improved or deteriorated.
- *Unreported outcome measures:* The CS rated the item "Is there any evidence to suggest that the authors measured more outcomes than they reported?" as "no" (low risk of bias). However, the ERG noted that some of the specific AE-related outcomes were pre-specified in the protocol on clincaltrials.gov, but results on these outcomes were not provided in the Finkel *et al* paper.[20] Findings relating to these outcomes are reported on clinicaltrials.gov.[22]

Results for early onset study (ENDEAR)

All of the outcomes listed in the final NICE scope[12] (see Table 3) are included in the CS for the ENDEAR study, except for complications (such as scoliosis and muscle contractures), stamina and fatigue and HRQoL. The clinical advisors to the ERG suggested that although scoliosis and muscle contractures are relevant outcomes for patients, they would be difficult to measure in short-term studies. Therefore, this omission was considered to be reasonable. As there are no validated questionnaires for stamina and fatigue for younger children, this omission was also considered to be reasonable. Results relating to AEs and HRQoL are presented in Sections 4.2.6 and 4.2.7.

The results of the ENDEAR study are presented in the CS using three different analyses sets (see Table 8). At the interim analysis for ENDEAR, the decision was made terminate the study early due to the benefit-risk assessment being in favour of nusinersen. Infants who completed the ENDEAR study were invited to enrol in the SHINE study, including those in the control arm.

Table 8: ENDEAR analysis sets (adapted from CS, Table 15)

Analysis	Number of patients	Description
Interim (15 June 2016)	Nusinersen: 51 Sham control: 27	Infants in the ITT set who were assessed at the day 183, 302, or 394 visit and had a time difference of at least 190 days between the date of first dose and the data cut-off date of the interim analysis
Final efficacy set (21 November 2016)	Nusinersen: 73; Sham control: 37	Infants in the ITT set who were assessed at the day 183, 302, or 394 visit and had a time difference of at least 190 days between the date of the first dose and the data cut-off date of the final analysis
Final ITT set (21 November 2016)	Nusinersen: 80; Sham control: 41	All infants who were randomised and received ≥1 dose of study drug

ITT – intention-to-treat

Motor function

Motor function was measured in the ENDEAR study using three measures: Module 2 of the Hammersmith Infant Neurological Examination (HINE-2 - the primary endpoint); the Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders (CHOP INTEND) and the Compound Muscle Action Potential (CMAP), an electrophysiological technique used to measure nerve function, were both secondary outcomes. Responders were infants with a greater number of motor milestone categories with improvement than worsening.[4] Motor function outcomes are shown in Table 9.

Table 9: ENDEAR motor function outcomes (adapted from CS, Table 19)

Outcome	Nusinersen	Control	Difference (95% CI) and *p*-value
Interim analysis (data cut-off 15 June 2016) (interim analysis set)			
HINE-2 proportion responders	21 (41%)	0 (0%)	41.18 (18.6, 61.20); $p<0.001$
Final analysis (data cut-off 21 November 2016) (efficacy analysis set)			
HINE- 2 proportion responders	37 (51%)	0 (0%)	[redacted]; $p<0.0001$
HINE -2 proportion with improvement in total score	49 (67%)	5 (14%)	
HINE -2 proportion with worsening in total score	1 (1%)	8 (22%)	
CHOP INTEND proportion with ≥ 4 point improvement	52 (71%)	1 (3%)	[redacted]; $p<0.001$
CHOP INTEND proportion with any improvement	53 (73%)	1 (3%)	
CHOP INTEND proportion with any worsening	5 (7%)	18 (49%)	
CMAP amplitude responders	26 (36%)	2 (5%)	$p=0.001$

CHOP INTEND - Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders; CI - confidence interval; CMAP - compound muscle action potential; HINE-2 - Module 2 of the Hammersmith Infant Neurological Examination

As shown in Table 9, a significantly greater percentage of patients in the nusinersen group achieved motor milestone responses compared with the control group, although many patients in the nusinersen group (49%) could not be classified as responders. In the nusinersen group, 22% of infants achieved full head control, 10% were able to roll over, 8% were able to sit independently and 1% were able to stand. In the control group, no infants achieved these milestones.[1]

Respiratory function

The only measure of respiratory function reported from the ENDEAR study was the annualised rate of serious respiratory events; 2.836 events were reported in the nusinersen group versus 3.065 events in the control group in the interim analysis (95% confidence intervals [CIs] not reported).[4] [redacted]

Ventilation

The ENDEAR study reported the number of hours of ventilator support as a measure of ventilation. In the interim analysis, the median percentage of time on ventilator support was lower in the nusinersen group (27.1%) compared with the control group (43.0%).[4] [redacted]. Outcomes relating to the endpoints of use of permanent assisted ventilation and time to death or permanent ventilation are presented in Table 10. A higher percentage of nusinersen patients had no use of permanent ventilation compared with the control group, although the difference was not statistically significant (p=0.13).

Mortality

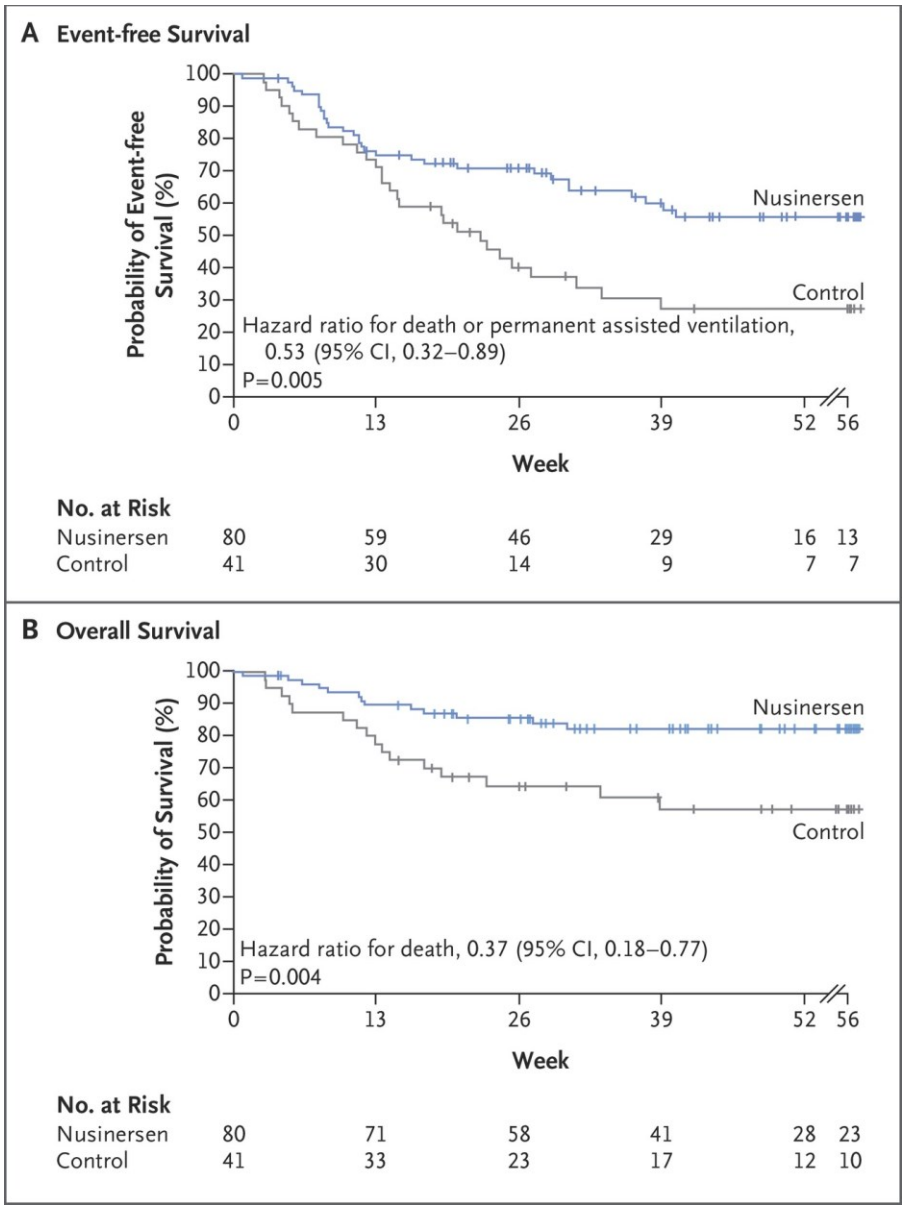
Measures of mortality within ENDEAR included event-free survival (EFS), defined as time to death or permanent ventilation (primary endpoint) and overall survival (OS); results for these outcomes are shown in Table 10. Statistically significant increases in both EFS (p=0.005) and OS (p=0.004) were observed for the nusinersen group. Figure 2 presents the associated Kaplan-Meier curves for these outcomes.

Table 10: ENDEAR study ventilation and survival outcomes (adapted from CS, Table 19)

Outcome	Nusinersen	Control	Difference (95% CI) or HR (95% CI) and *p*-value
No use of permanent assisted ventilation (ITT analysis set)	62 (78%)	28 (68%)	0.66 (0.32-1.37) *p*=0.13
EFS (ITT analysis set) (patients who had died or received permanent assisted ventilation)	31 (39%)	28 (68%)	HR: 0.53 (0.32, 0.89) *p*=0.005
OS (ITT analysis set) Dead Alive	 13 (16%) 67 (84%)	 16 (39%) 25 (61%)	HR: 0.37 (0.18, 0.77); *p*=0.004

ITT – intention-to-treat; EFS - event-free survival; HR – hazard ratio

Figure 2: ENDEAR Kaplan-Meier curves for EFS (A) and OS (B) (ITT population, final analysis) (reproduced from CS, Figure 15)



ITT – intention-to-treat; Source: Finkel 2017[20]

Number and length of hospitalisations

The number and length of hospitalisations was not included as an outcome in the NICE scope;[12] however, this outcome was included in the CS[1] (page 73) and is presented here for completeness. The adjusted annualised rates of hospitalisation in the nusinersen group were 4.378 (95% CI: 3.636 to 5.273) compared with 5.817 (95% CI: 3.636 to 5.273) hospitalisations/year in the control group (p=0.0959). Overall time spent hospitalised was significantly lower in the nusinersen group than the control group (LSM: 0.114 versus 0.207 [unit of time unclear from the CS]; LSM treatment difference: -0.093; 95% CI -0.151 to -0.034; p=0.0022).

Additional early onset study: CS3A

One additional early onset study, CS3A, was presented in the CS.[1] Table 11 below presents the study characteristics for CS3A.

Table 11: Summary of study characteristics for CS3A (based on data reported in CS Appendix L, Table 20)

Study ID	**CS3A**
Study objectives	Safety, tolerability, efficacy and PK
Study type/design	Phase II, open-label, multiple dose, single arm
Study population	Symptomatic, infantile onset SMA: 17 of 20 subjects (85%) had 2 copies of the *SMN2* gene (all 4 subjects in Cohort 1 and 13 subjects in Cohort 2); 2 subjects had 3 copies of the *SMN2* gene
Primary efficacy endpoint	Motor milestones (HINE Module 2)
Secondary efficacy endpoints	CHOP INTEND, OS and EFS
Intervention(s)	Nusinersen – Cohort 1: 6mg scaled equivalent loading dose, 12mg maintenance dose Cohort 2: 12mg scaled equivalent loading dose and 12mg maintenance dose Loading dose: days 1, 15, 85 Maintenance dose: day 253 and every 4 months thereafter
Number of patients dosed	TOTAL: 20 Cohort 1: 4 Cohort 2: 16 1 subject withdrew before dosing
Mean (median) age at baseline	141 (155) days (range 36–210 days)
Mean (median) age at symptom onset	60 (56) days

CHOP INTEND - Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders; HINE - Hammersmith Infant Neurological Examination; SMA – spinal muscular atrophy; SMN - survival of motor neurone; PK - pharmacokinetics

Key results for CS3A, as outlined in CS[1] Appendix L (pages 134-135) were:

- Change in HINE-2 score from baseline to last visit was significant for both cohorts combined (p=0.0002) and for participants in the 12mg dose group (p<0.0001).
- HINE-2 motor milestones increased steadily over time from a baseline mean score of 2.25 up to a mean increase of 9.40 milestones on day 694.
- CHOP-INTEND scores showed a mean increase of 11.5 points from baseline to last visit (p=0.0080, n=18)
- 15 of 20 subjects (75%) were alive and continuing the study at data cut-off.
- 13 subjects (65%) were free from permanent ventilation and continuing the study at data-cut-off.

4.2.3 Later onset studies

The CHERISH study is the main source of evidence for patients with later onset SMA. The characteristics of the CHERISH study are presented in Table 12.

Table 12: CHERISH study characteristics (adapted from CS, Table 5 and Table 7)

Study	Location (sites)	Design	Population	Interventions	Comparator	Primary outcome measure	Secondary outcome measures	Duration
CHERISH	24 centres in Canada, China, France, Germany, Italy, Japan, Korea, Spain, Sweden, USA	Phase III, randomised double-blind study in secondary care	Symptomatic later onset SMA (n=126); those who have or are most likely to develop SMA Type II or III	Nusinersen (n=84) administered as single intrathecal lumbar puncture injection. Single dose level 12mg delivered in 4 doses over 9 months using a loading regimen (days 1, 29. 85); maintenance dose given 6 months later (day 274)	Sham control (n=42)	HFMSE	≥ 3 point increase in HFMSE score WHO motor milestone Standing alone Walking with assistance RULM	Unclear; early termination of study after analysis of primary endpoint at the interim analysis; date from first treatment to last visit for last patient: 27 months[15]

HFMSE - Hammersmith Functional Motor Scale-Expanded; RULM - Revised Upper Limb Module; WHO - World Health Organization

Patients

Patients enrolled in the CHERISH study had later onset SMA with symptom onset after six months of age. The inclusion criteria for CHERISH were:

- Signed informed consent of parent(s) or guardian(s) and signed informed assent of child (if indicated per child's age and institutional guidelines)
- Genetic documentation of 5q-linked SMA due to homozygous gene deletion, mutation, or compound heterozygote of *SMN1*
- Onset of clinical signs and symptoms consistent with SMA at more than 6 months of age
- Age 2 to 12 years inclusive
- Able to sit independently but never had the ability to walk independently
- Hammersmith Functional Motor Scale-Expanded (HFMSE) score of 10 or higher and 54 or lower at screening
- Able to complete all study procedures, measurements, and visits and parent or guardian/child had adequately supportive psychosocial circumstances; estimated life expectancy more than 2 years from screening; met age-appropriate institutional criteria for use of anaesthesia/sedation if use was planned for study procedures
- For those individuals who may have reached reproductive maturity, females must have had a negative pregnancy test at screening and agree to employ adequate contraceptive measures for the duration of the study, and males were to be abstinent for the duration of the study.[1]

Exclusion criteria for the CHERISH study can be found in Appendix 1. Mercuri *et al*[23] state that one of the limitations of the study was the application of strict eligibility criteria (no severe contractures or scoliosis, outlying HFMSE scores, respiratory insufficiency or reliance on a gastric tube), which meant that the study population was more homogenous and younger than the population that is encountered in usual clinical practice. The baseline characteristics of the patients in the CHERISH study are shown in Table 13.

Table 13: CHERISH baseline demographics in the ITT population (reproduced from CS, Table 12)

Characteristic	**Nusinersen (N=84)**	**Sham-procedure control (N=42)**
Female, n (%)	46 (55)	21 (50)
White, n (%)	64 (76)	30 (71)
Median (range) age at screening, years	4.0 (2–9)	3.0 (2–7)
Median (range) age at symptom onset, months	10.0 (6–20)	11.0 (6–20)
Median (range) time from disease onset to enrolment, months	39.3 (8–94)	30.2 (10–80)
Median (range) age at SMA diagnosis, months	18.0 (0–48)	18.0 (0–46)

Characteristic	Nusinersen (N=84)	Sham-procedure control (N=42)
Median (range) time from diagnosis to enrolment, months	27.8 (2–86)	26.0 (2-72)
Median (range) disease duration, months	39.3 (8–94)	30.2 (10–80)
SMN2 copy number, 2/3/4/unknown, %	7/88/2/2	10/88/2/0
Children who have ever achieved motor milestone, n (%) Sat without support Walked with support Stood without support Walked ≥15 feet independently	 84 (100) 20 (24) 11 (13) 0	 42 (100) 14 (33) 12 (29) 0
Children using a wheelchair, n (%)	64 (76)	29 (69)
Mean (SD) HFMSE total score [a]	22.4 (8.3)	19.9 (7.2)
Mean (SD) WHO total score [a,b]	1.4 (1.0)	1.5 (1.0)
Mean (SD) RULM total score [a,c]	19.5 (6.2)	18.4 (5.7)

HFMSE - Hammersmith Functional Motor Scale-Expanded; ITT - intention-to-treat; RULM - Revised Upper Limb Module; SD - standard deviation; SMA - spinal muscular atrophy; SMN - survival motor neuron; WHO - World Health Organization; [a] Baseline is defined as the last non-missing value before the first dose of nusinersen or sham-procedure control. [b] If the baseline value as defined above was missing, then baseline was imputed as the median of the non-missing values of the stratum to which the child belongs: age<6 or ≥6 years. [c] One child had a missing value and this was imputed as the median baseline value of the child across all the multiply imputed datasets. Source: Mercuri 2018[23]

As stated in the CS,[1] overall, the groups were similar although there was an imbalance in the proportion of patients who had ever achieved a motor milestone and an imbalance in the median time from disease onset to study enrolment, with a longer delay in receiving therapy in the nusinersen group than the sham group. The nusinersen group had a slightly higher HFMSE total score at baseline, indicating slightly better motor function.

Intervention and comparator

Nusinersen was administered intrathecally as a single lumbar puncture injection using a loading dose on study days 1, 29 and 85, followed by maintenance dosing 6 months thereafter (starting on day 274). The sham control procedure was administered on days 1, 29, 85 and 274 using the same administration procedure as in the ENDEAR study. In the CHERISH study, however, if anaesthesia or sedation were used in a study site for the administration of nusinersen, then minimal sedation was used for the sham procedure.

Quality assessment for CHERISH

Table 14 presents the quality assessment of the CHERISH trial undertaken by the company and the ERG.

Table 14: Company and ERG quality assessment for CHERISH (adapted from CS, Table 18)

Quality assessment question	Company's quality assessment	ERG's quality assessment
Was randomisation carried out appropriately?	Yes	Yes: Performed using an interactive web response system.
Was the concealment of treatment allocation adequate?	Yes	Yes: Performed using an interactive web response system.
Were the groups similar at the outset of the study in terms of prognostic factors?	Partly: Baseline demography was balanced between the nusinersen and control groups. There was an imbalance in the proportion of patients who had ever achieved a milestone, with fewer patients in the nusinersen group than in the control group having stood without support, and having walked with support; more patients in the nusinersen group used a wheelchair than in the control group.	Unclear: Differences between groups were not examined statistically. It appears that fewer patients randomised to receive nusinersen had ever achieved a milestone, stood without support, and walked with support, and more nusinersen group patients using a wheelchair than among the control group. The nusinersen group had a slightly higher HFMSE total score at baseline.
Were the care providers, participants and outcome assessors blind to treatment allocation?	Yes	Partly: 51% of nusinersen and 57% sham patients received inhalational anaesthesia, and 86% nusinersen and 81% sham patients received intravenous sedation (see clarification response,[2] question A6). Therefore, as patients ranged from 2 to 9 years of age, some may not have been adequately blinded. Outcome assessors may have been able to determine which participants received a lumbar puncture due to related AEs.
Were there any unexpected imbalances in drop-outs between groups?	No	No
Is there any evidence to suggest that the authors measured more outcomes than they reported?	No	Unclear: Some of the specific AE-related outcomes were pre-specified in the protocol on clincaltrials.gov, but results on these outcomes were not provided in the Mercuri *et al* paper.[23] These outcomes are reported on clinicaltrials.gov.[24]
Did the analysis include an ITT analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	Yes	Yes: The imputation methods are reasonable; sensitivity analysis using other imputation methods yielded similar results.
Summary rating	**Low risk of bias**	**Moderate risk of bias**

AEs, adverse events; HFMSE, Hammersmith Functional Motor Scale-Expanded; ITT- intention-to-treat

Overall, the CS[1] rated CHERISH as a good quality study, with a low risk of bias. The ERG agrees with this in terms of randomisation, allocation concealment, and ITT analysis. The quality assessments undertaken by both the company and the ERG agree that there are differences between the nusinersen and control groups on some key variables at baseline. The quality assessments differ in terms of ratings of:

- *Blinding:* The CS rated this item as "yes" (low risk of bias). However, the ERG rated it as "partly" (moderate risk of bias) and noted that not all patients received inhalational anaesthesia (51% nusinersen and 57% sham control) or intravenous sedation (86% nusinersen and 81% sham control) (see clarification response,[2] question A6), and participants' ages ranged from 2 to 9 years, therefore, some participants may have been aware of which treatment they received (nusinersen or sham). In addition, outcome assessors may have been able to determine which participants had received a lumbar puncture according to which participants experienced AEs relating to this procedure.
- *Unreported outcomes:* The CS rated the item, "Is there any evidence to suggest that the authors measured more outcomes than they reported?" as "no" (low risk of bias). However, the ERG noted that some of the specific AE-related outcomes were pre-specified in the protocol on clincaltrials.gov, but results for these outcomes were not provided in the paper reported by Mercuri *et al*.[23] The findings relating to these outcomes are reported on clinicaltrials.gov.[24]

Results for later onset study (CHERISH)

Motor function, AEs and HRQoL were collected in the CHERISH study and are presented in the CS.[1] However, outcomes relating to respiratory function, complications, ventilation, stamina, fatigue and mortality, which were included in the NICE scope,[12] were not collected. Three separate efficacy sets were used in the CHERISH study (see Table 15).

Table 15: CHERISH efficacy sets (adapted from CS, Table 16)

Population	Number of patients	Description
Interim efficacy set (31 August 2016)	Nusinersen: 35 Control: 19	A subset of the ITT set who had been assessed at month 15 (i.e. the day 456 visit), which included all children with a day 456 visit and all children with a time difference of at least 463 days (456 days plus a 7-day window) between the date of first dose and the data cut-off date for the interim analysis (August 31, 2016). Used for the main interim analysis of motor milestones and also as a supportive analysis for the primary endpoint and all other secondary efficacy endpoints.
Efficacy set (3 March 2017)	Nusinersen: 66 Control: 34	Subset of children in the ITT set who had the opportunity to be assessed at the day 456 visit (i.e., month 15), which included all children with a day 456 visit and all children with a time difference of at least 463 days (456 days plus a 7-day window) between the date of first dose and the date for the final analysis. Used for the analysis of WHO motor milestones.
ITT set (3 March 2017)	Nusinersen: 84 Control: 42	All patients who were randomised and received ≥1 dose of the study drug or control procedure. Children were analysed in the treatment group to which they were randomised. Used for the change from baseline to month 15 in HFMSE score, percentage of HFMSE responders, and change in RULM score.

HFMSE – Hammersmith Functional Motor Scale-Expanded; ITT – intention-to-treat; RULM - Revised Upper Limb Module; WHO – World Health Organization

Motor function

Motor function was measured using HFMSE scores, the World Health Organization (WHO) criteria motor milestones and the Revised Upper Limb Module (RULM) measure. Outcomes relating to these motor function endpoints are presented in Table 16. HFMSE is a validated tool to assess motor function in children with SMA; higher scores indicate better function. The WHO motor milestones are a set of six gross motor milestones (sitting without support, standing with assistance, hands and knees crawling, walking with assistance, standing alone, walking alone) that are expected to be attained by 24 months in healthy children. The RULM measure was used to assess upper limb functional abilities in people with SMA.

Table 16: CHERISH motor function outcomes (adapted from CS, Table 20)

Outcome	Nusinersen	Control	Difference (95% CI) and *p*-value
Interim analysis (data cut-off 31 August 2016)			
HFMSE score: change from baseline in HFMSE (95% CI)	4.0 (2.9, 5.1)	-1.9 (-3.8, 0.0)	LSM change difference: 5.9 (3.7, 8.1); $p<0.001$
Final analysis (data cut-off 3 March 2017)			
HFMSE score: change from baseline in HFMSE (95% CI)	3.9 (3.0, 4.9)	-1.0 (-2.5, 0.5)	LSM change difference: 4.9 (3.1, 6.7); $p=0.0000001$[a]
Proportion of children with change(%) in HMSE score of ≥3 points (95% CI)	57 (46, 68)	26 (12, 40)	Odds ratio: 6 (2, 15); $p<0.001$
Motor milestones at 15 months: % who achieved ≥1 new motor milestone (95% CI)	20 (11,31)	6 (1, 20)	Difference in proportions14 (-7, 34); $p=0.08$
WHO criteria motor milestones at 15 months: LSM number of new motor milestones achieved per child (95% CI)	0.2 (0.1, 0.3)	-0.2 (-0.4, 0.0)	LSM difference 0.4 (0.2, 0.7); $p=0.0001$
WHO criteria motor milestones at 15 months: % who achieved standing alone (95% CI)	2 (0, 8)	3(0, 15)	Difference in proportions: -1 (-22, 19); $p>0.9999$
WHO criteria motor milestones at 15 months: % who achieved walking with assistance (95% CI)	2 (0, 8)	0 (0, 10)	Difference in proportions: 1.5 (-19.1, 22.0); $p>0.9999$
RULM: change from baseline at 15 months (95% CI)	4.2 (3.4, 5.0)	0.5 (-0.6, 1.6)	LSM difference: 3.7 (2.3, 5.0); $p=0.0000001$

CI - confidence interval; HFMSE - Hammersmith Functional Motor Scale-Expanded; LSM - least squares mean; RULM - Revised Upper Limb Module; WHO - World Health Organization

[a] Because the p-value for the primary endpoint was significant in the interim analysis, this endpoint was not formally tested for significance in the final analysis. The exploratory p-value is not reported in the full publication and is from Mercuri et al[23]

As shown in Table 16, compared with the control group, patients in the nusinersen group showed significant improvement in HFMSE scores from baseline, an increase in the number of new motor milestones achieved per child according to the WHO criteria and improvement in RULM score from baseline.

Additional late onset studies: CS1, CS10, CS2 and CS 12

Four additional late onset studies are presented in the CS: CS1, CS10 (extension for CS1), CS2 and CS12 (extension for CS2 and CS10).[1] The characteristics of these studies are shown in Table 17.

Table 17: Study characteristics for additional late onset studies (adapted from CS Appendix L, Table 20)

Study ID	CS1	CS10	CS2	CS12
Study objectives	Safety, tolerability, dose finding, and efficacy	Safety, tolerability, efficacy, and PK	Safety, tolerability, efficacy, and PK	Safety, tolerability, efficacy, and PK
Study type/design	Phase I, open-label, escalating dose	Phase I, open-label, single dose	Phase I, open-label, dose escalation, multiple dose	Phase I, open-label, multiple dose, single arm
Study population	Symptomatic, later onset SMA: 15 subjects (54%) had Type II SMA and 13 (46%) had Type III SMA	Symptomatic, later onset SMA in patients who previously participated in CS1: 10 subjects (56%) had Type II SMA and 8 subjects (44%) had Type III SMA	Symptomatic, later onset SMA: 13 subjects (38%) had Type II SMA and 21 (62%) had Type III SMA	Symptomatic, later onset SMA in CS10 and CS2: 22 subjects (47%) had Type II SMA and 25 (53%) had Type III SMA
Primary efficacy endpoint	HFMSE	HFMSE	HFMSE	HFMSE
Secondary efficacy endpoints	PedsQL, CMAP, MUNE	PedsQL, CMAP, MUNE	PedsQL, CMAP, MUNE, ULM, myometry, 6MWT, ACEND	6MWT, ULM, CMAP, PedsQL, ACEND
Intervention(s)	Nusinersen 1mg, 3mg, 6mg and 9mg single dose	Nusinersen – Cohort 1: 6mg on day 1 Cohort 2: 9mg on day 1	Nusinersen – Cohort 1: 3mg on days 1, 29, 85 Cohort 2: 6mg on days 1, 29 and 85 Cohort 3: 9mg on days 1, 85 Cohort 4: 12mg on days 1, 29 and 85 Total duration: approximately 8 months	Nusinersen 12mg Doses on days 1, 169, 351, and 533 Total duration: approximately 1.5 years
Number of patients dosed	**TOTAL: 28** 1mg cohort: 6 3mg cohort: 6 6mg cohort: 6 9mg cohort: 10	**TOTAL: 18** Cohort 1: 4 Cohort 2: 14	**TOTAL: 34** Cohort 1: 8 Cohort 2: 8 Cohort 3: 9 Cohort 4: 9	**TOTAL: 47** 12mg: 47
Mean (median) age at baseline	6.1 years (range 2–14 years)	6.6 years (range –11 years)	7.4 years (range 2–15 years)	8 years (range 3–17 years)
Mean (median) age at symptom onset	Not summarised	Not summarised	Not summarised	Not summarised

6MWT - 6-minute walk test; ACEND - Assessment of Caregiver Experience with Neuromuscular Disease; CMAP - Compound Muscle Action Potential; HFMSE - Hammersmith Functional Motor Scale-Expanded; MUNE - Motor Unit Number Estimation; PedsQL - Paediatric Quality of Life Inventory; PK - pharmacokinetics; SMA - spinal muscular atrophy; ULM - Upper Limb Module; PK - pharmacokinetics

Results from later onset studies

Key findings from these later onset studies were as follows (CS Appendix L, pages 137-139):

CS1 & CS10

- Dose-dependent improvement in HFMSE total score with a mean increase from baseline of 3.1 points (17.6%) at day 85 at the highest dose evaluated (9mg; note – the licensed dose is 12mg)
- 7 of 10 subjects with 9mg dose exhibited improvement of ≥ 3 points in the HFMSE.

CS2 & CS12

- For patients with Type II SMA with up to three years of treatment, there were improvements observed in motor function over time as measured by HFMSE scores and ULM test
- One patient with Type II SMA gained the ability to walk independently
- Two patients with Type III SMA regained the ability to walk independently
- For patients with Type III SMA with up to three years of treatment, HFMSE scores were stable over time
- Increases were observed in 6MWT distances.[25]

Results were not presented separately for Study CS2 and Study CS10 either in the CS or in publications related to these studies.[25, 26]

4.2.4 Ongoing studies

Three ongoing studies are described in the CS: NURTURE (study completion January 2022), SHINE (study completion August 2022), and EMBRACE (study completion April 2019, see Table 18).[1] The CS includes results for the NURTURE study only as data were not available for SHINE and EMBRACE. The CS states that the NURTURE study, in pre-symptomatic infants, is a supportive study.

Table 18: Summary of ongoing nusinersen studies (reproduced from CS, Table 30)

Study	Study title	Design	Subject population	Treatment groups	Interim analyses	Ongoing /updated analyses
SHINE	A Study for Participants With Spinal Muscular Atrophy (SMA) Who Previously Participated in Nusinersen (ISIS 396443) Investigational Studies.	Open-label extension study	Infantile and later onset SMA patients from ENDEAR and CHERISH, CS12 and CS3A	Nusinersen	Estimated dates for interim analyses: Q1 2018 Data cut-off: 30 June 2017	Estimated study completion: August 1, 2022
NURTURE	A Study of Multiple Doses of Nusinersen (ISIS 396443) Delivered to Infants With Genetically Diagnosed and Pre-symptomatic Spinal Muscular Atrophy (NURTURE)	Open-label, Phase II	Genetically diagnosed and pre-symptomatic SMA	Nusinersen	Estimated dates for interim analyses: Q1/Q2 2018 Data cut-off: June 2017	Estimated study completion: January 26 2022
EMBRACE	A Study to Assess the Safety and Tolerability of Nusinersen (ISIS 396443) in Participants With Spinal Muscular Atrophy (SMA). (EMBRACE)	Phase II, randomised, double-blind, sham-procedure controlled study	Patients with SMA who are not eligible to participate in the clinical studies ENDEAR and CHERISH	Nusinersen and Sham	Estimated dates for interim analyses: Part 1: August 10, 2017	Estimated study completion: April 1, 2019

SMA - spinal muscular atrophy; Q - quarter

Patients

The study characteristics for the NURTURE study in pre-symptomatic infants are presented in Table 19. In response to a request for clarification from the ERG2 (question A4), the company stated that 25 out of 30 screened infants have been enrolled. The 25 enrolled infants were identified through diagnosis of an affected sibling (n= 18), a newborn screening programme (n=3), prenatal testing (n=3) and known carrier status (n=1). The company's response to clarification question A82 stated that patients with any clinical signs or symptoms strongly suggestive of SMA at screening or immediately prior to the first dosing were excluded. Table 19 below shows data presented in the CS, for the first 20 patients entered in the NURTURE study only.

The inclusion criteria for NUTURE were:

- Age ≤6 weeks at first dose
- Genetic documentation of 5q SMA homozygous gene deletion or mutation or compound heterozygous mutation
- Genetic documentation of 2 or 3 copies of *SMN2*
- CMAP ≥1 mV at baseline
- Gestational age of 37–42 weeks for singleton births; gestational age of 34–42 weeks for twins.[1]

Table 19: NURTURE study characteristics (adapted from CS, Table 7 and NURTURE CSR[21])

Study	NURTURE (CS5)
Location (sites)	20 study sites in 10 countries including UK
Design	Phase II, open-label, multicentre, single arm study
Population	Pre-symptomatic infants genetically diagnosed with SMA (likely to develop infantile or later onset) (target enrolment: N= 25)
Interventions	Nusinersen (n= 20)
Comparator	None
Primary outcome measure	Respiratory intervention or death
Secondary outcome measures	• Proportion of patients developing clinically manifested SMA as defined by: o Age-adjusted weight <5th percentile or decrease of ≥2 major weight growth curve percentiles (3rd, 5th, 10th, 25th, or 50th) or a percutaneous gastric tube placement for nutritional support o Failure to achieve age-appropriate attainment of the 6 WHO motor milestones • OS, i.e. proportion of patients alive • Percentage of participants who attained motor milestones assessed as part of HINE-2 • Attainment of motor milestones as assessed by WHO criteria • Change from baseline in CHOP INTEND motor function scale • Change in baseline in growth parameters
Duration	Ongoing

CHOP-INTEND - Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders; HINE-2 - Module 2 of the Hammersmith Infant Neurological Examination; SMA - spinal muscular atrophy WHO- World Health Organisation

The baseline characteristics for the NURTURE study are presented in Table 20.

Table 20: Baseline characteristics for the NURTURE study (adapted from CS, Table 13, including additional data from the company's clarification response, question A9)

Characteristic	2 SMN2 copies **N=13** [a] ***(n=15)***	3 SMN2 copies **N=7** ***(n=10)***	Total **N=20** ***(n=25)***
Age at first dose, days, n			
≤14 >14 to ≤28 >28 Range	6 5 2 3–41	2 3 2 10–42	8 *(n=9)* 8 *(n=12)* 4 *(n=4)* 3–42
Mean CHOP INTEND total score Median (range) [b]	48.0 50.0 (25–60) c	53.8 56.0 (40–60) d	49.6 54.0 (25–60) e
Mean HINE total motor milestones Median (range) [b]	2.5 3.0 (0–5) c	4.2 4.0 (2–7) d	3.0 3.0 (0–7) e
Mean ulnar CMAP amplitude Median (range), mV [b]	2.62 2.15 (1.0–6.7) c	3.96 4.00 (2.7–4.9) d	2.99 2.85 (1.0–6.7) e
Mean peroneal CMAP amplitude Median (range), mV [b]	2.47 2.65 (0.2–4.2) f	4.88 4.40 (4.0–7) d	3.27 3.20 (0.2–7.0) g
Male, %			55
Region, n North America Europe Asia-Pacific			 13 4 3

CHOP INTEND - Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders; CMAP - compound muscle action potential; HINE - Hammersmith Infant Neurological Examination
NURTURE study interim analysis data cut-off date: October 21, 2016. [a] Included 1 set of twins each with 2 SMN2 copies; [b] Based on efficacy set of patients who completed the day 64 visit or longer (N=18) ; [c] N=13. [d] N=5. [e] N=18. [f] N=10. [g] N=15
Source: Crawford 2017[27] Numbers in italics are from clarification response.

In the NURTURE study, 13 patients had 2 SMN2 copies and would therefore be expected to develop a more severe SMA phenotype than subjects with 3 *SMN2* copies, although other genetic modifying factors will affect the type of SMA an individual will develop. Most patients were male, younger than one month and from the US.

Intervention and comparators

Nusinersen was administered intrathecally (12mg equivalent dose) by lumbar puncture with loading doses on days 1, 15, 29 and 64 and maintenance doses on days 183, 302, 421, 540, 659 and 778.

Quality assessment for NURTURE

Table 21 presents the quality assessment of the NURTURE study undertaken by the company and the ERG, based on the Newcastle-Ottawa Scale.[19]

Table 21: Company and ERG quality assessment for NURTURE (adapted from information in CS, Appendix D, pages 21-26) using the Newcastle-Ottawa Scale[19]

Quality assessment question	Company's quality assessment	ERG's quality assessment
Representativeness of the exposed cohort	[redacted]	Unclear
Selection of the non-exposed cohort	[redacted]	N/A (single-arm study)
Ascertainment of exposure	[redacted]	Patients were administered nusinersen as an intervention within the study. Administration was monitored (CS[1] page 48; CSR[21] pages 30-31).
Demonstration that outcome of interest was not present at start of study	Not assessed in CS	Primary outcome is time to respiratory intervention or death, which was not present at baseline (CS,[1] page 49; CSR,[21] page 37). WHO motor milestones were not achieved at baseline due to age (CS,[1] page 52; CSR,[21] page 76).
Comparability of cohorts on the basis of the design or analysis	[redacted]	N/A
Assessment of outcome	[redacted]	Standard clinician-assessed outcome measurements used (CS,[1] pages 28-19 and pages 85-88; CSR,[21] pages 37-40), open-label (CS,[1] pages 28, 48, and 97; CSR[21] page 27).
Was follow-up long enough for outcomes to occur?	[redacted]	Treatment occurred over 778 days (CS,[1] page 32; CSR,[21] page 31), and followed up to interim data cut-off for 421 days (CSR,[21] page 68), during which time motor outcomes occurred, but not death or ventilation, however the median time to death or permanent ventilation is 10.5 months in those with 2 copies of *SMN2* and 13 months overall (CSR[21] page 115), and therefore follow-up should have been long enough.
Adequacy of follow up of cohorts	[redacted]	No withdrawals as of the recent interim analysis (cut-off date 31st October 2016) in CS[1] page 49 and CSR[21] page 56.
Stars total	[redacted]	**5**

[redacted]. The ERG agrees with this in terms of ascertainment of exposure, assessment of outcome, whether follow-up was long enough for outcomes

to occur, and adequacy of follow-up cohort. The quality assessments undertaken by the company and the ERG differ in terms of ratings of:

- *Representativeness of cohort:* [redacted] however, the ERG rated this as "unclear", as information demonstrating how the NURTURE cohort compared with the wider SMA population was not presented in the CS.
- *Demonstration that outcome of interest was not present at start of study:* This item was not assessed in the CS, and the ERG judged NURTURE as "good" on this item.

Results for supportive study in pre-symptomatic infants (NURTURE)

Those infants assessed in the interim analysis had been in the study for a median of 317.5 days (range 2-524 days).

Motor function

Motor function was measured in the NURTURE study by HINE, CHOP INTEND and WHO motor milestones. HINE motor milestones were achieved in 16 of 18 subjects in the efficacy set (89%). At the data cut-off, 12 subjects achieved sitting independently, 9 subjects achieved standing with or without support and 6 subjects achieved walking with or without support.

From baseline, 16 of 18 subjects (89%) achieved and maintained improvements in the CHOP INTEND total score. An increase of ≥4 points in the CHOP INTEND total score from baseline, the chosen definition of a responder in the CS, was seen in 61% of subjects (n=11/18).

With regard to WHO motor milestones, at the last observed visit, 71% of patients had achieved sitting without support, 59% achieved standing with assistance, 29% walking with assistance, 18% standing alone and 12% walking alone. In response to a request for clarification from the ERG[2] (question A9), the company provided the following information: 22 (100%) of infants achieved the WHO motor milestone sitting without support and 8/13 (62%) achieved walking alone, among infants with enough observation time. It is unclear how "enough observation time" was determined.

Mortality and ventilation

All infants were alive and none required invasive ventilation, tracheostomy or non-invasive ventilation (NIV) for ≥6 hours/day continuously for ≥7 days. The company's clarification response[2] (question A9) reported that as of 5th July 2017, all infants were alive and none required tracheostomy or permanent ventilation. Two of 15 infants (13%) with 2 *SMN2* copies required respiratory intervention for ≥6 hours/day continuously for ≥7 days during an acute, reversible viral infection. One additional infant

with 2 *SMN2* copies required respiratory support for ≥6 hours/day continuously for ≥1 day but less than 7 days.

Information on other ongoing studies

The ERG requested further information relating to the SHINE and EMBRACE studies during the clarification stage of the appraisal. Interim results (data cut-off 30th June 2017) from SHINE (infantile onset patients only from ENDEAR) reported additional improvements in total and specific HINE-2 motor milestones and general motor function as measured by CHOP INTEND. Median time to death or permanent ventilation was 73 weeks. Those patients who were in the control group in ENDEAR and who began nusinersen in SHINE showed improvements in total HINE-2 motor milestones and CHOP INTEND scores. No data were presented for later onset patients (from CHERISH) taking part in the SHINE study. The CSR for SHINE was not provided by the company.

Information on the inclusion criteria for the EMBRACE study was provided in the company's clarification response[2] (question A15). Patients included in EMBRACE had genetic documentation of 5q SMA; onset of symptoms ≤6 months with 3 *SMN2* copies or onset of symptoms ≤6 months and aged >7 months at screening with 2 *SMN2* copies or onset of SMA symptoms >6 months and aged ≤18 months at screening with 2 or 3 *SMN2* copies. They did not meet the inclusion criteria for ENDEAR: symptom onset ≤6 months and aged ≤7 months at screening with 2 *SMN2* copies or CHERISH: symptom onset >6 months and aged 2-12 years at screening.

4.2.5 HRQoL

Three measures of HRQoL were assessed in the CHERISH study: the Paediatric quality of life inventory (PedsQL), the Clinical Global Impression of Improvement (CGI-I) and the Assessment of Caregiver Experience with Neuromuscular Disease (ACEND).

PedsQL score

PedsQL is a modular self-report and parent proxy report approach to measuring HRQoL in children and adolescents 2-18 years of age. [redacted]

CGI-I

The CGI-I is a clinician reported outcome measuring patient's global functioning after initiating treatment and uses a seven point ordinal scale from 1 (very much improved) to 7 (very much worse). Table 22 presents the CGI-I assessments for both investigator and caregiver in the CHERISH study.

[redacted]

Table 22 CHERISH study CGI-I assessment (investigator and caregiver) at month 15 (reproduced from CS, Table 22)

Outcome	Investigator assessment		Caregiver assessment	
CGI assessment N (%)	Nusinersen (N=66)	Sham control (N=34)	Nusinersen (N=64)	Sham control (N=34)
Very much improved	[redacted]	[redacted]	[redacted]	[redacted]
Much improved				
Minimally improved				
No change				
Minimally worse				
Much worse				
Very much worse				

CGI-I - Clinical Global Impression of Improvement; N - number

ACEND

ACEND quantifies the caregiver burden experienced by parents of children affected by severe muscular diseases including children with SMA.

[redacted]

4.2.6 Subgroups

The decision problem set out in the final NICE scope[12] states that subgroups to be given consideration are based on severity of disease and should include the following:

- Age of SMA onset
- SMA type
- SMA genotype (including *SMN2* copy number).

In the ENDEAR study, treatment effects for key outcome measures were evaluated for two pre-specified subgroups as well as above and below median disease duration:

- disease duration at screening (≤12 weeks, >12 weeks)
- age at symptom onset (≤12 weeks, >12 weeks)

Table 23 presents ENDEAR subgroups by disease duration at screening; Table 24 presents ENDEAR subgroups by age at symptom onset. With regard to time to death or permanent ventilation in patients below the median disease duration, the hazard ratio (HR) was 0.24 (95% CI 0.10 to 0.58, $p<0.001$), whilst for those above the median disease duration, the HR was 0.84 (95% CI 0.43 to 1.67, $p=0.4$).[1] (see Figure 3 and Figure 4).

Table 23: ENDEAR subgroups analyses according to disease duration at screening (≤12 weeks, >12 weeks)

Outcome (source)	≤ 12 weeks			>12 weeks		
	Control (n=18)	**Nusinersen (n=34)**	***p*-value**	**Control (n=23)**	**Nusinersen (n=46)**	***p*-value**
HINE-2, % responders (CS, Appendix E, Figure 6)	0 (n=16)	75 (n=32)	$p<0.0001$	0 (n=21)	32 (n=41)	$p=0.0026$
CHOP INTEND, % improvement ≥ 4 points) (CS, Appendix E, Figure 7)	0 (n=16)	88 (n=32)	$p<0.0001$	5 (n=21)	59 (n=41)	$p<0.0001$
CHOP INTEND % worsening >= 4 points (CS, Appendix E, Figure 7)	50 (n=16)	0 (n=32)	NR	43 (n=21)	5 (n=41)	$p<0.0001$
OS (CS, Appendix E, Table 1 and Figure 8)	-	-	[redacted]	[redacted]	[redacted]	[redacted]
EFS (CS, Appendix E, Figure 9)	-	-	HR:0.158 ($p=0.0004$)	-	-	HR=0.816, $p=0.5325$

CHOP-INTEND - Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders; EFS - event-free survival; HINE-2 - Module 2 of the Hammersmith infant Neurological Examination: OS - overall survival

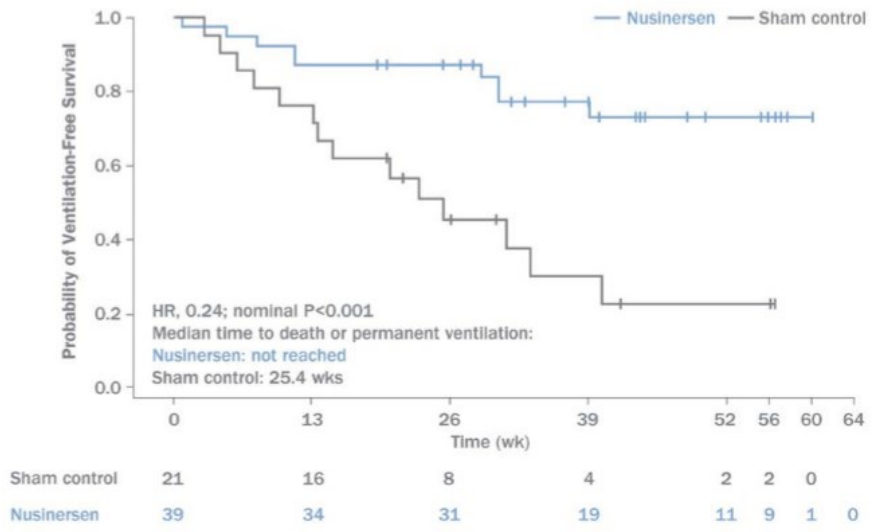
Table 24: ENDEAR subgroups analyses according to age at symptom onset (≤12 weeks, >12 weeks)

Outcome (source)	≤ 12 weeks			>12 weeks		
	Control (n=32)	**nusinersen (n=72)**	***p*-value**	**Control (n=8)**	**nusinersen (n=9)**	***p*-value**
OS (CS, Appendix E, Table 1)	-	-	HR:0.261 (95% CI: 0.1154-0.5919)	-	-	HR: 3.275 (95% CI: 0.509-21.3746)

OS - overall survival

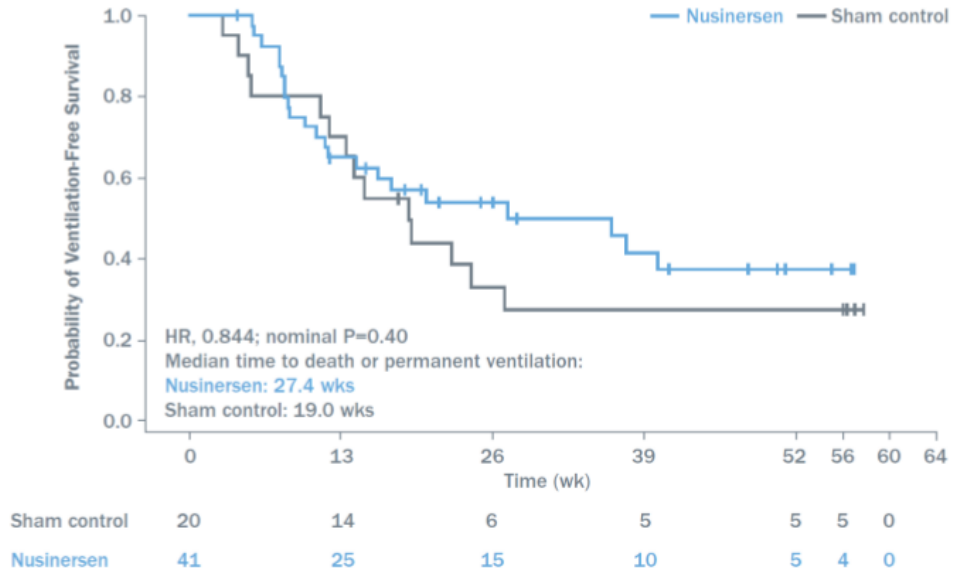
Overall, nusinersen demonstrated a benefit in all subgroups, apart from OS in the subgroup with age at onset of symptoms >12 weeks; however, the number of patients in this subgroup was small. For all outcomes, more pronounced treatment effects were observed for infants with disease duration ≤12 weeks at screening, however statistical tests for a difference between subgroups were not provided. In response to a request for clarification from the ERG[2] (question B6), the company provided results of Cox proportional hazards models and indicated that disease duration did not have a statistically significant effect on OS, while age of onset did have a statistically significant effect. Age was included as a continuous covariate and the company stated that "*it appears that survival in the sham arm is poor if age of onset is less than around 10 or 12 weeks, whereas survival on nusinersen may not be affected by age of onset.*" [2] Figure 3 and Figure 4 present Kaplan-Meier plots for time to death or permanent ventilation for subgroups by median disease duration at screening.

Figure 3: ENDEAR: Kaplan-Meier plots of time to death or permanent ventilation in the subgroup of infants below the median disease duration at screening (reproduced from CS, Figure 16)



HR - hazard ratio
Note: HR <1 indicates lower risk of event for the nusinersen group. The HR is calculated based on Cox regression adjusted for each infant's disease duration at screening; Source: Finkel 2017[20]

Figure 4: ENDEAR: Kaplan-Meier plots of time to death or permanent ventilation in the subgroup of infants above the median disease duration at screening (reproduced from CS, Figure 17)

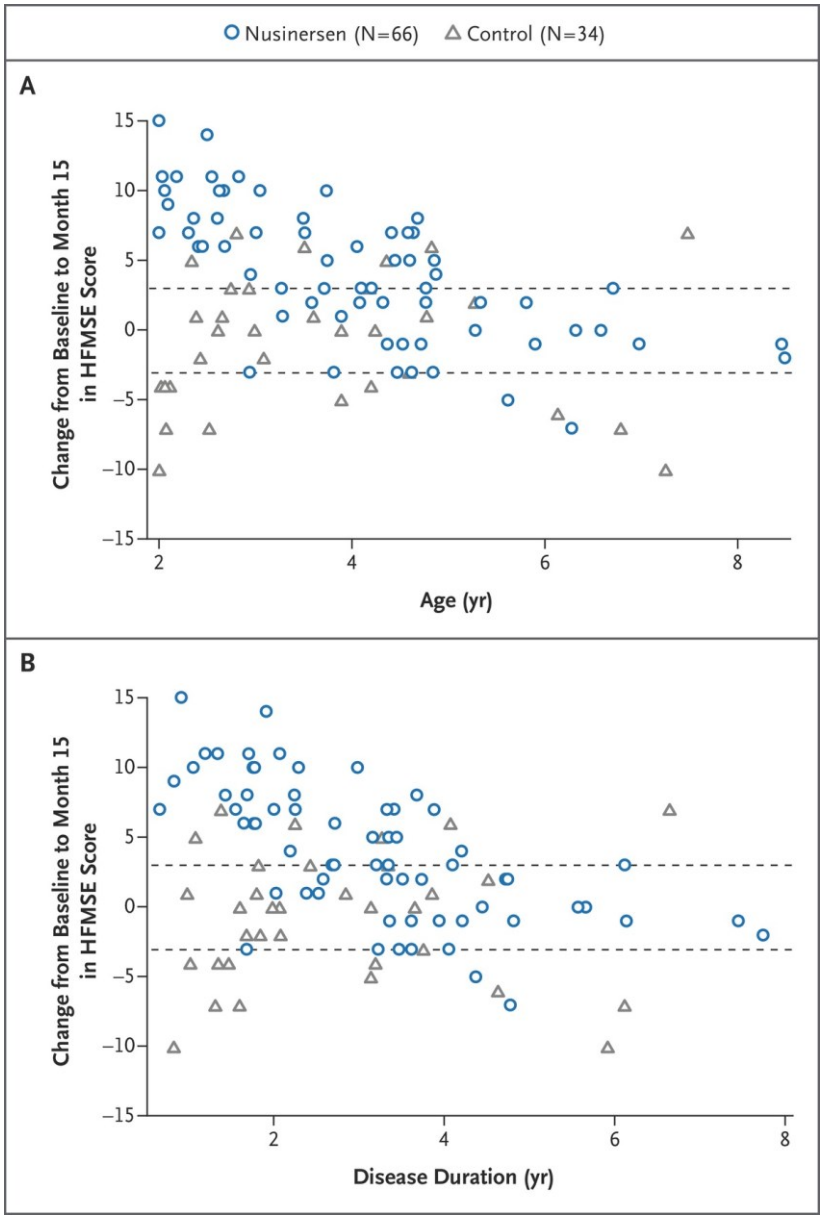


HR - hazard ratio
Note: HR <1 indicates lower risk of event for the nusinersen group. The HR is calculated based on Cox regression adjusted for each infant's disease duration at screening. Source: Finkel 2017[20]

Kaplan-Meier plots for OS and EFS by disease duration can be found in Appendix 2.

With regard to the CHERISH study, Figure 5 shows the change from baseline in HFMSE score according to age and disease duration. This illustrates that younger children who received treatment earlier in their disease course tended to have greater improvements. The treatment effects for each subgroup were not reported in the CS.

Figure 5: Change from baseline in total HFMSE score according to age (A) and disease duration (B) at screening (final analysis) (reproduced from CS, Figure 23)



HFMSE- Hammersmith Functional Motor Scale-Expanded; Disease duration is a child's age at screening minus the age at symptom onset. The analyses included children in the ITT population who did not have missing data for the 15-month assessment (66 in the nusinersen group and 34 in the control group). Dotted lines represent a ±3-point change in HFSME score, which is considered to be clinically meaningful. Source: Mercuri 2018[23]

The CS also included waterfall plots for HFMSE and RULM at 15 months (CS, Appendix E, Figures 10 and 11) again showing that younger children and those who received treatment earlier in their disease course tended to have greater improvements.

4.2.7 Safety and tolerability

Adverse events

The CS[1] presents an integrated safety analysis with data from eight completed or ongoing studies including a total of 260 patients (see Table 25). The studies with infantile onset patients included ENDEAR and CS3A; later onset studies included CHERISH and CS1, CS2, CS10 and CS12, while the pre-symptomatic group was from the NURTURE study only. Overall, the most commonly reported AEs in nusinersen-treated patients were either consistent with events occurring in the natural history of SMA, consistent with common conditions in the general population, consistent with common age-appropriate events or consistent with events observed in the context of lumbar puncture.[4]

Table 25: AEs from integrated safety analysis (reproduced from CS, Table 27)

N (%)	Nusinersen-treated patients				Sham-control-treated patients
	Infantile onset SMA	**Later onset SMA**	**Pre-symptomatic SMA**	**All nusinersen-treated patients**	
	ENDEAR & CS3A (N=100)	**CHERISH & CS1, 2, 10 & 12 (N=140)**	**NURTURE (N=20)**	**ENDEAR, CHERISH, NURTURE, CS1, 2, 3A, 10 & 12 (N=260)**	**ENDEAR & CHERISH (N=83)**
Summary of AEs					
AEs leading to discontinuation [a]	16 (16)	0 (0)	0 (0)	16 (6)	16 (19)
Treatment-related AEs	0 (0)	1 (<1)	0 (0)	1 (<1)	0 (0)
Common AEs No. of events No. of patients	 1,627 97 (97)	 1,187 134 (96)	 141 16 (80)	 2,955 247 (95)	 909 82 (99)
AEs by preferred term, with an incidence of >10% in nusinersen-treated patients					
Pyrexia	59 (59)	49 (35)	5 (25)	113 (43)	39 (47)
Upper respiratory tract infection	36 (36)	50 (36)	8 (40)	94 (36)	25 (30)
Nasopharyngitis	21 (21)	33 (24)	4 (20)	58 (22)	15 (18)
Vomiting	22 (22)	33 (24)	0 (0)	55 (21)	8 (10)
Headache	0 (0)	51 (36)	0 (0)	52 (20)	0 (0)
Constipation	37 (37)	0 (0)	2 (10)	50 (19)	14 (17)
Back pain	0 (0)	44 (31)	0 (0)	45 (17)	0 (0)
Cough	15 (15)	26 (19)	3 (15)	44 (17)	17 (20)
Pneumonia	30 (30)	0 (0)	2 (10)	41 (16)	14 (17)
Respiratory distress	28 (28)	0 (0)	0 (0)	31 (12)	12 (14)
Scoliosis	11 (11)	18 (13)	0 (0)	29 (11)	0 (0)
Diarrhoea	16 (16)	0 (0)	0 (0)	27 (10)	7 (8)
Respiratory failure	26 (26)	0 (0)	0 (0)	27 (10)	16 (19)
Post-lumbar puncture syndrome	0 (0)	26 (19)	0 (0)	26 (10)	0 (0)

AE - adverse event; SMA - spinal muscular atrophy; [a] All AEs leading to study discontinuation were events with fatal outcomes; Source: Mercuri et al[28]

In the integrated safety analysis, both nusinersen-treated patients and control patients experienced AEs. The most commonly reported AEs were those expected in patients with SMA or after lumbar puncture, such as headache, vomiting, back pain and post-lumbar puncture syndrome. Other common AEs occurring in ≥20% patients were (nusinersen versus control): pyrexia (43% vs 47%), upper respiratory infections (36% vs 30%) and nasopharyngitis (22% vs 18%). NURTURE (in pre-symptomatic infants) reported fewer AEs compared with symptomatic infants as would be expected with their healthier baseline condition.[4]

Within the ENDEAR study (CS,[1] Appendix F, Table 2), the incidence of AEs in nusinersen group and the control group was similar. However, the following AEs occurred more frequently in the nusinersen group (n=80) than in the control group (n=41): constipation (35% vs 22%), upper respiratory infection (30% vs 22%) and pneumonia (29% vs 17%). With regard to the CHERISH study (CS,[1] Appendix F, Table 3), again the incidence of AEs was similar in the nusinersen and control groups, except for the following AEs which occurred more frequently in the nusinersen group (n=84) than the control group (n=42): headache (29% vs 7%), vomiting (29% vs 12%), back pain (25% vs 0%) and epistaxis (7% vs 0%).

Serious adverse events and death

Serious adverse events (SAEs) and death were also presented from the integrated safety analysis including the same studies as described above (see Table 26).

Table 26: SAEs and death summary from integrated safety analysis (reproduced from CS, Table 28)

N (%)	Nusinersen-treated patients				Sham-control-treated patients
	Infantile onset SMA	Later onset SMA	Pre-symptomatic SMA	All nusinersen-treated patients	
	ENDEAR & CS3A (N=100)	CHERISH & CS1, 2, 10 & 12 (N=140)	NURTURE (N=20)	ENDEAR, CHERISH, NURTURE, CS1, 2, 3A, 10 & 12 (N=260)	ENDEAR & CHERISH (N=83)
Patient death	17 (17)	0 (0)	0 (0)	17 (7)	16 (19)
Incidence of SAEs	77 (77)	19 (14)	6 (30)	102 (39)	50 (60)
SAEs					
Respiratory, thoracic, and mediastinal disorders	63 (63)	4 (3)	2 (10)	69 (27)	33 (40)
Infections and infestations	60 (60)	13 (9)	4 (20)	77 (30)	29 (35)
Cardiac disorders	12 (12)	0 (0)	0 (0)	12 (5)	7 (8)
Metabolism and nutrition disorders	10 (10)	0 (0)	2 (10)	12 (5)	7 (8)
Gastrointestinal disorders	7 (7)	1 (<1)	1 (5)	9 (3)	7 (8)
General disorders and administrative site conditions	7 (7)	1 (<1)	1 (5)	9 (3)	1 (1)
Injury, poisoning, and procedural complications	3 (3)	3 (2)	0 (0)	6 (2)	3 (4)
Investigations	3 (3)	0 (0)	0 (0)	3 (1)	3 (4)
Nervous system disorders	3 (3)	0 (0)	0 (0)	3 (1)	0 (0)
Vascular disorders	2 (2)	0 (0)	0 (0)	2 (<1)	0 (0)
Immune system disorders	0 (0)	1 (<1)	0 (0)	1 (<1)	-
Musculoskeletal and connective tissue disorders	1 (1)	0 (0)	0 (0)	1 (<1)	-
Skin and subcutaneous tissue disorders	1 (1)	0 (0)	0 (0)	1 (<1)	0 (0)

SAE - serious adverse event

Overall, there were fewer deaths in the nusinersen-treated patients compared with the control patients (19% vs 7%) and fewer SAEs in the nusinersen patients compared with the control patients (39% vs 60%). Common SAEs affecting >20% of patients were respiratory, thoracic and mediastinal disorders (27% for nusinersen patients and 40% for control) and infections and infestations (30% in nusinersen

patients and 35% in control). The SAEs reported are consistent with those expected in patients with SMA and are not necessarily related to treatment.

Within the ENDEAR study (CS,[1] Appendix F, Table 2), there were fewer SAEs in the nusinersen group than the control group; however, specific AEs that occurred more frequently in the nusinersen group (n=80) than the control group (n=41) were: respiratory distress (26% vs 20%); pneumonia (24% vs 12%) and atelectasis (18% vs 10%). Within the CHERISH study (CS,[1] Appendix F, Table 3), all reported SAEs were higher in the control group than in the nusinersen group.

Additional safety issues

In the post-marketing setting, cases of meningitis have been noted following the administration of nusinersen, although numbers were not reported in the CS. [redacted] The US Food and Drug Administration (FDA) medical review for nusinersen[29] highlights some AEs with potentially severe consequences and recommends warnings regarding the risk of thrombocytopenia, coagulation abnormalities, renal toxicity, hyponatremia, decreased growth, rash and possible vasculitis, and hepatotoxicity.

4.3 Conclusions of the clinical effectiveness section

4.3.1 Completeness of the CS with regard to relevant clinical studies and relevant data within those studies

The CS[1] did not contain a systematic review as would be expected within a submission to the NICE STA process. As such, it is not entirely certain that all nusinersen studies have been identified, although the ERG is confident that all relevant studies of nusinersen for SMA have been included in the CS. In addition, a systematic review of studies relating to BSC, listed as the comparator in the NICE scope,[12] was not presented in the CS.

The studies included in the CS were well presented and included studies in three patient groups: (i) early onset (ENDEAR); (ii) late onset (CHERISH) and (iii) pre-symptomatic SMA (NURTURE), with ENDEAR and CHERISH being the key studies.

4.3.2 Interpretation of treatment effects reported in the CS in relation to relevant population, interventions, comparator and outcomes

The ERG is content that the relevant populations and intervention have been included in the CS, that is, infantile and later onset patients treated with nusinersen. However, the appropriate comparator, BSC

was not included. All relevant outcomes were included in the CS, apart from complications, stamina and fatigue.

In the ENDEAR study, the primary outcome measures were the proportion of motor milestone responders (HINE-2) and EFS (defined as time to death or permanent ventilation). With regard to HINE-2, a significantly greater percentage of patients in the nusinersen group achieved motor milestone responses than the control group. The proportion of HINE-2 responders in the interim analysis was 41% in the nusinersen group and 0% in the control group [difference: 41.18% (95% CI 18.6% to 61.20%, p<0.001). In the final efficacy set, the proportion of HINE-2 responders was 51% in the nusinersen group compared with 0% in the control group (difference=50.68%; 95% CI 31.81% to 66.48%, p<0.0001), although many patients in the nusinersen group (49% in final efficacy set) could not be classified as responders. For EFS (ITT analysis set), there was a statistically significant increase for the nusinersen group compared with the sham control group (HR=0.53; 95% CI 0.32 to 0.89; p=0.005).

In the CHERISH study, the primary outcome measure was motor function as measured by HFMSE. The change in HFMSE from baseline was significant in both the interim analysis (LSM change difference=5.9; 95% CI 3.7 to 8.1; p<0.001) and in the final efficacy set analysis (LSM change difference=4.9; 95% CI 3.1 to 6.7; p=0.0000001) for the nusinersen group compared with the control group.

The company's integrated safety analysis showed that both nusinersen-treated patients and control patients experienced AEs. The most commonly reported AEs were those expected in patients with SMA or after lumbar puncture, such as headache, vomiting, back pain and post-lumbar puncture syndrome. Overall, there were fewer deaths in the nusinersen treated patients compared to the control patients (19% vs 7%) and fewer SAEs in the nusinersen patients compared with the control patients (39% vs 60%).

Nusinersen appears to provide significant clinical benefit to patients and the safety profile reported in the studies was acceptable and generally more favourable than that for the sham control group. The patient groups in the study arms for the ENDEAR and CHERISH studies were broadly similar although the nusinersen groups had more severe symptoms and longer duration of treatment.

4.3.3 Uncertainties surrounding the reliability of the clinical effectiveness evidence

There are several areas of uncertainty in the clinical evidence. The dosage of nusinersen in the CHERISH study was different from the licensed dose in that the number of and timings for loading dose days were different as well as the timing for the maintenance dose (every 4 months for ENDEAR and every 6 months for CHERISH).

The use of three different analysis sets in both the ENDEAR and CHERISH studies made it difficult to interpret the study findings. Although, most outcomes listed in the NICE scope[12] were presented, with the exception of complications and stamina and fatigue, some outcomes were presented in only one study. Information on subgroups as set out in the NICE scope was provided although the data were limited.

The follow-up period in the studies was relatively short and no data were provided for patients in the post-marketing setting. The lack of long-term data means that it is unknown whether the effect size will change as the disease progresses and patients grow older. There is also a lack of data on the need for dose adjustments as patients grow older.

There are multiple phenotypes for SMA and no data were presented for patients with inborn symptoms (Type 0) or mild, adult onset SMA (Type IV). There is no information about how decisions should be made regarding treatment taking into account disease severity, duration and progression along with patient benefit. In addition, there is no information on the optimal dose of treatment. It is unclear when untreated pre-symptomatic patients, who are genetically diagnosed, would develop symptoms or how severe symptoms would be. Therefore, decisions regarding treatment are challenging in this patient group.

4.4 Additional work undertaken by ERG

No additional work on the clinical effectiveness section was undertaken by the ERG.

5. COST EFFECTIVENESS

This chapter presents a summary and critique of the company's health economic analyses of nusinersen for the treatment of early onset and later onset SMA. Section 5.1 presents a summary and critique of the results of the company's review of existing cost-effectiveness analyses. Section 5.2 summarises the scope of the company's *de novo* health economic analyses. Sections 5.3 and 5.4 detail the methods and results of the company's early onset and later onset models, respectively. Section 5.5 presents a critique of both health economic analyses. Section 5.6 presents the results of exploratory analyses undertaken by the ERG. Section 5.7 presents a discussion of the available economic evidence.

5.1 Company's review of published cost-effectiveness studies

The company conducted a combined search to identify studies of cost-effectiveness, HRQoL and resource use in relation to SMA (CS,[1] Appendices G, H and I; Sections 5, 6 and 7). The company's searches did not identify any economic evaluations of treatments for SMA.

During the clarification process[2] (question B1), the ERG queried the origin of the search filters which had been used to identify studies of each type. In their response, the company clarified that whilst they had not used any validated filters (e.g. those developed by McMaster University https://hiru.mcmaster.ca/hiru/HIRU_Hedges_MEDLINE_Strategies.aspx#Costs), the searches had been developed with input from an information specialist and terms were either based on the MeSH controlled vocabulary or drawn from previously published guidelines. The ERG notes that there is some overlap between the search terms used to identify economic evaluations and those for cost and resource use studies (CS,[1] Appendix G, Section 5.2.3), however, the ERG considers those included to be broadly fit for purpose.

With respect to the company's review of HRQoL studies, the search terms were grouped into two different sets - "utility studies" (including specific measures such as SF-36 and EQ-5D) and "human burden" in which broader terms such as "QoL" and "HRQL" were included. Most of the essential terms the ERG would expect to see in an HRQoL filter were included, although some published filters (e.g., the filter produced by the Canadian Agency for Drugs and Technologies in Health [CADTH] www.cadth.ca/resources/finding-evidence/strings-attached-cadths-database-search-filters#health) include a wider variety of measures. Unusually, the "human burden" terms were searched for only in article titles; the ERG notes that it is more conventional to search for terms in multiple fields such as abstracts and index terms. However, independent searches undertaken by the ERG did not identify any further published studies reporting on EQ-5D utilities in patients with SMA.

5.2 Model scope – early onset and later onset models

As part of its submission to NICE,[1] the company submitted two fully executable health economic models programmed in Microsoft Excel®. The scope of the company's health economic analyses is summarised in Table 27. The company's models assess the cost-effectiveness of nusinersen versus "real-world care" (hereafter referred to as usual care) in two populations: (i) patients with early onset (Type 1) SMA, based on the ENDEAR study,[14] and (ii) patients with later onset (Type II and III) SMA, based on the CHERISH study.[15] Both models evaluate the incremental health gains, costs and cost-effectiveness of nusinersen versus usual care from the perspective of the UK NHS and Personal Social Services (PSS). The early onset model adopts a 60-year time horizon, whilst the later onset model adopts an 80-year time horizon (see footnotes to Table 27). Cost-effectiveness is expressed in terms of the incremental cost per quality-adjusted life year (QALY) gained. All health outcomes and costs are discounted at a rate of 3.5% per annum. Unit costs are valued at 2015/16 prices.

Table 27: Scope of company's health economic analyses – early and later onset models

	Early onset model	Later onset model
Population	ITT population of the ENDEAR study[14] (Type I SMA). Mean starting age=5.58 months (0.47 years)	ITT population of the CHERISH study[15] (Types II and III SMA). Mean starting age=43.71 months (3.64 years)
Time horizon	60 years*	80 years
Intervention	Nusinersen	
Comparator	Usual care	
Outcome	Incremental cost per QALY gained	
Perspective	NHS and PSS	
Discount rate	3.5%	
Price year	2015/2016	

** Whilst the CS states that a 40-year time horizon was adopted for the early onset model, all results presented for this population in the CS relate to a 60-year time horizon. The company's clarification response[2] confirms that a 60-year time horizon was intended*

5.2.1 Population

Early onset model

The population within the early onset model (Type I SMA) reflects the ITT population enrolled into the ENDEAR study.[14] The mean age of the cohort at baseline in ENDEAR was 5.58 months (0.47 years); this is taken as the patient start age within the model. The initial distributions of patients within the modelled intervention and control groups are defined according to baseline HINE-2 scores for the nusinersen and sham groups within ENDEAR, respectively (note – the ERG considers the use of treatment-specific initial distributions to reflect an error, see Section 5.5).

Later onset model

The population within the later onset model (Type II and III SMA) reflects the ITT population enrolled into the CHERISH study.[15] The mean age of the cohort at baseline in CHERISH was 43.71 months

(3.64 years); this is taken as the patient start age within the model. The initial distributions of patients within the intervention and control groups are defined according to baseline HFMSE scores for the nusinersen and sham groups within CHERISH, respectively (note – again, the ERG considers the use of treatment-specific initial distributions to reflect an error, see Section 5.5).

The licensed indication for nusinersen is for the treatment of 5q SMA.[4] As discussed in Chapter 3, the company's economic analyses do not include patients with Type 0 or Type IV SMA; as such, the populations captured within the company's early onset and later onset models are narrower than the marketing authorisation for nusinersen. Despite this absence of evidence, the CS[1] states that the anticipated place of nusinersen is as a first-line treatment for all SMA patients as soon as possible after diagnosis.

5.2.2 Intervention

The intervention within both the early onset and later onset models is nusinersen administered as an intrathecal bolus injection via lumbar puncture.

Early onset model

Within the early onset model, nusinersen is assumed to be given as four loading doses on days 0, 14, 28 and 63, followed by one maintenance dose every four months thereafter. Each loading/maintenance dose is assumed to consist of 12mg nusinersen. This is based on the treatment schedule within the ENDEAR study[14] and is consistent with the marketing authorisation for nusinersen.[4] The company's model assumes that nusinersen will be discontinued either if the patient has achieved no motor milestones (or all milestones previously achieved are lost) by the end of month 13 (the end of study follow-up within ENDEAR) or if the patient undergoes scoliosis surgery and cannot subsequently undergo lumbar puncture.[1]

Later onset model

Within the later onset model, nusinersen is assumed to be given as four loading doses on days 1, 30, 60 and 90, followed by one maintenance dose every four months thereafter. Each loading/maintenance dose is assumed to consist of 12mg nusinersen. This treatment schedule differs from that used in the CHERISH study,[15] whereby loading doses were administered on days 1, 29 and 85, with subsequent maintenance doses on day 274 and every 6 months thereafter. Both the modelled treatment schedule in the later onset model and the treatment schedule applied in the CHERISH study differ from the dosing regimen specified in the marketing authorisation[4] (as detailed above). With reference to this issue, the CS states that *"as the use of the modelled dosing regimen could lead to greater benefit in clinical practice, the modelled results may represent a conservative estimate of treatment effect"* (CS,[1] page 167). The company's model assumes that nusinersen will be discontinued either if the patient has

achieved no milestones (or all milestones previously achieved are lost) by the end of month 15 (the end of study follow-up within CHERISH) or if patient undergoes scoliosis surgery and cannot subsequently undergo lumbar puncture.

Comparator

Within both the early onset and later onset SMA models, the comparator is assumed to be usual care; this includes respiratory, nutritional, gastrointestinal and orthopaedic interventions.[1]

5.3 Early onset model – methods and results

5.3.1 Model structure and logic – early onset model

The company's early onset model adopts a state transition approach, based on health states defined according to the HINE-2 instrument[30] (see Figure 6). The early onset model includes eight health states: (i) No milestones achieved; (ii) Mild milestones achieved; (iii) Moderate milestones achieved; (iv) Sits without support; (v) Stands with assistance; (vi) Walks with assistance; (vii) Stands/walks unaided and (viii) Dead. The HINE-2 scoring system is presented in Appendix 2; the company's classification of HINE-2 health states according to this scoring system is summarised in Table 28).

Figure 6: Company's early onset model structure (reproduced from CS, Figure 31)

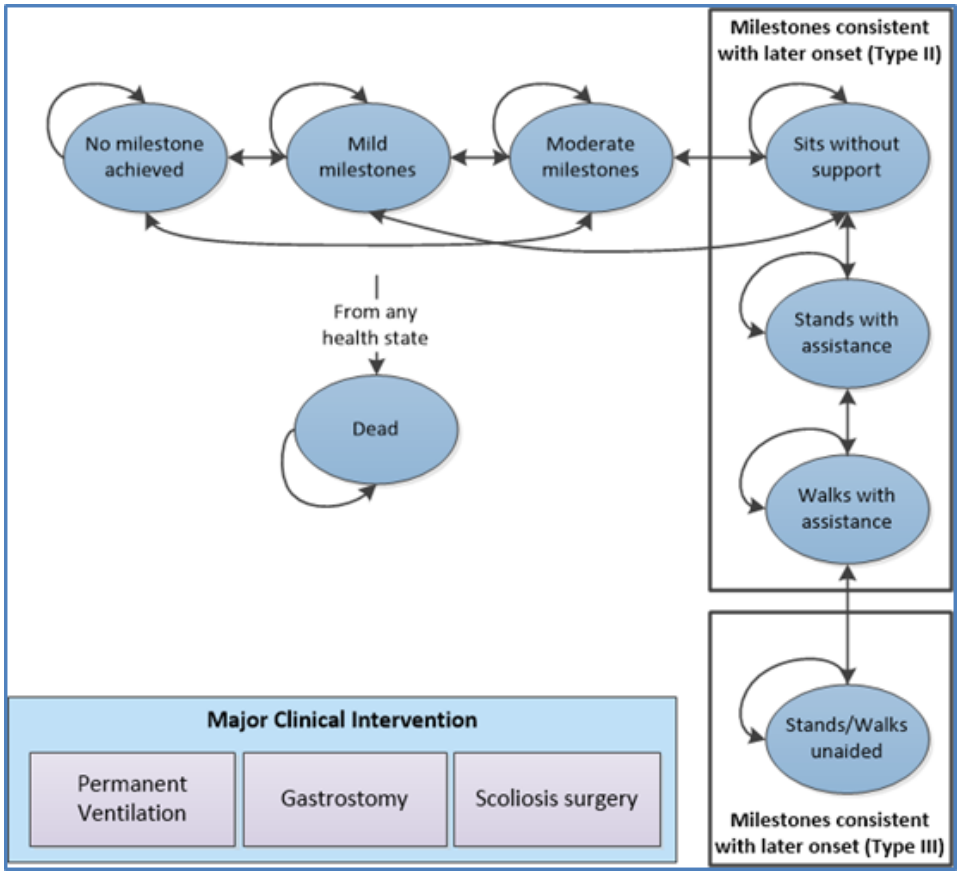


Table 28: Early onset model health states according to HINE-2 scoring (adapted from CS, Figure 31 footnotes and the company's clarification response)

Model health state	HINE-2 criteria for model health state
(i) No milestones	Patients have a score of 0 in all HINE-2 items. Voluntary grasp any score
(ii) Mild milestones	Patients have a score of 1 in at least one of the following items: head control, ability to kick, or crawling. Patients have a score of 0 in other items. Voluntary grasp any score.
(iii) Moderate milestones	Patients have any of the following scores in at least one of the following items: head control = 2; sitting = 1; ability to kick = 2 or 3; rolling = 1 or 2; crawling = 2; standing = 1; walking = 1.* Voluntary grasp any score.
(iv) Sits without support	Patients have a score of 2 or 3 or 4* in sitting ability and a score <2 in standing ability. Any score in other items except walking.
(v) Stands with assistance	Patients have a score of 2 in standing ability. Any score in other items except walking.
(vi) Walks with assistance	Patients have a score of 2 in walking. Any score in other items.
(vii) Stands/walks unaided	Patients have a score of 3 either in standing or walking ability. Any score in other items.

** Corrected by the company following clarification[2] (question B2)*

Model logic

The logic of the company's early onset model is described in the following sections.

Nusinersen group

Patients enter the model according to the observed baseline HINE-2 health state distribution for the nusinersen group in the ENDEAR study.[14] During the first four model cycles (up to the end of month 13), mortality risk is modelled using the predicted cumulative survival probabilities derived from a 1-knot Royston-Parmar spline model fitted to the observed survival data for the nusinersen group in ENDEAR. From model entry until the end of month 13, transitions between the seven HINE-2-based health states are governed by four cycle-specific transition matrices derived from observed count data within ENDEAR; these transition probabilities are then adjusted (normalised) during each cycle to account for the error between the predicted mortality probability from the spline model and the observed mortality probability within the nusinersen group of ENDEAR. From month 14 to the end of month 58, mortality is modelled using an exponential function estimated using survival outcomes for patients receiving non-invasive respiratory aid (NRA) from a retrospective chart review study reported by Gregoretti *et al;*[31] these data are adjusted to match the age of the ENDEAR population (see Section 5.3.3).

Mortality risk in all subsequent model cycles is based on an HR-adjusted Gompertz function fitted to general population mortality data[32] (HR=5,184.81). This time-dependent 3-step Type I SMA mortality function (1-knot spline [ENDEAR]→exponential [Gregoretti]→HR-adjusted Gompertz [general population, HR=5,184.81]) is applied to all patients in the three worst three health states (State [i] No milestones, State [ii] Mild milestones and State [iii] Moderate milestones). Beyond the end of follow-

up in ENDEAR, mortality risk for patients in the four best health states (State [iv] Sits without support, State [v] Stands with assistance, State [vi] Walks with assistance and State [vii] Stands/walks unaided) is adjusted to reflect an assumption of improved survival associated with Type II SMA, based on a 2-knot Royston-Parmar spline model fitted to data from an observational study reported by Zerres *et al*.[33] Beyond the end of follow-up within Zerres *et al*[33] (the end of month 622), this improved mortality for Type II SMA is modelled using a separate HR-adjusted Gompertz function fitted to general population mortality data (HR=26.41). Within these better health states, patients are allocated 90% of the mortality risk from the Type II mortality model (2-knot spline [Zerres]→HR-adjusted Gompertz [general population, HR=26.41]) and 10% of the mortality risk from the Type I mortality model (1-knot spline [ENDEAR]→exponential [Gregoretti]→HR-adjusted Gompertz [general population, HR=5,184.81]). From the end of month 13 onwards, all health state transitions are governed by two transition matrices: one corresponding to the cycle from the end of month 13 to the end of month 14, and one corresponding to all subsequent 4-monthly cycles. These two transition matrices were estimated using CHOP INTEND scores observed within the ENDEAR trial[14] and Study CS3A;[34] both matrices permit nusinersen-treated patients to either remain in their current state or to move to the next best health state; they do not allow for the deterioration of any patient's motor function from this timepoint onwards.

Patients are assumed to discontinue nusinersen if they do not achieve any milestones by the end of month 13 or if they undergo scoliosis surgery (at year 12 for non-ambulatory patients and at year 15 for ambulatory patients) and cannot subsequently undergo administration of nusinersen via lumbar puncture. Patients who discontinue nusinersen due to lack of efficacy are assumed to remain State (i) (No milestones) until death. Patients who discontinue nusinersen following scoliosis surgery are assumed to subsequently follow the final transition matrix for the sham group.[3]

Usual care group

Patients enter the model based on the baseline HINE-2 health state distribution for the sham group in the ENDEAR study.[14] During the first four cycles (up to the end of month 13), mortality risk is modelled using the predicted cumulative survival probabilities from a 1-knot Royston-Parmar spline model fitted to the survival data for the sham group within ENDEAR. Transitions between the seven HINE-2-based health states are governed by four cycle-specific matrices derived from observed count data within ENDEAR; these transition probabilities are then adjusted (normalised) during each cycle to account for the error between the predicted mortality probability from the spline model and the observed mortality probability within the sham group of ENDEAR.

From month 14 onwards, mortality is modelled using the same exponential (Gregoretti *et al*[31]) and HR-adjusted general population Gompertz (HR=5,184.81) function as that used in the nusinersen group (see above). In contrast to the assumptions applied to the nusinersen group, no mortality adjustment is

applied for patients in States (iv) to (vii) in the usual care group. After the end of month 13, all health state transitions are governed by two transition matrices: one corresponding to the cycle from the end of month 13 to the end of month 14, and one corresponding to all subsequent 4-monthly cycles. These matrices were estimated using CHOP INTEND scores observed within the ENDEAR trial[14] and Study CS3A;[34] these matrices permit patients on usual care to either remain in their current state or move to the next worst health state; they do not allow for the improvement of any patient's motor function from this timepoint onwards. A proportion of patients are assumed to undergo scoliosis surgery at year 10 if non-ambulant and at year 15 if ambulant; however, this event does not impact on the patient's health state occupancy, HRQoL or costs.

Estimation of health outcomes, costs and cost-effectiveness

Separate utilities are applied to each modelled health state. QALYs accrued by patients in each group are estimated by applying a vector of health utilities to the probability of being in each state during each model cycle. QALY losses for caregivers are estimated conditional on the patient's health state and include a QALY loss for bereavement on carers. The CS reports separate analyses including/excluding caregiver QALYs.

The early onset model includes the following cost components: (i) acquisition and administration costs for nusinersen; (ii) health state costs, including respiratory, gastrointestinal, nutritional and orthopaedic care (conditional on motor milestones achieved) and (iii) end-of-life care (applied as a once-only cost at the point of death).

Incremental cost-effectiveness is calculated in a pairwise fashion based on the difference in costs divided by the difference in QALYs for nusinersen and usual care.

5.3.2 Structural assumptions – early onset model

The company's early onset SMA model makes the following assumptions:

(i) Treatment using nusinersen will be discontinued if no milestones are achieved after 13 months (see clarification response,[2] question B27). The ERG notes that this assumption is applied only once, as patients receiving nusinersen are assumed never to transit to State (i) No milestones after this timepoint (see assumption [iv] below).

(ii) A proportion of patients discontinue nusinersen following scoliosis surgery.

(iii) After the end of month 13, an adjustment is applied to reflect improved survival for nusinersen patients in State (iv) Sits without support, State (v) Stands with assistance, State (vi) Walks with assistance and State (vii) Stands/walks unaided. These patients are allocated 90% of the mortality risk for Type II SMA and 10% of the mortality risk for Type I SMA. This adjustment

is not applied to patients reaching these states in the usual care group; instead, all patients in the usual care group are allocated 100% of the Type I mortality risk.

(iv) After the end of month 13, patients receiving nusinersen are assumed never to transit to a worse health state; rather, during any model cycle, patients can either remain in their current health state or transit to the next best health state. Beyond month 13, transition probabilities are based on the mean rate of improvement in CHOP INTEND score within ENDEAR and the mean CHOP INTEND scores within each HINE-2 state for the nusinersen group over the course of the ENDEAR study (supplemented using data from Study CS3A for State [v] Stands with assistance and State [vi] Walks with assistance). The rate of improvement in CHOP INTEND score is assumed to be constant with respect to time and monotonic across health states.

(v) After month 13, patients receiving usual care are assumed never to transit to an improved health state; rather, during any model cycle, patients can either remain in their current health state or transit to the next worst health state. Beyond month 13, transition probabilities are based on the mean rate of worsening in CHOP INTEND score within ENDEAR and the mean CHOP INTEND scores within each model health state for the sham group over the course of the ENDEAR study (supplemented using data from Study CS3A for State [v] Stands with assistance and State [vi] Walks with assistance). The rate of decline in CHOP INTEND score is assumed to be constant with respect to time and monotonic across health states.

(vi) After month 13, the probability of transiting from State (vi) Walks with assistance to State (vii) Walks/stands unaided is assumed to be the same as the probability of transiting from State (v) Stands with assistance to State (vi) Walks with assistance. The company considers this to be a conservative assumption.[2]

(vii) A proportion of ambulant patients undergo scoliosis surgery after 15 years.

(viii) The CS[1] states that the model assumes that a proportion of non-ambulant patients undergo scoliosis surgery at 12 years. Whilst this assumption is correctly implemented in the nusinersen group of the company's model, the model assumes that scoliosis surgery for non-ambulant patients receiving usual care occurs at 10 years. As separate costs and utility changes for scoliosis surgery are not included in the model, this does not impact on the model results.

(ix) Treatment costs are grouped according to milestones consistent with Type I SMA (State [i] No milestones, State [ii] Mild milestones and State [iii] Moderate milestones), Type II SMA (State [iv] Sits without support, State [v] Stands with assistance and State [vi] Walks with assistance) and Type III SMA (State [vii] Stands/walks unaided).

(x) The model does not include additional HRQoL impacts or costs associated with AEs. The CS[1] notes that no treatment-related AEs were observed in ENDEAR.

5.3.3 Evidence used to inform model parameters – early onset model

The main groups of parameters for the early onset model and the evidence used to inform these are summarised in Table 29. These are discussed in further detail in the subsequent sections.

Table 29: Evidence used to inform the company's early onset model

Parameter group	Evidence source
Initial HINE-2 health state distribution - nusinersen	Observed initial HINE-2 distribution in the nusinersen group of ENDEAR[14]
Initial HINE-2 health state distribution – usual care	Observed initial HINE-2 distribution in the sham group of ENDEAR[14]
Overall survival – nusinersen	1-knot Royston-Parmar spline model fitted to nusinersen group data from ENDEAR[14] switching (after month 13) to an exponential model fitted to adjusted NRA group data from Gregoretti *et al*[31] switching (after month 58) to an HR-adjusted general population Gompertz model (HR=5,184.81).[32] For States (iv) to (vii), after month 13, an adjustment of 0.90 is applied to reflect improved survival for Type II SMA based on a 2-knot spline fitted to data reported by Zerres *et al*[33] switching (after month 622) to an HR-adjusted general population Gompertz model (HR=26.41).[32]
Overall survival – usual care	1-knot Royston-Parmar spline model fitted to sham group of ENDEAR[14] switching (after month 13) to an exponential model fitted to adjusted NRA group data from Gregoretti *et al* switching (after month 58) to an HR-adjusted general population Gompertz model (HR=5,184.81). No adjustment is applied to reflect Type II SMA outcomes.
Transition probabilities – nusinersen (up to month 13)	Observed HINE-2 count data from ENDEAR[14] (without imputation)
Transition probabilities – usual care (up to month 13)	Observed HINE-2 count data from ENDEAR[14] (without imputation)
Transition probabilities – nusinersen (month 14 onwards)	Estimated mean rate of improvement in CHOP INTEND and mean CHOP INTEND scores by HINE-2 state in ENDEAR[14] for nusinersen group (supplemented using data from Study CS3A[34])
Transition probabilities – usual care (month 14 onwards)	Estimated mean rate of worsening in CHOP INTEND and mean CHOP INTEND scores by HINE-2 state in ENDEAR[14] for sham group (supplemented using data from Study CS3A[34])
Probability of undergoing surgery for scoliosis and age at time of surgery	Surgery probability based on assumption.[1] Timing of surgery loosely based on Haaker and Fujak[35]
Probability of discontinuing nusinersen after surgery for scoliosis	Assumption[1]
Patient utilities	PedsQL data collected in CHERISH[15] mapped to the EQ-5D using a published algorithm reported by Khan *et al*[36]
Baseline caregiver utility	Baseline caregiver utility based on Bastida *et al.*[37] Caregiver disutilities by health state estimated using Ara and Brazier[38] and mapped patient utilities from CHERISH. [15]
Nusinersen acquisition cost	CS[1]
Nusinersen administration costs	NHS Reference Costs 2015/16[39]
Health state costs	Bastida *et al*[37]
End-of-life care costs	NICE Guideline 61[40]

HINE-2 - Module 2 of the Hammersmith Infant Neurological Examination; HR – hazard ratio; CHOP INTEND - Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders; NRA - Non-invasive respiratory aid; EQ-5D – Euroqol 5-Dimensions; CS – company's submission

Overall survival – early onset SMA

Company's methods for estimating overall survival

As outlined in Section 5.3, OS is modelled using a piecewise approach with separate sources to inform different sections of the modelled time horizon. Extrapolation on the basis of external data was considered by the company to be "*more appropriate than extrapolating the survival models fitted to the observed trial period alone*" (CS,[1] page 122). The overall modelling approach is summarised in Table 30; further details of the external data and the modelling approach are provided below.

Table 30: Summary of survival models applied for extrapolation of OS

Survival interval	Treatment group		
	Usual care (N=41)	Nusinersen (N=80)	
		States (i) to (iii)	States (iv) to (vii)
OS time period 1 Month 0 to Month 13	ENDEAR sham arm* **1-knot spline combined model**	ENDEAR nusinersen arm† **1-knot spline combined model**	
OS time period 2 Month 14 to Month 58	Adjusted Gregoretti *et al*[31] NRA‡ **Exponential model**	Adjusted Gregoretti *et al*[31] NRA‡ **Exponential model**	Adjusted Gregoretti *et al*[31]‡ and Zerres *et al*[33] § **Gregoretti exponential (weight 0.1) Zerres 2-knot spline (weight 0.9)**
OS time period 3a Month 59 to Month 622	UK general population mortality data **HR-adjusted Gompertz (HR=5184.8)**	UK general population mortality data **HR-adjusted Gompertz (HR=5184.8)**	UK general population mortality and Zerres *et al*[33]§ **HR-adjusted Gompertz (HR=5184.8, weight 0.1) Zerres 2-knot spline (weight 0.9)**
OS time period 3b Month 623 to Month 720			UK general population mortality data **HR-adjusted Gompertz (HR=5184.8, weight 0.1) and HR-adjusted Gompertz (HR=26.4, weight 0.9)**

** Observed trial data, N=41*
† observed trial data, N=80
‡ N= 26, Type I SMA replicated from KM, adjusted
§ N=240, Type II SMA replicated from KM, no adjustment

Survival models

The company considered a range of common parametric models: exponential, Weibull, Gompertz, log normal, log logistic, generalised gamma and Royston-Parmar cubic splines fitted on the hazard scale with 1, 2, and 3 knots (described in the CS[1] as flexible spline-based Weibull models). Hybrid survival models were also considered for some situations but were not found to be appropriate (see CS,[1] Appendix P). For extrapolation based on UK general population mortality data, the company considered only the Weibull, Gompertz and Royston-Parmar cubic spline models.

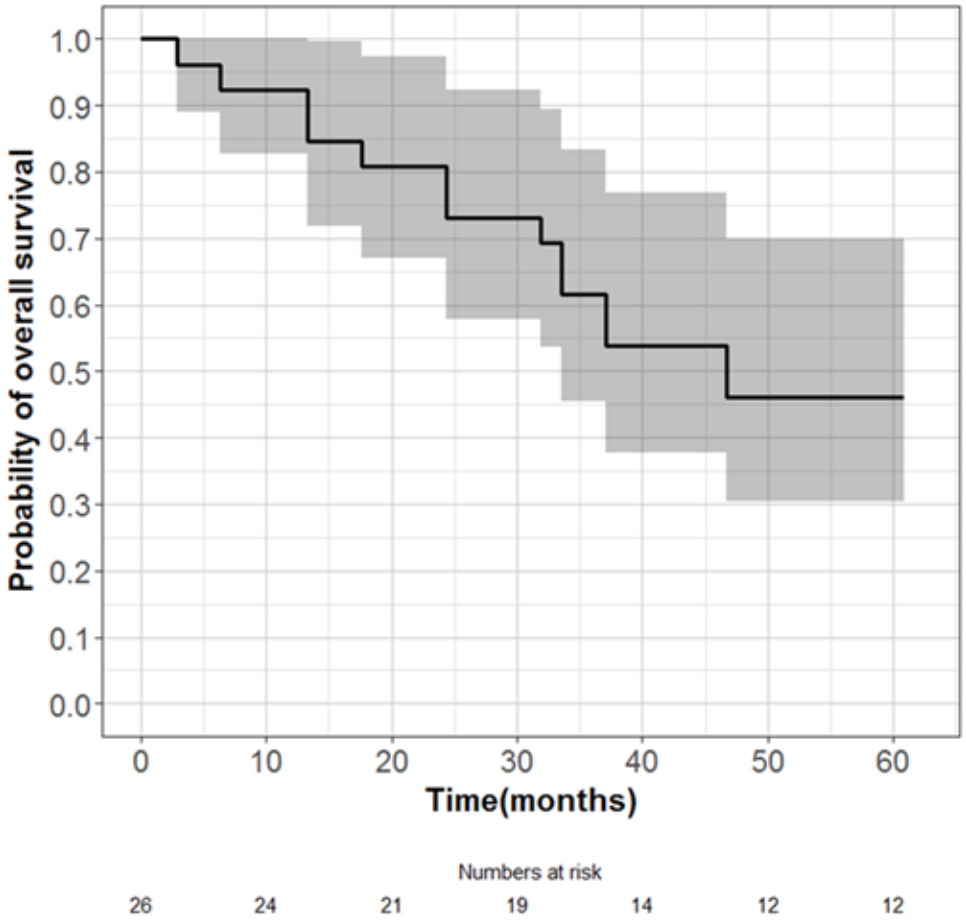
For the ENDEAR data,[14] two approaches were considered to account for differential survival probabilities in the nusinersen and sham arms: (i) a *combined model* with treatment group included as a covariate (described as *unstratified models* in the CS) and (ii) *stratified models* whereby all parameters are allowed to differ by treatment. The latter approach is equivalent to fitting separate models to each treatment group.

Models were fitted in R[41] using either the *eha* package (exponential, Weibull, log normal and log logistic models) or the *flexsurv* package (Gompertz, generalised gamma and Royston-Parmar spline models). Complementary log-log plots were produced to assess the proportional hazards assumption, and smoothed non-parametric estimates of the observed hazard rates were produced. Fit of the models was considered based on the Akaike Information Criterion (AIC), the Bayesian Information Criterion (BIC) and the Integrated Brier Score (IBS)[42] through bootstrap cross-validation., together with visual inspection of fit and consideration of the clinical plausibility of the extrapolated portion of the survival curves.

External data sources

The study reported by Gregoretti *et al*[31] is a retrospective chart review of 194 infantile onset SMA patients followed by 4 Italian centres between October 1, 1992 and December 31, 2010. Subgroup data on the 31 infants receiving non-invasive respiratory muscle aid (NRA) were deemed by the company to be the most reflective of current standard care. Individual patient-level data (IPD) were reconstructed from the published Kaplan-Meier curve. Gregoretti *et al* present data from birth whereas the mean age of patients at the start of treatment in ENDEAR[14] was 5.56 months (note – a slightly higher value of 5.58 months is assumed in the company's model). The company adjusted the reconstructed IPD by subtracting 5.56 from all event times, resulting in 5 individuals with negative event times who were excluded from the dataset (see clarification response,[2] question B11). The resulting adjusted survival curve is shown in Figure 7. Data from Zerres and Rudnik-Schöneborn[43] were also considered in a scenario analysis (see Section 5.3.5).

Figure 7: Kaplan-Meier estimates based on Gregoretti *et al*, adjusted for mean age of patients at the start of the ENDEAR trial (reproduced from CS Appendix P, Figure 55)



NRA - non-invasive respiratory aid; NT - no treatment; TV - tracheotomy and invasive mechanical ventilation.

For patients in States (iv) to (vii) in the nusinersen group, the company considered that motor milestones characteristic of later onset patients would be achieved, hence survival would be between that of Type I and Type II SMA patients. Type II mortality in time periods 2 and 3a was modelled based on the SMA Type II population of Zerres *et al*[33] and is briefly described in the CS[1] (Section 4.3.1, page 168 and Appendix P, page 212). This natural history study included 240 patients with Type II SMA, recruited from 1960 onwards. The company reconstructed IPD from the published Kaplan-Meier curve without performing any adjustment.

Beyond the end of follow-up in Gregoretti *et al.*[31] OS was modelled based on general population mortality data from the Office for National Statistics (ONS),[32] using average life tables for males and females. IPD were reconstructed using the algorithm reported by Guyot *et al.*[44] CS Appendix P (page 208) states *"Since only in survival after 19 years was of interest, infant mortality (children <3 years old) was removed from these data."* The ERG is unclear regarding the relevance and appropriateness of this statement.

Survival modelling results - early onset model

OS time period 1: ENDEAR follow-up (up to the end of month 13)

Model fit statistics for all parametric models fitted to the ENDEAR trial data[14] are summarised in Table 31. The predicted survival probabilities are illustrated in CS,[1] Appendix P, Figures 28 and 29. The company selected the combined model Royston-Parmar cubic spline with 1 knot for the base case, as it provided a good fit to the data and preserves the assumption of proportional hazards, which the company considered to be appropriate for the data. The CS states that the combined Royston-Parmar cubic spline with 2 knots and the combined Gompertz models also provided a good fit.

Table 31: Model fit statistics for parametric models fitted to ENDEAR OS data (adapted from CS Appendix P, Figure 30, Figure 31 and Figure 33)

Model	Combined/stratified	AIC	BIC	IBS
Cubic spline 1-knot	Combined (PH)	**251.4**	**256.9**	0.1556
Cubic spline 2-knot	Combined (PH)	**251.6**	**258.5**	0.1558
Gompertz	Combined (PH)	**251.9**	**256.0**	0.1556
Cubic spline 3-knot	Combined (PH)	253.5	261.7	NR
Gompertz	Stratified	253.8	259.2	0.1555
Cubic spline 1-knot	Stratified	255.2	263.4	NR
Log normal	Combined (AFT)	255.8	259.9	0.2192
Log normal	Stratified	256.5	262.0	0.1561
Cubic spline 2-knot	Stratified	256.9	267.8	NR
Generalised gamma	Combined (AFT)	257.2	262.7	NR
Log logistic	Combined (AFT)	257.7	261.8	0.2424
Cubic spline 3-knot	Stratified	257.9	271.6	NR
Weibull	Combined (PH)	259.2	263.4	0.2606
Log logistic	Stratified	259.3	264.8	0.1565
Exponential	Combined (PH)	259.8	262.5	0.2560
Weibull	Stratified	261.2	266.6	0.1558

AIC – Akaike Information Criterion; BIC – Bayesian Information Criterion; IBS - Integrated Brier Score, lower numbers are favourable; PH – proportional hazards; AFT – accelerated failure time; NR - not reported
Numbers in bold relate to highest rank (lowest AIC/BIC) or within 3 of lowest AIC/BIC

OS time period 2: From end of ENDEAR follow-up to end of Gregoretti et al follow-up

Model fit statistics for all parametric models fitted to the adjusted Gregoretti NRA data[31] are summarised in Table 32; fitted survival curves are provided in CS[1] Appendix P, Figures 57-62. The company selected the exponential model for the base case. The company considered that all models gave a good visual fit to the observed data but that only the exponential, Weibull and hybrid models gave plausible long-term predictions. The exponential model was considered to give the best fit; predicted hazard rates from this model were applied to the sham (usual care) group from month 14 to month 58.

OS for the treatment group was also informed by Zerres *et al*.[33] Model fit statistics for all parametric models fitted to the reconstructed Zerres *et al* data[33] are summarised in Table 33; predicted survival

probabilities are provided in CS[1] Appendix P, Figures 74 and 75. The combined Royston-Parmar spline model with 2 knots was selected for use in the company's base case as this model gave the best fit in terms of the AIC and the BIC.

For patients in model health states (iv) to (vii) who are receiving treatment using nusinersen, OS was then assumed to be between that of the survival prediction from Zerres *et al*[33] and Gregoretti *et al*[31] according to the weighting given in Equation [i].

$$S_{Nusinersen}(t) = 0.9\, S_{Zerres}(t) + 0.1\, S_{Gregorretti}(t) \qquad [i]$$

Justification of these weightings was provided through reference to an advisory board meeting on SMA held by the company,[45] although the ERG notes that the documentation provided by the company does not report the values of the weights applied in the model. The predicted hazards from the weighted combination of survival functions were applied to the treatment arm from months 14 to 58.

Table 32: Model fit statistics for parametric models fitted to adjusted Gregoretti *et al* NRA OS data (adapted from CS Appendix P, Figure 63, 64, 66)

Model	AIC	BIC	IBS
Exponential	**152.2**	**152.8**	0.16733
Log logistic	**153.2**	**154.5**	0.16952
Log normal	**153.3**	**154.5**	0.17039
Weibull	**153.8**	**155.1**	0.17053
Gompertz	**154.2**	**155.5**	0.17057
Generalised gamma	**155.2**	157.2	NR
Cubic spline 1-knot	155.6	157.5	0.17072
Cubic spline 2-knot	157.3	159.8	NR
Cubic spline 3-knot	157.5	160.7	NR
Cubic spline 4-knot	159.1	162.9	NR

AIC – Akaike Information Criterion; BIC – Bayesian Information Criterion; IBS - Integrated Brier Score, lower numbers are favourable; NR - not reported Numbers in bold relate to highest rank (lowest AIC/BIC) or within 3 of lowest AIC/BIC

Table 33: Model fit statistics for parametric models fitted to Zerres *et al* 1997 Type II OS data (adapted from CS Appendix P, Figure 77, Figure 78 and Figure 80)

Model	AIC	BIC	IBS
Cubic spline 2-knot	**1563.5**	**1574.3**	0.16246
Weibull	1583.2	1588.6	0.16303
Cubic spline 1-knot	1585.2	1592.6	0.16340
Gompertz	1587.2	1593.3	0.16338
Log logistic	1590.7	1596.1	0.16359
Log normal	1592.6	1598.0	0.16351
Exponential	1644.5	1647.2	0.16920

AIC – Akaike Information Criterion; BIC – Bayesian Information Criterion; IBS - Integrated Brier Score, lower numbers are favourable; NR - not reported Numbers in bold relate to highest rank (lowest AIC/BIC) or within 3 of lowest AIC/BIC

OS time period 3: From end of Gregoretti et al follow-up to end of time horizon, usual care arm and nusinersen states (i)-(iv)

Model fit statistics for all parametric models fitted to the general population mortality data are summarised in Table 34; fitted survival probabilities are provided in CS[1] Appendix P, Figure 67. The Gompertz model was preferred by the company on account of the theoretical justification of this distribution to model healthy populations and the simplicity of the model. The predicted hazards were compared with those from the exponential model fitted to the Gregoretti *et al* data,[31] providing an HR of 5184.8. This HR was applied to the Gompertz model derived from the general population in order to "*adjust the survival curve for a population matching that of Gregoretti*" (CS,[1] Section 3.3.4.1, page 126).

Table 34: Model fit statistics for parametric models fitted to reconstructed general population mortality data (adapted from CS Appendix P, Figures 68, 69 and 71)

Model	AIC	BIC	IBS
Cubic spline 2-knot	**85927.1**	**85921.8**	0.070502
Cubic spline 1-knot	85935.0	85931.1	0.70496
Gompertz	85961.6	85958.7	0.070488
Weibull	86295.9	86293.3	0.70716

AIC – Akaike Information Criterion; BIC – Bayesian Information Criterion; IBS - Integrated Brier Score, lower numbers are favourable; NR - not reported Numbers in bold relate to highest rank (lowest AIC/BIC) or within 3 of lowest AIC/BIC

OS time period 3a: From end of Gregoretti et al follow-up to end of Zerres et al, nusinersen states (iv)-(vii)

For nusinersen-treated patients reaching states (iv) to (vii), there is an additional stage due to differing durations of follow-up within Gregoretti *et al*[31] and Zerres *et al.*[33] After the end of Gregoretti *et al*, the portion of the OS informed by Gregoretti *et al* is replaced by the HR-adjusted general population survival shown in Equation [ii].

$$S_{Nusinersen}(t) = 0.9\, S_{Zerres}(t) + 0.1\, (S_{genpop}(t))^{1/5184.8} \qquad \text{[ii]}$$

OS time period 3b: From end of Zerres et al, nusinersen states (iv)-(vii)

Beyond the end of the Zerres *et al*[33] follow-up period, the portion of Equation [ii] informed by the Zerres *et al* survival curve is then replaced by the adjusted general population mortality resulting in a weighted combination of two Gompertz models shown in Equation [iii]. To estimate the adjustment factor, predicted hazard rates at 53 years were compared. The Gompertz model fitted to the general population gave a hazard rate of 0.00028, whilst the exponential model fitted to the Zerres *et al*[33] data gave a hazard rate of 0.00745; the estimated HR was 26.4.

$$S_{Nusinersen}(t) = 0.9(S_{genpop}(t))^{1/26.4} + 0.1\, (S_{genpop}(t))^{1/5184.8} \qquad \text{[iii]}$$

Transition probabilities

Transition probabilities were estimated using different approaches for the observed period of ENDEAR[14] and for subsequent cycles. Within the observed period, transitions were estimated directly using observed HINE-2 count data for each treatment group. Separate matrices were calculated for each of four cycles (day 1-64, day 65-183, day 184-302 and day 303-394). In response to a request for clarification,[3] the company stated that matrices were generated using the efficacy dataset without imputation of missing data; however, the ERG notes that these matrices contain count data for a larger number of patients than were included in the efficacy set.

Beyond the end of follow-up in ENDEAR (after the end of month 13), two transition matrices are applied: the first is applied for the interval from the end of month 13 to the end of month 14, whilst the second is applied to all subsequent 4-monthly cycles. These matrices were estimated by calculating the mean rate of change in CHOP INTEND score in each treatment group and the mean CHOP INTEND score within each HINE-2 model health state within each treatment group over the duration of ENDEAR. Data on mean CHOP INTEND score by HINE-2 state from Study CS3A[34] were used for State (v) Stands with assistance and State (vi) Walks with assistance due to limited data in ENDEAR (see Table 35). Transition probabilities for patients in the nusinersen and usual care groups were calculated using Equation [iv] and Equation [v], respectively.

$$TP\ (nusinersen)\ = MIN[1{,}1 + \left(\frac{Rate\ CHI\ increase\ (per\ month)\ .\ cycle\ length\ (months)}{Mean\ CHI\ next\ best\ state - Mean\ CHI\ current\ state}\right) \quad \text{[iv]}$$

$$TP(usual\ care)\ = MIN[1{,}1 + \left(\frac{Rate\ CHI\ decrease\ (per\ month)\ .\ cycle\ length\ (months)}{Mean\ CHI\ current\ state - Mean\ CHI\ next\ worst\ state}\right) \quad \text{[v]}$$

CHI - CHOP INTEND score

Table 35: CHOP INTEND data used to inform transition probabilities beyond month 13

MEAN CHOP INTEND SCORE			
HINE-2 health state	**Nusinersen**	**Sham**	**Source**
No milestones	24.59	20.19	ENDEAR[14]
Mild milestones	32.98	26.83	
Moderate milestones	41.45	37.11	
Sits without support	46.67	48.00	
Stands with assistance	52.67	52.67	Study CS3A[34]
Walks with assistance	63.00	63.00	
Walks unaided	-	-	
RATE OF IMPROVEMENT/WORSENING			
	Nusinersen	**Sham**	
Monthly CHI rate	[redacted]	[redacted]	ENDEAR[14]

Estimated transition matrices for the first four model cycles (based on the observed count data from ENDEAR) are shown in Table 36, Table 37, Table 38 and Table 39. Table 40 and Table 41 present the transition matrices applied after the end of month 13.

Table 36: Transition matrices for nusinersen (top) and sham (bottom), HINE-2 observed count data, ENDEAR trial, days 1-64 (taken from company's model)

NUSINERSEN GROUP (patients alive with data n=[redacted])								
From\To state	No milestones	Mild milestones	Moderate milestones	Sits without support	Stands with assistance	Walks with assistance	Stands/walks unaided	Dead
No milestones	[redacted]	[redacted]	[redacted]					[redacted]
Mild milestones	[redacted]	[redacted]	[redacted]					[redacted]
Moderate milestones			[redacted]					[redacted]
Sits without support	[redacted]							
Stands with assistance					[redacted]			
Walks with assistance						[redacted]		
Stands/walks unaided							[redacted]	
Dead								[redacted]
SHAM GROUP (patients alive with data n=[redacted])								
From\To state	No milestones	Mild milestones	Moderate milestones	Sits without support	Stands with assistance	Walks with assistance	Stands/walks unaided	Dead
No milestones	[redacted]	[redacted]	[redacted]					[redacted]
Mild milestones	[redacted]	[redacted]	[redacted]					
Moderate milestones	[redacted]	[redacted]	[redacted]					
Sits without support				[redacted]				
Stands with assistance					[redacted]			
Walks with assistance						[redacted]		
Stands/walks unaided							[redacted]	
Dead								[redacted]

** No observed transitions from state during cycle; Blank cells indicate zero probability*
n - number

Table 37: Transition matrices for nusinersen (top) and sham (bottom), HINE-2 observed count data, ENDEAR trial, days 65-183 (taken from company's model)

NUSINERSEN GROUP (patients alive with data n=)								
From\To state	No milestones	Mild milestones	Moderate milestones	Sits without support	Stands with assistance	Walks with assistance	Stands/walks unaided	Dead
No milestones								
Mild milestones								
Moderate milestones								
Sits without support								
Stands with assistance								
Walks with assistance								
Stands/walks unaided								
Dead								
SHAM GROUP (patients alive with data n=)								
From\To state	No milestones	Mild milestones	Moderate milestones	Sits without support	Stands with assistance	Walks with assistance	Stands/walks unaided	Dead
No milestones								
Mild milestones								
Moderate milestones								
Sits without support								
Stands with assistance								
Walks with assistance								
Stands/walks unaided								
Dead								

** No observed transitions from state during cycle; Blank cells indicate zero probability*
n - number

Table 38: Transition matrices for nusinersen (top) and sham (bottom), HINE-2 observed count data, ENDEAR trial, days 184-302 (taken from company's model)

NUSINERSEN GROUP (patients alive with data n=)								
From\To state	No milestones	Mild milestones	Moderate milestones	Sits without support	Stands with assistance	Walks with assistance	Stands/walks unaided	Dead
No milestones								
Mild milestones								
Moderate milestones								
Sits without support								
Stands with assistance								
Walks with assistance								
Stands/walks unaided								
Dead								
SHAM GROUP (patients alive with data n=)								
From\To state	No milestones	Mild milestones	Moderate milestones	Sits without support	Stands with assistance	Walks with assistance	Stands/walks unaided	Dead
No milestones								
Mild milestones								
Moderate milestones								
Sits without support								
Stands with assistance								
Walks with assistance								
Stands/walks unaided								
Dead								

** No observed transitions from state during cycle; Blank cells indicate zero probability*
n - number

Table 39: Transition matrices for nusinersen (top) and sham (bottom), HINE-2 observed count data, ENDEAR trial, days 303-394 (taken from company's model)

NUSINERSEN GROUP (patients alive with data n=[redacted])								
From\To state	No milestones	Mild milestones	Moderate milestones	Sits without support	Stands with assistance	Walks with assistance	Stands/walks unaided	Dead
No milestones	[redacted]	[redacted]	[redacted]					
Mild milestones	[redacted]	[redacted]	[redacted]					
Moderate milestones	[redacted]		[redacted]					
Sits without support			[redacted]	[redacted]	[redacted]			
Stands with assistance					[redacted]			
Walks with assistance						[redacted]		
Stands/walks unaided							[redacted]	
Dead								[redacted]
SHAM GROUP (patients alive with data n=[redacted])								
From\To state	No milestones	Mild milestones	Moderate milestones	Sits without support	Stands with assistance	Walks with assistance	Stands/walks unaided	Dead
No milestones	[redacted]							
Mild milestones		[redacted]						
Moderate milestones			[redacted]					
Sits without support				[redacted]				
Stands with assistance					[redacted]			
Walks with assistance						[redacted]		
Stands/walks unaided							[redacted]	
Dead								[redacted]

** No observed transitions from state during cycle; Blank cells indicate zero probability*
n - number

Table 40: Transition matrices for nusinersen (top) and sham (bottom), extrapolation based on CHOP INTEND score in ENDEAR trial, months 13-14 (taken from company's model)

NUSINERSEN GROUP (patients alive with data n=n/a)							
From\To state	No milestones	Mild milestones	Moderate milestones	Sits without support	Stands with assistance	Walks with assistance	Stands/walks unaided
No milestones	[redacted]						
Mild milestones		[redacted]	[redacted]				
Moderate milestones			[redacted]	[redacted]			
Sits without support				[redacted]	[redacted]		
Stands with assistance					[redacted]	[redacted]	
Walks with assistance						[redacted]	[redacted]
Stands/walks unaided							[redacted]
SHAM GROUP (patients alive with data n=n/a)							
From\To state	No milestones	Mild milestones	Moderate milestones	Sits without support	Stands with assistance	Walks with assistance	Stands/walks unaided
No milestones	[redacted]						
Mild milestones	[redacted]	[redacted]					
Moderate milestones		[redacted]	[redacted]				
Sits without support			[redacted]	[redacted]			
Stands with assistance				[redacted]	[redacted]		
Walks with assistance					[redacted]	[redacted]	
Stands/walks unaided						[redacted]	[redacted]

Blank cells indicate zero probability
n – number; n/a - not applicable

Table 41: Transition matrices for nusinersen (top) and sham (bottom), extrapolation based on CHOP INTEND score in ENDEAR trial, all 4-month cycles after month 14 (taken from company's model)

NUSINERSEN GROUP (patients alive with data n=n/a)							
From\To state	No milestones	Mild milestones	Moderate milestones	Sits without support	Stands with assistance	Walks with assistance	Stands/walks unaided
No milestones							
Mild milestones							
Moderate milestones							
Sits without support							
Stands with assistance							
Walks with assistance							
Stands/walks unaided							
SHAM GROUP (patients alive with data n=n/a)							
From\To state	No milestones	Mild milestones	Moderate milestones	Sits without support	Stands with assistance	Walks with assistance	Stands/walks unaided
No milestones							
Mild milestones							
Moderate milestones							
Sits without support							
Stands with assistance							
Walks with assistance							
Stands/walks unaided							

Blank cells indicate zero probability
n – number; n/a - not applicable

Probability of undergoing surgery for scoliosis and age at time of scoliosis surgery

The company's assumptions regarding scoliosis surgery are summarised in Table 42. The company's early onset model assumes that within the nusinersen group, 1% of surviving patients will undergo scoliosis surgery at year 12 if non-ambulant or at year 15 if ambulant. Twenty percent of patients receiving nusinersen who undergo scoliosis surgery are assumed to subsequently discontinue treatment. Within the usual care group, the model assumes that 1% of surviving patients will undergo scoliosis surgery at year 10 if non-ambulant or at year 15 if ambulant. The probabilities of undergoing scoliosis surgery and subsequently discontinuing nusinersen were based assumptions.[1] The timing of surgery appears to have been loosely based on a paper describing SMA and its management by Haaker and Fujak.[35]

Table 42: Scoliosis surgery parameters included in the early onset model

Parameter	Nusinersen	Usual care	Source
Percentage of patients undergoing surgery for scoliosis	1%	1%	Assumption[1]
Percentage of patients discontinuing nusinersen following scoliosis surgery	20%	n/a	Assumption[1]
Time of surgery since model start (non-ambulant)	12 years	10 years	Haaker and Fujak[35]
Time of surgery since model start (ambulant)	15 years	15 years	Haaker and Fujak[35]

HRQoL - patient utilities

Neither the ENDEAR trial nor the CHERISH trial included the use of a preference-based instrument to assess HRQoL. In addition, the company's review of published HRQoL studies[1] did not identify any suitable studies. The CS[1] highlights that the derivation of HRQoL estimates for patients with SMA is challenging due to the nature of the condition and the age of the population.

Initially, the company explored the use of a *de novo* case vignette study (Lloyd *et al*[46]) to estimate health utilities associated with each of the health states within the model. The company held interviews with five clinical experts to draft case studies representing each of the modelled health states. The company subsequently held further interviews with five clinical experts to value the health states using the EQ-5D-Y (using the adult EQ-5D tariff) and the PedsQL Neuromuscular Module. However, the valuations produced negative utility scores for most of the states and the CS states that some of the rankings of health state valuations were counterintuitive. Further details are given in the documentation relating to the expert advisory board meeting,[45] although the ERG notes that the issues relating to counterintuitive rankings relate to states which are not used in the company's final models (see clarification response,[1] question B5). As a consequence of the reservations raised by several of the clinical experts consulted, the company decided not to use these utilities within either the early onset or later onset models.

The clinical experts consulted by the company expressed a preference to instead use the PedsQL data collected as part of the CHERISH study in later onset SMA patients.[15] These data were mapped onto the EQ-5D using an algorithm published by Khan *et al.*[36] The PedsQL to EQ-5D mapping algorithm was estimated using data from a cross-sectional survey conducted in four secondary schools in England amongst children aged 11–15 years of age. The selected ordinary least squares (OLS) mapping algorithm was calculated relative to the EQ-5D utility for the general population based on a predictive equation with coefficients on age, the square of age and sex. The resulting mapped EQ-5D utility values were assumed to apply for later onset patients and were adapted for the early onset model based on an assumed correspondence of health states between early onset and later onset models (see Table 43).

Table 43: Patient utilities used in the early onset model

Early onset SMA model (HINE-2-based health states)	Later onset SMA model (HFMSE-based health states)	Mapped utility value
No milestones	Sits without support but does not roll	[redacted]
Mild milestones	Sits and rolls independently	
Moderate milestones	Sits and rolls independently	
Sits without support	Sits and crawls on hands and knees	
Stands with assistance	Stands or walks with assistance	
Walks with assistance	Stands without assistance	
Stand or walks without assistance	Walks without assistance	

SMA – spinal muscular atrophy; HINE-2 - Module 2 of the Hammersmith Infant Neurological Examination; HFMSE - Hammersmith Functional Motor Scale-Expanded

HRQoL – caregiver disutilities

The early onset model includes disutilities for caregivers of SMA patients; these are assumed to be dependent on the motor milestones achieved by the patient during each model cycle. Caregiver disutilities were calculated using: (i) the mean caregiver EQ-5D score reported in a cross-sectional study of patients with SMA in France, Germany, Spain and United Kingdom (Bastida *et al*[37]); (ii) an estimate of the mean utility of the general population[38] (assuming a constant age of 30.88 years, 80% female) and (iii) the mapped patient utilities estimated for each health state (see Table 43). The company first estimated health utilities for caregivers conditional on the patient's health state by subtracting the difference in patient utilities between selected HINE-2 health states from the baseline caregiver utility reported by Bastida *et al*.[37] Caregiver disutilities were then calculated by subtracting the caregiver utility estimate from the mean general population utility estimate. The derivation of each health state-specific disutility is shown in Table 44.

Table 44: Parent/carer utilities used in the early onset model

HINE-2 health state	Patient utility	Caregiver utility	Caregiver disutility*	Calculation and assumptions
(i) No milestones	[redacted]	[redacted]	[redacted]	Bastida *et al*[37] baseline caregiver utility minus difference between State (ii) Mild milestones and State (i) No milestones states
(ii) Mild milestones	[redacted]	[redacted]	[redacted]	Based directly on Bastida *et al*[37] caregiver utility
(iii) Moderate milestones	[redacted]	[redacted]	[redacted]	Based directly on Bastida *et al*[37] caregiver utility
(iv) Sits without support	[redacted]	[redacted]	[redacted]	Bastida *et al*[37] baseline caregiver utility minus difference between State (ii) Moderate milestones and State (iv) Sits without support
(v) Stands with assistance	[redacted]	[redacted]	[redacted]	Bastida *et al*[37] baseline caregiver utility minus difference between State (iii) Moderate milestones states and State (v) Stands with assistance
(vi) Walks with assistance	[redacted]	[redacted]	[redacted]	Assumed to be the same as State (v) Stands with assistance
(vii) Stand or walks without assistance	[redacted]	[redacted]	[redacted]	Assumed to be the same as State (v) Stands with assistance
Baseline parameters				
Bastida *et al*[37] caregiver utility		[redacted]	-	-
General population utility[38]		0.92	-	Caregiver age=30.88 years, 80% female
Bereavement		-	-0.04	-

** Calculated as general population utility minus caregiver utility*

Resource use and costs

The company's early onset model includes the following cost components: (i) nusinersen acquisition and administration costs; (ii) health state costs and (iii) end-of-life costs.

Drug acquisition and administration costs

The acquisition cost for nusinersen is £75,000 per vial.[1, 13]

The company's model assumes that nusinersen is administered via lumbar puncture. Forty percent of all nusinersen administrations are assumed to be given in an inpatient setting, 30% are assumed to be given in an outpatient setting and the remaining 30% are assumed to be given in a day case setting. The costs for lumbar puncture were taken from NHS Reference Costs 2015/2016[39] using HRG codes HC72A (Diagnostic Spinal Puncture, 19 years and over), HC72B (Diagnostic Spinal Puncture, between 6 and 18 years) and HC72C (Diagnostic Spinal Puncture, 5 years and under). The company calculated weighted mean administration costs of £1,359 for patients aged 5 years and under, £1,295 for those aged between 6 and 18 years and £606 for those aged 19 years and over (see Table 45).

Table 45: Estimated nusinersen administration costs

Description	Mean cost	NHS Reference Costs 2015/16 code[39]
Age 5 years and under		
Inpatient	£1,690	EL - HC72C
Outpatient	£577	OPROC - HC72C (service code 421)
Day case	£1,700	DC - HC72C
Weighted mean cost	**£1,359**	
Age 6 to 18 years		
Inpatient	£1,658	EL - HC72B
Outpatient	£560	OPROC - HC72B (service code 421)
Day case	£1,546	DC - HC72B
Weighted mean cost	**£1,295**	
Age 18 years and over		
Inpatient	£918	EL - HC72A
Outpatient	£204	OPROC - HC72A (service code 400)
Day case	£593	DC - HC72AB
Weighted mean cost	**£606**	

EL - elective inpatient; OPROC - outpatient procedures; DC - day case

Health state costs

Health state costs were based on data from the cross-sectional SMA study reported by Bastida *et al.*[37] Within this study, the main caregivers of children/adolescents diagnosed with SMA completed a self-administered questionnaire providing information related to sociodemographics, the costs of professional private care, the need for informal care, expenditure and resource utilisation related to SMA.[1] The company took the health state costs data from Bastida *et al*[37] (reported Euros, year 2014) and converted these values to Pounds Sterling (year 2016) using an exchange rate also provided in Bastida *et al*[37] and changes in consumer prices between 2014 and 2016 (see Table 46).

Table 46: Estimated annual costs by category of resource use in Type I, II and III SMA patients (reproduced from CS Table 41)

Description	Type I SMA		Type II SMA		Type III SMA	
	€ 2014	£ 2016	€ 2014	£ 2016	€ 2014	£ 2016
Drugs	[redacted]					
Medical tests						
Medical visits						
Hospitalisations						
GP & emergency						
Health material						
Social services						
Total						

SMA – spinal muscular atrophy

The data provided by Bastida *et al*[37] were divided into a number of resource classifications: drugs; medical tests; medical visits; hospitalisations; general practitioner (GP) & emergency visits, health material and social services; a brief description of what is included in each of these classifications is provided below:

- Drugs - costs for drugs such as creatine, gabapentin, hydroxyurea, vitamin supplements and calcium.
- Medical tests - costs associated with blood tests, urinalysis, electrocardiogram, magnetic resonance imaging, range of motion tests, spirometry and x-rays of the chest, back and hip.
- Medical visits - costs associated with home visits and hospital outpatient appointments with urologist, neurologist, psychiatrist, dermatologist, nephrologist, respiratory consultant, nutritionist, occupational therapist, traumatologist, specialists in palliative care and respiratory physiotherapist.
- Hospitalisations - costs associated with any hospital inpatient treatment.
- GP & emergency - costs related to appointments with GP, practice nurses or emergency treatments.
- Health material - costs associated with the provision of orthosis, prosthesis, wheelchairs, adjustable beds, shower chairs, humidifiers, portable oxygen, food supplements and gastric feeding cannulas, pulse oximetry and communication aids.
- Social services - costs associated with care provided by a day centre or occupational centre, respiratory physiotherapists, occupational physiotherapists, psychosocial care for the family are respite care in residential centres.[1]

The company then divided each of these costs according to four main therapy areas using proportions based either on expert medical opinion or assumptions (see Table 47).

Table 47: Allocation of costs by resource classification

Description	Respiratory care	Gastrointestinal care	Nutritional care	Orthopaedic care
Drugs	50%	50%	0%	0%
Medical tests	25%	25%	25%	25%
Medical visits	[redacted]	[redacted]	[redacted]	[redacted]
Hospitalisations	[redacted]	[redacted]	[redacted]	[redacted]
GP & emergency	[redacted]	[redacted]	[redacted]	[redacted]
Health material	25%	25%	25%	25%
Social services	25%	25%	25%	25%

This was done for each of the three types of SMA. The company applied the estimated costs for each SMA type to health states describing outcomes consistent with those SMA types (see Table 48).

Table 48: Annual health state costs, early onset model

Cost component	Milestones consistent with Type I SMA (State [i] No milestones; State [ii] Mild milestones; State [iii] Moderate milestones)	Milestones consistent with Type II SMA (State [iv] Sits without support; State [v] Stands with assistance; State [vi] Walks with assistance)	Milestones consistent with Type III SMA (State [vii] Stands/walks unaided).
Respiratory care	[redacted]	[redacted]	[redacted]
Gastrointestinal care	[redacted]	[redacted]	[redacted]
Nutritional care	[redacted]	[redacted]	[redacted]
Orthopaedic care	[redacted]	[redacted]	[redacted]
Total	[redacted]	[redacted]	[redacted]

The ERG notes that the company's approach to breaking down the costs by type of care is irrelevant as the sum of the costs shown in Table 48 (after manipulation) is the same as the sum of the costs presented in Table 46 (before manipulation).

End-of-life costs

The company's early onset model includes a once-only end-of-life cost of £11,839. The source of this cost is not described in the CS;[1] text contained in the executable model indicates that this value was informed by NICE Guideline 61.[40]

5.3.4 Methods for model evaluation

The CS[1] presents the results of the early onset model in terms of the incremental cost per QALY gained for nusinersen versus usual care. Separate results are presented for: (i) analyses including patient health gains only and (ii) analyses including patient health gains and caregiver QALY losses. The company's base case incremental cost-effectiveness ratios (ICERs) are based on the deterministic version of the model. The CS also includes the results of probabilistic sensitivity analysis (PSA), deterministic sensitivity analyses (DSAs), scenario analyses and subgroup analyses. The results of the PSA are presented in the form of a cost-effectiveness plane and cost-effectiveness acceptability curves (CEACs), based on 1,000 Monte Carlo simulations. The probabilistic ICER is also presented. The distributions applied in the company's PSA are summarised in Table 49. The results of the DSAs are presented in the form of a tornado diagram for specified model parameters. Scenario analyses were undertaken to explore the impact of alternative time horizons, and alternative assumptions surrounding mortality risk, transition probabilities, costs and HRQoL.

Table 49: Distributions used in company's PSA, early onset model

Parameter group	Distribution	ERG comment
Initial HINE-2 health state distribution - nusinersen	Fixed	These parameters are subject to uncertainty. Given the multinomial nature of the data, a Dirichlet distribution (applied to the combined ENDEAR population) would be appropriate.
Initial HINE-2 health state distribution – usual care	Fixed	
Overall survival – nusinersen early onset SMA	Multivariate normal	The adjustment factor for Type II mortality in the better states is fixed at its mean value.
Overall survival – usual care early onset SMA	Multivariate normal	-
Transition probabilities – nusinersen (up to month 13)	Dirichlet	Priors are included for some but not all unobserved transitions.
Transition probabilities – usual care (up to month 13)	Dirichlet	
Transition probabilities – nusinersen (month 14 onwards)	Dirichlet	
Transition probabilities – usual care (month 14 onwards)	Dirichlet	
Probability of undergoing surgery for scoliosis	Beta	Inappropriately characterised using treatment-specific parameters.
Age at time of surgery	Normal	Inappropriately characterised using treatment-specific parameters.
Probability of discontinuing nusinersen after surgery for scoliosis	Beta	-
Patient utilities	Beta	All utilities sampled using the same random number, thereby inducing over-correlation between states.[47]
Baseline caregiver utilities	Beta	No uncertainty is included in the Bastida *et al*[37] baseline caregiver disutility.
Nusinersen acquisition cost	Fixed	-
Nusinersen administration costs	Normal (cost) and Dirichlet (administration setting)	-
Health state costs	Gamma	-

HINE-2 – Module 2 of the Hammersmith Infant Neurological Examination; ERG – Evidence Review Group

5.3.5 Company's model results – early onset model

This section presents the results of the company's early onset model, evaluated over a 60-year time horizon.

Central estimates of cost-effectiveness – early onset model

Table 50 presents the central estimates of cost-effectiveness derived from the company's model (including health gains accrued by patients only). Based on a re-run of the probabilistic version of the model by the ERG, nusinersen is expected to generate an additional 5.29 QALYs at an additional cost

of £2,160,048 per patient; the corresponding ICER for nusinersen versus usual care is £408,712 per QALY gained. The deterministic version of the model produces a similar ICER of £407,605 per QALY gained for nusinersen versus usual care. The inclusion of caregiver QALY losses (see Table 51) leads to a slightly lower probabilistic ICER of £404,270 per QALY gained; the deterministic ICER is estimated to be £402,361 per QALY gained.

Table 50: Company's model results, early onset model (including patient health gains only)

Probabilistic model					
Option	**QALYs**	**Costs**	**Inc. QALYs**	**Inc. Costs**	**Incremental cost per QALY gained**
Nusinersen	7.73	£2,229,863	5.29	£2,160,048	**£408,712**
Usual care	2.45	£69,814.82	-	-	-
Deterministic model					
Option	**QALYs**	**Costs**	**Inc. QALYs**	**Inc. Costs**	**Incremental cost per QALY gained**
Nusinersen	7.86	£2,258,852	5.37	£2,187,311	**£407,605**
Usual care	2.49	£71,540	-	-	-

Inc. - incremental; QALY - quality-adjusted life year

Table 51: Company's model results, early onset model (including patient health gains and caregiver QALY losses)

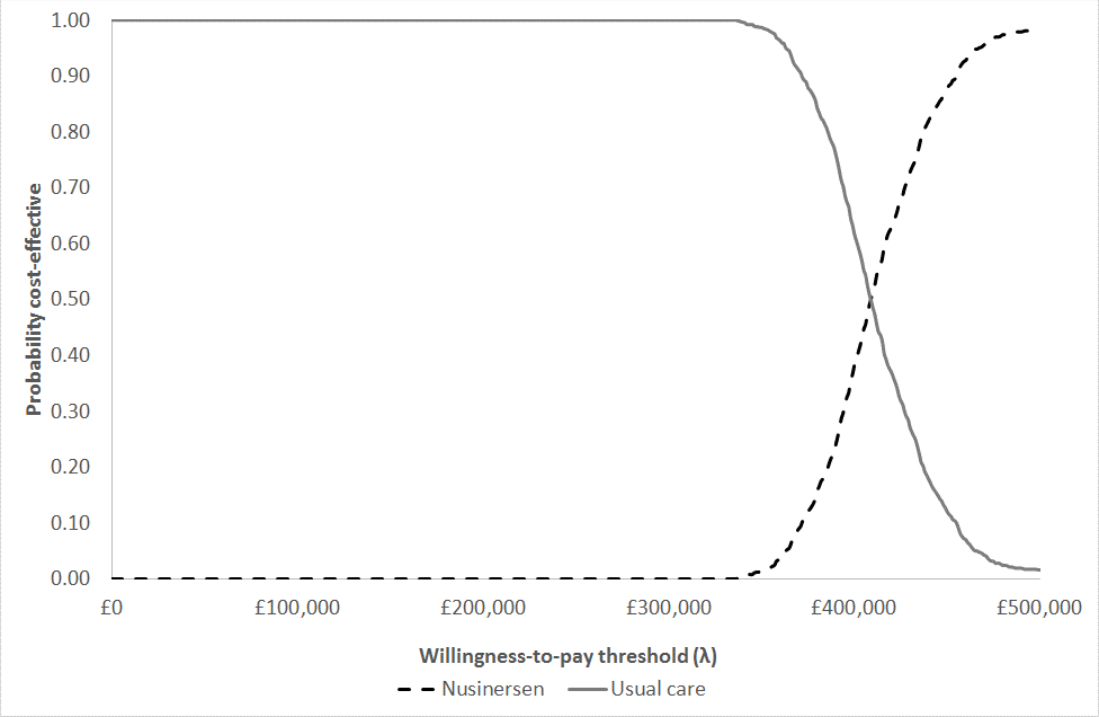
Probabilistic model					
Option	**QALYs**	**Costs**	**Inc. QALYs**	**Inc. Costs**	**Incremental cost per QALY gained**
Nusinersen	7.49	£2,229,863	5.34	£2,160,048	**£404,270**
Usual care	2.14	£69,814.82	-	-	-
Deterministic model					
Option	**QALYs**	**Costs**	**Inc. QALYs**	**Inc. Costs**	**Incremental cost per QALY gained**
Nusinersen	7.61	£2,258,852	5.44	£2,187,311	**£402,361**
Usual care	2.17	£71,540	-	-	-

Inc. - incremental; QALY - quality-adjusted life year

Company's probabilistic sensitivity analysis - early onset model

Figure 8 presents CEACs for nusinersen and usual care for the early onset population. As shown in the figure, the probability that nusinersen produces more net benefit than usual care at willingness-to-pay (WTP) thresholds below £337,000 per QALY gained is approximately zero.

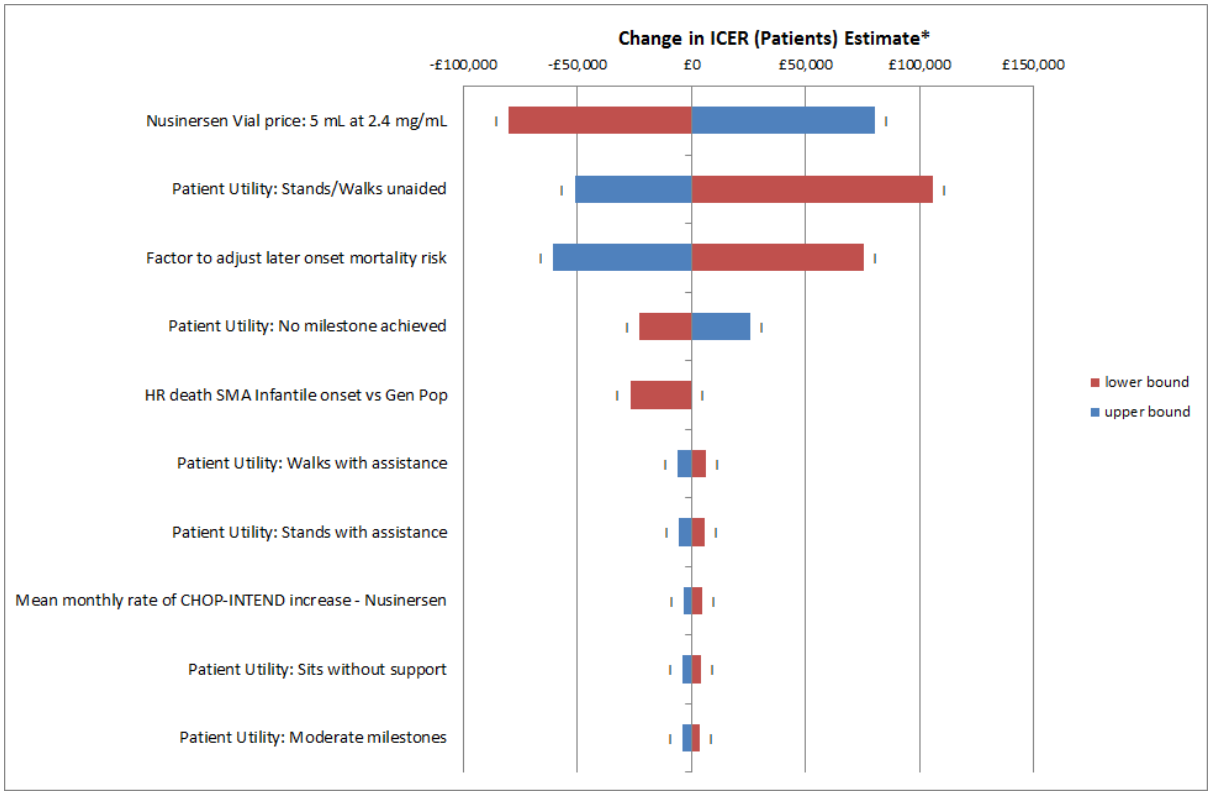
Figure 8: CEACs, early onset model, patient health gains only



Company's deterministic sensitivity analyses - early onset model

Figure 9 presents the results of the company's DSAs in the form of a tornado diagram (change in ICER from baseline). As shown in the figure, the most influential model parameters relate to the acquisition cost of nusinersen, the health utility associated with State (vii) Stands/walks unaided, and the Type II SMA mortality adjustment factor applied to the better health states. The lowest ICER generated from the company's one-way DSAs is £327,347 per QALY gained (nusinersen vial price=£60,000) whilst the highest ICER is £513,324 per QALY gained (health utility State [vii] Stands/walks unaided = [redacted]).

Figure 9: Company's DSA tornado diagram, early onset model, patient health gains only



CHOP INTEND - Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders; ICER – incremental cost-effectiveness ratio; HR – hazard ratio

Scenario analysis results - early onset model

Table 52 details the results of the company's scenario analyses. As shown in the table, the early onset model is very sensitive to the assumptions regarding the Type II mortality adjustment applied to States (iv) to (vii). The lowest ICER for nusinersen versus usual care is estimated to be £347,082 per QALY gained when only patient health gains are considered, and £345,578 per QALY gained when caregiver QALY losses are included (mortality adjustment factor=1.00). The highest ICER for nusinersen versus usual care is estimated to be £872,257 per QALY gained, when only patient health gains are considered, and £802,469 per QALY gained when caregiver QALY losses are included (mortality adjustment factor=0.00).

Table 52: Scenario analysis results, early onset model

Scenario	ICER (patient health gains only)	ICER (patient health gains and caregiver QALY losses)
Base case (deterministic)	£407,605	£402,361
Time horizon=10 years	£564,659	£543,695
Time horizon=20 years	£436,278	£428,375
Time horizon=30 years	£410,888	£405,315
Do not apply higher long-term risk of death based on SMA Type I - adjusted general mortality rates	£380,658	£376,357
OS beyond trial follow-up based on Zerres 1995 + 2 knots & 60-year time horizon	£379,804	£376,289
OS treatment effects - taper HR to 1.0 over 12 months	£405,766	£400,680
Apply discontinuation to State (i) No milestones and State (ii) Mild milestones	£406,096	£402,138
Do not apply Type II mortality rates from Zerres *et al* to patients in motor milestones characteristic of later onset	£872,257	£802,469
Mortality risk factor=0.50	£578,554	£556,339
Mortality risk factor=1.00	£347,082	£345,578
Assumption that proportion of patients on treatment reach a plateau (0% worsen)	£417,355	£412,445
Assumption that proportion of patients on treatment reach a plateau (10% worsen)	£421,445	£417,806
Source for usual care arm CHOP INTEND rate of decline - Finkel *et al*. 2012	£407,315	£402,328
All nusinersen administration inpatient	£409,438	£404,170
All nusinersen administration day case	£409,015	£403,752
Health state costs include costs of major clinical events only	£442,838	£437,140
Cost source – Klug *et al*	£405,194	£399,980
Patient utility based on vignettes	£421,703	£394,298
Patient utility based on Bastida upper bound	£450,353	£476,009
Patient utility based on Bastida lower bound	£503,295	£788,019
Patient utility based on PedsQL type 2 (<25 months disease duration)	£387,628	£364,333

SMA - spinal muscular atrophy; OS - overall survival; CHOP INTEND - Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders; PedsQL - Paediatric Quality of Life Inventory; ICER – incremental cost-effectiveness ratio

Subgroup analysis - early onset model

Table 53 presents the results of the company's subgroup analysis based on disease duration (≤12 weeks and >12 weeks). It should be noted that the results of the subgroup analyses presented in the CS[1] are incorrect and should be disregarded; the results presented in Table 53 are based on additional information provided by the company following the clarification process.[3]

Table 53: Subgroup analysis results, early onset model

Subgroup	ICER (patient health gains only)	ICER (patient health gains and caregiver QALY losses)
ITT population, each arm (base case)*	£407,605	£402,361
ITT population, both arms (base case)†	£409,235	£404,015
≤12 weeks disease duration each arm*	£375,237	£370,915
≤12 weeks disease duration both arms†	£375,775	£371,458
>12 weeks disease duration each arm*	£484,614	£473,247
>12 weeks disease duration both arms†	£485,766	£474,355

** "thresholds" defining HINE-2 health states based on mean CHOP INTEND scores in each treatment group;*
† "thresholds" defining HINE-2 health states based on mean CHOP INTEND scores across both treatment groups
ITT – intention-to-treat; ICER – incremental cost-effectiveness ratio; QALY – quality-adjusted life year

5.4 Later onset model – methods and results

5.4.1 Model structure and logic – later onset model

The company's later onset model follows a conceptual design which is broadly similar to the early onset model described in the previous section (see Figure 10). The later onset model adopts a state transition approach based on health states defined according to the HFMSE instrument.[48] The later onset model includes seven health states: (i) Sits without support but does not roll; (ii) Sits and rolls independently; (iii) Sits and crawls with hands and knees; (iv) Stands/walks with assistance; (v) Stands unaided; (vi) Walks unaided and (vii) Dead. The domains of the HFMSE are presented in Appendix 3. The classification of health states within the company's later onset model according to HFMSE scores is summarised in Table 54.

Figure 10: Company's later onset model structure (reproduced from CS, Figure 43)

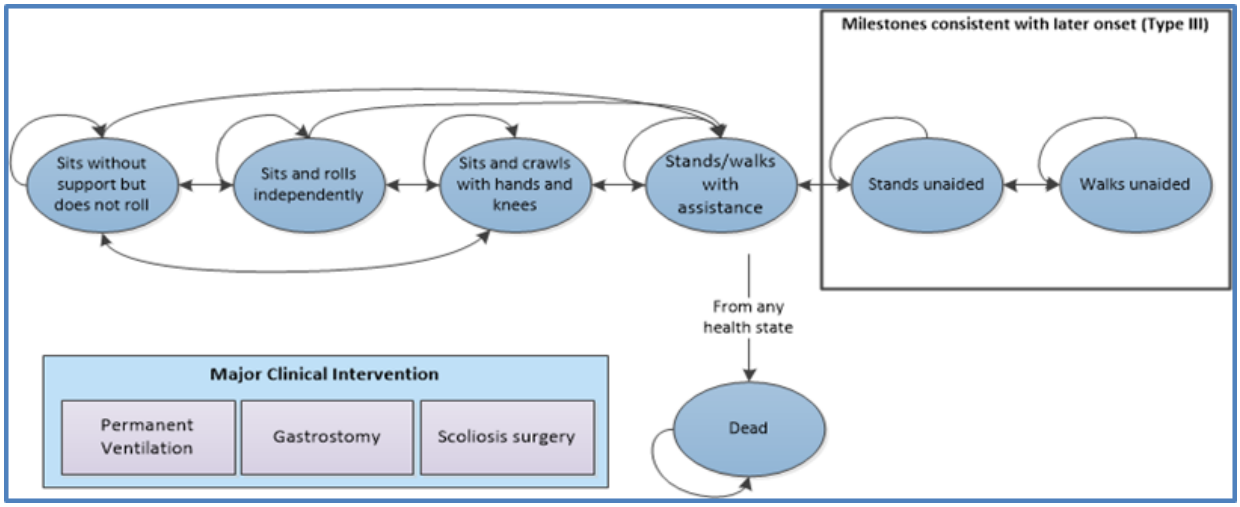


Table 54: Model health states according to HFMSE score (adapted from CS, Figure 43 footnotes)

Model health state	HFMSE criteria for model health state
(i) Sits without support but does not roll	Patients sit according to the WHO criteria and have a score <2 in Rolls Prone to Supine right and left in HFMSE score
(ii) Sits and rolls independently	Patients sit according to the WHO criteria and have a score of 2 in Rolls Prone to Supine right or Rolls Prone to Supine left in HFMSE score
(iii) Sits and crawls with hands and knees	Based on WHO criteria (see Appendix 3)
(iv) Stands/walks with assistance	
(v) Stands unaided	
(vi) Walks unaided	

WHO – World Health Organization

Model logic

The logic of the company's later onset model is described in the sections below.

Nusinersen group

Patients enter the model based on the baseline HFMSE health state distribution for the nusinersen group in the CHERISH study.[15] During the first five model cycles (up to the end of month 15), mortality risk is assumed to be zero, based on the observed number of deaths within the nusinersen group of CHERISH. From model entry until the end of month 15, transitions between the six HFMSE-based health states are governed by five cycle-specific transition matrices derived from observed count data within CHERISH.

From the end of month 15 to the end of month 623, mortality is modelled using a 2-knot Royston-Parmar spline model fitted to survival data for Type II patients reported by Zerres *et al*[33] (the same data used in the early onset model); beyond this timepoint, mortality is modelled using an HR-adjusted Gompertz function fitted to general population mortality data[32] (HR=26.41). This time-dependent 3-stage Type II SMA mortality function (zero risk [CHERISH]→2-knot spline [Zerres]→ HR-adjusted Gompertz[general population, HR=26.41]) is applied to all patients in the four worst health states (State [i] Sits without support but does not roll; State [ii] Sits and rolls independently; State [iii] Sits and crawls with hands and knees and State [iv] Stands/walks with assistance). Mortality risk for patients in the two better health states (State [vi] Stands unaided and State [vii] Walks unaided) is adjusted by a factor of 0.50 to reflect an assumption of improved survival associated with Type III SMA based on a Gompertz model fitted to general population mortality data (without HR adjustment).[32] After the end of month 15, all health state transitions are governed by a single transition matrix estimated using the HFMSE scores observed within the CHERISH trial,[15] Study CS2 and Study CS12.[25] This matrix permits nusinersen-treated patients to either remain in their current state or move to the next best health state, but does not allow for the deterioration of any patient's motor function from this timepoint onwards. Patients are assumed to discontinue nusinersen if they do not achieve milestones better than State (i) Sits without

support but does not roll by the end of month 15, or if they undergo scoliosis surgery (at year 12 for non-ambulatory patients and year 15 for ambulatory patients) and cannot subsequently undergo administration of nusinersen via lumbar puncture. Patients who discontinue nusinersen due to lack of efficacy are assumed to remain in State (i) Sits without support but does not roll state until death. Patients who discontinue nusinersen following scoliosis surgery are assumed to subsequently follow the post-trial transition matrix for the sham group.[3]

Usual care group

Patients enter the model based on the baseline HFMSE health state distribution for the sham group in CHERISH.[15] During the first five model cycles (up to the end of month 15), mortality risk is assumed to be zero, based on the observed number of deaths within the sham group of CHERISH. From model entry until the end of month 15, transitions between the six HFMSE-based health states are governed by five cycle-specific transition matrices derived from observed count data within CHERISH.

From month 15 onwards, mortality is modelled using the same data and assumptions as those applied within the nusinersen group, including the survival advantage assumed for States [v] and [vi]. After the end of month 15, all health state transitions are governed by a single transition matrix estimated using the HFMSE scores observed within CHERISH,[15] Study CS2 and Study CS12.[25] This matrix permits patients on usual care to either remain in their current state or to transit to the next worst health state, but does not allow for the improvement of any patient's motor function from this timepoint onwards (hence the survival advantage in the better two states only applies to those already in those states by the end of month 15). A proportion of patients are assumed to undergo scoliosis surgery at year 10 if non-ambulant and at year 15 if ambulant; however, this does not impact on the patient's health state occupancy, HRQoL or costs.

Estimation of health outcomes, costs and cost-effectiveness

Separate utilities are applied to each modelled health state. QALYs accrued by patients in each group are estimated by applying a vector of health utilities to the probability of being in each state during each model cycle. QALY losses for caregivers are estimated based on the patient's health state (including a QALY loss for bereavement). Analyses are presented separately which include/exclude caregiver QALY losses.

The model includes the following cost components: (i) acquisition and administration costs for nusinersen and (ii) health state costs, including respiratory, gastrointestinal, nutritional and orthopaedic care (conditional on motor milestones). In contrast with the early onset model, end-of-life care costs are not included.

Incremental cost-effectiveness is calculated in a pairwise fashion based on the difference in costs divided by the difference in QALYs for nusinersen and usual care.

5.4.2 Structural assumptions – later onset model

(i) Treatment using nusinersen is assumed to be discontinued if the patient has not progressed beyond State (i) Sits without support but does not roll state after 15 months. As with the early onset model, this assumption is applied only once as patients receiving nusinersen are assumed never to transit to this state after this timepoint (see assumption [v]).

(ii) A proportion of patients discontinue nusinersen following scoliosis surgery.

(iii) Patients cannot die in either treatment group until after month 15.

(iv) After month 15, an adjustment is applied to reflect improved survival for patients in State (v) Stands unaided and State (vi) Walks unaided. These patients are allocated 50% of the mortality risk for Type III SMA and 50% of the mortality risk for Type II SMA. Unlike the early onset model, this adjustment is applied to both the nusinersen and usual care groups.

(v) After month 15, patients receiving nusinersen are assumed never to transit to a worse health state; rather, during any model cycle, they can either remain in their current health state or transit to the next best health state. Beyond this timepoint, transition probabilities are based on the mean rate of improvement in HFMSE score within CHERISH and the mean HFMSE score within each model health state for the nusinersen group over the course of the CHERISH trial and Studies CS2 and CS12. The rate of improvement in HFMSE score is assumed to be constant with respect to time and monotonic across health states.

(vi) After month 15, patients receiving usual care are assumed never to transit to an improved health state; rather, during any model cycle, they can either remain in their current health state or transit to the next worst health state. Beyond this timepoint, transition probabilities are based on the mean rate of worsening in HFMSE score within CHERISH and the mean HFMSE scores within each model health state for the usual care group over the course of the CHERISH trial and Studies CS2 and CS12. The rate of worsening in HFMSE score is assumed to be constant with respect to time and monotonic across health states.

(vii) A proportion of ambulant patients undergo scoliosis surgery after 15 years.

(viii) The CS[1] states that the model assumes that a proportion of non-ambulant patients undergo scoliosis surgery at 12 years. However, the implemented model assumes that scoliosis surgery may occur at 10 years for the usual care group. As separate costs and utility changes for scoliosis surgery are not included in the model, this does not impact on the model results.

(ix) Treatment costs are grouped according to milestones consistent with Type II SMA ([i] Sits without support but does not roll; [ii] Sits and rolls independently; [iii] Sits and crawls with hands and knees; [iv] Stands/walks with assistance) and Type III SMA ([v] Stands unaided; [vi] Walks unaided).

(x) The model does not include additional HRQoL impacts or costs associated with AEs. The CS notes that the ENDEAR trial did not observe any treatment-related AEs.

5.4.3 Evidence used to inform model parameters – later onset model

The main groups of parameters for the later onset model and the evidence used to inform these are summarised in Table 55. These are discussed in further detail in the subsequent sections.

Table 55: Evidence used to inform the company's later onset model

Parameter group	Evidence source
Initial HFMSE health state distribution – nusinersen	Observed initial HFMSE distribution in the nusinersen group of CHERISH[15]
Initial HFMSE health state distribution – usual care	Observed initial HFMSE distribution in the sham group of CHERISH[15]
Overall survival – nusinersen	Zero risk (based on CHERISH) switching (after month 15) to a 2-knot Royston-Parmar spline model fitted to data reported by Zerres *et al*[33] switching (after month 623) to an HR-adjusted general population Gompertz model (HR=26.41).[32] For States (v) and (vi), after month 15, an adjustment of 0.50 is applied to reflect improved survival for Type III SMA based an unadjusted general population Gompertz model.[32]
Overall survival – usual care	Health state-dependent mortality probabilities are the same as those for the nusinersen group
Transition probabilities – nusinersen (up to month 15)	Observed HFMSE count data from CHERISH[15] (without imputation)
Transition probabilities – usual care (up to month 15)	Observed HFMSE count data from CHERISH[15] (without imputation)
Transition probabilities – nusinersen (month 16 onwards)	Estimated mean rate of improvement for nusinersen group in HFMSE and mean HFMSE scores in CHERISH[15] (supplemented using data from Study CS2 and Study CS12[25])
Transition probabilities – usual care (month 16 onwards)	Estimated mean rate of worsening for sham group in HFMSE and mean HFMSE scores in CHERISH[15] (supplemented using data from Study CS2 and Study CS12[25])
Probability of undergoing surgery for scoliosis and age at time of surgery	Probability based on estimate for scoliosis surgery in Type II SMA reported by Bladen *et al.*[49] Timing of surgery loosely based on Haaker and Fujak.[35]
Probability of discontinuing nusinersen after surgery for scoliosis	Assumption[1]
Patient utilities	PedsQL data collected in CHERISH[15] mapped to the EQ-5D using a published algorithm reported by Khan *et al*[36]
Baseline caregiver utilities	Baseline caregiver utility based on Bastida *et al.*[37] Caregiver disutilities by health state estimated using Ara and Brazier[38] and mapped patient utilities from CHERISH.[15]
Nusinersen acquisition cost	CS[1]
Nusinersen administration costs	NHS Reference Costs 2015/16[39]
Health state costs	Bastida *et al*[37]
End-of-life care costs	Not included in model

HFMSE - Hammersmith Functional Motor Scale-Expanded; HR – hazard ratio; SMA – spinal muscular atrophy; EQ-5D – Euroqol 5-Dimensions; CS – company's submission

Overall survival –later onset SMA

OS was modelled using similar approach to that adopted for the early onset model with separate sources used to inform each of the two different sections of the modelled time horizon. The overall modelling approach is summarised in Table 56. The company assumed that mortality risk for patients achieving State (v) Stands unaided and State (vi) Walks unaided would be between that of Type II SMA patients and the general population.

Model fit statistics for the Zerres *et al* data[33] and general population mortality data have been previously described in Section 5.2.4.

Table 56: Summary of survival models applied for extrapolation of overall survival

Time period	Both treatment groups	
	States (i) to (iv)	**States (v) and (vi)**
Month 0 to Month 15	CHERISH **No deaths**	
OS time period 1 Month 16 To Month 623	Zerres *et al*[33*] **2-knot spline**	Zerres *et al*[33*] **2-knot spline (weight 0.5)** UK general population mortality **unadjusted Gompertz** **(weight 0.5)**
OS time period 2 Month 623 to Month 960	UK general population mortality **HR-adjusted Gompertz** **(HR=26.4)**	UK general population mortality **unadjusted Gompertz** **(weight 0.5)** **HR-adjusted Gompertz** **(HR=26.4, weight 0.5)**

** N= 240, Type II SMA replicated from KM, no adjustment*
OS – overall survival; HR – hazard ratio

Transition probabilities

Similar to the early onset model, transition probabilities for the later onset model were estimated using different approaches for the observed period of CHERISH[15] and for subsequent cycles. Within the observed period, transitions were based directly on observed HFMSE count data for each treatment group. Separate matrices were calculated for five cycles (day 1-92, day 93-169, day 170-274, day 275-365 and day 366-456). All patients remained alive and none were lost to follow-up over the course of the trial.

Beyond the end of study follow-up, a single treatment-specific transition matrix is applied for all subsequent 4-monthly cycles. In contrast to the early onset model which attempts to map from the HINE-2 to CHOP INTEND, the later onset model uses HFMSE data from CHERISH to estimate milestone achievement/loss within the unobserved period (additional data from Study CS2 and CS12 were also used for State [vi] Walks unaided). Transition probabilities for patients in the nusinersen and

usual care groups were calculated using Equation [vi] and Equation [vii], respectively. The data used to estimate these transition probabilities are shown in Table 57.

$$TP\ (nusinersen)\ = MIN[1{,}1 + \left(\frac{Rate\ HFMSE\ increase\ (per\ month)\ .\ cycle\ length\ (months)}{Mean\ HFMSE\ next\ best\ state - Mean\ HFMSE\ current\ state}\right) \quad \text{[vi]}$$

$$TP(usual\ care)\ = MIN[1{,}1 + \left(\frac{Rate\ HFMSE\ decrease\ (per\ month)\ .\ cycle\ length\ (months)}{Mean\ HFMSE\ current\ state - Mean\ HFMSE\ next\ worst\ state}\right) \quad \text{[vii]}$$

Table 57: HFMSE data used to inform transition probabilities after month 15

MEAN HFMSE SCORE			
HFMSE health state	**Nusinersen**	**Sham**	**Source**
Sits without support but does not roll	17.7	15.9	CHERISH[15]
Sits and rolls independently	24.6	24.0	
Sits and crawls with hands and knees	34.5	26.7	
Stands/walks with assistance	38.4	26.7	
Stands unaided	40.3	31.5	
Walks unaided	51.0	38.8	CHERISH,[15] CS2 and CS12[25]
RATE OF IMPROVEMENT/WORSENING			
	Nusinersen	**Sham**	
Monthly HFMSE rate	[redacted]	[redacted]	CHERISH[15]

HFMSE - Hammersmith Functional Motor Scale-Expanded

Estimated transition probabilities for the first five model cycles (based on the observed count data from CHERISH) are shown in Table 58, Table 59, Table 60, Table 61 and Table 62. Table 63 presents the transition matrices applied for each 4-month cycle after the end of month 15.

Table 58: Transition matrices for nusinersen (top) and sham (bottom), HFMSE observed count data, CHERISH trial, days 1-92

NUSINERSEN GROUP (patients alive with data n=[redacted])							
From\To state	Sits without support but does not roll	Sits and rolls independently	Sits and crawls with hands and knees	Stands/walks with assistance	Stands unaided	Walks unaided	Dead
Sits without support but does not roll	[redacted]	[redacted]		[redacted]			
Sits and rolls independently	[redacted]	[redacted]					
Sits and crawls with hands and knees	[redacted]		[redacted]				
Stands/walks with assistance		[redacted]		[redacted]	[redacted]		
Stands unaided					[redacted]		
Walks unaided						[redacted]	
Dead							[redacted]
SHAM GROUP (patients alive with data n=[redacted])							
From\To state	Sits without support but does not roll	Sits and rolls independently	Sits and crawls with hands and knees	Stands/walks with assistance	Stands unaided	Walks unaided	Dead
Sits without support but does not roll	[redacted]	[redacted]					
Sits and rolls independently	[redacted]	[redacted]					
Sits and crawls with hands and knees		[redacted]	[redacted]				
Stands/walks with assistance				[redacted]	[redacted]		
Stands unaided				[redacted]	[redacted]	[redacted]	
Walks unaided						[redacted]	
Dead							[redacted]

** No observed transitions from state during cycle; Blank cells indicate zero probability*
N - number

Table 59: Transition matrices for nusinersen (top) and sham (bottom), HFMSE observed count data, CHERISH trial, days 93-169

NUSINERSEN GROUP (patients alive with data n=[redacted])							
From\To state	Sits without support but does not roll	Sits and rolls independently	Sits and crawls with hands and knees	Stands/walks with assistance	Stands unaided	Walks unaided	Dead
Sits without support but does not roll	[redacted]	[redacted]	[redacted]	[redacted]			
Sits and rolls independently	[redacted]	[redacted]	[redacted]	[redacted]			
Sits and crawls with hands and knees			[redacted]				
Stands/walks with assistance				[redacted]	[redacted]		
Stands unaided					[redacted]		
Walks unaided						[redacted]	
Dead							[redacted]
SHAM GROUP (patients alive with data n=[redacted])							
From\To state	Sits without support but does not roll	Sits and rolls independently	Sits and crawls with hands and knees	Stands/walks with assistance	Stands unaided	Walks unaided	Dead
Sits without support but does not roll	[redacted]	[redacted]		[redacted]			
Sits and rolls independently		[redacted]					
Sits and crawls with hands and knees			[redacted]				
Stands/walks with assistance	[redacted]			[redacted]		[redacted]	
Stands unaided				[redacted]	[redacted]	[redacted]	
Walks unaided					[redacted]		
Dead							[redacted]

** No observed transitions from state during cycle; Blank cells indicate zero probability*
N - number

Table 60: Transition matrices for nusinersen (top) and sham (bottom), HFMSE observed count data, CHERISH trial, days 170-274

NUSINERSEN GROUP (patients alive with data n=[redacted])							
From\To state	Sits without support but does not roll	Sits and rolls independently	Sits and crawls with hands and knees	Stands/walks with assistance	Stands unaided	Walks unaided	Dead
Sits without support but does not roll	[redacted]	[redacted]					
Sits and rolls independently	[redacted]	[redacted]	[redacted]	[redacted]			
Sits and crawls with hands and knees			[redacted]	[redacted]			
Stands/walks with assistance			[redacted]	[redacted]			
Stands unaided					[redacted]		
Walks unaided						[redacted]	
Dead							[redacted]
SHAM GROUP (patients alive with data n=[redacted])							
From\To state	Sits without support but does not roll	Sits and rolls independently	Sits and crawls with hands and knees	Stands/walks with assistance	Stands unaided	Walks unaided	Dead
Sits without support but does not roll	[redacted]	[redacted]					
Sits and rolls independently	[redacted]	[redacted]					
Sits and crawls with hands and knees		[redacted]	[redacted]				
Stands/walks with assistance	[redacted]			[redacted]			
Stands unaided					[redacted]	[redacted]	
Walks unaided				[redacted]		[redacted]	
Dead							[redacted]

** No observed transitions from state during cycle; Blank cells indicate zero probability*
N - number

Table 61: Transition matrices for nusinersen (top) and sham (bottom), HFMSE observed count data, CHERISH trial, days 275-365

NUSINERSEN GROUP (patients alive with data n=[redacted])							
From\To state	Sits without support but does not roll	Sits and rolls independently	Sits and crawls with hands and knees	Stands/walks with assistance	Stands unaided	Walks unaided	Dead
Sits without support but does not roll	[redacted]	[redacted]					
Sits and rolls independently	[redacted]	[redacted]					
Sits and crawls with hands and knees			[redacted]	[redacted]			
Stands/walks with assistance			[redacted]	[redacted]			
Stands unaided					[redacted]	[redacted]	
Walks unaided						[redacted]	
Dead							[redacted]
SHAM GROUP (patients alive with data n=[redacted])							
From\To state	Sits without support but does not roll	Sits and rolls independently	Sits and crawls with hands and knees	Stands/walks with assistance	Stands unaided	Walks unaided	Dead
Sits without support but does not roll	[redacted]						
Sits and rolls independently	[redacted]	[redacted]					
Sits and crawls with hands and knees	[redacted]	[redacted]					
Stands/walks with assistance				[redacted]	[redacted]		
Stands unaided					[redacted]		
Walks unaided						[redacted]	
Dead							[redacted]

** No observed transitions from state during cycle; Blank cells indicate zero probability*
N - number

Table 62: Transition matrices for nusinersen (top) and sham (bottom), HFMSE observed count data, CHERISH trial, days 366-456

NUSINERSEN GROUP (patients alive with data n=[redacted])							
From\To state	Sits without support but does not roll	Sits and rolls independently	Sits and crawls with hands and knees	Stands/walks with assistance	Stands unaided	Walks unaided	Dead
Sits without support but does not roll	[redacted]	[redacted]					
Sits and rolls independently	[redacted]	[redacted]	[redacted]				
Sits and crawls with hands and knees	[redacted]	[redacted]	[redacted]	[redacted]			
Stands/walks with assistance			[redacted]	[redacted]			
Stands unaided					[redacted]		
Walks unaided						[redacted]	
Dead							[redacted]
SHAM GROUP (patients alive with data n=[redacted])							
From\To state	Sits without support but does not roll	Sits and rolls independently	Sits and crawls with hands and knees	Stands/walks with assistance	Stands unaided	Walks unaided	Dead
Sits without support but does not roll	[redacted]	[redacted]					
Sits and rolls independently	[redacted]	[redacted]					
Sits and crawls with hands and knees			[redacted]				
Stands/walks with assistance	[redacted]			[redacted]			
Stands unaided					[redacted]		
Walks unaided					[redacted]	[redacted]	
Dead							[redacted]

** No observed transitions from state during cycle; Blank cells indicate zero probability*
N - number

Table 63: Transition matrices for nusinersen (top) and sham (bottom), extrapolation based on HFMSE score in CHERISH trial, all 4-month cycles after month 15

NUSINERSEN GROUP (patients alive with data n=n/a)						
From\To state	Sits without support but does not roll	Sits and rolls independently	Sits and crawls with hands and knees	Stands/walks with assistance	Stands unaided	Walks unaided
Sits without support but does not roll						
Sits and rolls independently						
Sits and crawls with hands and knees						
Stands/walks with assistance						
Stands unaided						
Walks unaided						
SHAM GROUP (patients alive with data n=n/a)						
From\To state	Sits without support but does not roll	Sits and rolls independently	Sits and crawls with hands and knees	Stands/walks with assistance	Stands unaided	Walks unaided
Sits without support but does not roll						
Sits and rolls independently						
Sits and crawls with hands and knees						
Stands/walks with assistance						
Stands unaided						
Walks unaided						

Blank cells indicate zero probability
n/a - not applicable

Probability of undergoing surgery for scoliosis and age at time of surgery

The assumptions regarding the timing of scoliosis surgery and the probability of discontinuing nusinersen treatment within the later onset model are the same as those for the early onset model (see Section 5.3.3). One clinical advisor to the ERG noted that patients with Type II SMA would typically undergo scoliosis surgery earlier than assumed in the model. The later onset model assumes that 43% of patients undergo scoliosis surgery at each assumed surgery timepoint, based on a survey-based study reported by Bladen *et al.*[49]

HRQoL - patient utilities

The source and derivation of the health state utility values in the later onset model are the same as those for the early onset model, albeit based on different health state descriptions (see Table 43).

HRQoL - caregiver utilities

Within the later onset model, caregiver disutilities were estimated using a similar approach and the same data as those used in the early onset model. The derivation of each health state-specific disutility is shown in Table 64.

Table 64: Parent/carer utilities used in the later onset model

HFMSE health state	Patient utility	Caregiver utility*	Caregiver disutility	Calculation and assumptions
Sits without support but does not roll	[redacted]	[redacted]	[redacted]	Bastida *et al*[37] baseline caregiver utility minus difference between State (ii) Sits and rolls independently and State (i) Sits without support but does not roll
Sits and rolls independently	[redacted]	[redacted]	[redacted]	Based on weighted mean of Type II and Type III caregiver utility reported by Bastida *et al*[37]
Sits and crawls with hands and knees	[redacted]	[redacted]	[redacted]	Bastida *et al*[37] baseline caregiver utility minus difference between State (ii) Sits and rolls independently and State (iii) Sits and crawls with hands and knees
Stands/walks with assistance	[redacted]	[redacted]	[redacted]	Bastida *et al*[37] baseline caregiver utility minus difference between State (ii) Sits and rolls independently and State (iv) Stands/walks with assistance
Stands unaided	[redacted]	[redacted]	[redacted]	Assumed to be the same as State (iv) Stands/walks with assistance
Walks unaided	[redacted]	[redacted]	[redacted]	Bastida *et al*[37] baseline caregiver utility minus difference between State (ii) Sits and rolls independently and State (vi) Walks unaided. Disutility constrained at zero.
Baseline parameters				
Bastida *et al*[37] caregiver utility		[redacted]	-	-
General population utility[38]		0.92	-	Caregiver age=30.88 years, 80% female
Bereavement		-	-0.04	-

** Calculated as general population utility minus caregiver utility*

Resource use and costs

The company's later onset model includes the following cost components: (i) nusinersen acquisition and administration costs and (ii) health state costs. End-of-life care costs are not included in the later onset model.

Drug acquisition and administration costs

As with the early onset model, the cost of nusinersen is assumed to be £75,000 per vial. As noted in Chapter 3, the model assumes that nusinersen is given as four loading doses during the first 3-month cycle, with 4-monthly maintenance doses thereafter, based on the licensed treatment schedule[4] rather than the treatment schedule used in CHERISH.[15] Nusinersen administration costs are based on the same age-based calculations as those used in the early onset model (see Section 5.3.3).

Health state costs

Consistent with the early onset model, health state costs are based on estimates reported in Bastida *et al*[37] (see Table 65).

Table 65: Annual health state costs, later onset model

Cost component	Milestones consistent with Type II SMA ([i] Sits without support but does not roll; [ii] Sits and rolls independently; [iii] Sits and crawls with hands and knees; [iv] Stands/walks with assistance)	Milestones consistent with Type III SMA ([v] Stands unaided; [vi] Walks unaided)
Respiratory care	[redacted]	[redacted]
Gastrointestinal care	[redacted]	[redacted]
Nutritional care	[redacted]	[redacted]
Orthopaedic care	[redacted]	[redacted]
Total	[redacted]	[redacted]

SMA – spinal muscular atrophy

5.4.4 Methods for model evaluation

The CS[1] presents the results of the later onset model in terms of the incremental cost per QALY gained for nusinersen versus usual care. Results are presented separately for: (i) analyses including patient health gains only and (ii) analyses including patient health gains and caregiver QALY losses. The company's base case ICERs are based on the deterministic version of the model. The CS also includes the results of PSA, DSAs, scenario analyses and subgroup analyses. The results of the PSA are presented in the form of a cost-effectiveness plane and CEACs, based on 1,000 Monte Carlo simulations. The probabilistic ICER is also presented. The distributions applied in the company's PSA are summarised

in Table 66. The results of the DSAs are presented in the form of a tornado diagram for specified model parameters. Scenario analyses were undertaken to explore the impact of alternative time horizons and alternative assumptions surrounding mortality risk, transition probabilities and costs; no scenario analyses are presented around HRQoL estimates.

Table 66: Distributions used in company's PSA, later onset model

Parameter group	Distribution	ERG comment
Initial HFMSE health state distribution – nusinersen	Fixed	The initial distributions are subject to uncertainty. Given the multinomial nature of the data, a Dirichlet distribution (applied to the combined CHERISH population) would be appropriate.
Initial HFMSE health state distribution – usual care	Fixed	
Overall survival – nusinersen	Multivariate normal	-
Overall survival – usual care	Multivariate normal	-
Transition probabilities – nusinersen (up to month 15)	Dirichlet	Priors are included for some but not all unobserved transitions.
Transition probabilities – usual care (up to month 15)	Dirichlet	
Transition probabilities – nusinersen (month 16 onwards)	Dirichlet	
Transition probabilities – usual care (month 16 onwards)	Dirichlet	
Probability of undergoing surgery for scoliosis	Beta	Inappropriately characterised using treatment-specific parameters.
Age at time of surgery	Normal	Inappropriately characterised using treatment-specific parameters.
Probability of discontinuing nusinersen after surgery for scoliosis	Beta	-
Patient utilities	Beta	All utilities sampled using the same random number, thereby inducing over-correlation between states.[47]
Baseline caregiver utilities	Beta	No uncertainty is included in the Bastida *et al*[37] baseline caregiver disutility
Nusinersen acquisition cost	Fixed	-
Nusinersen administration costs	Normal (cost) and Dirichlet (administration setting)	-
Health state costs	Gamma	-

HFMSE - Hammersmith Functional Motor Scale-Expanded; ERG – Evidence Review Group

5.4.5 Company's cost-effectiveness results – later onset model

This section presents the results of the company's later onset model.

Central estimates of cost-effectiveness – later onset model

Table 67 presents the central estimates of cost-effectiveness derived from the company's updated model (including patient health gains only). Based on a re-run of the probabilistic version of the model by the ERG, nusinersen is expected to generate an additional 2.28 QALYs at an additional cost of £2,938,441 per patient: the corresponding ICER for nusinersen versus usual care is £1,286,149 per QALY gained. The deterministic version of the model produces a slightly lower ICER of £1,252,991 per QALY gained for nusinersen versus usual care. The inclusion of caregiver QALY losses leads to a markedly lower probabilistic ICER of £933,088 per QALY gained (see Table 68); the deterministic ICER is lower at £898,164 per QALY gained.

Table 67: Company's model results, later onset model (patient health gains only)

Probabilistic model					
Option	**QALYs**	**Costs**	**Inc. QALYs**	**Inc. Costs**	**Incremental cost per QALY gained**
Nusinersen	16.85	£3,120,835	2.28	£2,938,441	**£1,286,149**
Usual care	14.56	£182,394	-	-	-
Deterministic model					
Option	**QALYs**	**Costs**	**Inc. QALYs**	**Inc. Costs**	**Incremental cost per QALY gained**
Nusinersen	16.88	£3,148,754	2.37	£2,964,442	**£1,252,991**
Usual care	14.52	£184,312	-	-	-

Inc. – incremental; QALY – quality-adjusted life year

Table 68: Company's model results, later onset model (patient health gains and caregiver QALY losses)

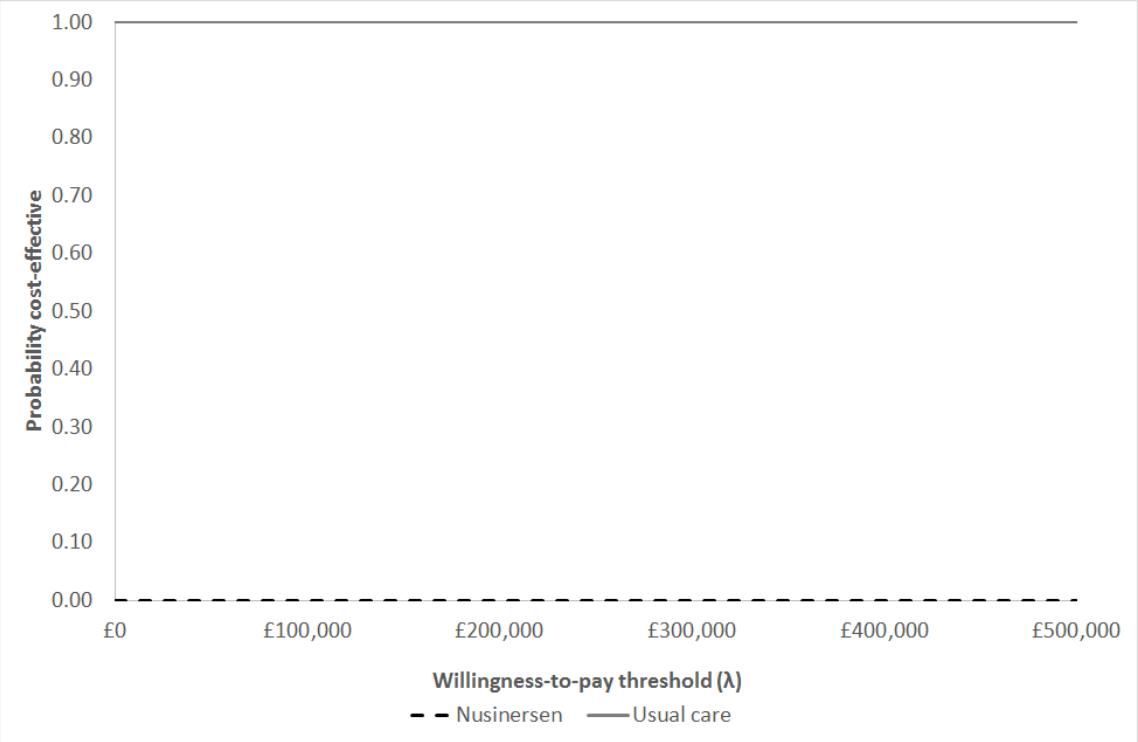
Probabilistic model					
Option	**QALYs**	**Costs**	**Inc. QALYs**	**Inc. Costs**	**Incremental cost per QALY gained**
Nusinersen	15.65	£3,120,835	3.15	£2,938,441	**£933,088**
Usual care	12.50	£182,394	-	-	-
Deterministic model					
Option	**QALYs**	**Costs**	**Inc. QALYs**	**Inc. Costs**	**Incremental cost per QALY gained**
Nusinersen	15.66	£3,148,754	3.30	£2,964,442	**£898,164**
Usual care	12.36	£184,312	-	-	-

Inc. – incremental; QALY – quality-adjusted life year

Company's probabilistic sensitivity analysis - later onset model

Figure 11 presents CEACs for nusinersen and usual care for the later onset population. As shown in the figure, the probability that nusinersen produces more net benefit than usual care is approximately zero even at WTP thresholds of £500,000 per QALY gained.

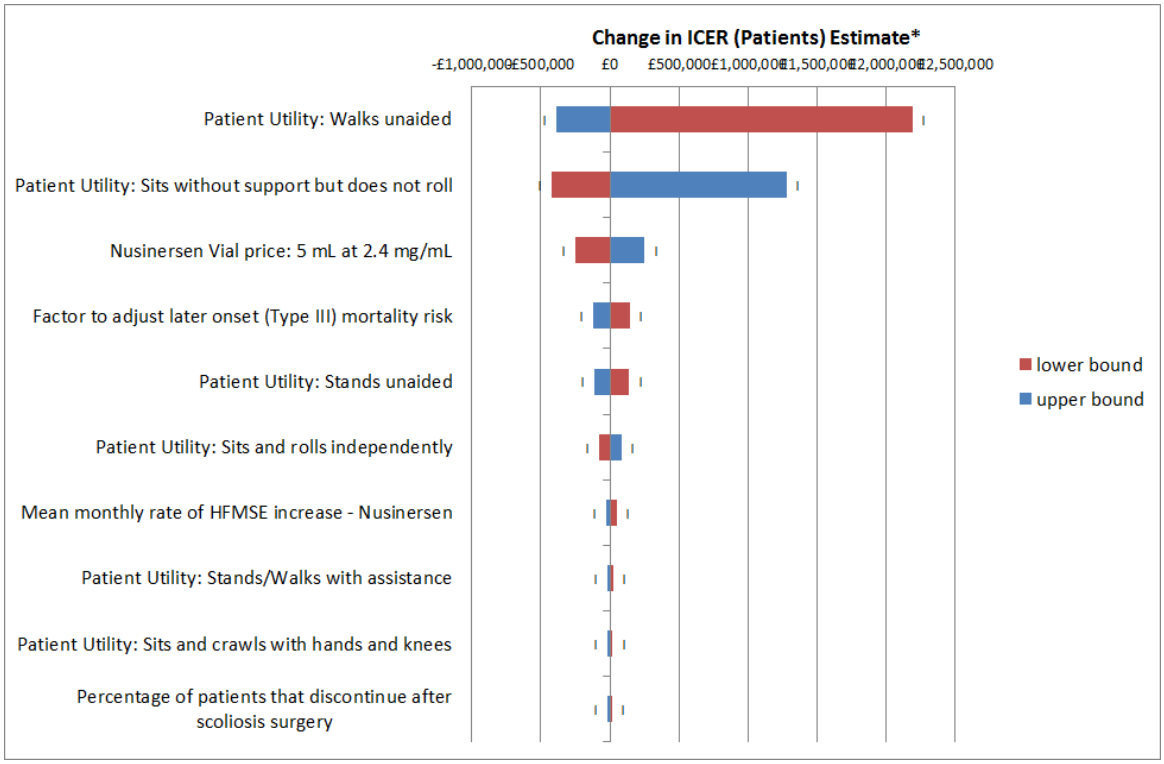
Figure 11: CEACs, later onset model, patient health gains only



Company's deterministic sensitivity analyses - later onset model

Figure 12 presents the results of the company's DSAs in the form of a tornado diagram (change in ICER from baseline). As shown in the figure, the most influential model parameters relate to the patient utility values for State (vi) Walks unaided and for State (i) Sits without support but does not roll. The lowest ICER generated from the company's one-way DSAs is £832,517 per QALY gained (patient utility for State [i] Sits without support but does not roll = [redacted]) whilst the highest ICER is £3,445,079 per QALY gained (patient utility for State [vi] Walks unaided = [redacted]).

Figure 12: Company's DSA tornado diagram, later onset model, patient health gains only



HFMSE - Hammersmith Functional Motor Scale-Expanded; ICER – incremental cost-effectiveness ratio; HR – hazard ratio

Scenario analysis results - later onset model

Table 69 presents the results of the company's scenario analyses. As shown in the table, the ICER for nusinersen is highly sensitive to the assumptions regarding mortality risk in the best two health states and the model time horizon. The lowest ICER for nusinersen versus usual care is estimated to be £734,749 per QALY gained when only patient health gains are included, and £614,044 per QALY gained when caregiver QALY losses are included in the analysis. These ICERs relate to the scenario in which general population mortality risk is attributed to all patients in States (v) and (vi) (mortality adjustment factor = 1.00). The highest ICER for nusinersen versus usual care is estimated to be £2,394,639 per QALY gained when only patient health gains are included, and £1,473,743 per QALY gained when caregiver disutilities are included in the analysis; these ICERs relate to the scenario in which the time horizon is truncated at 20 years.

Table 69: Scenario analysis results, later onset model

Scenario	ICER (patient health gains only)	ICER (patient health gains and caregiver QALY losses)
Base case (deterministic)	£1,252,991	£898,164
Time horizon=20 years	£2,394,639	£1,473,743
Time horizon=40 years	£1,528,733	£1,027,641
Time horizon=60 years	£1,280,983	£911,120
Societal cost perspective	£1,150,976	£825,038
Do not apply higher long-term risk of death based on SMA Type II adjusted general mortality rates	£1,227,736	£886,694
Do not apply general population mortality rates to patients in motor milestones characteristic of later onset (Type III) patients	£2,324,278	£1,285,987
Mortality risk factor=0.75	£969,170	£753,553
Mortality risk factor=1.00	£734,749	£614,044
Assumption a proportion of patients on treatment reach a plateau; 0% of those reaching an improvement plateau start getting worse	£1,371,100	£983,437
Assumption a proportion of patients on treatment reach a plateau; 10% of those reaching an improvement plateau start getting worse	£1,393,262	£997,921
Usual care arm HFMSE rate of decline based on Kaufmann *et al*[50]	£1,268,258	£911,947
All nusinersen administration inpatient	£1,258,656	£902,225
All nusinersen administration day case	£1,255,928	£900,269
Health state costs includes costs of major clinical events only	£1,276,308	£914,878
Cost estimates based on Klug *et al*[51]	£1,258,136	£901,852

SMA – spinal muscular atrophy; HFMSE - Hammersmith Functional Motor Scale-Expanded; ICER – incremental cost-effectiveness ratio

Subgroup analysis - later onset model

Table 70 presents the results of the company's subgroup analyses for the later onset model (disease duration <25 months or ≥25 months). The results suggest that the ICER for nusinersen versus usual care is less favourable in patients with longer disease duration (≥25 months).

Table 70: Subgroup analysis results, later onset model

Subgroup	ICER (patient health gains only)	ICER (patient health gains and caregiver QALY losses)
ITT population, each arm (base case)*	£1,252,991	£898,164
ITT population, both arms (base case) †	£1,265,944	£924,891
<25 months disease duration, each arm*	£1,263,457	£892,985
<25 months disease duration, both arms†	£1,201,673	£863,535
≥25 months disease duration, each arm*	£1,712,437	£1,220,287
≥25 months disease duration, both arms†	£1,615,299	£1,165,000

** "thresholds" defining HFMSE health states based on mean scores in each treatment group; † "thresholds" defining HFMSE health states based on mean scores across both treatment groups*

5.5 Critical appraisal of the company's health economic analyses

This section presents a critical appraisal of the health economic analyses of nusinersen for the treatment of early onset and later onset SMA presented within the CS.[1] Section 5.5.1 details the methods used by the ERG to interrogate and critically appraise the company's submitted health economic analyses. Section 5.5.2 discusses the extent to which the company's analyses adhere to the NICE Reference Case. Section 5.5.3 presents a detailed critique of the ERG's main issues and concerns relating to the company's analyses.

5.5.1 Methods for reviewing the company's health economic analyses

The ERG adopted a number of approaches to explore, interrogate and critically appraise the company's submitted economic analyses and the underlying health economic models upon which these were based. These included:

- Consideration of key items contained within published economic evaluation and health economic modelling checklists[52, 53] to critically appraise the company's models and analyses.
- Scrutiny of the company's models by health economic modellers and discussion of issues identified amongst the members of the ERG.
- Double-programming of the deterministic version of the company's models to fully assess the logic of the company's model structures, to draw out any unwritten assumptions and to identify any apparent errors in model implementation.
- Examination of the correspondence between the description of the models reported within the CS[1] and the executable models.
- Replication of the base case results, PSAs, DSAs and scenario analyses presented within the CS.[1]
- Where possible, checking of parameter values used in the company's models against their original data sources.
- The use of expert clinical input to judge the credibility of the company's assumptions underpinning the company's models.

5.5.2 Adherence of the company's economic analyses to the NICE Reference Case (early and later onset models)

The company's economic analyses of nusinersen for the treatment of early onset and later onset SMA are partially in line with the NICE Reference Case.[54] The ERG notes that the analyses exclude patients with Type 0 and Type IV SMA; patients with these SMA types are included in the marketing authorisation and the final NICE scope.[12] In addition, the evidence used to inform the clinical effectiveness evidence for nusinersen and the longer-term prognosis of patients with SMA are not based on formal systematic reviews. These issues are discussed in further detail in Section 5.5.3.

Table 71: Adherence of the company's economic analyses to the NICE Reference Case (early onset and later onset models)

Element	Reference case	ERG comments
Defining the decision problem	The scope developed by NICE[12]	The company's economic analyses relate to the ITT populations of the ENDEAR study[14] (Type I SMA) and the CHERISH study[15] (Types II and III SMA). Taken together, this population is narrower than the population defined in the final NICE scope and the marketing authorisation for nusinersen (people with 5q SMA). No economic evidence is presented for patients with Type 0 or Type IV SMA. The ERG notes that the model states are defined according to motor function milestones which may not fully capture the impact of other outcomes defined in the NICE scope[12] (e.g. respiratory function and the requirement for ventilation).
Comparator(s)	As listed in the scope developed by NICE	The company's economic analyses define the comparator as real world care (symptomatic or usual care), based on the sham arms of the ENDEAR and CHERISH trials[14, 15] and use observational data to inform survival outcomes beyond trial follow-up. The scope defines the comparator as BSC. The ERG and its clinical advisors consider this to be reasonable but note that there may be variation in how Type I SMA patients are managed, which may lead to differences between observed and predicted survival estimates. The ERG's clinical advisors commented that in the real world, the ability to provide BSC and the choices made by families may differ from a clinical trial situation. They also noted that families entering into trials are likely to be more motivated in seeking proactive support for their infants/children than many in routine clinical care.
Perspective on outcomes	All direct health effects, whether for patients or, when relevant, carers	Health gains accrued by patients are valued in terms of QALYs gained. Additional analyses are presented including QALY losses for caregivers.
Perspective on costs	NHS and PSS	The analysis adopts an NHS and PSS perspective.
Type of economic evaluation	Cost-utility analysis with fully incremental analysis	The results of the analyses are presented in terms of the incremental cost per QALY gained for nusinersen versus usual care.
Time horizon	Long enough to reflect all important differences in costs or outcomes between the technologies being compared	The early onset model adopts a 60-year time horizon. The later onset model adopts an 80-year time horizon. Within both models, approximately 100% of patients have died by the end of the modelled time horizon.
Synthesis of evidence on health effects	Based on systematic review	The company did not undertake a systematic review of clinical effectiveness evidence. The model is informed by the pivotal RCTs of nusinersen[14, 15] as well as observational data.[31-33] The methods for identifying these observational studies are unclear from the CS.[1]

Element	Reference case	ERG comments
Measuring and valuing health effects	Health effects should be expressed in QALYs. The EQ-5D is the preferred measure of HRQoL in adults.	Patient utilities were derived by mapping the PedsQL data from the CHERISH trial[15] to the EQ-5D using an algorithm reported by Khan *et al.*[36] Health utilities for the early onset model were based on an assumed correspondence between the HFMSE and HINE-2 defined health states. The mapping algorithm was derived using valuations from healthy schoolchildren. The ERG has concerns regarding the validity of these estimates and notes that alternative sources are available, although these are also subject to issues concerning face validity. Caregiver utilities were based on a single estimate from Bastida *et al*[37] and a large number of assumptions using the mapped patient utilities from CHERISH.[15]
Source of data for measurement of HRQoL	Reported directly by patients and/or carers	
Source of preference data for valuation of changes in HRQoL	Representative sample of the UK population	
Equity considerations	An additional QALY has the same weight regardless of the other characteristics of the individuals receiving the health benefit	No additional equity weighting is applied to estimated QALY gains. The CS[1] argues that nusinersen meets NICE's end-of-life criteria within the early onset population.
Evidence on resource use and costs	Costs should relate to NHS and PSS resources and should be valued using the prices relevant to the NHS and PSS	Resource components included in the company's models reflect those relevant to the NHS and PSS. Unit costs were valued at 2015/16 prices.
Discount rate	The same annual rate for both costs and health effects (currently 3.5%)	Costs and health effects are discounted at a rate of 3.5% per annum.

SMA - spinal muscular atrophy; ITT - intention-to-treat; QALY - quality-adjusted life year; HRQoL - health-related quality of life; PSS - Personal Social Services; EQ-5D - Euroqol 5-Dimensions; HINE-2 - Module 2 of the Hammersmith Infant Neurological Examination; HFMSE - Hammersmith Functional Motor Scale-Expanded; NICE - National Institute for Health and Care Excellence; ERG - Evidence Review Group

5.5.3 Main issues identified within the critical appraisal

Box 1 summarises the main issues identified within the ERG's critical appraisal of the company's economic analyses. These issues are discussed in further detail in the subsequent sections.

Box 1: Main issues identified within the critical appraisal undertaken by the ERG

(1) Absence of economic evidence relating to Type 0 and Type IV SMA
(2) Model verification, errors and complexity of programming approach
(3) Concerns regarding model structures which focus only on motor milestones
(4) Highly favourable assumptions regarding the expected trajectory of nusinersen-treated patients through modelled motor milestone health states
(5) Highly favourable assumptions regarding the expected survival of nusinersen-treated patients
(6) Issues relating to estimated patient utilities
(7) Arbitrary calculations underpinning caregiver disutilities
(8) Issues relating to health state costs
(9) Representation of uncertainty

(1) Absence of economic evidence relating to Type 0 and Type IV SMA

The marketing authorisation for nusinersen states that treatment is indicated for the treatment of 5q SMA.[4] This population is also defined in the final NICE scope.[12] The company's early onset model relates to patients with Type I SMA, whilst the later onset model relates to patients with Types II and III SMA. The CS does not present any economic analyses for patients with Type 0 or Type IV SMA. With respect to this issue, the CS states: *"Patients with type 0 and type IV (adult onset) SMA are omitted from the submission, despite market authorisation,(1) as there is no clinical evidence for nusinersen in type 0 and type IV that meets the requirements for technology appraisal at the current time"* (CS,[1] page 9). However, the CS[1] (page 21) also states that the anticipated place of nusinersen in therapy is as first-line treatment for all SMA patients. The ERG's clinical advisors stated that they would not treat Type 0 SMA patients with nusinersen, except in the context of clinical trials. The advisors also stated that they would not treat Type IV SMA patients using nusinersen as it is unlikely that these patients would obtain benefit from treatment.

(2) Model verification, errors and complexity of programming approach

Concerns regarding complexity of the company's model implementation

The company's models were programmed in such a complex way that the key formulae (including the Markov trace) were largely impenetrable to the ERG. This caused significant problems for the ERG not only in terms of verifying that the model had been implemented as intended and without error, but more fundamentally in terms of understanding what assumptions had been applied within the models. The extent of these issues is evident from a single Markov trace calculation in the nusinersen group of the early onset model (see Box 2). This formula includes 14 =IF() statements, 38 =SUMPRODUCT() functions and 73 =TRANSPOSE() functions. The early onset model includes several hundred similar equations to calculate the Markov trace for the nusinersen group. The trace calculations for patients who have undergone scoliosis surgery are approximately twice as long as the example given in Box 2. The later onset model is also subject to similar complicated programming issues.

Box 2: Example formula from a single cell of the company's early onset model trace

*=IF(txt_disc=2,IF(os_f_type2=2,SUMPRODUCT(TRANSPOSE($F25:$M25),IF($C26<=$GF$7,F$419:F$426,F$433:F$440))*(1-$DE26),SUMPRODUCT(TRANSPOSE($F25:$H25),IF($C26<=$GF$7,F$419:F$421,F$433:F$435))*(1-$DE26)+SUMPRODUCT(TRANSPOSE($I25:$L25),IF($C26<=$GF$7,F$422:F$425,F$436:F$439))*(1-$DA26)+$M25*IF($C26<=$GF$7,F$426,F$440)*(1-$DE26)),IF($C26<=$GO$12,IF(os_f_type2=2,(SUMPRODUCT(TRANSPOSE($F25:$M25),TRANSPOSE($BH25:$BO25),F$419:F$426)+SUMPRODUCT(TRANSPOSE($F25:$M25),TRANSPOSE($BQ25:$BX25),F$458:F$465))*(1-$DE26),(SUMPRODUCT(TRANSPOSE($F25:$H25),TRANSPOSE($BH25:$BJ25),F$419:F$421)+SUMPRODUCT(TRANSPOSE($F25:$H25),TRANSPOSE($BQ25:$BS25),F$458:F$460))*(1-$DE26)+(SUMPRODUCT(TRANSPOSE($I25:$L25),TRANSPOSE($BK25:$BN25),F$422:F$425)+SUMPRODUCT(TRANSPOSE($I25:$L25),TRANSPOSE($BT25:$BW25),F$461:F$464))*(1-$DA26)+$M25*($BO25+$BX25)*F$426*(1-$DE26)),IF(HS_Stop_txt=1,IF(os_f_type2=2,(SUMPRODUCT(TRANSPOSE($G25:$M25),TRANSPOSE($BI25:$BO25),F$420:F$426)+SUMPRODUCT(TRANSPOSE($G25:$M25),TRANSPOSE($BR25:$BX25),F$459:F$465))*(1-$DE26)+$F25*($BH25+$BQ25)*F$419*(1-$DC26),(SUMPRODUCT(TRANSPOSE($G25:$H25),TRANSPOSE($BI25:$BJ25),F$420:F$421)+SUMPRODUCT(TRANSPOSE($G25:$H25),TRANSPOSE($BR25:$BS25),F$459:F$460))*(1-$DE26)+(SUMPRODUCT(TRANSPOSE($I25:$L25),TRANSPOSE($BK25:$BN25),F$422:F$425)+SUMPRODUCT(TRANSPOSE($I25:$L25),TRANSPOSE($BT25:$BW25),F$461:F$464))*(1-$DA26)+$M25*($BO25+$BX25)*F$426*(1-$DE26)+$F25*($BH25+$BQ25)*F$419*(1-$DC26)),IF(HS_Stop_txt=2,IF(os_f_type2=2,(SUMPRODUCT(TRANSPOSE($H25:$M25),TRANSPOSE($BJ25:$BO25),F$421:F$426)+SUMPRODUCT(TRANSPOSE($H25:$M25),TRANSPOSE($BS25:$BX25),F$460:F$465))*(1-$DE26)+(SUMPRODUCT(TRANSPOSE($F25:$G25),TRANSPOSE($BH25:$BI25),F$419:F$420)+SUMPRODUCT(TRANSPOSE($F25:$G25),TRANSPOSE($BQ25:$BR25),F$458:F$459))*(1-$DC26),(SUMPRODUCT(TRANSPOSE($H25),TRANSPOSE($BJ25),F$421)+SUMPRODUCT(TRANSPOSE($H25),TRANSPOSE($BS25),F$460))*(1-$DE26)+(SUMPRODUCT(TRANSPOSE($F25:$G25),TRANSPOSE($BH25:$BI25),F$419:F$420)+SUMPRODUCT(TRANSPOSE($F25:$G25),TRANSPOSE($BQ25:$BR25),F$458:F$459))*(1-$DC26)+(SUMPRODUCT(TRANSPOSE($I25:$L25),TRANSPOSE($BK25:$BN25),F$422:F$425)+SUMPRODUCT(TRANSPOSE($I25:$L25),TRANSPOSE($BT25:$BW25),F$461:F$464))*(1-$DA26)+$M25*($BO25+$BX25)*F$426*(1-$DE26)),IF(os_f_type2=2,(SUMPRODUCT(TRANSPOSE($G25:$L25),TRANSPOSE($BI25:$BN25),F$420:F$425)+SUMPRODUCT(TRANSPOSE($G25:$L25),TRANSPOSE($BR25:$BW25),F$459:F$464))*(1-$DE26)+(SUMPRODUCT(TRANSPOSE($F25),TRANSPOSE($BH25),F$419)+SUMPRODUCT(TRANSPOSE($F25),TRANSPOSE($BQ25),F$458))*(1-$DC26)+$M25*($BO25+$BX25)*F$426*(1-$DC26),(SUMPRODUCT(TRANSPOSE($G25:$H25),TRANSPOSE($BI25:$BJ25),F$420:F$421)+SUMPRODUCT(TRANSPOSE($G25:$H25),TRANSPOSE($BR25:$BS25),F$459:F$460))*(1-$DE26)+(SUMPRODUCT(TRANSPOSE($F25),TRANSPOSE($BH25),F$419)+SUMPRODUCT(TRANSPOSE($F25),TRANSPOSE($BQ25),F$458))*(1-$DC26)+(SUMPRODUCT(TRANSPOSE($I25:$L25),TRANSPOSE($BK25:$BN25),F$422:F$425)+SUMPRODUCT(TRANSPOSE($I25:$L25),TRANSPOSE($BT25:$BW25),F$461:F$464))*(1-$DA26)+$M25*($BO25+$BX25)*F$426*(1-$DC26)))))+IF(os_f_type2=2,SUMPRODUCT(TRANSPOSE($F25:$M25),TRANSPOSE($AY25:$BF25),F$445:F$452)*(1-$DC26),SUMPRODUCT(TRANSPOSE($F25:$H25),TRANSPOSE($AY25:$BA25),F$445:F$447)*(1-$DC26)+SUMPRODUCT(TRANSPOSE($I25:$L25),TRANSPOSE($BB25:$BE25),F$448:F$451)*(1-$DA26)+$M25*$BF25*F$452*(1-$DC26)))*

The ERG sought clarification regarding the justification for the company's programming approach (see clarification response,[2] question B20). In response, the company acknowledged that the formulae are unnecessarily complicated, but noted that: (a) the model had to be developed "from scratch" due to the absence of existing economic models of treatments for SMA, and (b) the model was developed iteratively and became more complex due to the inclusion of elements such as scoliosis surgery and different model extrapolation approaches. The ERG does not consider that either of these explanations presents a sufficient justification for the complicated programming approach adopted.

Double-programming of the company's early onset and later onset models

During the early stages of the appraisal, the ERG raised concerns with NICE regarding the complex implementation of the company's models. In response, the company held a tutorial telephone call with the ERG and NICE which helped to clarify the intended logic and assumptions of the models. Subsequently, the ERG was able to double-program simplified versions of the Markov traces for both treatment groups in the early and later onset models (excluding the possibility of scoliosis surgery, thereby reducing the complexity of both models). In addition, the ERG was able to use the Markov traces generated from the company's models to replicate the remaining model structure and to estimate ICERs for both the early and later onset SMA populations. The results of these two double-programming exercises are shown in Table 72 and Table 73.

Table 72: Comparison of the company's model and the ERG's double-programmed Markov traces, end of trial follow-up to end of time horizon (excludes the possibility of scoliosis surgery)

Health state	Mean health state sojourn time (years, from month 13-end of time horizon)			
	Nusinersen		Usual care	
	Company's Markov trace	ERG's double-programmed Markov trace	Company's Markov trace	ERG's double-programmed Markov trace
Early onset model				
No milestone achieved	2.55	2.55	9.35	9.35
Mild milestone	0.19	0.19	0.06	0.06
Moderate milestone	0.48	0.48	0.05	0.05
Sits without support	0.78	0.78	0.00	0.00
Stands with assistance	1.45	1.45	0.00	0.00
Walks with assistance	1.44	1.44	0.00	0.00
Stands/walks unaided	29.47	29.47	0.00	0.00
Later onset model				
Sits without support but does not roll	14.56	14.56	31.21	31.22
Sits and rolls independently	0.77	0.77	2.61	2.61
Sits and crawls with hands and knees	0.47	0.47	0.45	0.45
Stands/walks with assistance	0.29	0.29	0.03	0.03
Stands unaided	1.86	1.86	0.53	0.53
Walks unaided	22.39	22.38	0.20	0.20

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Table 73: Comparison of the company's model results and the ERG's estimated ICERs using the company's Markov traces

	Company's model			ERG's double-programmed model		
Early onset model						
Option	**Inc. QALYs**	**Inc. costs**	**ICER**	**Inc. QALYs**	**Inc. costs**	**ICER**
Nusinersen	7.86	£2,258,362	**£407,679**	7.86	£2,272,097	**£410,240**
Usual care	2.49	£71,540	-	2.49	£71,540	-
Later onset model						
Option	**Inc. QALYs**	**Inc. costs**	**ICER**	**Inc. QALYs**	**Inc. costs**	**ICER**
Nusinersen	16.88	£3,148,754	**£1,252,991**	16.88	£3,299,874	**£1,315,176**
Usual care	14.52	£184,312	-	14.52	£188,309	

Inc. - incremental; QALY - quality-adjusted life year; ICER - incremental cost-effectiveness ratio

On the basis of these double-programming exercises, the ERG is broadly satisfied that the company's base case analyses have been implemented correctly and without significant error. The only potential exception relates to discontinuation following scoliosis surgery; due to the programming approach, the ERG had difficulty in understanding exactly how this is applied. This may explain the discrepancies between the company's model results and those generated from the ERG's double-programming exercise. The ERG notes that the replicated model traces and the replicated cost and QALY calculations implemented by the ERG are very straightforward.

Through a combination of model scrutiny and the ERG's double-programming exercise, the ERG identified the following errors in the company's early onset and later onset models:

(i) *Inconsistent assumptions regarding end-of-life costs between the early and later onset models.* End-of-life costs are included in the early onset model but not in the later onset model. Given that all patients die, the ERG considers the inclusion of these costs to be largely irrelevant, as the only way in which this parameter could impact on the ICER is through discounting these costs at different death times between treatment groups. The company's clarification response[2] (question B31) shows that the inclusion of end-of-life costs has only a negligible impact on the ICER for nusinersen; within this analysis, the ICER for nusinersen is reduced by £236.

(ii) *Discrepancies between the company's model traces and the ERG's double-programmed model traces.* The ERG's double-programmed Markov traces are very similar but not identical to those generated using the company's models. It is unclear whether these discrepancies are the result of rounding errors or minor programming errors in the company's models. The ERG considers that these discrepancies are likely to have a negligible impact on the ICER for nusinersen.

(iii) *Ambiguity regarding intended model time horizon in the early onset model.* The CS[1] states that a 40-year time horizon was used for the early onset model; however, the submitted model and all results presented in the CS correspond to a 60-year time horizon. In response to a request

for clarification (see clarification response,[2] question B32) the company stated that they had intended to use a 60-year time horizon. The ERG notes that the impact of using a 40-year or 60-year time horizon has a minimal impact on the ICER for nusinersen as almost all patients have died within 40 years.

(iv) *Use of different initial distributions between treatment groups in both the early and later onset models.* The initial health state distribution at model entry is based on the treatment-specific distributions in the ENDEAR and CHERISH studies[14, 15] (see Figure 13 and Figure 14). In response to a request for clarification from the ERG (see clarification response,[2] question B22), the company stated that this approach was taken *"to ensure that the model followed the trial data more accurately."* However, the ERG considers this to represent an error that introduces a potential selection bias whereby the patients' initial health state is prognostic of outcomes. The ERG believes that it would have been more appropriate to apply a common initial distribution based on the overall health state distribution within each trial. This issue is tested in the ERG's exploratory analyses and is shown not to significantly impact upon the ICER for nusinersen (see Section 5.6).

Figure 13: Initial HINE-2 health state distribution of patients in the company's early onset model (based on ENDEAR)

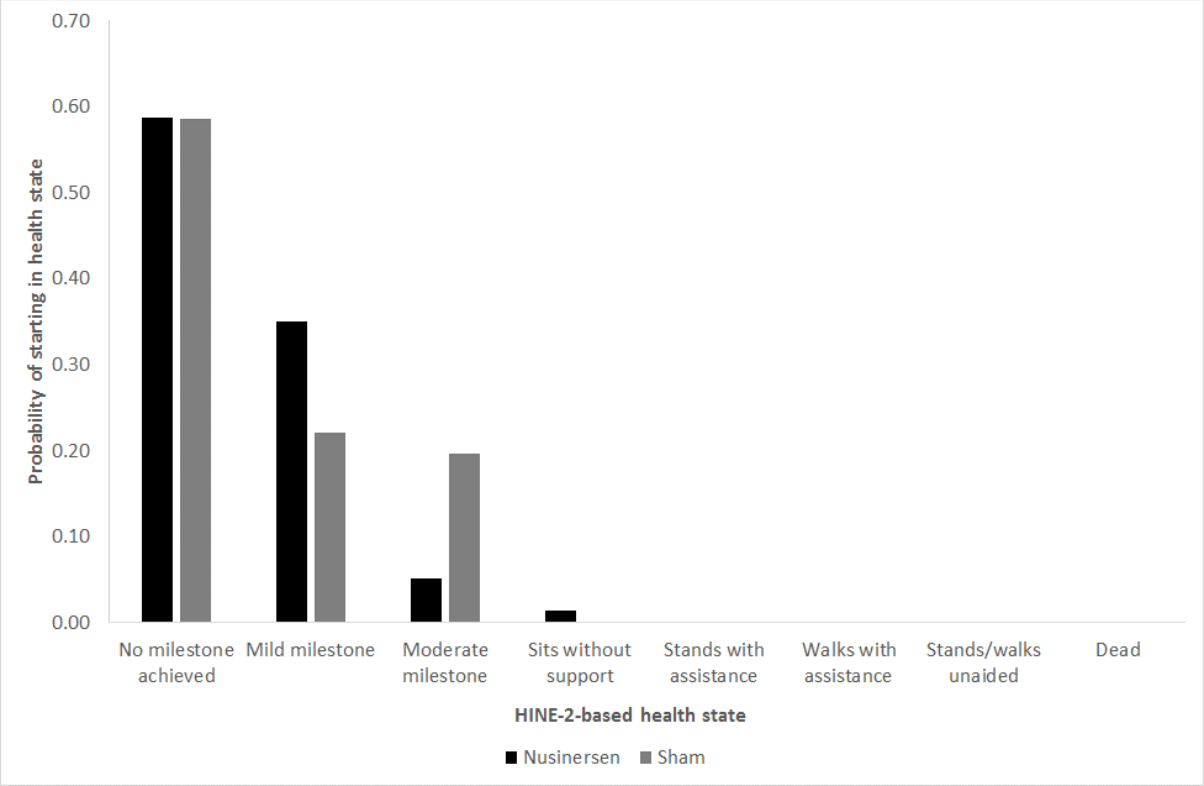
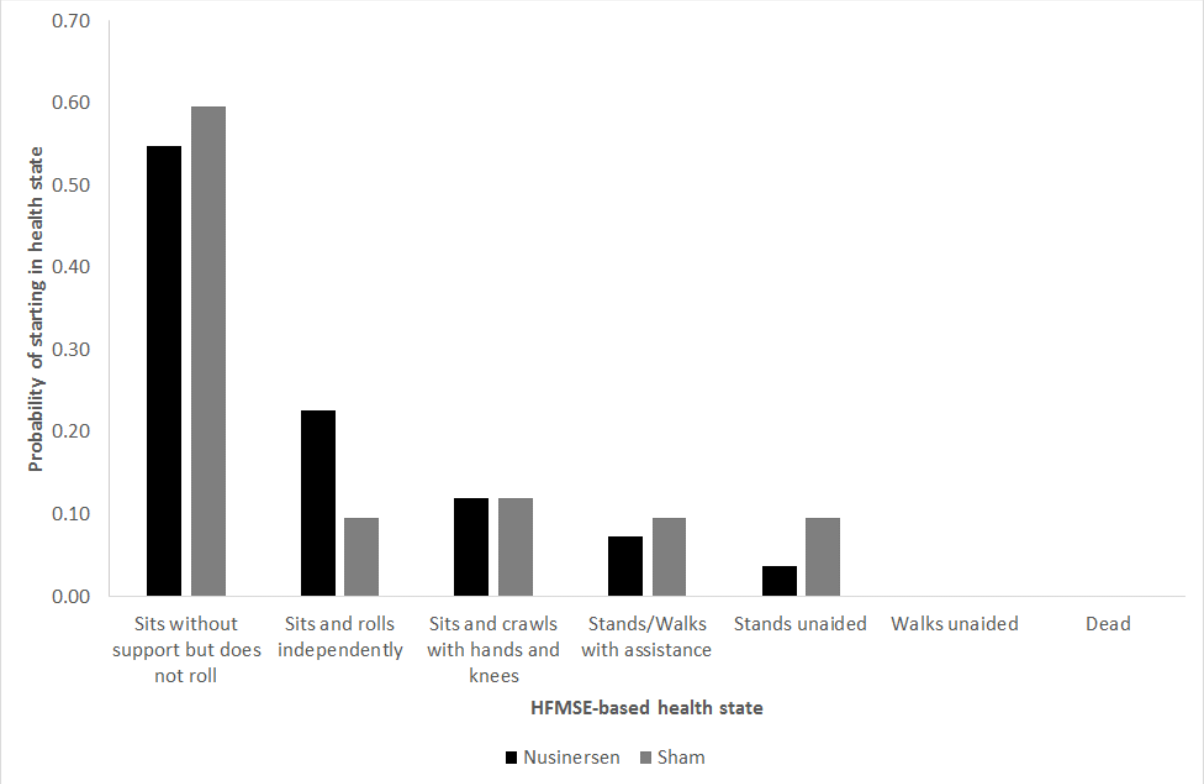


Figure 14: Initial HFMSE health state distribution of patients in the company's later onset model (based on CHERISH)



Correspondence between the written submission and the model

Overall, the implemented model structure and inputs correspond to the description in the CS.[1] However, the ERG notes that the CS is unclear with respect to: (a) how patients' trajectories are modelled after discontinuing due to scoliosis surgery (including the use of tunnel states which are not described in the CS); (b) when scoliosis surgery is applied (once only or during each cycle).

The ERG was able to generate probabilistic ICERs using the company's models which are similar to those reported within the CS. The ERG was also able to replicate the results of the company's deterministic base case analyses, DSAs and scenario analyses. As noted in Section 5.3, the results of the subgroup analyses for the early onset population presented in the CS are incorrect; corrected results were provided by the company following the clarification process (shown in Table 53).[3]

Correspondence of the model inputs and the original sources of parameter values

The ERG attempted to reproduce the transition matrices beyond the end of ENDEAR and CHERISH using the data reported in the CS (see Table 35 and Table 57); the resulting matrices were slightly different to those used in the company's models. It is likely, but not definite, that this is a consequence of rounding errors.

The source of the assumed cost of end-of-life care is not mentioned in the CS, but is cited in the model. The ERG was unable to locate the cost estimate within the NICE Guideline 61 resource use template.[40]

The documentation relating to the UK SMA advisory board meeting[45] (the source of the Type II and Type III mortality adjustment assumptions) does not report the actual adjustment factors applied to the better health states (early onset model, mortality adjustment factor = 0.90; later onset model, mortality adjustment factor = 0.50).

The ERG attempted to replicate IPD from Gregoretti *et al*,[31] and to adjust the data as described by the company. The resulting Kaplan-Meier estimates showed some deviation, as illustrated in Figure 21. This is likely to reflect expected uncertainty in the replication process rather than an error.

All other inputs applied in the base case analysis appear to reflect the original source material.

(3) Concerns regarding model structures which focus only on motor milestones

The ERG has some concerns regarding the structures of the early and later onset models. Both models focus exclusively on the achievement/loss of motor milestones (and death). Clinical advisors to the ERG agreed that the achievement/loss of motor milestones is important in SMA and that the company's model structures are broadly reasonable in terms of functional symptoms of SMA. The clinical advisors also commented that HINE-2 and HFMSE are appropriate instruments through which to classify motor milestones in SMA. They also noted that CHOP INTEND, which is used to inform the long-term extrapolation of motor function in the early onset model, is an appropriate functional scale for infants with Type I SMA, but may be less relevant for older or fragile children or for those with the ability to sit. The clinical advisors further commented that other symptoms and outcomes besides motor function may also be important - in particular, aspects of SMA relating to respiratory function, the explicit use of ventilation and the possibility of infections; these factors are not explicitly captured in either of the company's model structures. The clinical advisors also stated that motor function is not the sole determinant of HRQoL and that the ability to participate in activities and a lack of negative symptoms (e.g. pain and infection) may be more important than motor function. Despite these concerns, the ERG considers that both models are consistent with key outcomes measured in the ENDEAR and CHERISH trials[14, 15] and that alternative characterisations of the disease would likely be hindered by a lack of evidence.

(4) Highly favourable assumptions regarding the expected trajectory of nusinersen-treated patients through modelled motor milestone health states

Within the early onset model, transition probabilities beyond the end of follow-up in ENDEAR[14] are based on the rate of change in CHOP INTEND score over the trial duration, and mean CHOP INTEND

scores conditional on HINE-2 model health state within ENDEAR (supplemented with additional data from Study CS3A[34] for the best two health states). These mean CHOP INTEND scores are treated as thresholds that define whether the patient is in the current state or the next best/worst health state. A similar approach is used within the later onset model, whereby transition probabilities are derived using the rate of change in HFMSE score over the course of the CHERISH trial,[15] together with mean HFMSE scores for each HFMSE model health state within CHERISH (supplemented using data from Study CS2 and CS12[25] for the best health state). In both models, patients receiving nusinersen are assumed either to improve or stay in the same state (deterioration is not permitted), whilst patients in the usual care group are assumed either to worsen or stay in the same state (improvement is not permitted).

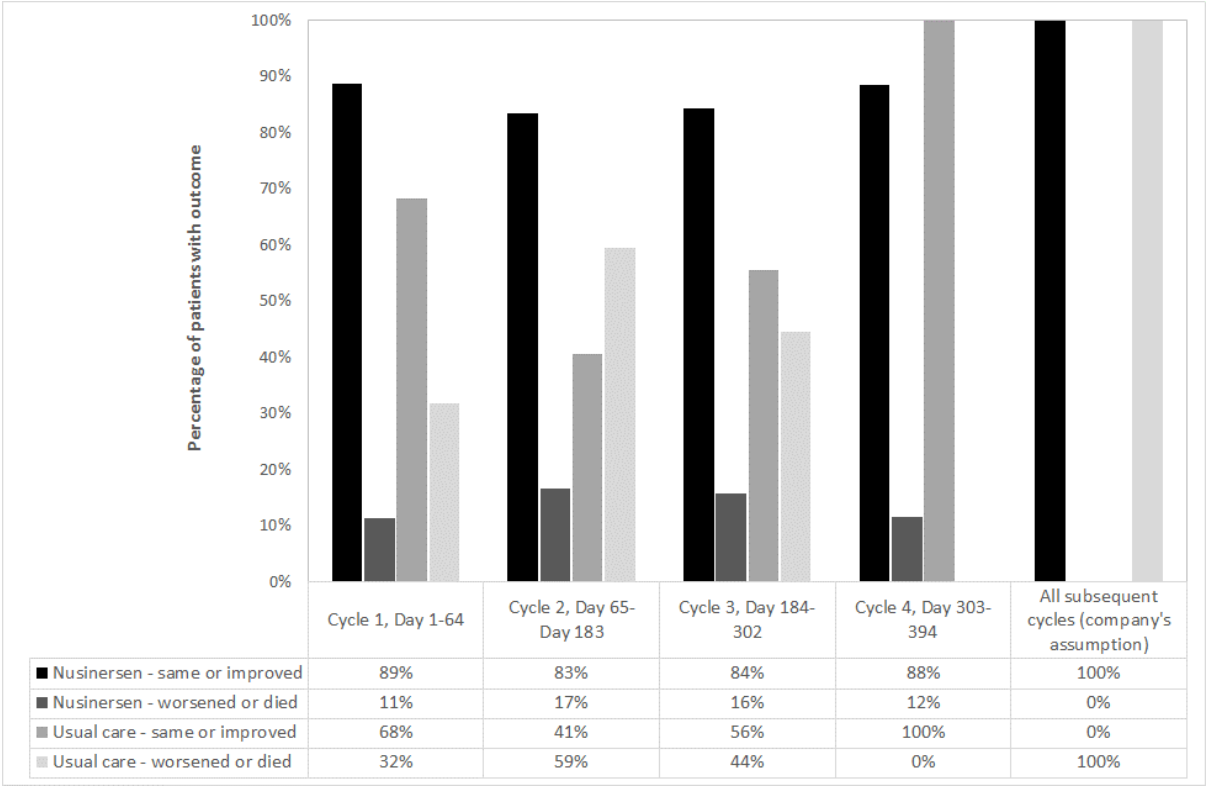
The ERG has several concerns regarding the company's approach for estimating transition probabilities; these concerns are detailed below.

(a) Highly favourable assumptions regarding improvements for nusinersen-treated patients beyond the end of the ENDEAR and CHERISH trials

Clinical advisors to the ERG considered that the company's assumption that patients receiving usual care would not experience improvements in motor milestones beyond the observed follow-up periods of ENDEAR and CHERISH may be broadly reasonable, although they noted that Type III patients in CHERISH may develop some further motor skills. However, the advisors noted that there is considerable uncertainty surrounding the long-term benefits of nusinersen on motor function and that it is possible that patients may lose milestones despite treatment with nusinersen. They considered this to represent a key uncertainty in the clinical evidence base and noted that improving motor milestones increases the burden on the respiratory system.

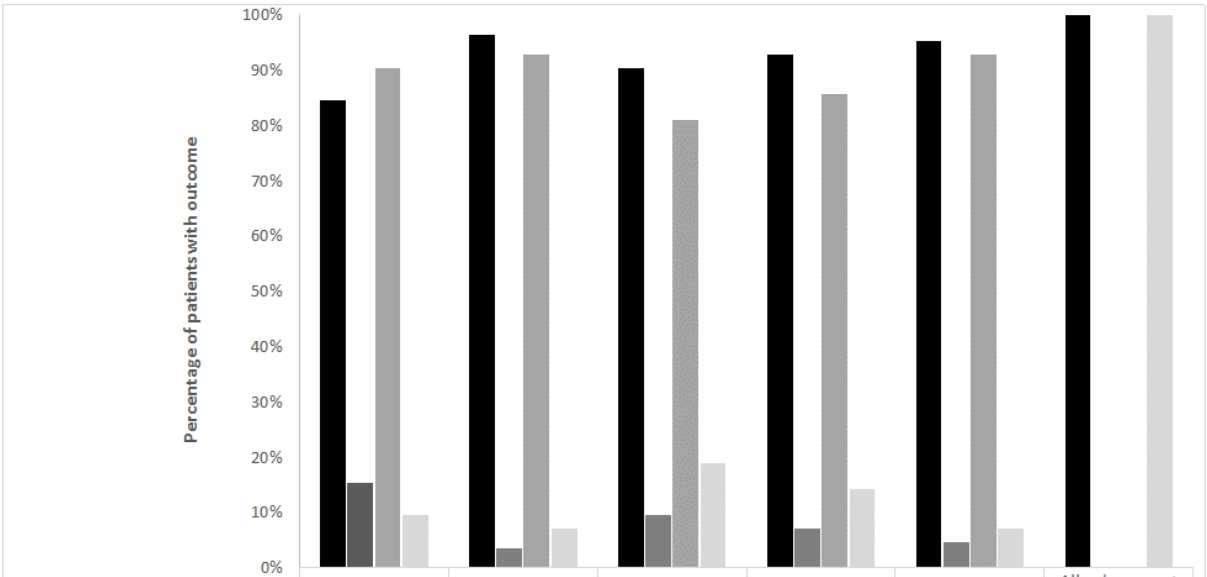
The ERG also notes that the company's assumptions of no deterioration for nusinersen and no improvement for usual care do not reflect the observed clinical trial data. Figure 15 presents observed data from ENDEAR[14] relating to the probability that a patient who is alive and at risk either: (a) stays in the same health state or improves or (b) worsens or dies. Figure 16 presents the equivalent data from CHERISH.[15] As shown in both figures, during every time interval, a proportion of surviving patients receiving nusinersen transited to a worse health state. In addition, during all cycles except for cycle 4 (the interval between days 303 and 394) in ENDEAR,[14] a proportion of surviving patients receiving the sham procedure transited to an improved health state, whilst in CHERISH,[15] a proportion of patients receiving sham transited to an improved state during every cycle. As such, the observed data do not support the assumptions employed in the extrapolated periods of the company's model.

Figure 15: Observed and assumed transitions between HINE-2 health states over time, early onset model



	Cycle 1, Day 1-64	Cycle 2, Day 65-Day 183	Cycle 3, Day 184-302	Cycle 4, Day 303-394	All subsequent cycles (company's assumption)
Nusinersen - same or improved	89%	83%	84%	88%	100%
Nusinersen - worsened or died	11%	17%	16%	12%	0%
Usual care - same or improved	68%	41%	56%	100%	0%
Usual care - worsened or died	32%	59%	44%	0%	100%

Figure 16: Observed and assumed transitions between HFMSE health states over time, later onset model



	Cycle 1, Day 1-92	Cycle 2, Day 93-169	Cycle 3, Day 170-274	Cycle 4, Day 275-365	Cycle 5, Day 366-456	All subsequent cycles (company's assumption)
Nusinersen - same or improved	85%	96%	90%	93%	95%	100%
Nusinersen - worsened or died	15%	4%	10%	7%	5%	0%
Usual care - same or improved	90%	93%	81%	86%	93%	0%
Usual care - worsened or died	10%	7%	19%	14%	7%	100%

In response to a request for clarification from the ERG,[2] the company provided additional information regarding the assumption of continued improvement for patients receiving nusinersen beyond the end of the trials:

[redacted] *the mean rate of improvement in CHOP INTEND was continued beyond the end of ENDEAR trial follow-up although, given the uncertainty around this parameter, a proportion of nusinersen patients can be assumed to reach a plateau or deteriorate. In the RWC arm, the base case assumes that the deterioration in CHOP INTEND observed in the ENDEAR trial continues beyond the end of trial follow-up. A lower rate of deterioration can be applied in the model by selecting the natural history study by Finkel et al. (2014) in infantile onset SMA or Kaufman et al. (2012) in later onset SMA."* (Company's clarification response,[2] question B16a).

However, in their response to clarification question (B16b), the company noted that the clinicians attending the advisory board meeting believed that [redacted] The clinical advisors to the ERG stated that it is more likely that outcomes for patients receiving nusinersen would follow a distribution whereby some would improve, whilst others would worsen. Therefore, the assumptions employed within the company's models regarding long-term improvements in motor function for patients receiving nusinersen do not fully reflect clinical advice received by the company or the ERG. Rather, the company's approach to extrapolating transition probabilities for the nusinersen group within both models appears to be unrealistically optimistic. Within the later onset model, the company's approach to extrapolating transition probabilities for the usual care group may be unduly pessimistic, at least for some Type III SMA patients.

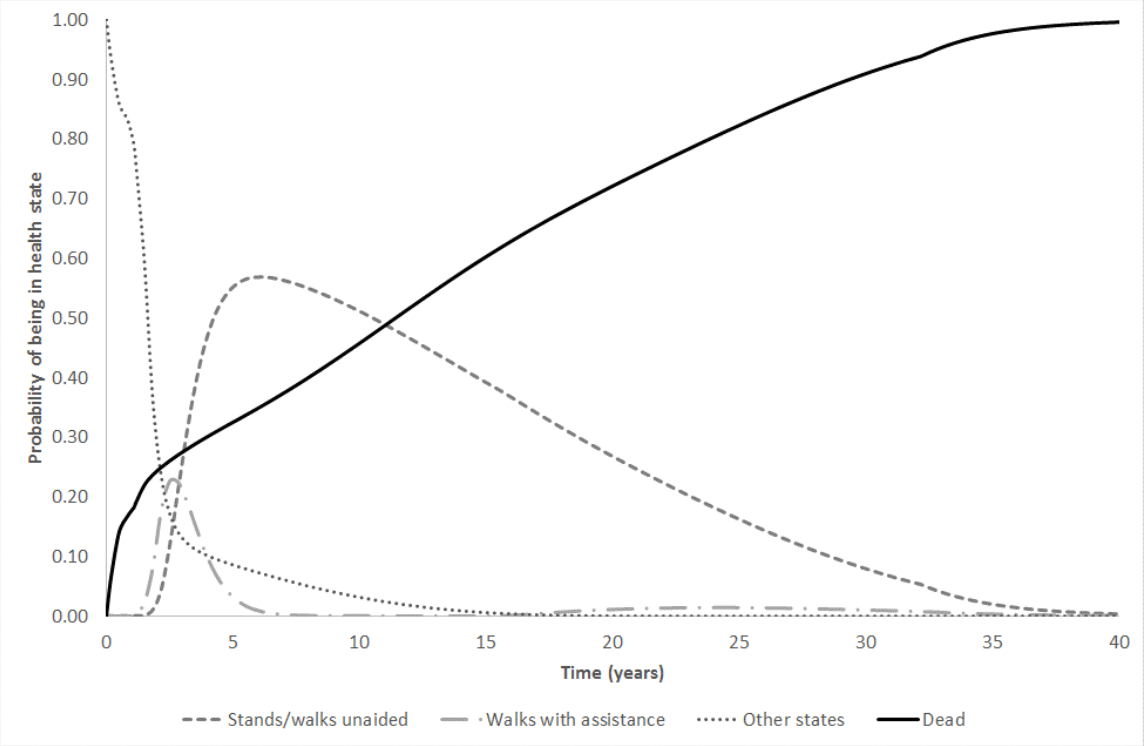
(b) Model predictions that all surviving patients will reach the best health states were not observed within the ENDEAR and CHERISH trials

Figure 17 shows the model-predicted health state occupancy within the nusinersen group over the time horizon within the early onset model; Figure 18 presents the equivalent estimates for the later onset model. As shown in Figure 17, within the nusinersen group, the vast majority of surviving patients reach the best health state (HINE-2 State [vii] Stands/walks unaided) within the first five years of the model time horizon. As a consequence of the assumption regarding no deterioration within the nusinersen group and the very low probability of undergoing scoliosis surgery and discontinuing treatment, almost all patients remain in this state until death. However, within ENDEAR, no patients achieved milestones which would locate them in the best two health states, and by the end of trial follow-up, only one patient

had reached State (v) Stands with assistance at any timepoint. The health state projections predicted by the early onset model therefore appear highly favourable given the observed data. The ERG notes that these favourable projections are driven by the company's combined use of CHOP INTEND data in the unobserved period and the assumption that motor function cannot deteriorate for patients receiving nusinersen.

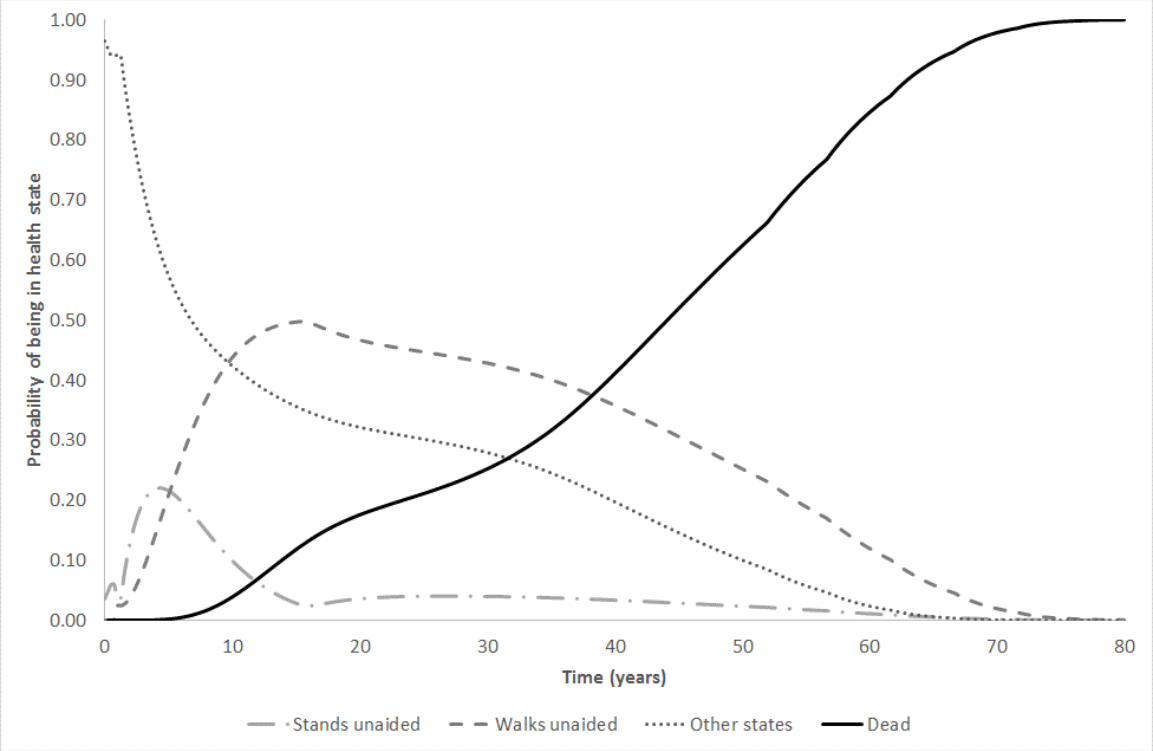
Similarly, within the later onset model, approximately 49.8% of patients reach the best health state (State [vi] Walks unaided) by around 15 years (see Figure 18). However, only two patients reached this milestone within the nusinersen group of CHERISH. The ERG notes that the company's later onset model predictions are driven by the assumption that the motor function for nusinersen-treated patients cannot deteriorate.

Figure 17: Health state occupancy over time, early onset model, nusinersen group



Note: Stands/walks unaided is the best state; Walks with assistance is the second best state

Figure 18: Health state occupancy over time, later onset model, nusinersen group



Note: Walks unaided is the best state; Stands unaided is the second best state

(c) Concerns regarding the company's approach to calculating transition probabilities

Within the early onset model, the company's approach for deriving transition probabilities for the unobserved period relies on an assumption of perfect correlation between CHOP INTEND and HINE-2 health state. The CHOP INTEND scores represent a threshold for being in the current state or the next best/worst state. However, the company's approach applies a different set of thresholds depending on treatment group (the mean CHOP INTEND scores for each health state are different for the nusinersen and usual care groups, see Table 35). The ERG considers the joint interpretation of these two assumptions to be unclear.

In response to a request for clarification from the ERG,[2] the company stated that: *"There won't necessarily be a direct relationship between the changes on one measure and the changes in the other both because they are measuring different aspects of motor ability and because of the different properties of the two measurement scales. For example, considering patients' absolute scores, patients are closer to zero on the HINE-2 scale than on the CHOP INTEND scale at baseline, thus limiting the scope for further reductions in score over time with HINE-2."* (Company's clarification response,[2] question B17b). The company's response calls to question the appropriateness of assuming a perfect correlation between the HINE-2 and CHOP INTEND instruments. A similar issue regarding the

definition of health states with treatment-specific HFMSE thresholds also applies to the company's later onset model (see Table 57).

The rate of improvement/worsening in CHOP INTEND and HFMSE are assumed to be constant with respect to time and are applied monotonically to each permitted transition. Figure 14 of the company's clarification response[2] and Figure 21 of the CS[1] suggest that the mean change in CHOP INTEND score in each group in ENDEAR and the mean change in HFMSE in CHERISH are not constant.

In addition, as shown in Equations [iv] to [vii], the company's calculation approach involves applying a constraint which prevents the estimated transition probabilities from exceeding 1.0. This constraint is necessary in the usual care group of the early onset model for the transition from State (v) Stands with assistance to State (iv) Sits without support. Based on the company's calculation, the unconstrained transition probability is [redacted] ([redacted]*4]/[52.7-48.0]); the ERG has concerns with the appropriateness of the calculation, given that this value exceeds 1.0. A further issue applies to the transition between State (iv) Stands/walks with assistance and State (iii) Sits and crawls with hands and knees within the company's later onset model, whereby the threshold between states is the same hence the denominator is zero; this calculation returns a #DIV/0! error unless a constraint is applied (see Table 57). These issues raise further questions regarding the appropriateness of the approach used to calculate transition probabilities within both models.

On the basis of the above issues, the ERG considers the company's extrapolation to be highly optimistic, mathematically unsound and inconsistent with the available evidence from ENDEAR and CHERISH.

(5) Highly favourable assumptions regarding the expected survival of nusinersen-treated patients

The company use a complex multi-stage approach for extrapolation using external data. As described by the company, it is widely recommended that longer-term data should be used to inform the extrapolation of clinical trial data with limited follow up.[55, 56] However, the ERG has concerns regarding how this has been implemented by the company and considers that a simpler approach would have greater plausibility and would provide more transparent survival predictions. The main points are summarised below; these are discussed in further detail in the following sections.

(i) Complexity of modelling approach
- Not clearly described. Assumptions not clearly stated or justified
- Some standard parametric models fitted to the observed data provided plausible predictions

(ii) Use of external data from Gregoretti *et al*[31] to inform early onset model

- Assumption that after adjustment for age, mortality is the same in Gregoretti *et al*[31] and ENDEAR[14] is not plausible
- Uncertainty due to reconstruction of IPD from published Kaplan-Meier curve

(iii) Use of external data from Zerres *et al*[33] to inform later onset model

- Assumption that mortality is the same as in CHERISH is not justified

(iv) Use of general population mortality

- Assumption that long-term mortality is systematically different between the studies and the general population (by assuming a constant HR) is not plausible

(v) Assumptions regarding treatment effect

- Description that a conservative HR of 1.0 is applied is misleading due to the implementation of the Type II adjustment

(vi) Concerns regarding SMA Type II adjustment

- No observed data to justify the use of Zerres *et al*[33] data or the adjustment factors used.

(i) Complexity of modelling approach

Jackson *et al*[49] present a framework for survival extrapolation using external data which is referenced by the company in justifying their approach (see clarification response,[2] question B9). If the external population has the same mortality at all times (or in the long-term) as that of the external population, then survival estimates from the external population can be used directly without adjustment. This assumption permits the direct use of data from Gregoretti *et al*[31] and Zerres *et al*[33] in the early onset and late onset models, respectively. Alternatively, OS may be assumed to be different, but systematically similar in such a way that the external data can be adjusted to estimate OS in the target population. This assumption permits the application of the adjusted general population mortality data. The validity of these assumptions is paramount to the reliability of the survival predictions; however, no clear justification for either assumption was presented by the company. The ERG considers that the plausibility of these assumptions is questionable and considers each case in further detail below.

Given the concerns regarding the use of external data, the ERG considers that a simpler approach based on extrapolating parametric models fitted to observed trial data may have been both more informative and more transparent than the approach adopted by the company. Consideration of appropriate external data is important; however, it could be used more simply to judge the plausibility of models fitted to observed data, or to inform certain parameters.[56] In their response to clarification questions from the ERG[2] (question B9), the company states that some parametric models provided plausible extrapolations and so the ERG considers that using these would be a reasonable approach. Details of which models provided plausible predictions were not provided by the company.

As summarised in Section 5.3.3, the company provides a detailed account of model fitting to each observed data source; however, the long-term fitted survival probabilities are of limited relevance given that composite functions are applied in the model. The survival functions as applied in the model are shown in Figure 19 and Figure 20 for the early onset and late onset models, respectively.

With respect to the early onset usual care group, one clinician believed that the survival curve was reasonable. The second advisor believed that the curve was optimistic compared with the patients seen in her clinical practice and commented that in routine care, many families do not have the resources to manage NIV or aggressive management and instead 'opt' for a palliative approach. The advisor also noted that in some areas, resources and experience in supporting small infants with SMA are limited. With respect to the early onset nusinersen group, one clinician stated that the survival curve reflected a "big assumption" whilst the other believed it was optimistic as she would not expect any patients to survive to 35 years. One of the advisors had particular concerns regarding the plausibility of the company's mortality adjustment in the better states of the early onset model, and noted that longer-term evidence from the SHINE and NURTURE studies may provide useful information.

Figure 19: Fitted survival curves, early onset model

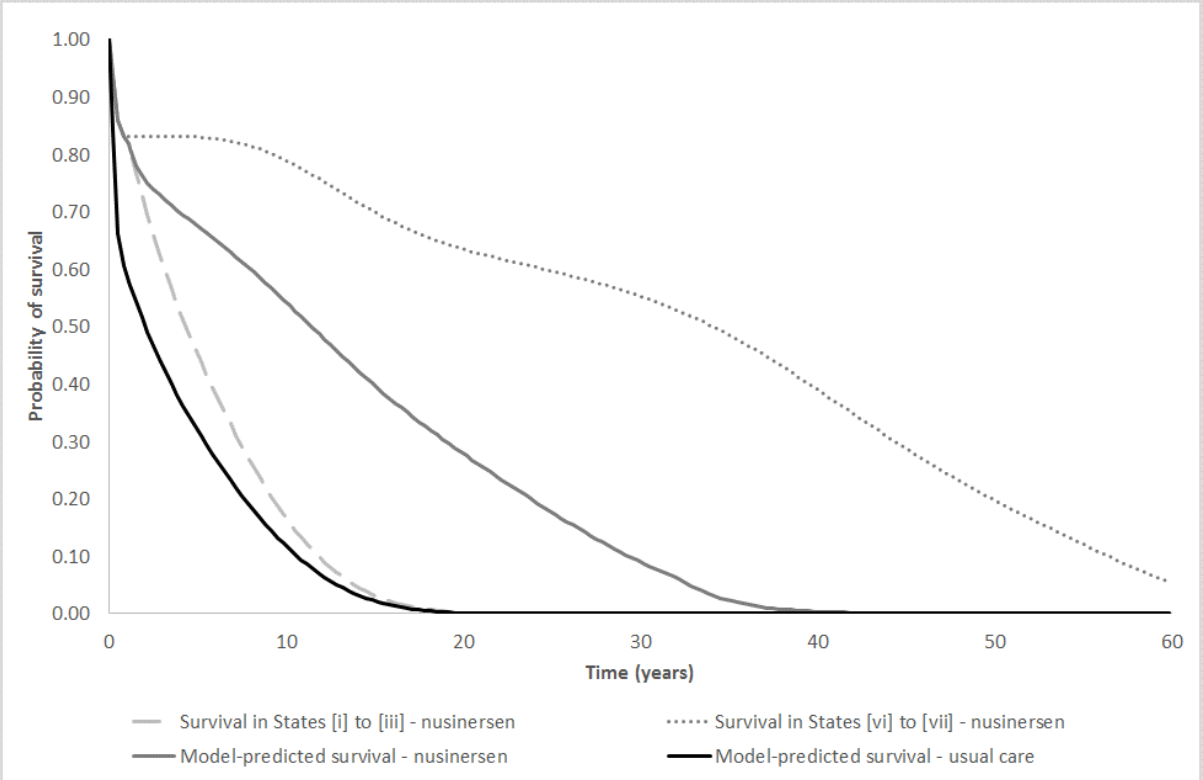
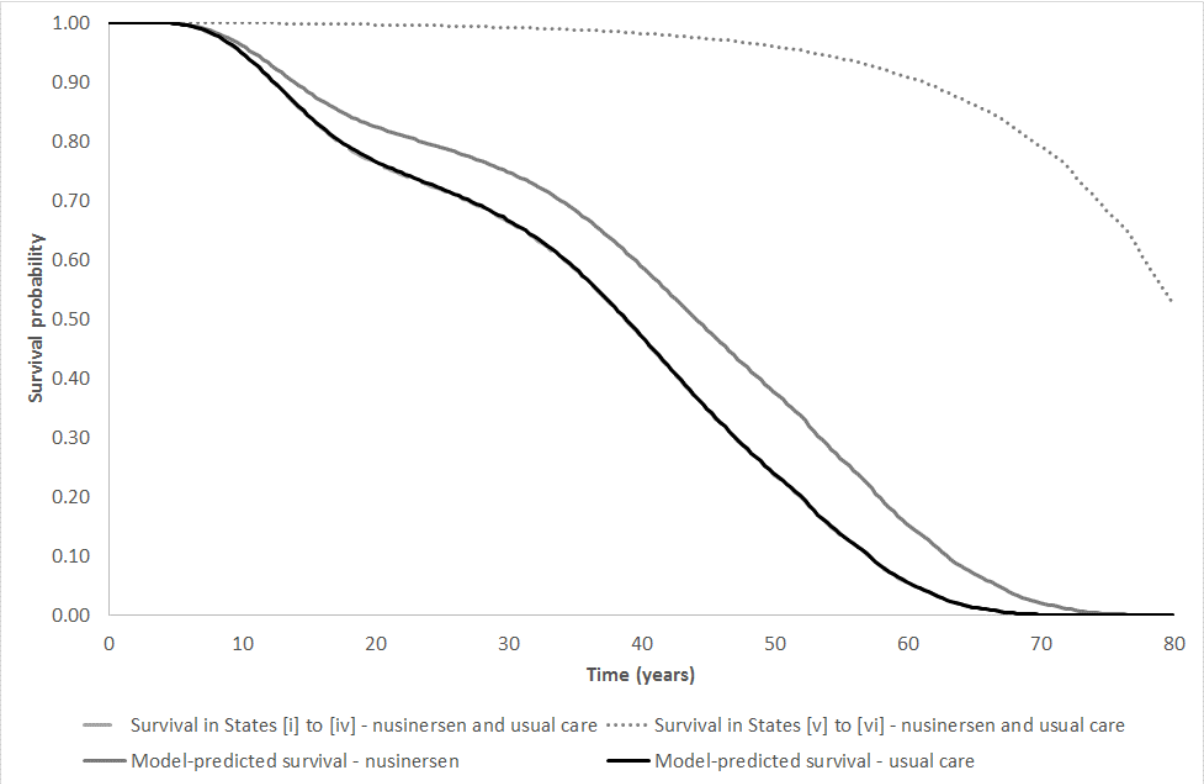


Figure 20: Fitted survival curves, later onset model



Note: the mortality adjustment has almost no effect in the usual care group due to the small proportion of patients in the best two states by the end of month 15

(ii) Use of external data from Gregoretti et al[31]

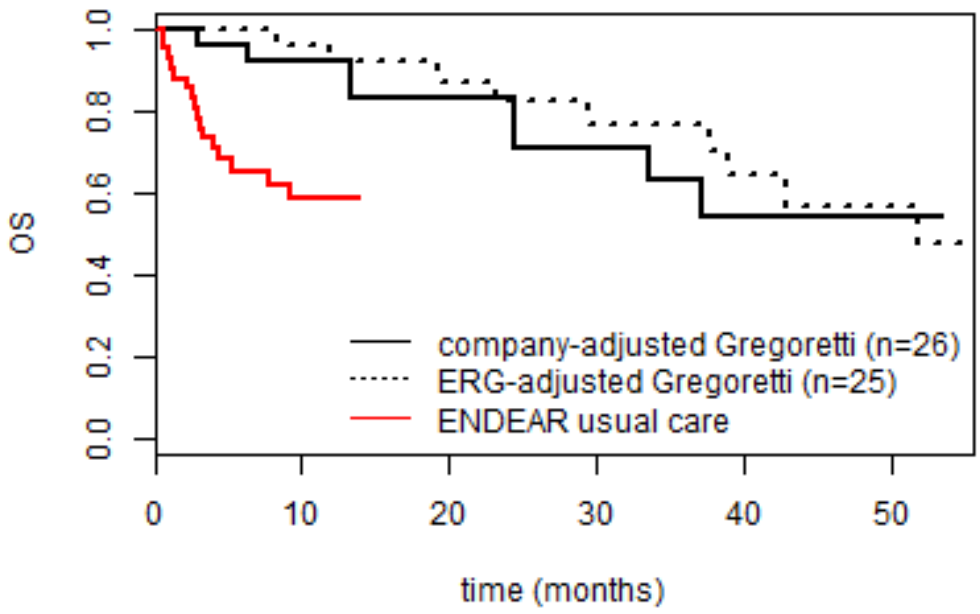
The ERG has concerns regarding the use of data from Gregoretti *et al*[31] to represent the usual care arm in ENDEAR. Of the 31 patients receiving NRA, 21 patients (67.8%) were over 3 months (~13 weeks) old at onset of symptoms, whereas in ENDEAR, patients tended to be younger at symptom onset (mean age of symptom onset of 9.6 weeks, range 1-20 weeks). As discussed in the original publication, mortality in the NRA cohort was higher (45.2%) than reported elsewhere.[57-59] The study authors comment that NIV and mechanically assisted coughing were used differently over the years of the study; the clinical advisors to the ERG noted that the reported outcomes from the study are poorer than would be expected in current clinical practice.

In order to fit parametric survival models, IPD were reconstructed by the company using the algorithm reported by Guyot *et al*.[44] The accuracy of the reconstruction depends on the amount of information provided in the original publication. In the case of Gregoretti *et al,*[31] the authors provide the total number of events (14 out of 31 patients died) but a number at risk table was not provided which results in a reconstruction with a higher degree of uncertainty. This is highlighted in Figure 21 by the difference between the ERG's reconstruction and that reported in Figure 34 of the CS.[1] A further limitation of the reconstructed IPD is the lack of information about important individual-level covariates. The company

adjusted the data to account for differences in the mean age of the populations, resulting in a reduction in the sample size from 31 to 26. However, there is potential for other confounding factors to remain.

The observed OS from ENDEAR and the adjusted Gregoretti *et al* NRA data are shown in Figure 21. There is a marked difference in OS between the two populations which indicates that the age-correction performed by the company was not sufficient to account for differences in baseline characteristics between the two groups. The company's clarification response[2] states that survival was "*greater than that expected from the clinical advice we received for UK patients and the sample size was small. From this paper there is insufficient information to draw conclusions on why survival was higher in the Italian patient population compared to the UK patient population*." (Company's clarification response,[2] question B12).

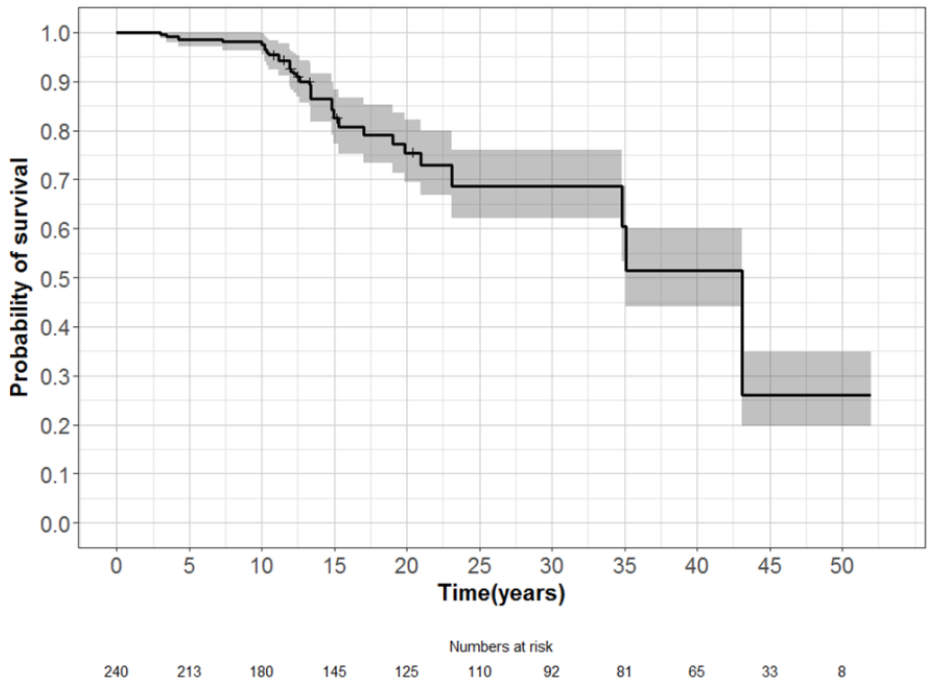
Figure 21: Kaplan-Meier OS estimates from adjusted Gregoretti *et al* and ENDEAR



(iii) Use of external data from Zerres et al[33]

The company's Kaplan-Meir curve of reconstructed IPD from Zerres *et al*[33] is shown in Figure 22. At 15 months, OS is 100%, as was observed in CHERISH. However, insufficient information was presented in Zerres *et al*[33] and the CS to allow the ERG to determine whether key characteristics of the two populations were similar.

Figure 22: Kaplan-Meier curve based on reconstructed IPD from Zerres *et al* (reproduced from CS, Figure 44)



The clinical advisors to the ERG noted that it is unclear whether any respiratory support was provided in the Zerres *et al* cohort. As this study predates publications on effective NIV use in paediatric cohorts, this is unlikely to reflect patients treated in current clinical practice.

(iv) Use of general population mortality

Beyond the trial data, OS is informed by general population mortality life tables.[32] OS is assumed to be systematically different between Gregoretti *et al* and the general population, or between Zerres *et al* and the general population, as characterised by a constant HR. The company acknowledge that the assumption of proportional hazards is not expected to hold; however, they state that "*this is a conservative approach since we would expect hazard rates to get closer to those from the general population with time. However, the available data did not provide information on how the hazard ratio may change over time*" (Company's clarification response,[2] question B13).

(v) Assumptions regarding treatment effect

The treatment effect in the first 13 months of the early onset model is derived from observed data in ENDEAR.[14] The company's preferred model (1-knot spline) provides a constant HR. Beyond the observed trial data, the company state that a conservative HR of 1.0 is applied in the base case; however, this is misleading as survival in the nusinersen treatment group is largely driven by an assumed switch to the Type II SMA mortality curve (proportion = 0.90).

(vi) Concerns regarding SMA type assumption

Survival for nusinersen-treated patients reaching model health states (iv) to (vii) was assumed to lie close to that observed in a Type II SMA population, with a weight of 0.90 applied to the survival prediction from Zerres *et al*[33] and a weight of 0.10 applied to the prediction from Gregoretti *et al.*[31] Justification of these weightings was provided by referencing an advisory board meeting on SMA.[45] However, no further details on how this figure was agreed or elicited were provided, despite a request from the ERG in clarification question B8.[2] Clinical advisors to the ERG considered that this was a large and optimistic assumption. The clinical advisors noted that there is a trade-off between gaining motor ability and placing a greater burden on the respiratory system, the impact of which is not clear.

(6) Issues relating to estimated patient utilities

(a) Poor face validity of patient utilities

The ERG considers that the mapped utility values used in the company's early and later onset models (see Table 43) have poor face validity. The worst states (early onset model - State [i] No milestones; later onset model - State [i] Sits without support but does not roll) are associated with a utility of [redacted], whilst the best states (early onset model - State [vii] Stand or walks without assistance; later onset model - State [vi] Walks without assistance) are associated with a utility of [redacted] The ERG considers that it is implausible that over the course of 10 years, a notional patient with SMA who never develops any motor milestones would accrue [redacted] undiscounted QALYs.

The ERG's clinical advisors also did not consider the company's patient utility values to be plausible, and noted in particular the high valuations for the worse states and the limited range of utility gain between the valuations for the best and worst states. They stated that although the utility of [redacted] for an infantile onset type I SMA patient who has achieved no milestones may be reasonable during the first few months of life (before motor function develops in healthy children), this would not be valid as the child gets older. One clinical advisor also commented that whilst mobility may have some influence on HRQoL, the ability of patients to participate in usual activities and a lack of negative symptoms (such as pain and infections) are likely to be key determinants of HRQoL.

(b) Issues relating to using mapped PedsQL data to represent utilities for patients with SMA

The algorithm used by the company (Khan *et al*[36]) mapped the PedsQL to the EQ-5D-Y (valued using the adult EQ-5D tariff). There are two main limitations associated with using the mapped values to generate utility values for patients with SMA.

Firstly, the study in which the mapping algorithm was developed was based on healthy schoolchildren aged 11-15 years. This population is very different to the populations represented within the company's models. The ERG believes that a healthy population completing both the PedsQL and EQ-5D-Y would

likely have very different responses to patients with early onset SMA or later onset SMA. Most of the children recruited into the mapping study had no problems in any dimensions of the EQ-5D-Y (percentage in Khan *et al*[36] with no problems in each domain - 95% mobility, 98% self-care, 95% usual activities, 76% pain/discomfort and 83% anxiety depression) and high PedsQL scores (scores of ≥80 in physical, emotional, social and school functioning, where the maximum score is 100). CHERISH PedsQL scores are not reported in the CS or the appendices, but they are unlikely to be as high as this in a population where severe motor function problems are characteristic of the disease. It is therefore unlikely that a mapping function developed in such a different population would be appropriate for the patient population under consideration. Khan *et al*[36] note that *"the performance of these algorithms in childhood populations, which differ according to age or clinical characteristics to our own, remains to be evaluated."*

Secondly, Khan *et al*[36] comment that they had few responses at the more severe end of the EQ-5D; this will have impacted upon the accuracy of the derived mapping functions. Mapping may overestimate the utility values for those at the severe end, primarily due to lack of data to accurately fit a regression model. The high utility values reported in the CS may well be a reflection of this problem.

In response to a request for clarification regarding to appropriateness of the mapping algorithm (see clarification response,[2] question B25), the company acknowledged that the Khan *et al*[36] mapping algorithm is *"not ideal"*, but noted that as the PedsQL was the only HRQoL questionnaire administered in either clinical trial (ENDEAR or CHERISH), mapping should be undertaken. The ERG disagrees and notes that two alternative sources could have been used: Bastida *et al*[37] and Lloyd *et al*[46] (previously described in Section 5.3.3). Whilst these studies used parents/clinicians as a proxy for SMA patients, both studies include valuations for health states associated with SMA.

Within Bastida *et al,*[37] mean values from UK respondents were reported to be [redacted] for Type I, [redacted] for Type II and [redacted] for SMA Type III (see Table 74). Health state valuations were highly variable between respondents from each country. Within Lloyd *et al*,[46] clinicians' valuations of health states for Type I SMA health states ranged from -0.33 to 0.71, whilst valuations for Type II SMA health states ranged from -0.13 to 0.72. The clinical advisors to the ERG commented that whilst Bastida *et al*[37] and Lloyd *et al*[46] are not subject to the same methodological problems as the mapping analysis, they also appear to have limited face validity, in particular, due to the very low (negative) valuations for patients in the worst health states which undermines the HRQoL of non-ambulant patients. The clinical advisors further commented that the valuations from these studies may not reflect those of other clinicians and families of SMA patients.

Table 74: EQ-5D utilities (parent proxy) reported by Bastida *et al*

SMA type	UK	Spain	France	Germany
All SMA types	[redacted]	[redacted]	[redacted]	[redacted]
Type I SMA	[redacted]	[redacted]	[redacted]	[redacted]
Type II SMA	[redacted]	[redacted]	[redacted]	[redacted]
Type III SMA	[redacted]	[redacted]	[redacted]	[redacted]

SMA - spinal muscular atrophy

Table 75: Elicited utilities from Lloyd *et al* vignette study

SMA Type I health states and associated HRQoL scores	
Health state	**Utility value**
Baseline	-0.12
Worsened	-0.24
Improvement	-0.17
Reclassified as SMA Type II	-0.04
Stands with assistance	0.04
Walks with assistance*	0.52
Reclassified as SMA Type III*	0.71
SMA after scoliosis surgery	-0.22
Gastric/nasogastric tube	-0.17
Requires ventilation	-0.33
SMA Type II health states and associated HRQoL scores	
HFMSE health state	**Utility value**
Baseline	0.04
Worsened	-0.13
Mild improvement	0.04
Moderate improvement	0.10
Stands/walks with assistance*	0.39
Stands/walks unaided	0.72
Loss of ambulation with/without assistance*	-0.12

SMA - spinal muscular atrophy; HRQoL – health-related quality of life
** Denotes health states where 2 index scores were calculated for one of the participants*

Overall, the ERG considers that none of the sources are ideal, but prefers the vignette study[46] as this broadly aligns with the final models' health states and is based on EQ-5D assessments of clinical experts in SMA. The ERG also notes that owing to the company's extrapolation assumptions regarding no deterioration in motor function for nusinersen-treated patients and no motor function improvement for patients receiving usual care, the utility values for the best and worst states have the greatest influence on the ICER in both the early and later onset models.

(7) Arbitrary calculations underpinning caregiver disutilities

Carer health utility values are based on self-reported EQ-5D-5L values of carers of patients with SMA (Bastida *et al*[37]). No detail is provided on the scoring of the EQ-5D-5L. Caregiver health utility values are adjusted by patient disutility between different states; the difference between this adjusted utility value and general population utility is used to calculate the caregiver disutility. The reasons for adjusting

are not clear from the CS.[1] The ERG has three main issues relating to the company's approach to estimating caregiver disutilities:

(i) Caregiver utilities are estimated based on differences in patient utility between HINE-2/HFMSE health states. However, it is unclear whether the impact of achieving a particular milestone for a patient would be equal to that for a carer, and the assumption that the ordering of health states for patients is the same as that for impacts on caregivers health is not adequately justified in the CS. One clinical advisor to the ERG considered that some degree of correlation might be expected, but noted that caregiver burden would be driven by other factors besides restricted motor function e.g. the incidence of recurrent infections and pain, educational development, availability of support and emotional burden. The other clinical advisor stated that impacts on carers are *"very individual and impossible to tease out."*

(ii) The calculations used in the company's model are arbitrary and most are informed by utilities for other states than the one being valued.

(iii) The ERG and its clinical advisors do not consider the patient utilities obtained from the mapping study to have face validity. This has a direct impact on the face validity of the company's estimated caregiver disutilities.

Given that Bastida *et al*[37] reports EQ-5D utilities from caregivers according to SMA type (see Table 75), it is unclear why these estimates were not used directly for health states defined by milestones associated with SMA type (as is assumed for the health state costs).

Table 76: Caregiver utilities reported by Bastida *et al*[37]

SMA type	Caregiver utility value			
	UK	Spain	France	Germany
All SMA types	[redacted]	[redacted]	[redacted]	[redacted]
Type I SMA	[redacted]	[redacted]	[redacted]	[redacted]
Type II SMA	[redacted]	[redacted]	[redacted]	[redacted]
Type III SMA	[redacted]	[redacted]	[redacted]	[redacted]

SMA - spinal muscular atrophy

(8) Issues relating to health state costs

The ERG notes the following issues relating to the costs included in the company's models:

(i) End-of-life costs are included in the early onset model, but not the later onset model. This is inconsistent.

(ii) The model does not include a cost associated with scoliosis surgery. The inclusion of scoliosis surgery costs is, however, unlikely to have a significant impact on the ICER for nusinersen.

(iii) Health state costs are taken from the cross-sectional study reported by Bastida *et al.*[37] Clinical advisors to the ERG noted that the estimated costs for Type I SMA and Type II SMA milestones appeared to be low, given the high degree of dependency associated with these

patients and the resources required to manage their condition. Both clinical advisors noted that the costs of managing SMA are likely to be dependent on age. This is not captured in the company's models.

(9) Representation of uncertainty

As highlighted in Table 49 and Table 66, the company's PSA in both the early and later onset models is subject to limitations, specifically:

(i) Several uncertain model parameters (for example, the initial distributions and the mortality adjustment factors) are held fixed at their mean values. These values are uncertain and should be characterised using probability distributions.

(ii) Health utilities are sampled using a single random number. This leads to over-correlation between each individual health state utility value;[47] as such, the uncertainty surrounding these parameters will be underestimated.

(iii) Priors are included for some but not all unobserved transitions (the ERG presumes that this is to ensure that the assumptions concerning improvement/deterioration of motor function are maintained in the PSA).

However, the ERG notes that correcting these issues is likely to have a negligible impact on the probabilistic ICER for nusinersen.

More generally, the post-trial transition probabilities, the patient health utilities and the mortality risks applied in both the early and later onset models are all highly uncertain. The ERG does not consider the company's exploration of the impact of this uncertainty to be sufficient.

5.6 Exploratory analyses undertaken by the ERG

5.6.1 ERG's exploratory analyses - methods

The ERG undertook eight sets of exploratory analyses; the same analyses were applied to both the early and later onset models. The ERG's preferred analysis includes: (i) the use of a common initial distribution across health states for both treatment groups; (ii) the inclusion of end-of-life costs for the later onset population; (iii) the use of patient utilities from Lloyd *et al*[46] and (iv) the application of caregiver utilities by SMA type (from Bastida *et al*[37]) to states relating to SMA milestones. Additional sensitivity analyses were undertaken using the ERG's analysis to explore: (i) the use of alternative HRQoL estimates for patients; (ii) the exclusion of the mortality adjustment factor applied to the better health states and (iii) alternative assumptions regarding long-term transition probabilities. The methods used to implement these analyses are described below; technical details for implementing the analyses in the company's models are presented in Appendix 4.

Exploratory analysis 1: Use of the average initial distribution for both treatment groups

Within this analysis, the initial distributions were set equal to the weighted average probability of being in each state in both groups at baseline in ENDEAR[14] and CHERISH.[15] The correction of this error is applied to all subsequent exploratory analyses.

Exploratory analysis 2: Inclusion of end-of-life costs for the later onset model

In order to maintain consistency between the early and later onset models, end-of-life costs were included in the later onset model. No amendment was made to the early onset model as these costs were already included.

Exploratory analysis 3: Use of patient utilities from the vignette study

As discussed in Section 5.5, the ERG has concerns regarding the validity of the utilities based on mapping the PedsQL data to the EQ-5D. Within this analysis, the data reported in the abstract by Lloyd *et al*[46] for Type I SMA are applied to the early onset model and the values for Type II SMA are applied to the later onset model (see Table 77). The ERG recognises that, based on clinical advice, the values for the worse health states also appear to be subject to face validity issues.

Table 77: Health utilities from vignette study applied in ERG's exploratory analyses

Early onset model		
HINE-2 health state	**Mapped PedsQL utility (company's base case[1])**	**Utilities elicited within vignette study[46]**
No milestones achieved	[redacted]	-0.24
Mild milestones	[redacted]	-0.12
Moderate milestones	[redacted]	-0.17
Sits without support	[redacted]	-0.04
Stands with assistance	[redacted]	0.04
Walks with assistance	[redacted]	0.52
Stands/Walks unaided	[redacted]	0.71
Later onset model		
HFMSE health state	**Mapped PedsQL utility (company's base case[1])**	**Utilities elicited within vignette study[46]**
Sits without support but does not roll	[redacted]	0.04*
Sits and rolls independently	[redacted]	0.04†
Sits and crawls with hands and knees	[redacted]	0.10‡
Stands/Walks with assistance	[redacted]	0.39
Stands unaided	[redacted]	0.72
Walks unaided	[redacted]	0.72

HINE-2 - Module 2 of the Hammersmith Infant Neurological Examination; HFMSE - Hammersmith Functional Motor Scale-Expanded; PedsQL - Paediatric Quality of Life Inventory

** Assumed to reflect "Baseline" state in vignette study; † Assumed to reflect "Mild improvement" state in vignette study; ‡ Assumed to reflect "Moderate improvement" state in vignette study*

Exploratory analysis 4: Application of caregiver utilities by SMA type from Bastida et al[37] to states relating to SMA milestones in both the early and later onset models

As discussed in Section 5.5 (critical appraisal point 7), the ERG considers that the company's approach to incorporating health state-dependent caregiver disutilities is arbitrary and lacks adequate justification. Given that caregiver EQ-5D values are reported by SMA type within Bastida *et al*,[37] the ERG considers the use of these data directly to be more appropriate than the values applied within the company's models.

Table 78: Caregiver utilities applied in the ERG's exploratory analyses

Early onset model		
HINE-2 health state	**Caregiver utility applied in company's base case[1])**	**Caregiver utilities from Bastida *et al*[37] applied in ERG exploratory analysis**
No milestones achieved	[redacted]	[redacted]
Mild milestones		
Moderate milestones		
Sits without support		
Stands with assistance		
Walks with assistance		
Stands/Walks unaided		
Later onset model		
HFMSE health state	**Caregiver utility applied in company's base case[1])**	**Caregiver utilities from Bastida *et al*[37] applied in ERG exploratory analysis**
Sits without support but does not roll	[redacted]	[redacted]
Sits and rolls independently		
Sits and crawls with hands and knees		
Stands/Walks with assistance		
Stands unaided		
Walks unaided		

HINE-2 - Module 2 of the Hammersmith Infant Neurological Examination; HFMSE - Hammersmith Functional Motor Scale-Expanded; ERG - Evidence Review Group
** Based on SMA Type I ; † Based on SMA Type II; ‡ Based on SMA Type III*

Exploratory analysis 5: ERG-preferred analysis

The ERG's preferred analysis combines exploratory analyses (i) to (iv). It should be noted that this analysis does not address the ERG's concerns regarding the company's modelled survival and motor function trajectories. As such, the ERG's "preferred" ICERs are very likely to be underestimated in both SMA populations.

Exploratory analysis 6: Use of alternative patient HRQoL estimates (Bastida et al[37] and expert clinical judgement)

Two alternative analyses were undertaken to explore the impact of using different HRQoL estimates for patients with SMA:

(6a) Analysis using utilities reported by Bastida *et al.*[37] Within this analysis, the UK patient utilities by SMA type reported by Bastida *et al*[37] (Type I utility=[redacted]; Type II utility=[redacted]; Type III utility=[redacted]) are applied to the model health states defined by milestones consistent with these SMA types.

(6b) Analysis using HRQoL estimates obtained from ERG clinical advisors. Within this analysis, the clinical advisors to the ERG were asked to provide plausible estimates of HRQoL for the health states included in the company's early and later onset models (see Table 79). It should be noted that these HRQoL estimates should be interpreted with caution as they are not preference-based.

Table 79: Clinical advisors' estimates of HRQoL associated with model health states

Early onset model	
HINE-2 health state	**HRQoL estimate**
No milestones achieved	0.20
Mild milestones	0.25
Moderate milestones	0.35
Sits without support	0.60
Stands with assistance	0.65
Walks with assistance	0.75
Stands/Walks unaided	0.85
Later onset model	
HFMSE health state	**HRQoL estimate**
Sits without support but does not roll	0.60
Sits and rolls independently	0.60
Sits and crawls with hands and knees	0.60
Stands/Walks with assistance	0.75
Stands unaided	0.85
Walks unaided	0.85

HRQoL - health-related quality of life; HINE-2 - Module 2 of the Hammersmith Infant Neurological Examination; HFMSE - Hammersmith Functional Motor Scale-Expanded

Exploratory analysis 7: Exclusion of mortality adjustment factors for better health states

Within this analysis, the mortality adjustment factors applied to the better health states were set equal to zero. The ERG also believes that there would be value in exploring alternative simpler parametric models for OS rather than applying complex piecewise methods using multiple external data sources as the company noted that some of these were plausible; however, these models were not reported in the CS.[1]

Exploratory analysis 8: Alternative assumptions regarding long-term transition probabilities

Five alternative scenario analyses were undertaken using the ERG's preferred models to explore the impact of long-term transition probabilities on the cost-effectiveness of nusinersen versus usual care:

(8a) 5% nusinersen patients lose milestones during each cycle (subtracted proportionally from those improving and those remaining in their current state)

(8b) 10% nusinersen patients lose milestones during each cycle (subtracted proportionally from those improving and those remaining in their current state)

(8c) 20% nusinersen patients lose milestones during each cycle (subtracted proportionally from those improving and those remaining in their current state)

(8d) All patients remain their final health state after the end of follow-up in ENDEAR[14]/CHERISH[15] (applied to both treatment groups)

(8e) All patients lose all milestones previously achieved immediately after the end of follow-up in ENDEAR[14]/CHERISH[15] (applied to both treatment groups). The ERG notes that this latter analysis is particularly pessimistic.

5.6.2 Results of the ERG's exploratory analyses – early onset SMA

The results of the ERG's preferred analysis are presented in Table 80. Additional exploratory analyses undertaken using the ERG's preferred model are presented in Table 81. All exploratory analyses were undertaken using the deterministic version of the company's model; the ERG expects that the probabilistic ICERs would be slightly higher.

As shown in Table 80, the application of a common initial distribution has only a minor impact on the ICER for nusinersen. The use of utilities from the vignette study[46] increases the ICER when only patient health gains are considered, but decreases the ICER when caregiver QALY losses are also included. The use of caregiver utilities by SMA type reported by Bastida *et al*[37] increases the ICER considerably. When these amendments are combined within the ERG's preferred analysis, nusinersen is expected to produce 5.2 incremental QALYs at an additional cost of £2,192,722 per patient compared with usual care. The inclusion of caregiver QALY losses reduces the incremental health gain to 3.47 QALYs. The ICERs for nusinersen versus usual care are estimated to be £421,303 per QALY gained (including patient health gains only) and £631,583 per QALY gained (including patient health gains and caregiver QALY losses).

It should be noted that the ERG's preferred analysis does not include any modification to the company's optimistic assumptions regarding survival and motor function trajectories; as such, it is very likely that the true ICERs for nusinersen will be higher. The additional exploratory analyses presented in Table 81 indicate that the use of alternative patient utilities from Bastida *et al*,[37] the exclusion of the mortality adjustment factor and the inclusion of assumptions regarding nusinersen-treated patients losing milestones have the propensity to considerably increase the ICER for nusinersen.

Table 80: ERG preferred analysis, early onset

Option	QALYs (patient)	QALYs (patient+ caregiver)	Cost	Inc. QALYs (patient)	Inc. QALYs (patient+ caregiver)	Inc. cost	ICER (patient)	ICER (patient+ caregiver)
Company's base case								
Nusinersen	7.86	7.61	£2,258,852	5.37	5.44	£2,187,311	**£407,605**	**£402,361**
Usual care	2.49	2.17	£71,540	-	-	-	-	-
ERG exploratory analysis 1 – mean initial distribution applied to both treatment group								
Nusinersen	7.87	7.63	£2,264,226	5.38	5.45	£2,192,722	**£407,417**	**£402,159**
Usual care	2.49	2.18	£71,504	-	-	-	-	-
ERG exploratory analysis 2 - include end-of-life cost								
Nusinersen	7.87	7.63	£2,264,226	5.38	5.45	£2,192,722	**£407,417**	**£402,159**
Usual care	2.49	2.18	£71,504	-	-	-	-	-
ERG exploratory analysis 3 – patient utilities based on vignette study (Lloyd *et al*[46])								
Nusinersen	4.42	4.15	£2,264,226	5.20	5.56	£2,192,722	**£421,303**	**£394,023**
Usual care	-0.78	-1.42	£71,504	-	-	-	-	-
ERG exploratory analysis 4 - caregiver utilities based on Bastida *et al*[37]								
Nusinersen	7.87	5.88	£2,264,226	5.38	3.65	£2,192,722	**£407,417**	**£600,882**
Usual care	2.49	2.23	£71,504	-	-	-	-	-
ERG exploratory analysis 5 - ERG preferred analysis (including ERG analyses 1, 2, 3 and 4)								
Nusinersen	4.42	2.43	£2,264,226	5.20	3.47	£2,192,722	**£421,303**	**£631,583**
Usual care	-0.78	-1.04	£71,504	-	-	-	-	-

ERG - Evidence Review Group; QALY - quality-adjusted life year; ICER - incremental cost-effectiveness ratio; Inc. - incremental

Table 81: Additional exploratory analyses undertaken using the ERG preferred model, early onset

Option	QALYs (patient)	QALYs (patient+ caregiver)	Cost	Inc. QALYs (patient)	Inc. QALYs (patient+ caregiver)	Inc. cost	ICER (patient)	ICER (patient+ caregiver)
ERG exploratory analysis 6a - patient utilities based on Bastida *et al*[37]								
Nusinersen	3.87	1.88	£2,264,226	3.23	1.49	£2,192,722	**£679,469**	**£1,467,413**
Usual care	0.64	0.38	£71,504	-	-	-	-	-
ERG exploratory analysis 6b - patient HRQoL estimates based on clinical judgement								
Nusinersen	6.69	4.70	£2,264,226	5.99	4.25	£2,192,722	**£366,289**	**£515,511**
Usual care	0.70	0.44	£71,504	-	-	-	-	
ERG exploratory analysis 7 - no mortality adjustment								
Nusinersen	1.16	0.45	£1,188,262	1.95	1.49	£1,116,759	**£573,922**	**£750,195**
Usual care	-0.78	-1.04	£71,504	-	-	-	-	-
ERG exploratory analysis 8a- 5% nusinersen patients lose milestones each cycle								
Nusinersen	4.00	2.27	£2,229,247	4.79	3.31	£2,157,744	**£450,926**	**£652,213**
Usual care	-0.78	-1.04	£71,504	-	-	-	-	-
ERG exploratory analysis 8b- 10% nusinersen patients lose milestones each cycle								
Nusinersen	3.45	1.98	£2,175,120	4.23	3.02	£2,103,616	**£496,787**	**£696,405**
Usual care	-0.78	-1.04	£71,504	-	-	-	-	-
ERG exploratory analysis 8c- 20% nusinersen patients lose milestones each cycle								
Nusinersen	2.01	1.04	£1,957,022	2.79	2.09	£1,885,518	**£674,945**	**£904,003**
Usual care	-0.78	-1.04	£71,504	-	-	-	-	-
ERG exploratory analysis 8d – all patients stay in final state indefinitely after end of ENDEAR								
Nusinersen	-0.66	-1.03	£1,660,017	0.09	-0.01	£1,588,513	**£16,788,055**	**Dominated**
Usual care	-0.76	-1.02	£71,504	-	-	-	-	-
ERG exploratory analysis 8e – all patients lose all milestones after end of ENDEAR								
Nusinersen	-1.03	-1.37	£567,615	-0.25	-0.33	£496,111	**Dominated**	**Dominated**
Usual care	-0.78	-1.04	£71,504	-	-	-	-	-

ERG - Evidence Review Group; QALY - quality-adjusted life year; ICER - incremental cost-effectiveness ratio; Inc. - incremental

5.6.3 Results of the ERG's exploratory analyses – later onset SMA

The results of the ERG's preferred analysis are presented in Table 82. Additional exploratory analyses undertaken using the ERG's preferred model are presented in Table 83.

As shown in Table 82, the application of a common initial distribution and the inclusion of end-of-life care costs slightly reduces the ICER nusinersen in the later onset population. The use of utilities for later onset SMA from the vignette study[46] significantly reduces the ICER for nusinersen. In contrast, the inclusion of caregiver utilities by SMA type from Bastida *et al*[37] drastically reduces the net QALY gains accrued when caregiver QALY losses are included in the analysis. When these amendments are combined within the ERG's preferred analysis, nusinersen is expected to produce 7.37 incremental QALYs at an additional cost of £3,014,078 per patient compared with usual care. The inclusion of caregiver QALY losses reduces the net incremental health gain to 4.76 QALYs. The ICERs for nusinersen versus usual care are estimated to be £408,769 per QALY gained (including patient health gains only) and £632,850 per QALY gained (including patient health gains and caregiver QALY losses).

Again, the ERG's preferred analysis for the later onset population does not include any modification to the company's optimistic assumptions regarding survival and motor function trajectories; as such, it is very likely that the true ICERs for nusinersen will be higher. The additional exploratory analyses presented in Table 83 indicate that the use of alternative patient utilities from Bastida *et al,*[37] the use of HRQoL estimates from the ERG's clinical advisors, and the inclusion of assumptions regarding nusinersen-treated patients losing milestones have the propensity to result in considerably higher ICERs for nusinersen. The ERG notes that the exclusion of the mortality adjustment factor results in less favourable ICERs for nusinersen, however the impact is less marked than that for the early onset model.

Table 82: ERG preferred analysis, later onset

Option	QALYs (patient)	QALYs (patient+ caregiver)	Cost	Inc. QALYs (patient)	Inc. QALYs (patient+ caregiver)	Inc. cost	ICER (patient)	ICER (patient+ caregiver)
Company's base case								
Nusinersen	16.88	15.66	£3,148,754	2.37	3.30	£2,964,442	**£1,252,991**	**£898,164**
Usual care	14.52	12.36	£184,312	-	-	-	-	-
ERG exploratory analysis 1 – mean initial distribution applied to both treatment group								
Nusinersen	16.95	15.76	£3,200,341	2.47	3.47	£3,014,655	**£1,221,051**	**£869,639**
Usual care	14.48	12.29	£185,686	-	-	-	-	-
ERG exploratory analysis 2 - include end-of-life cost								
Nusinersen	16.95	15.76	£3,203,766	2.47	3.47	£3,014,078	**£1,220,817**	**£869,472**
Usual care	14.48	12.29	£189,688	-	-	-	-	-
ERG exploratory analysis 3 – patient utilities based on vignette study (Lloyd *et al*[46])								
Nusinersen	8.53	7.34	£3,200,341	7.37	8.37	£3,014,655	**£408,847**	**£360,122**
Usual care	1.15	-1.03	£185,686	-	-	-	-	-
ERG exploratory analysis 4 - caregiver utilities based on Bastida *et al*[37]								
Nusinersen	16.95	13.54	£3,200,341	2.47	-0.14	£3,014,655	**£1,221,051**	**Dominated**
Usual care	14.48	13.68	£185,686	-	-	-	-	-
ERG exploratory analysis 5 - ERG preferred analysis (including ERG analyses 1, 2, 3 and 4)								
Nusinersen	8.53	5.12	£3,203,766	7.37	4.76	£3,014,078	**£408,769**	**£632,850**
Usual care	1.15	0.36	£189,688	-	-	-	-	-

ERG - Evidence Review Group; QALY - quality-adjusted life year; ICER - incremental cost-effectiveness ratio; Inc. - incremental

Table 83: Additional exploratory analyses undertaken using the ERG preferred model, later onset

Option	QALYs (patient)	QALYs (patient+ caregiver)	Cost	Inc. QALYs (patient)	Inc. QALYs (patient+ caregiver)	Inc. cost	ICER (patient)	ICER (patient+ caregiver)
ERG exploratory analysis 6a - patient utilities based on Bastida *et al*[37]								
Nusinersen	6.97	3.56	£3,203,766	4.80	2.19	£3,014,078	**£627,612**	**£1,375,278**
Usual care	2.16	1.37	£189,688	-	-	-	-	-
ERG exploratory analysis 6b - patient HRQoL estimates based on clinical judgement								
Nusinersen	15.44	12.03	£3,203,766	3.54	0.93	£3,014,078	**£850,597**	**£3,231,764**
Usual care	11.89	11.10	£189,688	-	-	-	-	
ERG exploratory analysis 7 - no mortality adjustment								
Nusinersen	7.49	4.42	£2,929,515	6.34	4.07	£2,739,998	**£432,191**	**£673,128**
Usual care	1.15	0.35	£189,517	-	-	-	-	-
ERG exploratory analysis 8a- 5% nusinersen patients lose milestones each cycle								
Nusinersen	6.78	4.03	£2,756,403	5.63	3.67	£2,566,715	**£455,934**	**£699,062**
Usual care	1.15	0.36	£189,688					
ERG exploratory analysis 8b- 10% nusinersen patients lose milestones each cycle								
Nusinersen	4.97	2.88	£2,296,390	3.81	2.52	£2,106,702	**£552,283**	**£834,754**
Usual care	1.15	0.36	£189,688					
ERG exploratory analysis 8c- 20% nusinersen patients lose milestones each cycle								
Nusinersen	2.49	1.28	£1,539,734	1.34	0.92	£1,350,046	**£1,011,268**	**£1,459,562**
Usual care	1.15	0.36	£189,688					
ERG exploratory analysis 8d – all patients stay in final state indefinitely after end of CHERISH								
Nusinersen	2.85	1.72	£2,993,988	0.81	0.73	£2,809,679	**£3,465,629**	**£3,831,118**
Usual care	2.04	0.98	£184,309	-	-	-	-	-
ERG exploratory analysis 8e – all patients lose all milestones after end of CHERISH								
Nusinersen	0.91	0.20	£721,228	0.04	0.03	£529,189	**£14,994,339**	**£18,436,952**
Usual care	0.88	0.17	£192,038	-	-	-	-	-

ERG - Evidence Review Group; QALY - quality-adjusted life year; ICER - incremental cost-effectiveness ratio; Inc. - incremental

5.7 Discussion

The CS[1] includes a systematic review of published economic evaluations of treatments for SMA together with two *de novo* health economic evaluations of nusinersen for the treatment of early onset and later onset SMA. The company's review did not identify any economic evaluations of treatments for SMA.

The company's early onset model assesses the cost-effectiveness of nusinersen versus usual care for the treatment of patients with early onset SMA (initial age = 5.58 months), based on the ENDEAR trial. The incremental health gains, costs and cost-effectiveness of nusinersen are evaluated over a 60-year time horizon from the perspective of the NHS and PSS. The company's early onset model adopts a state transition approach, with health states defined by motor function milestones based on the HINE-2 instrument. The model parameters were largely informed by: HINE-2 and CHOP INTEND outcomes collected within ENDEAR;[14] mortality outcomes from ENDEAR[14] and other observational data (Gregoretti *et al*,[31] Zerres *et al*[33] and general population life tables[32]); a mapping exercise to translate PedsQL outcomes collected in the CHERISH trial to the EQ-5D;[1, 36] a cross-sectional study of the costs and caregiver HRQoL impacts of SMA[37] and standard costing sources.[39] The model assumes that treatment using nusinersen will be discontinued for patients who do not achieve any milestones (or lose previously achieved milestones) after 13 months, and for patients undergoing scoliosis surgery who cannot subsequently receive nusinersen administration via lumbar puncture. The company's early onset model employs two key assumptions: (i) after month 13, nusinersen-treated patients who reach health states consistent with Type II/III SMA milestones gain an additional survival advantage, and (ii) after month 13, the motor function of nusinersen-treated patients cannot deteriorate, whilst the motor function of patients receiving usual care cannot improve.

Based on a re-run of the probabilistic version of the company's early onset model by the ERG, nusinersen is expected to generate an additional 5.29 QALYs at an additional cost of £2,160,048 per patient; the corresponding ICER for nusinersen versus usual care is £408,712 per QALY gained. The inclusion of caregiver QALY losses leads to a slightly lower probabilistic ICER of £404,270 per QALY gained. The probability that nusinersen produces more net benefit than usual care at WTP thresholds below £337,000 per QALY gained is approximately zero. The company's subgroup analyses suggest that the cost-effectiveness profile for nusinersen may be improved in early onset SMA patients with shorter disease duration (≤12 weeks subgroup ICER≈£375,000 per QALY gained, ICER includes patient health gains only).

The company's later onset model assesses the cost-effectiveness of nusinersen versus usual care for the treatment of patients with later onset SMA (initial age = 43.71 months), based on the CHERISH trial. The incremental health gains, costs and cost-effectiveness of nusinersen are evaluated over an 80-year

time horizon from the perspective of the NHS and PSS. The company's later onset model adopts a state transition approach, with health states defined by motor function milestones based on the HFMSE instrument. The model parameters were largely informed by: HFMSE outcomes collected within CHERISH;[15] mortality outcomes from CHERISH[15] and other observational data (Zerres *et al*[33] and general population life tables[32]), and the same cost and HRQoL sources as those used in the early onset model[37, 39] (see above). The company's model assumes that treatment using nusinersen will be discontinued for patients who do not achieve milestones beyond the Sits without support but does not roll state after 15 months, and for patients undergoing scoliosis surgery who cannot subsequently receive nusinersen administration via lumbar puncture. The later onset model includes two key assumptions: (i) after month 15, patients in either treatment group who reach health states consistent with Type III SMA milestones 15 gain an additional survival advantage, and (ii) after month 15, the motor function of nusinersen-treated patients cannot deteriorate, whilst the motor function of patients receiving usual care cannot improve.

Based on a re-run of the probabilistic version of the company's later onset model by the ERG, nusinersen is expected to generate an additional 2.28 QALYs at an additional cost of £2,938,441 per patient: the corresponding ICER for nusinersen versus usual care is £1,286,149 per QALY gained. The inclusion of caregiver QALY losses leads to a markedly lower probabilistic ICER of £933,088 per QALY gained. The probability that nusinersen produces more net benefit than usual care is approximately zero even at WTP thresholds of £500,000 per QALY gained. The company's subgroup analyses are inconclusive with respect to whether the cost-effectiveness profile for nusinersen is improved for later onset SMA patients with shorter disease duration (<25 months).

The ERG's critical appraisal identified a number of issues relating to the company's economic analyses and the evidence used to inform them. The most pertinent of these include: (i) the absence of economic evidence relating to Type 0 and Type IV SMA; (ii) the unnecessary complexity of the company's implemented models; (iii) highly favourable assumptions regarding the expected trajectory of nusinersen-treated patients through modelled motor milestone health states; (iv) highly favourable assumptions regarding the expected survival of nusinersen-treated patients; (v) poor face validity of patient utilities used in the models, and (vi) arbitrary calculations underpinning the caregiver disutilities used in the models.

The ERG undertook eight sets of exploratory analyses using the deterministic version of the company's models. The ERG's preferred scenario includes: (i) the use of a common initial distribution across health states for both treatment groups; (ii) the inclusion of end-of-life costs for the later onset population; (iii) the use of patient utilities from the vignette study[46] and (iv) the application of caregiver utilities by SMA type from Bastida *et al*[37] to states relating to SMA milestones in both the early and later onset models.

Importantly, the preferred analyses do not address the ERG's concerns regarding the optimistic assumptions underpinning the company's modelled survival and motor function trajectories; as such, it is very likely that the true ICERs for nusinersen will be higher. In order to address this uncertainty, additional sensitivity analyses were undertaken to explore the use of alternative patient utilities, the exclusion of the mortality adjustment factors and alternative long-term transition probabilities.

The ERG's preferred analyses within the early onset population results in ICERs for nusinersen versus usual care of £421,303 per QALY gained (including patient health gains only) and £631,583 per QALY gained (including patient health gains and caregiver QALY losses). The ERG's additional exploratory analyses lead to ICERs ranging from £366,289 per QALY gained to dominated.

The ERG's preferred ICER for nusinersen versus usual care in the later onset population is estimated to be £408,769 per QALY gained (including patient health gains only). The inclusion of caregiver QALY losses increases the ICER to £632,850 per QALY gained. The ERG's additional exploratory analyses lead to ICERs ranging from £432,191 per QALY gained to in excess of £18.4million per QALY gained.

6. END OF LIFE

NICE end of life supplementary advice should be applied in the following circumstances and when all the criteria referred to below are satisfied:

- The treatment is indicated for patients with a short life expectancy, normally less than 24 months and;
- There is sufficient evidence to indicate that the treatment offers an extension to life, normally of at least an additional 3 months, compared to current NHS treatment.

The CS[1] makes the case that NICE's end of life criteria apply to the infantile onset SMA population, but not for the later onset population. The ERG agrees that the later onset population does not meet the end of life criteria. The evidence presented in this chapter therefore relates only to the early onset (Type I) SMA population. Table 84 presents the main evidence for nusinersen relating to NICE's end of life criteria; additional evidence from natural history studies is presented in Table 32 of the CS.[1]

Table 84: Evidence supporting the application of end of life criteria presented in the CS (adapted from CS, Table 31)

Criterion	Evidence available
Nusinersen is indicated for patients with a short life expectancy, normally less than 24 months	Survival is highly dependent upon the nature and extent of supportive care, which may vary by country, institution and physician and patient preference. The median age for death or permanent respiratory support (a composite endpoint used in clinical trials and natural history studies in this population) is approximately 9–13 months.[60] [redacted]
There is sufficient evidence to indicate that nusinersen offers an extension to life, normally of at least an additional 3 months, compared with current NHS treatment	Infants in the ENDEAR study who received nusinersen had a significantly higher likelihood of EFS (final analysis: HR for death or the use of permanent assisted ventilation, 0.53; p=0.005) and OS (HR for death, 0.37; p=0.004) than infants who underwent a sham procedure, despite the fact that more infants in the nusinersen group than in the control group were receiving ventilatory support at baseline. The median time to death or the use of permanent assisted ventilation was 22.6 weeks in the control group and was not reached in the nusinersen group; the median time to death was not reached in either group (ITT population at end of study). In addition, at the latest data cut-off, all pre-symptomatic children in NURTURE (including those with 2 *SMN2* copy number) are still alive.

ITT- intention-to-treat; SMA - spinal muscular atrophy; SMN – survival motor neuron

With respect to the criterion relating to short life expectancy, the CS[1] makes the following points:

- There are no published studies on the natural history of SMA in English or UK populations.

- Survival of Type I SMA patients is highly dependent upon the nature and extent of supportive care received. This may vary between countries, institutions and according to physician and patient preferences.
- "Proactive" supportive care can prolong survival (for example, due to nutritional support using gastrostomy tubes and NIV or tracheostomy/ventilator support). [redacted]
- Changes in standard of care over time and the variable use of tracheostomy and invasive mechanical ventilation lead to variations in reported survival rates.
- The CS[1] makes the case that "survival free of permanent ventilation", which is generally accepted as intubation or tracheostomy with mechanical ventilation or >16 hours/day NIV support for >14 consecutive days (16+/14+) in the absence of an acute reversible illness or following surgery, may be a more relevant endpoint, as permanent ventilation may not be provided in England.
- On the basis of natural history studies included in the CS,[1] the median time to death or permanent respiratory support is reported to be 9-13 months. [redacted]

  Further details of the studies used to inform these estimates are provided in CS[1] Table 32.

The clinical advisors to the ERG did not share the same view regarding the expected survival of Type I SMA patients. One clinical advisor considered that the low survival rates for Type I SMA patients cited in the CS[1] are outdated and reflect an era before the use of ventilation, and noted that some less severe Type Ic SMA patients diagnosed between 3 and 6 months may survive to school age. The shift is seen in a greater proportion receiving ventilation. In contrast, the second clinical advisor considered that the mean survival for Type I SMA patients is likely to be less than 2 years and noted that she did not have any SMA patients who were older than 2 years of age (almost all of these patients had or have Type Ib SMA). This advisor noted that practice has changed and that the availability of improved expertise and equipment with NIV to support younger children will lead to longer survival. The clinical advisors commented that survival free of permanent ventilation is a useful surrogate outcome for severe impairment and weakness which allows for comparisons between studies. However, the advisors considered that ventilation for >16 hours a day is arguably better than death and that parents of infants with SMA may also share this view.

The ERG notes that the mean predicted survival for the usual care group of the company's early onset model is 3.87 years; on the basis of the company's model, the short life expectancy criterion is not met. As discussed in Section 5.5.3, one of the ERG's clinical advisors considered this predicted survival trajectory to be overly optimistic and expected the function to be steeper. Despite the differences in clinical opinion received by the ERG, it should be noted that the company's statement that "patients rarely survive to their second birthday" is inconsistent with the company's own model predictions.

With respect to the criterion relating to a life extension of 3 months or greater, the CS[1] notes the following:

- In ENDEAR, the median time to death or the use of permanent assisted ventilation was 22.6 weeks in the control group and was not reached in the nusinersen group. Overall, the risk of death or the use of permanent assisted ventilation was 47% lower in the nusinersen group than in the control group (hazard ratio, 0.53; 95% CI, 0.32–0.89; *p*=0.005)
- Despite a poorer prognosis in the nusinersen group of ENDEAR at baseline, the overall risk of death was 63% lower in the nusinersen group compared with the sham group (HR=0.37 [95% CI: 0.18, 0.77])
- Despite a poorer prognosis in the nusinersen group of ENDEAR at baseline, a lower proportion of infants receiving nusinersen received permanent assisted ventilation compared with those receiving sham (23% versus 32%, HR=0.66, *p*=0.13)
- All pre-symptomatic infants in NURTURE were alive and none had required respiratory intervention (invasive or NIV for ≥6 hours/day, continuously for ≥7 days or tracheostomy).

The company's early onset model suggests that nusinersen extends mean survival by 9.12 years compared with usual practice.

Both clinical advisors noted that there was considerable uncertainty regarding the expected survival duration for Type I patients receiving nusinersen and considered the model-predicted survival trajectory for the nusinersen group to be overly optimistic (see Section 5.5.3). However, they did believe that it was plausible that nusinersen would extend survival by at least 3 months. The clinical advisors also noted that there were infants treated with nusinersen who had gains in motor function but progressive deterioration in respiratory function; this has implications for long-term survival, especially as it is not yet clear whether these motor milestones will be maintained.

7. OVERALL CONCLUSIONS

Clinical effectiveness conclusions

The CS[1] did not contain a systematic review as would be expected in a submission to the NICE STA process. As such, it is not entirely certain that all nusinersen studies have been identified, although the ERG is confident that all relevant studies of nusinersen for SMA have been included in the CS. No information was provided for the BSC comparator listed in the NICE scope.[12] Two key RCTs were presented in the CS: ENDEAR, in early (infantile) onset SMA patients and CHERISH, in later onset SMA patients.

Nusinersen appears to provide significant clinical benefit to patients and the safety profile reported in the studies was acceptable and generally more favourable than that for the sham control group. The patient groups in the study arms for the ENDEAR and CHERISH studies were broadly similar although the nusinersen groups had more severe symptoms and longer duration of treatment.

Cost-effectiveness conclusions

With respect to the early onset model, the ERG's preferred assumptions increase the ICER for nusinersen versus usual care (including patient health gains only) from £407,605 per QALY gained (the company's base case) to £421,303 per QALY gained. When caregiver QALY losses are included in the analysis, the ERG's preferred assumptions increase the ICER from £402,361 per QALY gained (the company's base case) to £631,583 per QALY gained.

With respect to the later onset model, the ERG's preferred assumptions decrease the ICER for nusinersen versus usual care (including patient health gains only) from £1,252,991 per QALY gained (the company's base case) to £408,769 per QALY gained. When caregiver QALY losses are included in the analysis, the ERG's preferred assumptions reduces the ICER from £898,164 per QALY gained (the company's base case) to £632,850 per QALY gained. The main driver of these differences between the ICERs generated by the company and the ERG relates to the HRQoL impact on patients and caregivers.

The ERG's preferred analyses do not include any modification to the optimistic assumptions underpinning the company's modelled survival and motor function trajectories. The ERG's additional exploratory analyses show that the use of less optimistic assumptions has the propensity to markedly increase the ICERs for nusinersen in both populations.

The long-term probabilities of achieving, maintaining and losing motor function for nusinersen-treated patients, the long-term survival advantage of nusinersen and the relationship between motor function

and HRQoL in patients with SMA are all highly uncertain. However, the ERG also notes that given the acquisition cost of nusinersen, the level of decision uncertainty with respect to NICE's usual thresholds for cost-effectiveness is low.

7.1 Implications for research

Longer-term studies are required to determine the full impact of nusinersen on survival and motor function outcomes and AEs for patients with SMA; SHINE may provide useful information on these outcomes. Future clinical studies of nusinersen for the treatment of SMA should include a preference-based measure of HRQoL for patients (if applicable) and/or caregivers. Future research studies may also be worthwhile to determine whether nusinersen offers benefits to patients with Type 0 SMA and patients with Type IV SMA.

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9. APPENDICES

Appendix 1: Exclusion criteria for ENDEAR and CHERISH studies

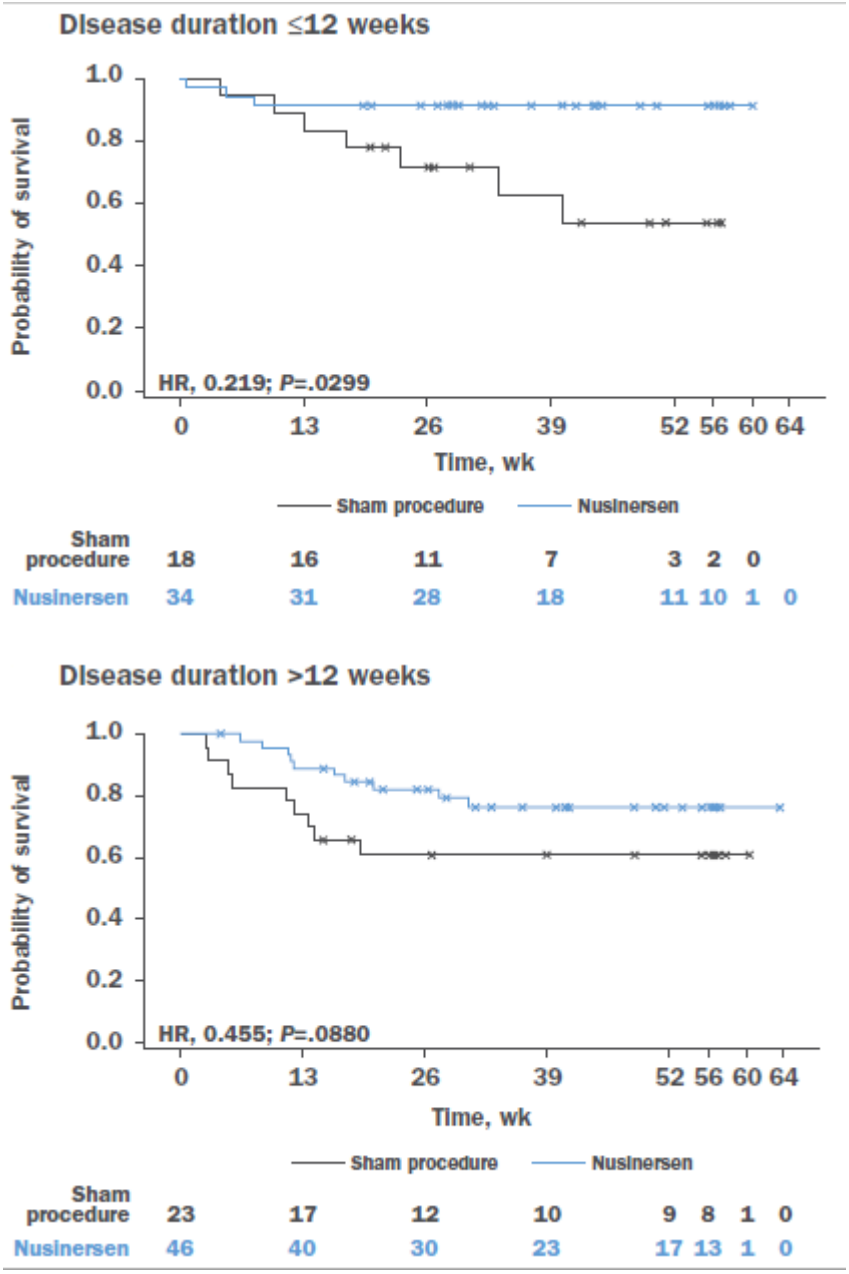
Table 85: Exclusion criteria for ENDEAR and CHERISH (adapted from Table 8, CS, page 34)

Exclusion criteria	ENDEAR	CHERISH
	• Peripheral oxygen desaturation (oxygen saturation below 96% without ventilation support) during screening • SMA symptoms within the first week of birth • Presence of an active infection requiring systemic antiviral or antibacterial treatment during screening • History of brain or spinal cord disease that would interfere with lumbar puncture, CSF circulation, or safety assessments • Presence of an implanted CSF drainage shunt or central nervous system catheter; abnormalities in haematology or clinical chemistry parameters at screening that would prevent inclusion as assessed by the site investigator • Treatment of SMA with an investigational drug, biological agent, or device within 30 days of screening • History of gene therapy, prior ASO therapy, or cell transplantation • The parent/guardian is unable to understand a basic description of the study or does not agree to comply with the schedule of assessments as defined by the protocol • The infant's caregiver does not adhere to the standard-of-care guidelines • Presence of a medical condition that would interfere with the infant's ability to participate in the study as assessed by the site investigator.	• Respiratory insufficiency at screening (defined by the medical necessity for invasive or non-invasive ventilation for >6 hours during a 24-hour period) • Medical necessity for a gastric feeding tube, where most feeds are given by this route; severe contractures (any contracture that, according to the investigator, could interfere with HFMSE) or severe scoliosis (Cobb Angle >40 degrees) evident on X-ray examination at screening • Hospitalisation for surgery (i.e., scoliosis surgery, other surgery), pulmonary event, or nutritional support within 2 months of screening or planned during the duration of the study • Presence of an untreated or inadequately treated active infection

ASO – antisense oligonucleotide, CSF - cerebrospinal fluid; SMA - spinal muscular atrophy

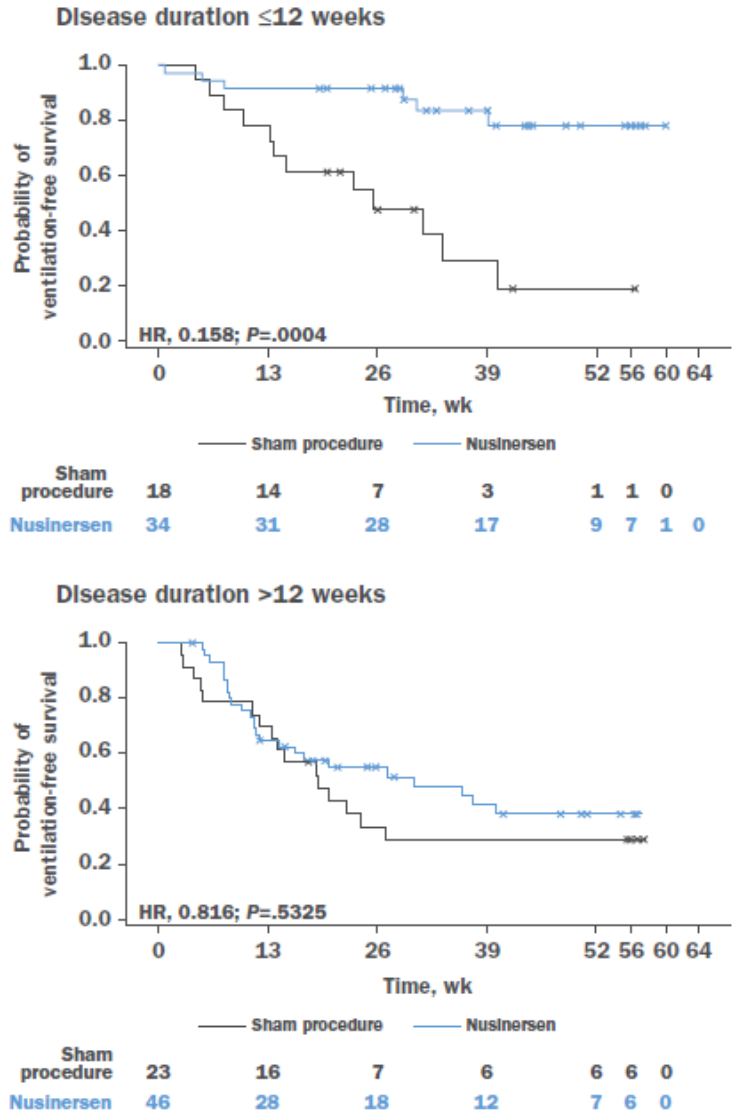
Appendix 2: Overall survival and event free survival by disease duration subgroup

Figure 23: Overall survival by disease duration (reproduced from CS, Appendix E, Figure 8)



HR- hazard ratio

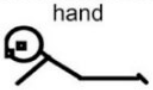
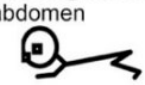
Figure 24: Event free survival by disease duration subgroup (reproduced from CS, Appendix E, Figure 9)



HR- Hazard ratio

Appendix 3: Instruments used to inform transition probabilities within the company's models

Table 86: HINE-2 classification (reproduced from CS Figure 5)

Head control	Unable to maintain head upright normal up to 3m	Wobbles normal up to 4m	Maintained upright all the time normal from 5m		
Sitting	Cannot sit	With support at hips  normal at 4m	Props  normal at 6m	Stable sit  normal at 7-8m	Pivots (rotates)  normal at 9m
Voluntary grasp – note side	No grasp	Uses whole hand	Index finger and thumb but immature grasp	Pincer grasp	
Ability to kick in supine	No kicking	Kicks horizontally but legs do not lift	Upward (vertically)  normal at 3m	Touches leg  normal at 4-5m	Touches toes  normal at 5-6m
Rolling	No rolling	Rolling to side (normal at 4m)	Prone to supine (normal at 6 m)	Supine to prone (normal at 6 m)	
Crawling or bottom shuffling	Does not lift head	On elbow  (normal at 3 m)	On outstretched hand  (normal at 4m)	Crawling flat on abdomen  (normal at 8m)	Crawling on hands and knees  (normal at 10m)
Standing	Does not support weight	Supports weight (normal at 4m)	Stands with support (normal at 7m)	Stands unaided (normal at 12m)	
Walking		Bouncing (normal at 6m)	Cruising (walks holding on) (normal at 12m)	Walking independently (normal by 15m)	

Source: De Sanctis et al[30] and CS[1]

Table 87: CHOP INTEND domains and scoring

CHOP INTEND item	CHOP INTEND activities	Scoring within CHOP INTEND item
1	Spontaneous movement (upper extremity)	0-4
2	Spontaneous movement (lower extremity)	0-4
3	Hand grip	0-4
4	Head in midline with visual stimulation	0-4
5	Hipadductors	0, 2 or 4
6	Rolling elicited from legs	0-4
7	Rolling elicited from arms	0-4
8	Shoulder and elbow flexion and horizontal abduction	0-4
9	Shoulder flexion and elbow flexion	0-4
10	Unnamed – relates to knee extension	0-4
11	Hip flexion and foot dorsiflexion	0, 2, 3 or 4
12	Head control	0-4
13	Elbow flexion	0, 2 or 4 (score with item 14)
14	Neck flexion	0, 2 or 4 (score with item 13)
15	Head/neck extension (Landau)	0, 2 or 4
16	Spinal incurvation (Galant)	0, 2 or 4
Total score, best score on each side for each item (maximum 64 points)		

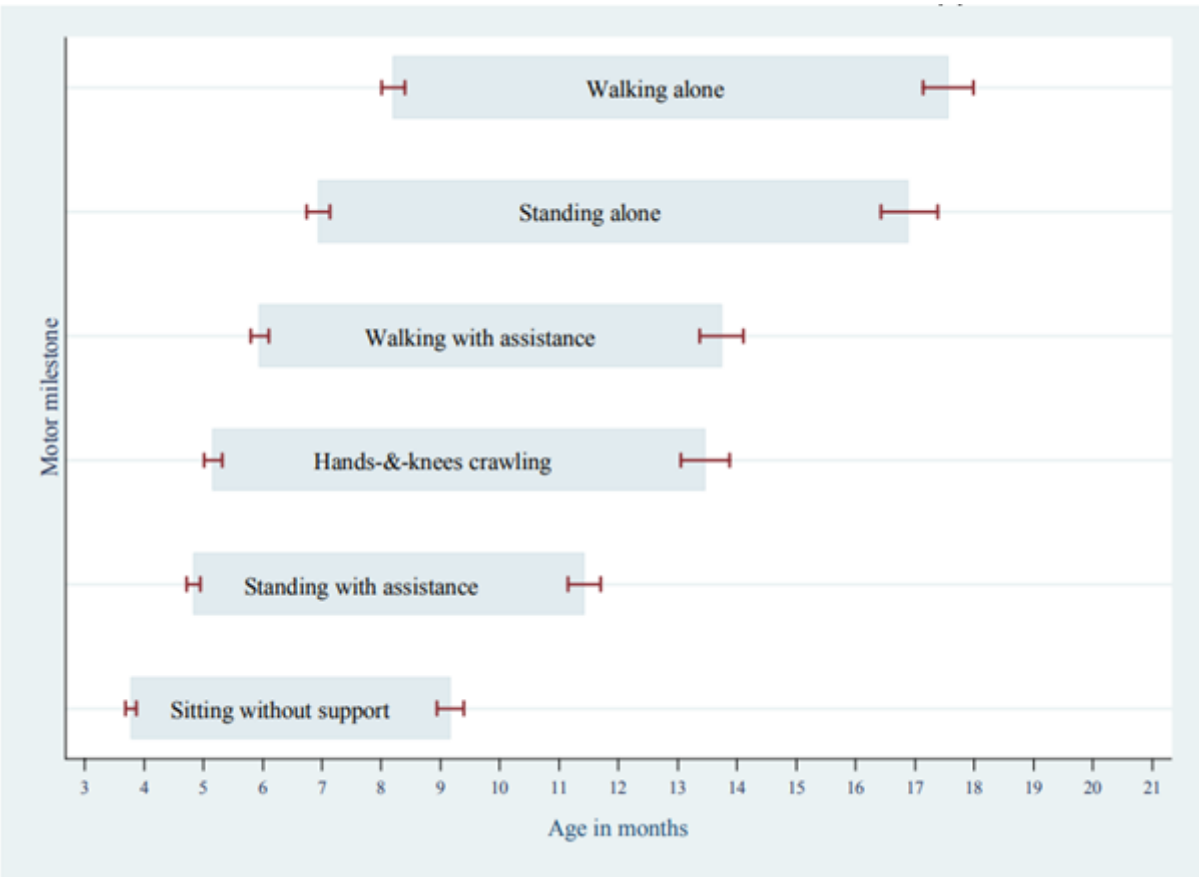
Source: Glanzman et al[62]

Table 88: HFMSE domains and scoring

HMFSE item	HMFSE activities	Scoring within HMFSE item
1	Able to sit on chair or with legs off bed with or without hand support	0, 1 or 2
2	Able to sit on floor cross legged or legs stretched in front	0, 1 or 2
3	Able to bring hands to face at eye level	0, 1 or 2
4	Able to bring hands to head	0, 1 or 2
5	Roll to side	0, 1 or 2
6-9	Roll	0, 1 or 2
10	Able to lie down from sitting	0, 1 or 2
11	Able to raise head when lying prone	0, 1 or 2
12-13	Able to prop on forearms or extend arms	0, 1 or 2
14	Able to sit up from lying	0, 1 or 2
15	Able to four-point kneel	0, 1 or 2
16	Able to crawl	0, 1 or 2
17	Lift head from supine	0, 1 or 2
18	Stand with support	0, 1 or 2
19	Stand without support	0, 1 or 2
20	Able to walk	0, 1 or 2
21-22	Able to flex hip from supine	0, 1 or 2
23-26	Able to half knee	0, 1 or 2
27	Able to go from standing to sitting	0, 1 or 2
28	Able to squat	0, 1 or 2
29	Able to jump	0, 1 or 2
30-33	Go up and down stairs	0, 1 or 2

Source: Pera et al[63]

Table 89: WHO motor milestones



Source: WHO Multicentre Growth Reference Study Group[64]

Appendix 4: Methods for implementing the ERG's exploratory analyses

(a) Infant onset model

Exploratory analysis 1

Replace the values in worksheet "Markov Nusinersen T1" cells F335:N335 and worksheet "Markov RWC T1" cells F335 to N335 with the values presented in Table 90.

Table 90: ERG analysis 1 - baseline distribution for early onset model

Health state	Baseline proportion
No milestones	0.59
Mild milestones	0.31
Moderate milestones	0.10
Sits without support	0.01
Stands with assistance	0.00
Walks with assistance	0.00
Stands/walks unaided	0.00
Loss	0.00
Dead	0.00

Exploratory analysis 2

No amendment is required for the early onset model.

Exploratory analysis 3

For the early onset model, go to worksheet "Utility T1" drop-down box in row 11, select "Clinical experts – EQ-5D-Y vignette study"

Exploratory analyses 4

Go to worksheet "Utility T1" cells I18 to I25. Replace with the values shown in Table 91.

Table 91: ERG exploratory analysis 4 - caregiver utilities for early onset model (Bastida)

Health state	Caregiver utility
No milestones	[redacted]
Mild milestones	
Moderate milestones	
Sits without support	
Stands with assistance	
Walks with assistance	
Stands/walks unaided	
Loss of later onset motor function	0.00

Exploratory analysis 5

Apply all changes from ERG exploratory analyses 1-4, as described above. Analyses 6-8 should start from this version of the model.

Exploratory analyses 6a

Go to worksheet "Utility T1" cells F18:F25. Replace with values shown in Table 92.

Table 92: ERG exploratory analysis 6a – patient utilities for early onset model (Bastida)

Health state	Patient utility
No milestones	[redacted]
Mild milestones	
Moderate milestones	
Sits without support	
Stands with assistance	
Walks with assistance	
Stands/walks unaided	
Loss of later onset motor function	0.00

Exploratory analysis 6b

Go to worksheet "Utility T1" cells F18:F25. Replace with values shown in Table 93

Table 93: ERG exploratory analysis 6b – patient utilities for early onset model (ERG's clinical advisors)

Health state	HRQoL estimate
No milestones	0.20
Mild milestones	0.25
Moderate milestones	0.35
Sits without support	0.60
Stands with assistance	0.65
Walks with assistance	0.75
Stands/walks unaided	0.85
Loss of later onset motor function	0.00

Exploratory analysis 7

Go to worksheet "Efficacy T1" cell I104. Set value equal to zero.

Exploratory analysis 8

For exploratory analysis 8a, 8b and 8c, replace the values in worksheet "Markov Nusinersen T1" cells F419:L425 with the values presented in Table 94, Table 95 and Table 96, respectively. For exploratory analysis 8d and 8e, replace the values in worksheet "Markov Nusinersen T1" cells F419:L425 and worksheet "Markov RWC T1" cells F419:L425 with the values presented in Table 97 and Table 98, respectively.

Table 94: Transition matrix for ERG exploratory analysis 8a - 5% of nusinersen-treated patients deteriorate to next worst state

From\To state	No milestones	Mild milestones	Moderate milestones	Sits without support	Stands with assistance	Walks with assistance	Stands/walks unaided
No milestones	[redacted]						
Mild milestones	[redacted]	[redacted]	[redacted]				
Moderate milestones		[redacted]	[redacted]	[redacted]			
Sits without support			[redacted]	[redacted]	[redacted]		
Stands with assistance				[redacted]	[redacted]	[redacted]	
Walks with assistance					[redacted]	[redacted]	[redacted]
Stands/walks unaided						[redacted]	[redacted]

Table 95: Transition matrix for ERG exploratory analysis 8b - 10% of nusinersen-treated patients deteriorate to next worst state

From\To state	No milestones	Mild milestones	Moderate milestones	Sits without support	Stands with assistance	Walks with assistance	Stands/walks unaided
No milestones	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Mild milestones	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Moderate milestones	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Sits without support	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Stands with assistance	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Walks with assistance	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Stands/walks unaided	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Table 96: Transition matrix for ERG exploratory analysis 8c - 20% of nusinersen-treated patients deteriorate to next worst state

From\To state	No milestones	Mild milestones	Moderate milestones	Sits without support	Stands with assistance	Walks with assistance	Stands/walks unaided
No milestones	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Mild milestones	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Moderate milestones	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Sits without support	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Stands with assistance	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Walks with assistance	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Stands/walks unaided	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Table 97: Transition matrix for ERG exploratory analysis 8d – all patients remain in the state achieved at the end of ENDEAR follow-up

From\To state	No milestones	Mild milestones	Moderate milestones	Sits without support	Stands with assistance	Walks with assistance	Stands/walks unaided
No milestones	[redacted]						
Mild milestones		[redacted]					
Moderate milestones			[redacted]				
Sits without support				[redacted]			
Stands with assistance					[redacted]		
Walks with assistance						[redacted]	
Stands/walks unaided							[redacted]

Table 98: Transition matrix for ERG exploratory analysis 8e – all patients revert to no milestones state at the end of ENDEAR follow-up

From\To state	No milestones	Mild milestones	Moderate milestones	Sits without support	Stands with assistance	Walks with assistance	Stands/walks unaided
No milestones	[redacted]						
Mild milestones	[redacted]						
Moderate milestones	[redacted]						
Sits without support	[redacted]						
Stands with assistance	[redacted]						
Walks with assistance	[redacted]						
Stands/walks unaided	[redacted]						

(b) Later onset model

Exploratory analysis 1

Replace the values in worksheet "Markov Nusinersen T1" cells F335:N335 and worksheet "Markov RWC T1" cells F335 to N335 with the values presented in Table 99.

Table 99: ERG analysis 1 - baseline distribution for later onset model

Health state	Baseline proportion
Sits without support but does not roll	0.56
No improvement	0.00
Sits and rolls independently	0.18
Sits and crawls with hands and knees	0.12
Stands/Walks with assistance	0.08
Stands unaided	0.06
Walks unaided	0.00
Loss	0.00
Dead	0.00

Exploratory analysis 2

Go to worksheet "Cost T2" drop-down box in row 170. Select "Apply".

Exploratory analysis 3

Go to worksheet "Utility T2" cells F18:F25. Replace values with those presented in Table 100.

Table 100: ERG exploratory analysis 3 – patient utilities for later onset model (vignette)

Health state	Patient utility
Sits without support but does not roll	0.04
No improvement	0.00
Sits and rolls independently	0.04
Sits and crawls with hands and knees	0.10
Stands/Walks with assistance	0.39
Stands unaided	0.72
Walks unaided	0.72
Loss	0.00

Exploratory analyses 4

Go to worksheet "Utility T2" cells I18: I25. Replace values with those presented in Table 101.

Table 101: ERG exploratory analysis 4 - caregiver utilities for later onset model (Bastida)

Health state	Caregiver utility
Sits without support but does not roll	[redacted]
No improvement	
Sits and rolls independently	
Sits and crawls with hands and knees	
Stands/Walks with assistance	
Stands unaided	
Walks unaided	
Loss	

Exploratory analysis 5

Apply all changes from ERG exploratory analyses 1-4, as described above. Analyses 6-8 should start from this version of the model.

Exploratory analyses 6a

Go to worksheet "Utility T2" cells F18:F25. Replace values with those presented in Table 102.

Table 102: ERG exploratory analysis 6a – patient utilities for later onset model (Bastida)

Health state	Patient utility
Sits without support but does not roll	[redacted]
No improvement	
Sits and rolls independently	
Sits and crawls with hands and knees	
Stands/Walks with assistance	
Stands unaided	
Walks unaided	
Loss	

Exploratory analyses 6a

Go to worksheet "Utility T2" cells F18:F25. Replace values with those presented in Table 103.

Table 103: ERG exploratory analysis 6b – patient utilities for later onset model (ERG's clinical advisors)

Health state	HRQoL estimate
Sits without support but does not roll	0.60
No improvement	0.00
Sits and rolls independently	0.60
Sits and crawls with hands and knees	0.60
Stands/Walks with assistance	0.75
Stands unaided	0.85
Walks unaided	0.85
Loss	0.00

Exploratory analysis 7

Go to worksheet "Efficacy T2" cell I185. Set value equal to zero.

Exploratory analysis 8

For exploratory analysis 8a, 8b and 8c, replace the values in worksheet "Markov Nusinersen T2" cells F416:M423 with the values presented Table 104, Table 105 and Table 106, respectively. For exploratory analysis 8d and 8e, replace the values in worksheet "Markov Nusinersen T2" cells F416:M423 and worksheet "Markov RWC T2" cells F416:M423 with the values presented in Table 107 and Table 108, respectively.

Table 104: Transition matrix for ERG exploratory analysis 8a - 5% of nusinersen-treated patients deteriorate to next worst state

From\To state	Sits without support but does not roll	No improvement	Sits and rolls independently	Sits and crawls with hands and knees	Stands/walks with assistance	Stands unaided	Walks unaided
Sits without support but does not roll	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
No improvement	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Sits and rolls independently	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Sits and crawls with hands and knees	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Stands/walks with assistance	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Stands unaided	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Walks unaided	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Table 105: Transition matrix for ERG exploratory analysis 8b - 10% of nusinersen-treated patients deteriorate to next worst state

From\To state	Sits without support but does not roll	No improvement	Sits and rolls independently	Sits and crawls with hands and knees	Stands/walks with assistance	Stands unaided	Walks unaided
Sits without support but does not roll	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
No improvement	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Sits and rolls independently	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Sits and crawls with hands and knees	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Stands/walks with assistance	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Stands unaided	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Walks unaided	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Table 106: Transition matrix for ERG exploratory analysis 8c - 20% of nusinersen-treated patients deteriorate to next worst state

From\To state	Sits without support but does not roll	No improvement	Sits and rolls independently	Sits and crawls with hands and knees	Stands/walks with assistance	Stands unaided	Walks unaided
Sits without support but does not roll	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
No improvement	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Sits and rolls independently	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Sits and crawls with hands and knees	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Stands/walks with assistance	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Stands unaided	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Walks unaided	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Table 107: Transition matrix for ERG exploratory analysis 8d – all patients remain in the state achieved at the end of CHERISH follow-up

From\To state	Sits without support but does not roll	No improvement	Sits and rolls independently	Sits and crawls with hands and knees	Stands/walks with assistance	Stands unaided	Walks unaided
Sits without support but does not roll	1.000						
No improvement							
Sits and rolls independently			1.000				
Sits and crawls with hands and knees				1.000			
Stands/walks with assistance					1.000		
Stands unaided						1.000	
Walks unaided							1.000

Table 108: Transition matrix for ERG exploratory analysis 8e – all patients revert to no milestones state at the end of CHERISH follow-up

From\To state	Sits without support but does not roll	No improvement	Sits and rolls independently	Sits and crawls with hands and knees	Stands/walks with assistance	Stands unaided	Walks unaided
Sits without support but does not roll	1.000						
No improvement							
Sits and rolls independently	1.000						
Sits and crawls with hands and knees	1.000						
Stands/walks with assistance	1.000						
Stands unaided	1.000						
Walks unaided	1.000						

National Institute for Health and Care Excellence
Centre for Health Technology Evaluation

Pro-forma Response

ERG report

Nusinersen for treating spinal muscular atrophy [ID1069]

You are asked to check the ERG report from the School of Health and Related Research (ScHARR), The University of Sheffield to ensure there are no factual inaccuracies contained within it.

If you do identify any factual inaccuracies you must inform NICE by **5pm, Tuesday 12 June 2018** using the below proforma comments table. All factual errors will be highlighted in a report and presented to the Appraisal Committee and will subsequently be published on the NICE website with the Evaluation report.

The proforma document should act as a method of detailing any inaccuracies found and how and why they should be corrected.

Issue 1 ENDEAR study results

Description of problem	Description of proposed amendment	Justification for amendment	Response
Page 2, Section 1.2, Second paragraph	Please include an additional sentence: "One participant in the nusinersen group was withdrawn from the trial before treatment."	The participant numbers in the treatment and control arm do not correspond to the ENDEAR sample size (N=122).	It is not clear in the CS that one patient withdrew before treatment (see Appendix D, section 2.2). This has not been amended, however the committee can see the additional information from the company's fact check response.
Page 4, Section 1.2	Please amend as follows: "Overall, there were fewer deaths in the nusinersen-treated patients than the control patients (7% vs 19%) and fewer serious adverse events (SAEs) in the nusinersen-treated patients compared with the control patients (39% vs 60%)."	The presented numbers do not correspond to the ENDEAR study results: error in values presented in the percentage of deaths in the nusinersen-treated and control patient group.	These figures are taken directly from Table 28, and compare all nusinersen-treated patients from the integrated safety analysis with control patients. This does not refer to the ENDEAR trial, but states "overall". No change is required.
Page 25, Table 7	Please remove following statement and amend rating if appropriate: Outcome assessors may have been able to determine which participants received a lumbar puncture due to related AEs.	Biogen do not believe this to be true. In the ENDEAR study no AE suggested either treatment pathway. Could the ERG clarify which AE they have in mind which would "unblind" the study participant?	This is already correct, no change required. Page 90: "commonly reported AEs were consistent with events typically observed in patients with SMA or complications of lumbar puncture."

Issue 2 Primary and secondary outcome measures

Description of problem	Description of proposed amendment	Justification for amendment	Response
Page 22 of the ERG report, Table 5; 7th column (Primary outcome measure) where it states: Proportion of motor milestone responders (HINE-2) Event-free survival (EFS) Time to death or permanent ventilation	Please change to: Proportion of motor milestone responders (HINE-2) Event-free survival (EFS) i.e time to death or permanent ventilation	In Table 5 event free survival and time to death or permanent ventilation appear as separate endpoints whereas event free survival is defined as time to death or permanent ventilation (please see Table 7 in the company submission [CS]).	This has been amended.
Page 22, Table 5; 8th column (Secondary outcome measures)	Please also add the following secondary outcome: Time to death or permanent ventilation in the 2 subgroups of participants above and below the study median disease duration	Not all the secondary efficacy outcomes are listed in Table 5 of the ERG report (please see Table 7 in the CS).	This has been amended.

Issue 3 Definition of responders

Description of problem	Description of proposed amendment	Justification for amendment	Response
Page 27 of the ERG report where it states: Responders were infants with a	Please change to: HINE-2 responders were infants with a ≥2-point increase [or maximal score]	The ERG haven't provided the full definition for HINE-2 responders (see Section 2.3.3.1, Section 2.6.1 and	The abbreviated definition (from the EMA documentation) was chosen for readability. The full

greater number of motor milestone categories with improvement than worsening.[4]	in the ability to kick, OR ≥1-point increase in the motor milestones of head control, rolling, sitting, crawling, standing or walking, AND improvement in more categories of motor milestones than worsening. Furthermore, not the whole HINE scale was used – voluntary grasp was discounted.	Section 2.6.2 of the CS and Table 2 [footnotes] in the SmPC where the full definitions are provided).	definition has been added to the footnote for Table 9.

Issue 4 Incorrect reference

Description of problem	Description of proposed amendment	Justification for amendment	Response
Page 8 of the ERG report where it states: SMA is rare and is recognised as an orphan disease by the European Medicines Agency (EMA).[4]	Please amend the cited reference to "European Medicines Agency. Nusinersen - EPAR – public assessment report. EMA: London; 2017"	The reference cited is "European Medicines Agency. Nusinersen - summary of product characteristics. EMA: London; 2017" whereas it should be the EPAR – public assessment report (available from http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Public_assessment_report/human/004312/WC500229706.pdf). Please note that are some instances in the ERG report where the SmPC is correctly cited; therefore please only correct for the occurrences	The ERG believes that the SmPC is an annex to the EPAR. This is indicated by the title of the hyperlink in the product information tab on the EMA website and because the SmPC document begins with "ANNEX 1." We have amended the bibliography to reflect this.
Page 24 of the ERG report where it states: Overall, demographic and baseline disease characteristics and SMA history of the intention-to-treat (ITT) population in the ENDEAR study are consistent with a population highly likely to develop Type I SMA.[4]			
Page 25 of the ERG report, Table 7, 2nd and 3rd row, 3rd column where it states: Yes: performed using an interactive voice/web response system.[4, 21]			
Page 25 of the ERG report, Table 7, 8th row, 3rd			

column where it states: Yes: Participants who died or withdrew were counted as non-responders.[4]		stated in the left hand column and not throughout.	
Page 25 of the ERG report where it states: Responders were infants with a greater number of motor milestone categories with improvement than worsening.[4]			
Page 28 of the ERG report where it states: The only measure of respiratory function reported from the ENDEAR study was the annualised rate of serious respiratory events; 2.836 events were reported in the nusinersen group versus 3.065 events in the control group in the interim analysis (95% confidence intervals [CIs] not reported).[4]			
Page 28 of the ERG report where it states: The ENDEAR study reported the number of hours of ventilator support as a measure of ventilation. In the interim analysis, the median percentage of time on ventilator support was lower in the nusinersen group (27.1%) compared with the control group (43.0%).[4]			
Page 40 of the ERG report where it states: NURTURE (in pre-symptomatic infants) reported fewer AEs compared with symptomatic infants as would be expected with their healthier baseline condition.[4]			
Page 50 of the ERG report where it states: Overall, the most commonly reported AEs in nusinersen-treated patients were either consistent with events occurring in the natural history of SMA,			

consistent with common conditions in the general population, consistent with common age-appropriate events or consistent with events observed in the context of lumbar puncture.[4]			
Page 53 of the ERG report where it states: NURTURE (in pre-symptomatic infants) reported fewer AEs compared with symptomatic infants as would be expected with their healthier baseline condition.[4]			

Issue 5 SHINE CSR

Description of problem	Description of proposed amendment	Justification for amendment	Response
Page 46 of the ERG report where it states: The CSR for SHINE was not provided by the company.	Please change to: The CSR for SHINE was not provided by the company because it was not available at the time of the submission and clarification questions.	The CSR could not be provided because it was not available (see the answer to the clarification question A14). We feel the ERG should acknowledge this in their report.	This is not a factual inaccuracy. Irrespective of the reasons for not providing the CSR, the CSR was not provided by the company.

Issue 6 Adverse events

Description of problem	Description of proposed amendment	Justification for amendment	Response
Page 53 of the ERG report where it states: Within the ENDEAR study (CS,[1] Appendix F, Table 2), the incidence of AEs in	Please change to: Within the ENDEAR study (CS,[1] Appendix F, Table 2), the incidence of AEs in nusinersen group and the control group	The wording of “however” and “except” implies that there were no AEs which occurred more frequently in the control group versus the nusinersen group.	This is not a factual inaccuracy. No amendment is required as the text is factually accurate and aims to highlight where there may be

nusinersen group and the control group was similar. **However**, the following AEs occurred more frequently in the nusinersen group (n=80) than in the control group (n=41): constipation (35% vs 22%), upper respiratory infection (30% vs 22%) and pneumonia (29% vs 17%). With regard to the CHERISH study (CS,[1] Appendix F, Table 3), again the incidence of AEs was similar in the nusinersen and control groups, **except for the following AEs which occurred more frequently in the nusinersen group** (n=84) than the control group (n=42): headache (29% vs 7%), vomiting (29% vs 12%), back pain (25% vs 0%) and epistaxis (7% vs 0%).	was similar. The following AEs occurred more frequently in the nusinersen group (n=80) than in the control group (n=41): constipation (35% vs 22%), upper respiratory infection (30% vs 22%) and pneumonia (29% vs 17%). With regard to the CHERISH study (CS,[1] Appendix F, Table 3), again the incidence of AEs was similar in the nusinersen and control groups. The following AEs occurred more frequently in the nusinersen group (n=84) than the control group (n=42): headache (29% vs 7%), vomiting (29% vs 12%), back pain (25% vs 0%) and epistaxis (7% vs 0%).	However, this is not the case. For example, in ENDEAR for nusinersen versus control: Respiratory failure (25% vs 39%); acute respiratory failure (14% vs 24%); gastroesophageal reflux disease (12% vs 20%); decreased oxygen saturation (12% vs 24%); cough (11% vs 20%); dysphagia (11% vs 22%) (see Appendix F Table 2 in the CS). For example, in CHERISH for nusinersen versus control: Upper respiratory tract infection (30% vs 45%); nasopharyngitis (24% vs 36%) (see Appendix F Table 3 in the CS).	treatment-related adverse events.
Page 55: [redacted]	Please amend to: [redacted]	Clarification for completion	This is not a factual inaccuracy. The Committee can see this additional information from the company's fact check response.

Issue 7 Best supportive care as the comparator

Description of problem	Description of proposed amendment	Justification for amendment	Response
Page 55/56 of the ERG report where it states: However, the appropriate comparator, BSC was not included.	Please change to: CHERISH and ENDEAR were head-to-head trials versus sham in addition to BSC; however no other studies evaluating BSC were included.	CHERISH and ENDEAR were head-to-head trials versus sham in addition to best supportive care (BSC). Therefore, it is inaccurate to say that the appropriate comparator was not included. We feel the ERG should acknowledge that the trials included BSC.	This is not a factual inaccuracy. The comparator in the CS is sham procedure control group. Although BSC was included as part of this, no details of BSC are provided. No studies of BSC outside of the sham control were included in the CS.

Issue 8 Description of the economic model

Description of problem	Description of proposed amendment	Justification for amendment	Response
Page 5, 'Later onset model', 1st paragraph, final sentence: The later onset model includes two key assumptions: (i) patients in either treatment group who reach health states consistent with Type III SMA milestones by month 15 follow general population mortality rates, and (ii) after month 15, the motor function of nusinersen-treated patients cannot deteriorate, whilst the motor function of patients receiving usual care cannot improve.	Please amend to: The later onset model includes two key base case assumptions: (i) the mortality rates of patients in either treatment group who reach health states consistent with Type III SMA milestones lie between those of Type II and Type III patients, and (ii) after month 15, the motor function of nusinersen-treated patients cannot deteriorate, whilst the motor function of patients receiving usual care cannot improve.	Clarification of the treatment of mortality for patients who achieve Type III motor milestones and that these are base case assumptions	The ERG agrees. The suggested amendment has been made throughout.

Page 5: The company's later onset model adopts a state transition approach, with health states defined by motor function milestones based on the HFMSE instrument.	Please amend to: The company's later onset model adopts a state transition approach, with health states defined by motor function milestones based on the HFMSE instrument and the WHO criteria.	The change is for completeness. No impact on results. The statement should also include the WHO criteria . However, Table 54 (page 92) does mention that the health states (iii) to (vi) are based on the WHO criteria.	The ERG agrees. The suggested amendment has been made.
Table 3, p.15 'Outcomes' row, final column: Complications of SMA (including, for example, scoliosis and muscle contractures), and stamina and fatigue, are not included as these outcomes were not collected in the pivotal clinical trials	Please amend to: Complications of SMA (including, for example, muscle contractures, stamina and fatigue) are not included as these outcomes were not collected in the pivotal clinical trials	Scoliosis is included in the economic models	The entire table and its contents are reproduced directly from Table 1 of the CS. No amendment has been made. In addition, whilst scoliosis is included in the model, it is not associated with specific costs or outcomes.
Page 63, first paragraph, final sentence: they do not allow for the deterioration of any patient's motor function from this timepoint onwards.	Please amend to: they do not allow, in the base case, for the deterioration of any patient's motor function from this timepoint onwards.	Clarification: this is a base case assumption (can be relaxed in scenario analysis)	This is not a factual inaccuracy. The ERG believes that it is fairly obvious that the model description relates to the base case analysis. The scenario analyses which relax these assumptions are briefly described in the sections called "Methods for model evaluation" and the results can be seen in the results section. No amendment has been made.
Page 63 'Usual care group', 2nd paragraph, 2nd sentence: In contrast to the assumptions applied to the nusinersen group, no mortality adjustment is applied for patients in States (iv) to (vii) in the usual care group.	Please remove this statement.	In the nusinersen group, mortality is adjusted for those in health states (iv) to (vii). However, in the usual care group, there are no patients in these health states beyond month 6. Therefore an adjustment is not relevant.	There is no adjustment of mortality risk in the comparator group. This is not a factual inaccuracy.

Page 64, first paragraph, final sentence: however, this event does not impact on the patient's health state occupancy, HRQoL or costs.	Please remove this statement.	Varying the assumptions related to scoliosis surgery changes the model results.	The company's statement is incorrect. Note that this sentence relates specifically to the usual care group, not the nusinersen group. In the usual care group, changing the time at which patients undergo scoliosis surgery or the proportion of who undergo surgery has no impact on the model results.
Page 64-65 5.3.2 Structural assumptions – early onset model, bullet iii), final sentence: This adjustment is not applied to patients reaching these states in the usual care group; instead, all patients in the usual care group are allocated 100% of the Type I mortality risk.	Please remove this statement, alternatively the following could be said: No mortality adjustment is applied because patients in the usual care arm do not reach health states (iv) to (vii) in the base case analysis. However, the formula in the model does apply the adjustment to patients in health states (iv) to (vii) in the usual care group. Hence, if in a scenario analysis the patients in the usual care arm do reach health states (iv) to (vii), then the mortality adjustment will be applied.	For completeness. No impact on results	The ERG's model description relates to the base case analysis and the ICERs associated with it. In this base case scenario, no adjustment is applied. Therefore, this is not factually inaccurate.
Page 65, bullet (iv) 1st sentence: After the end of month 13, patients receiving nusinersen are assumed never to transit to a worse health state	Please amend to: After the end of month 13, patients receiving nusinersen are assumed, in the base case, never to transit to a worse health state	This assumption can be relaxed.	The model description naturally relates to the base case. No amendment has been made.

Page 65, bullet (viii) final sentence: As separate costs and utility changes for scoliosis surgery are not included in the model, this does not impact on the model results.	Please remove this statement.	Varying the assumptions related to scoliosis surgery changes the model results.	The company's statement is incorrect. Note that this sentence relates specifically to the usual care group, not the nusinersen group. In the usual care group, changing the time at which patients undergo scoliosis surgery or the proportion of who undergo surgery has no impact on the model results.
Page 73, in response to a request for clarification, the company stated that matrices were generated using the efficacy dataset without imputation of missing data; however, the ERG notes that these matrices contain count data for a larger number of patients than were included in the efficacy set.	Please remove this statement.	The response was misunderstood. In the response we were just clarifying that the trial analyses based on the efficacy set did not use any imputation for missing visits due to study closure. In the third paragraph we mentioned that the model used the ITT population, and then we presented what the model's results would have been if missing visits due to study closure were imputed using Last Observation Carried Forward (LOCF).	The statement in the ERG report (accurate or not) reflects the company's clarification response. On the basis of the additional information presented in this fact check, this suggests that the reasons for the number of surviving patients with data declining over time have not been provided. As such, we cannot provide a correction. We suggest that the company clarifies this issue during the committee meeting.
Page 85, 1st sentence: The ERG notes that the company's approach to breaking down the costs by type of care is irrelevant as the sum of the costs shown in **Error! Reference source not found.** (after manipulation) is the same as the sum of the costs presented in **Error! Reference source not found.** (before manipulation).	Please remove this statement.	The manipulation is intended to illustrate how the distribution by resource category (as in Bastida et al.) is converted into the distribution by therapy area presented in the model.	This is not a factual inaccuracy. The values before manipulation are the same as the values after manipulation. No amendment has been made.
Page 86 (table 49) Priors are included for some but not	Please amend to: In the usual care arm, priors were not	Clarification on model structure	The ERG disagrees with the company's suggested amendment.

all unobserved transitions.	included for transitions that were considered improbable according to natural history.		The original statement is correct and accurate.
Page 92, 'Nusinersen group', final paragraph penultimate sentence: This matrix permits nusinersen-treated patients to either remain in their current state or move to the next best health state, but does not allow for the deterioration of any patient's motor function from this timepoint onwards.	Please amend to: This matrix permits nusinersen-treated patients to either remain in their current state or move to the next best health state but, in the base case, does not allow for the deterioration of any patient's motor function from this timepoint onwards.	This is a base case assumption which can be relaxed in scenario analysis.	The model description naturally relates to the base case. No amendment has been made.
Page 93, 'Usual care group, 2nd paragraph, 1st sentence: From month 15 onwards, mortality is modelled using the same data and assumptions as those applied within the nusinersen group, including the survival advantage assumed for States [v] and [vi].	Please amend to: As some patients in both arms of the model occupy states [v] and [vi] at most timepoints, mortality is modelled using the same data and assumptions as those applied within the nusinersen group, including the survival advantage assumed for States [v] and [vi].	Provides justification for this approach	This is not a factual inaccuracy. No amendment has been made.
Page 93, 'Usual care group', 2nd paragraph, final sentence: however, this does not impact on the patient's health state occupancy, HRQoL or costs.	Please remove this statement.	Altering the assumptions about the proportion of patients undergoing scoliosis surgery changes the results of the model.	The company's statement is incorrect. Note that this sentence relates specifically to the usual care group, not the nusinersen group. In the usual care group, changing the time at which patients undergo scoliosis surgery or the proportion of who undergo surgery has no impact on the model results.
Page 94, 5.4.2 Structural	Please remove this statement.	The explanation for this is that in the	This is not a factual inaccuracy. It

assumptions – later onset model, bullet (iv): Unlike the early onset model, this adjustment is applied to both the nusinersen and usual care groups		later onset model, both nusinersen and usual care patients occupy the better health states whereas this is not the case in the infantile onset model.	reflects the trajectory of patients in the base case.
Page 94, 5.4.2 Structural assumptions – later onset model, bullet (v): After month 15, patients receiving nusinersen are assumed never to transit to a worse health state	Please amend to: After month 15, patients receiving nusinersen are assumed, in the base case, never to transit to a worse health state	This assumption is relaxed in scenario analysis.	The model description naturally relates to the base case. No amendment has been made.
Page 94, 5.4.2 Structural assumptions – later onset model, bullet (viii): As separate costs and utility changes for scoliosis surgery are not included in the model, this does not impact on the model results.	Remove this statement	Changing assumptions around scoliosis surgery alters the model results	The company's statement is incorrect. Note that this sentence relates specifically to the usual care group, not the nusinersen group. In the usual care group, changing the time at which patients undergo scoliosis surgery or the proportion of who undergo surgery has no impact on the model results.
Page 95, Table 55, last line, second column: Not included in model	Please amend to: Not included in the base case model.	Results can be generated including end of life costs	This is not factually inaccurate – the table clearly relates to the base because other evidence sources are used in the scenario analyses (as described elsewhere in the ERG report).
Page 105, 'Resource use and costs', second sentence: End-of-life care costs are not included in the later onset model.	Please amend to: End-of-life costs are not included in the base case calculations for the later onset model.	Results can be generated including end-of-life costs	The model description naturally relates to the base case. No amendment has been made.

Page 106, Table 66, 1st row, third column: The initial distributions are subject to uncertainty. Given the multinomial nature of the data, a Dirichlet distribution (applied to the combined CHERISH population) would be appropriate.	Query inclusion of this statement	Might not be the best solution if the aim is to keep the distribution the same in both groups and consistent with CHERISH.	These parameters are uncertain and this uncertainty should be reflected in the model. The Dirichlet could have been applied to a single combined distribution. Samples from this distribution could then be applied in both treatment groups.
Page 112, Table 71, 'Time horizon' row, third column: Within both models, approximately 100% of patients have died by the end of the modelled time horizon.	Please amend to: In the infantile onset model, 100% of patients have died by the end of the time horizon. In the later onset model, all usual care patients and almost all nusinersen patients have died.	Clarification of survival in each model	With respect to the nusinersen group of the later onset model, at 959 months (~79.92 years), 99.99% of the cohort have died. The ERG believes that it is reasonable to treat this as "all patients". No amendment has been made.
Page 119, section 5.5.3 - Text that does not describe the facts accurately. The ERG report states that "The assumed cost of end-of-life care is not mentioned in the CS, but is cited in the model."	We suggest omitting that sentence from the report.	Alignment of ERG report with CS: the cost per patients of £11,839 for end-of-life care is quoted in the CS "20180315_Nusinersen (Spinraza)_NICE_Main Submission Document B_[CIC]" on the page 147 in the Table 48.	The ERG report should have stated that the source of this cost is not mentioned in the CS. This minor correction has been included in the report.
Page 119 The ERG attempted to reproduce the transition matrices beyond the end of ENDEAR and CHERISH using the data reported in the CS (see Table 35 and Table 57); the resulting matrices were slightly different to those used in the company's models. It is likely, but not definite, that this is a		This is a clarification of the ERG statement and has no impact on results. The numbers used in the model calculations did use all the numbers after the decimal point. This would explain the slight differences.	The ERG agrees that this may explain the discrepancies although this is not certain. No amendment has been made.

consequence of rounding errors.			
Page 120 The ERG was unable to locate the cost estimate within the NICE Guideline 61 resource use template.		This is a clarification of the ERG statement and has no impact on results. The estimate was based on the total cost of dying in hospital, total cost of dying at home, and number of patients reported in the NG61. The calculation is performed on the background sheet "Country specifics sheet" based on the assumption that 20% of patients die in hospital, and 80% die at home.	As noted in the ERG report, the source of this cost estimate was not reported in the CS. No amendment has been made.
Page 120 The clinical advisors further commented that other symptoms and outcomes besides motor function may also be important - in particular, aspects of SMA relating to respiratory function, the explicit use of ventilation and the possibility of infections; these factors are not explicitly captured in either of the company's model structures. The clinical advisors also stated that motor function is not the sole determinant of HRQoL and that the ability to participate in activities and a lack of negative symptoms (e.g. pain and infection) may be more important than motor function.		Clarification of ERG statement: Although the explicit use of ventilation is not captured in the base case analysis, the model does include the option to use the combined outcome of permanent ventilation or death as a proxy of survival without permanent ventilation. Also, in a scenario analysis the health state costs were estimated based on the costs of major clinical events, including permanent ventilation (based on ENDEAR), gastrostomy, and scoliosis surgery.	This is not a factual inaccuracy. The CS and the ERG report present the results of the scenario analyses undertaken by the company.
Page 121, bullet (4), final sentence: (deterioration is not permitted)	Please amend to: (deterioration is not permitted in the base case)	This assumption can be relaxed.	The model description naturally relates to the base case. No amendment has been made.

Page 121, bullet (a), second paragraph, first sentence: no deterioration for nusinersen	Please amend to: no deterioration in the base case for nusinersen	This assumption can be relaxed.	The model description naturally relates to the base case. No amendment has been made.
Page 123 Therefore, the assumptions employed within the company's models regarding long-term improvements in motor function for patients receiving nusinersen do not fully reflect clinical advice received by the company or the ERG. Rather, the company's approach to extrapolating transition probabilities for the nusinersen group within both models appears to be unrealistically optimistic. Within the later onset model, the company's approach to extrapolating transition probabilities for the usual care group may be unduly pessimistic, at least for some Type III SMA patients.		This is a clarification of the ERG statement and the scenarios available affect model results. The model does include several scenario analyses which allow exploring this uncertainty. There is a dropdown in the "Efficacy T1" and "Efficacy T2" (row 111 and 93, respectively) sheets which allows the user to explore different motor function trajectories for patients in the nusinersen arm. The user can enter the time at which a proportion of patients will stop improving and the proportion of patients that will progress as in the usual care arm.	The model description naturally relates to the base case. No amendment has been made.
Page 127, bullet (ii): Assumption that after adjustment for age, mortality is the same in Gregoretti *et al*[31] and ENDEAR[14] is not plausible	Please remove this sub-bullet.	It is not assumed that mortality in the two studies is the same. Gregoretti et al is used to extrapolate survival beyond the ENDEAR trial in the absence of long term clinical trial data.	The statement has been modified to reflect the point that this assumption only applies to the extrapolated period.
Page 127, bullet (iii): Assumption that mortality is the same as in CHERISH is not justified	Please remove this statement.	It is not assumed that mortality is the same in Zerres et al. as in CHERISH. The former is being used	The statement has been modified to reflect the point that this assumption only applies to the extrapolated

		to extrapolate beyond the latter in the absence of long term clinical trial data.	period.
Page 127, bullet (vi): No observed data to justify the use of Zerres *et al*[33] data or the adjustment factors used	Please remove this statement.	Zerres et al is being used because of the absence of data or a gold standard.	This is not a factual inaccuracy. As pointed out by the company, there is an absence of data to justify the assumption used.
Page 127 bullet (i) Complexity of modelling approach, second sentence: If the external population has the same mortality at all times (or in the long-term) as that of the external population, then survival estimates from the external population can be used directly without adjustment	Please amend this sentence.	Request for clarification of this sentence.	It is unclear which aspect of this statement the company finds unclear. The ERG does not consider that the sentence requires clarification. No amendment has been made.
Page 127: In their response to clarification questions from the ERG2 (question B9), the company states that some parametric models provided plausible extrapolations and so the ERG considers that using these would be a reasonable approach.	The authors appear to partially quote our response to question B9, missing some crucial detail. This statement should be: "In their response to clarification questions from the ERG2 (question B9), the company states that some parametric models provided plausible extrapolations, but did not fit the data well, and so the ERG considers that using these would be a reasonable approach."	Validity of chosen parametric models. May have impact on robustness of results. We think it is therefore worth raising the question whether the ERG consider using poorly fitting models a reasonable approach? The ERG does not appear to have addressed the problem of where models that fit the data well produce unrealistically high survival and other models that produce plausible survival predictions do not fit the data well. To us this suggests that hazard rates are likely to increase after follow-up in a way which cannot be predicted by the data in the randomised	The ERG agrees that in the absence of long-term trial data it is appropriate to consider the use of relevant external data, which may be used directly if appropriate. However, as stated in the Jackson *et al* paper cited by the company, "the necessary assumptions about how the populations differ, and how short-term trends might continue into the long term, must be clearly stated expressed and examined for plausibility and consistency with external data". The ERG does not consider that this has been demonstrated in this case, hence we suggested that a simpler

		controlled trial (RCT). If 'plausible' models are used that did not fit the RCT data well then it is highly likely that survival will be underestimated. The ERG's recommendation appears to be disagreement with the recent publications of Jackson et al. (2017) and Guyot et al. (2017) that argue the case for the direct use of external data to inform the extrapolation rather than use external data to help justify the choice of model as suggested by Latimer (2013) (NICE DSU Technical Support Document 14).	approach that is more transparent about the sources of uncertainty may have been considered. Jackson *et al* also refer to the NICE guidelines and that "external information could simply be used to inform the choice of model for extrapolation". The ERG does not consider that using poorly fitting models is a reasonable approach. However, a model that provides a less good fit to a small period of observed data, is not necessarily a poorly fitting model over the entire time horizon. The text has been amended to reflect this issue.
Page 131 bullet (v), last sentence: however, this is misleading as survival in the nusinersen treatment group is largely driven by an assumed switch to the Type II SMA mortality curve (proportion = 0.90)	Pleaser remove this statement.	It is a conservative assumption in the context of the treatment effect observed in the trial, irrespective of other assumptions used in extrapolating survival.	The ERG believes that it is misleading to describe a modelling approach as being conservative and then overriding it with a highly optimistic mortality adjustment. For example, Table 34 of the CS "Key features of the economic analysis – infantile onset" describes this "conservative" HR but does not mention the application of a mortality adjustment factor in the better health states. This does not

			seem very balanced.
Page 135, bullet (8)(i): End-of-life costs are included in the early onset model, but not the later onset model. This is inconsistent.	Please amend to: End-of-life costs are included in the early onset model, but not in the base case calculations for the later onset model.	Results can be generated including end-of-life costs	The model description naturally relates to the base case. No amendment has been made.
Page 135: The model does not include a cost associated with scoliosis surgery. .	Please amend to: The model base case analysis does not explicitly include a cost associated with scoliosis surgery, which was assumed to be captured by Bastida's estimates. However, the model included a scenario analysis which calculates health state costs based on the cost of major clinical events such as permanent ventilation, gastrostomy, and scoliosis surgery.	This is a clarification of cost of scoliosis surgery and has no impact on results	The model description naturally relates to the base case. No amendment has been made.
Page 136, bullet (9)(i): Several uncertain model parameters (for example, the initial distributions and the mortality adjustment factors) are held fixed at their mean values. These values are uncertain and should be characterised using probability distributions.	Please use different examples.	It isn't necessarily desirable to vary the initial distributions of patients in the probabilistic sensitivity analysis (PSA) if consistency with the trial is an objective. The mortality adjustment factors are modelling assumptions (they are not sampled data) and uncertainty around them is explored in scenario analysis.	The objective of the PSA should be to provide a faithful characterisation of the uncertainty surrounding the model parameters. All uncertain parameters should therefore be included. This includes the initial distribution and the mortality adjustment factors.
Page 136, bullet (9)(ii): the uncertainty surrounding these parameters will be underestimated	Please remove this statement	Uncertainty around health utilities are explored primarily through scenario analysis.	This is not a factual inaccuracy. The company's comment misses the point - the text relates to the PSA, not the scenario analyses.
Page 138, Exploratory analysis 5: ERG-preferred analysis, sentences 2	Please remove this statement	The model does include several scenario analyses which allow	This is not a factual inaccuracy. Irrespective of what the model has

and 3: It should be noted that this analysis does not address the ERG's concerns regarding the company's modelled survival and motor function trajectories. As such, the ERG's "preferred" ICERs are very likely to be underestimated in both SMA populations.		exploring this uncertainty. There is a dropdown in the "Efficacy T1" and "Efficacy T2" (row 111 and 93, respectively) sheets which allows the user to explore different motor function trajectories for patients in the nusinersen arm. The user can enter the time at which a proportion of patients will stop improving and the proportion of patients that will progress as in the usual care arm.	functionality to do, the ERG's "preferred analysis" does not modify the highly optimistic assumptions regarding mortality and motor function. The point of the subsequent analyses (#6-#8) is to show that even though data are absent, relaxing these assumptions may lead to considerably higher ICERs for nusinersen.
Page 139: The ERG also believes that there would be value in exploring alternative simpler parametric models for OS rather than applying complex piecewise methods using multiple external data sources as the company noted that some of these were plausible; however, these models were not reported in the CS.		This is a clarification of the ERG comment. The model included the option to use the parametric models for OS without applying long term data or the adjusted general population mortality rates.	This is not a factual inaccuracy. Alternative simpler approaches were not explored by the company.
Page 140, section 5.6.2, second sentence: the ERG expects that the probabilistic ICERs would be slightly higher.	Please remove this statement.	Probabilistic results could have been extracted from the model.	This is not a factual inaccuracy.
Page 143, section 5.6.3, third paragraph, first sentence: as such, it is very likely that the true ICERs for nusinersen will be higher.	Please remove this statement.	The distinction between the "preferred analysis" and the "true ICERs" is difficult to maintain when the additional exploratory analysis could have been included in the preferred analysis (but weren't for reasons unexplained).	This is not a factual inaccuracy. The ERG's "preferred analysis" does not modify the highly optimistic assumptions regarding mortality and motor function. The reason that ERG exploratory analyses #6-#8 were included was to show that even though data are absent, relaxing these assumptions may lead to considerably higher ICERs

			for nusinersen.
Page 146, section 5.7, second paragraph, final sentence: The company's early onset model employs two key assumptions: (i) nusinersen-treated patients who reach health states consistent with Type II/III SMA milestones by month 13 gain an additional survival advantage, and (ii) after month 13, the motor function of nusinersen-treated patients cannot deteriorate, whilst the motor function of patients receiving usual care cannot improve.	Please amend to: The company's early onset model employs two key assumptions: (i) nusinersen-treated patients who reach health states consistent with Type II/III SMA milestones gain an additional survival advantage, and (ii) after month 13 in the base case, the motor function of nusinersen-treated patients cannot deteriorate, whilst the motor function of patients receiving usual care cannot improve.	Clarification	The ERG agrees. An amendment has been made.
Page 147, 1st paragraph, final sentence: The later onset model includes two key assumptions: (i) patients in either treatment group who reach health states consistent with Type III SMA milestones by month 15 follow general population mortality rates, and (ii) after month 15, the motor function of nusinersen-treated patients cannot deteriorate, whilst the motor function of patients receiving usual care cannot improve.	Please amend to: The later onset model includes two key assumptions: (i) patients in either treatment group who reach health states consistent with Type III SMA milestones follow general population mortality rates, and (ii) after month 15, the motor function of nusinersen-treated patients cannot deteriorate in the base case, whilst the motor function of patients receiving usual care cannot improve.	Clarification	The ERG agrees. An amendment has been made.
Page 152, section 7, 'Cost-effectiveness conclusions', second paragraph, second sentence: When caregiver QALY losses are included in the analysis, the ERG's preferred assumptions increase the ICER from £898,164 per QALY gained (the company's base case) to £632,850	Please amend to: When caregiver QALY losses are included in the analysis, the ERG's preferred assumptions reduce the ICER from £898,164 per QALY gained (the company's base case) to £632,850 per QALY gained. The main	Correction of increase to reduction	The ERG agrees – this is a typographical error. An amendment has been made.

per QALY gained. The main driver of these differences between the ICERs generated by the company and the ERG relates to the HRQoL impact on patients and caregivers.	driver of these differences between the ICERs generated by the company and the ERG relates to the HRQoL impact on patients and caregivers.		

Issue 9 Scope of the appraisal

Description of problem	Description of proposed amendment	Justification for amendment	Response
Table 3, p.15 'Outcomes' row, final column: Complications of SMA (including, for example, scoliosis and muscle contractures), and stamina and fatigue, are not included as these outcomes were not collected in the pivotal clinical trials	Please alter to: Complications of SMA (including, for example, muscle contractures, stamina and fatigue) are not included as these outcomes were not collected in the pivotal clinical trials	Although scoliosis was not included in the pivotal clinical trials, it is included in the economic models.	We have not amended this because the entire table and its contents are reproduced directly from Table 1 of the CS.
Section 3.4, p.18, Outcomes First sentence: The CS[1] includes evidence relating to all of these outcomes except for: (i) stamina and fatigue, and (ii) complications of SMA.	Please change to: The CS[1] includes evidence relating to all of these outcomes except for: (i) stamina and fatigue.	Scoliosis is included in the economic models.	This is not a factual inaccuracy. The CS does not include any scoliosis-related outcomes from the nusinersen studies. Given that no cost or HRQoL impact for scoliosis surgery is included in the model, it serves only as a means of taking patients off nusinersen.

Issue 10 Confidential mark-up

Description of problem	Description of proposed amendment	Justification for amendment	Response
Tables 36-41 on pages 74-79 Table 58-63 on pages 98-103 Refers to transition matrices for both early and late onset models should be marked as academic in confidence (AIC). This also includes ERG exploratory analyses in tables 104-108 on pages 170-172.	Please highlight figures in tables as AIC	These figures should be treated as academic in confidence.	The additional highlighting has been added to the ERG report.

Nusinersen for treating spinal muscular atrophy: A Single Technology Appraisal Erratum

Produced by	School of Health and Related Research (ScHARR), The University of Sheffield
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Date completed	20th June 2018

Table 1: ENDEAR analysis sets (adapted from CS, Table 15)

Analysis	Number of patients	Description
Interim (15 June 2016)	Nusinersen: 51 Sham control: 27	Infants in the ITT set who were assessed at the day 183, 302, or 394 visit and had a time difference of at least 190 days between the date of first dose and the data cut-off date of the interim analysis
Final efficacy set (21 November 2016)	Nusinersen: 73; Sham control: 37	Infants in the ITT set who were assessed at the day 183, 302, or 394 visit and had a time difference of at least 190 days between the date of the first dose and the data cut-off date of the final analysis
Final ITT set (21 November 2016)	Nusinersen: 80; Sham control: 41	All infants who were randomised and received ≥1 dose of study drug

ITT – intention-to-treat

Motor function

Motor function was measured in the ENDEAR study using three measures: Module 2 of the Hammersmith Infant Neurological Examination (HINE-2 - the primary endpoint); the Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders (CHOP INTEND) and the Compound Muscle Action Potential (CMAP), an electrophysiological technique used to measure nerve function, were both secondary outcomes. Responders were infants with a greater number of motor milestone categories with improvement than worsening[4] (see footnote to Table 9). Motor function outcomes are shown in Table 2.

Table 2: ENDEAR motor function outcomes (adapted from CS, Table 19)

Outcome	Nusinersen	Control	Difference (95% CI); *p*-value
Interim analysis (data cut-off 15 June 2016) (interim analysis set)			
HINE-2 proportion responders	21 (41%)	0 (0%)	41.18 (18.6, 61.20); $p<0.001$
Final analysis (data cut-off 21 November 2016) (efficacy analysis set)			
HINE- 2 proportion responders	37 (51%)	0 (0%)	[redacted] $p<0.0001$
HINE -2 proportion with improvement in total score	49 (67%)	5 (14%)	
HINE -2 proportion with worsening in total score	1 (1%)	8 (22%)	
CHOP INTEND proportion with ≥ 4 point improvement	52 (71%)	1 (3%)	[redacted] $p<0.001$
CHOP INTEND proportion with any improvement	53 (73%)	1 (3%)	
CHOP INTEND proportion with any worsening	5 (7%)	18 (49%)	
CMAP amplitude responders	26 (36%)	2 (5%)	$p=0.001$

CHOP INTEND - Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders; CI - confidence interval; CMAP - compound muscle action potential; HINE-2 - Module 2 of the Hammersmith Infant Neurological Examination
Note: HINE-2 responders were infants with a ≥2-point increase [or maximal score] in the ability to kick, OR ≥1-point increase in the motor milestones of head control, rolling, sitting, crawling, standing or walking, and improvement in more categories of motor milestones than worsening.

- Assumption that after adjustment for age, long-term mortality is the same in Gregoretti *et al*[31] and ENDEAR[14] is not plausible
- Uncertainty due to reconstruction of IPD from published Kaplan-Meier curve

(iii) Use of external data from Zerres *et al*[33] to inform later onset model

- Assumption that long-term mortality is the same as in CHERISH is not justified

(iv) Use of general population mortality

- Assumption that long-term mortality is systematically different between the studies and the general population (by assuming a constant HR) is not plausible

(v) Assumptions regarding treatment effect

- Description that a conservative HR of 1.0 is applied is misleading due to the implementation of the Type II adjustment

(vi) Concerns regarding SMA Type II adjustment

- No observed data to justify the use of Zerres *et al*[33] data or the adjustment factors used.

(i) Complexity of modelling approach

Jackson *et al*[49] present a framework for survival extrapolation using external data which is referenced by the company in justifying their approach (see clarification response,[2] question B9). If the external population has the same mortality at all times (or in the long-term) as that of the external population, then survival estimates from the external population can be used directly without adjustment. This assumption permits the direct use of data from Gregoretti *et al*[31] and Zerres *et al*[33] in the early onset and late onset models, respectively. Alternatively, OS may be assumed to be different, but systematically similar in such a way that the external data can be adjusted to estimate OS in the target population. This assumption permits the application of the adjusted general population mortality data. The validity of these assumptions is paramount to the reliability of the survival predictions; however, no clear justification for either assumption was presented by the company. The ERG considers that the plausibility of these assumptions is questionable and considers each case in further detail below.

Given the concerns regarding the use of external data, the ERG considers that a simpler approach based on extrapolating parametric models fitted to observed trial data may have been both more informative and more transparent than the approach adopted by the company. Consideration of appropriate external data is important; however, it could be used more simply to judge the plausibility of models fitted to observed data, or to inform certain parameters.[56] In their response to clarification questions from the ERG[2] (question B9), the company states that some parametric models provided plausible extrapolations (although they did not provide the best fit to the observed data) and so the ERG considers that using these may be a reasonable approach. Details of which models provided plausible predictions were not provided by the company.

Supplementary analyses: NICE Cost-effectiveness results for nusinersen with confidential patient access scheme

The following analyses are a re-run of the cost-effectiveness analyses provided as part of the NICE manufacturer submission (15th March 2018), using the proposed simple discount patient access scheme (PAS) for nusinersen of [redacted] per vial, a [redacted] discount to the list price of £75,000 per vial. The results are aligned with the original NICE submission but limited to key analyses impacted by the PAS.

B.1 Infantile-Onset SMA

1.1 Base case results

1.1.1 Base case incremental cost-effectiveness analysis results

Table 1 reports the deterministic results for lifetime costs, life years gained and patient QALYs per patient for nusinersen vs. RWC and the associated incremental cost-effectiveness ratios (ICERs) for list and PAS prices for nusinersen. At list price, the discounted incremental costs are estimated to be £2,187,311, with discounted incremental QALYs of 5.37 for the patient and 5.44 with caregiver utilities included. The resulting ICER at list price is around £408,000 per QALY gained (patients only) or £402,361 with caregivers included (Table 2). With the application of the proposed PAS, the incremental costs are reduced by [redacted], resulting in an ICER of approximately [redacted] (patients) and [redacted] (patients & caregivers) per QALY gained.

Table 1. Base case results – infantile onset SMA, patient QALYs with and without PAS

Technology	Total costs (£)	Total LYG	Total QALYs	Inc. costs (£)	Inc. LYG	Inc. QALYs	ICER inc. (£/QALY)
List Price							
RWC	71,540	3.39	2.49				
Nusinersen	2,258,852	9.34	7.86	2,187,311	5.95	5.37	407,605
PAS Price							
RWC	71,540	3.39	2.49				
Nusinersen	[redacted]	9.34	7.86	[redacted]	5.95	5.37	[redacted]

Abbreviations: ICER, incremental cost-effectiveness ratio; inc., incremental; LYG, life years gained; QALYs, quality-adjusted life years; RWC, real-world care; SMA, spinal muscular atrophy

Table 2. Base case results – infantile onset SMA, patient and carer QALYs with and without PAS

Technology	Total costs (£)	Total LYG	Total QALYs	Inc. costs (£)	Inc. LYG	Inc. QALYs	ICER inc. (£/QALY)
List Price							
RWC	71,540	3.39	2.17				
Nusinersen	2,258,852	9.34	7.61	2,187,311	5.95	5.44	402,361
PAS Price							
RWC	71,540	3.39	2.17				
Nusinersen	[redacted]	9.34	7.61	[redacted]	5.95	5.44	[redacted]

Abbreviations: ICER, incremental cost-effectiveness ratio; inc., incremental, LYG, life years gained; QALYs, quality-adjusted life years; RWC, real-world care; SMA, spinal muscular atrophy

1.2 Sensitivity analyses

1.2.1 Probabilistic sensitivity analysis

Table 3 reports the probabilistic results in the same format as the deterministic results. The probabilistic costs, life years and QALYs are the mean of 1,000 iterations of the model. Figure 1 shows the 1,000 simulations of incremental costs and QALYs as a scatter plot on the cost-effectiveness plane using the proposed PAS price. Each simulation is shown by a blue diamond while the deterministic and probabilistic means are shown by a red square and red diamond, respectively. Due to the magnitude of the ICER, it was not thought useful to present the cost-effectiveness acceptability curve relative to NICE's conventional reference points of cost-effectiveness.

Table 3. Probabilistic results - infantile onset, patient QALYs with PAS

Technology	Total costs (£)	Total LYG	Total QALYs	Inc. costs (£)	Inc. LYG	Inc. QALYs	ICER inc. (£/QALY)
RWC	70,754	3.33	2.45				
Nusinersen	[redacted]	9.19	7.73	[redacted]	5.86	5.28	[redacted]

Abbreviations: ICER, incremental cost-effectiveness ratio; inc., incremental; LYG, life years gained; QALYs, quality-adjusted life years; RWC, real-world care

Figure 1. Scatter plot - infantile onset SMA with PAS

Abbreviations: QALY, quality-adjusted life years

1.2.2 Deterministic sensitivity analysis

Table 4 reports the OWSA for the 10 variables which have the largest ranges of impact on the ICER at the PAS price from a patient perspective, excluding the discount rates on costs and outcomes (which are the 2 most important variables overall). For each variable, the table reports the base case value, the upper and lower bounds used in OWSA and the ICERs at the upper and lower bounds of the variable. Figure 2 presents the same information graphically in the form of a tornado diagram.

Table 4. One-way sensitivity analysis - infantile onset with PAS

Parameter	Base case	Lower bound	Upper bound	ICER at variable's	
				Lower bound	Upper bound
Nusinersen vial price: 5 mL at 2.4 mg/mL	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Patient utility: Stands/Walks unaided	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Factor to adjust later onset mortality risk	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Patient Utility: No milestone achieved	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
HR death SMA Infantile onset vs Gen Pop	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Patient utility: Walks with assistance	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Patient utility: Stands with assistance	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Mean monthly rate of CHOP-INTEND increase – Nusinersen	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Patient utility: Sits without support	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Patient Utility: Moderate milestones	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: CHOP INTEND, Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders; ICER, incremental cost-effectiveness ratio; RWC, real-world care;

Figure 2. Tornado diagram - infantile onset with PAS

*The quadrant where the ICER falls is shown in the graph: I = quadrant 1; II = quadrant 2 (intervention dominated); III = quadrant 3 (less expensive and less effective); IV = quadrant 4 (intervention dominates)
Abbreviations: ICER, incremental cost-effectiveness ratio; RWC, real-world care

1.2.3 Scenario analysis

The exploration of uncertainty related to choice of methods or data sources was categorised as scenario analysis. For example, Zerres and Rudnik-Schöneborn (1995)(125) was used to extrapolate survival beyond the time horizon of the trial as an alternative to Gregoretti et al. (2013)(11). While the latter was used in the base case as it provided subgroup data that more accurately reflected that of the standard of care in the UK, Zerres and Rudnik-Schöneborn (1995)(125) was considered due to its size (445 patients) and duration of follow-up (20 years).

Table 5 reports a range of scenario analyses for infantile onset SMA, indicating the base case approach, scenarios investigated and the associated estimates of cost per QALY gained on the basis of patient and combined patient and carer perspectives. The ICERs can be compared against the base case incremental costs per patient QALY gained and cost per patient and carer QALY gained of £407,605 and £402,361, respectively. The results including carer QALYs are included here for completeness although they are only slightly lower than those using the patient perspective alone.

Table 5. Scenario analysis - infantile onset SMA with and without PAS

Input parameter	Base case analysis setting	Scenarios	List Price ICER (£)	PAS ICER (£)
			Patient perspective (upper), combined patient and carer perspective (lower)	
Base case ICER			**407,605** **402,361**	[redacted]
Time horizon (years)	Lifetime (60 years)	10	564,659 543,695	[redacted]
		20	436,278 428,375	[redacted]
		30	410,888 405,315	[redacted]
Cost perspective	Health and social care	Societal	419,253 413,851	[redacted]
Efficacy Setting				
Apply higher long-term risk of death based on SMA type I - adjusted general mortality rates	Apply	Don't Apply	380,658 376,357	[redacted]
OS beyond trial follow-up	Gregoretti 2013 -NRA	Zerres 1995 + 2 knots &	379,804 376,289	[redacted]
OS treatment effects	Apply HR =1.00 after trial follow-up	Taper to 1.0 over a defined period (12 months)	405,766 400,680	[redacted]
Health states from which patients discontinue	*No Milestones* (I)	*No Milestones and Mild Milestones*	406,096 402,138	[redacted]
Apply type II mortality rates from Zerres et al. 1997 to patients in motor milestones characteristic of later onset	Apply	Don't apply	872,257 802,469	[redacted]
Mortality risk factor	0.9	0.5	578,554 556,339	[redacted]
		1.00	347,082 345,578	[redacted]
Assumption that proportion of patients on treatment reach a plateau	No	Yes 0%	417,355 412,445	[redacted]

Input parameter	Base case analysis setting	Scenarios	List Price ICER (£)	PAS ICER (£)
			Patient perspective (upper), combined patient and carer perspective (lower)	
% of patients reaching an improvement plateau which start getting worse				
Assumption that proportion of patients on treatment reach a plateau % of patients reaching an improvement plateau which start getting worse	No	Yes 10%	421,445 417,806	[redacted]
Source for RWC arm CHOP INTEND rate of decline	ENDEAR	Finkel et al. 2012	407,315 402,328	[redacted]
Drug administration cost settings				
Inpatient/outpatient/day case	40% 30% 30%	100% 0% 0%	409,438 404,170	[redacted]
		0% 0% 100%	409,015 403,752	[redacted]
Health state cost settings				
Scenarios for health state costs	From published sources	Cost major clinical events only	442,838 437,140	[redacted]
Cost source	Bastida et al. 2016	Klug et al. 2016	405,194 399,980	[redacted]
Utility settings				
Patient	PedsQL type 2 (ITT)	Vignettes	421,703 394,298	[redacted]
		Bastida upper bound	450,353 476,099	[redacted]
		Bastida lower bound	503,295 788,019	[redacted]
		PedsQL type 2 (<25 months disease duration)	387,628 364,333	[redacted]

Abbreviations: CHOP INTEND, Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders; HINE, Hammersmith Infant Neurological Examination; HR, hazard ratio; ICER, incremental cost-effectiveness ratio; OS, overall survival; PedsQL, Paediatric Quality of Life Inventory; RWC, real-world care; SMA, spinal muscular atrophy;

1.2.4 Summary of sensitivity analyses results

OWSA primarily illustrates the significance of utility estimates as a source of uncertainty in the cost-effectiveness estimates. In particular, the utility for the ***Stand/Walks Unaided*** health state, in which the nusinersen cohort spends an average of 9.60 years per patient (undiscounted) compared with 0 years under RWC, generates the largest range of ICERS in OWSA. Extrapolation of survival beyond the time horizon of the ENDEAR trial was another area of considerable uncertainty. The mortality rate applied to infantile onset patients achieving later onset motor milestones generated a wide range of ICERs. However, at the upper end of its range in OWSA (and its most favourable possible value with mortality equivalent to that of type II patients), this variable gave an ICER which was slightly under £350,000 per QALY gained at list price. At the PAS price, the equivalent ICER fell to below [redacted] per QALY gained

Similarly, in scenario analyses, there were few parameters for which the scenario reduced the ICER below £400,000 or [redacted] per QALY gained, for the list and PAS price, respectively, primarily those related to mortality. This was observed when not applying a higher long-term mortality risk from other causes relative to the general population, and when applying data from Zerres and Rudnik-Schöneborn (1995)(125) rather than Gregoretti et al. (2013)(11) to extrapolate survival beyond the end of follow-up in the ENDEAR trial. For extrapolation beyond the ENDEAR study in infantile onset SMA, the latter scenario reduces the ICER to around £380,000 (or [redacted]).The scenario showing that patients achieving later onset motor milestones share the mortality experience of type II patients replicates the results of OWSA on this variable.

The scenario using the utilities obtained from the case vignette study, because of the linkage between the variation in patient utilities and carer utilities, reduces the ICER below £400,000 per QALY when carer QALYs are included at list price; the with PAS equivalent was approximately [redacted] per QALY gained. However, what is known about the disease and the burden on carers, including expert clinical advice at the UK advisory board(33), suggests that a utility does not adequately capture the impact on carers and that this approach is likely to understate the benefits of nusinersen.(109–113) More generally, the estimates of cost effectiveness presented here do not address the underlying limitations of the QALY as a single summary measure of benefit. Because of the conceptual and practical difficulties of measuring utilities, and the associated drawbacks of QALYs in this patient group, we caution against reducing the benefit of nusinersen to a single metric.

1.3 Subgroup analysis

Subgroup analysis was conducted for the two pre-specified subgroups based on disease duration in the ENDEAR trial (Table 6). Cost effectiveness was modelled by applying the transition probabilities specific to the patient counts of the subgroups. Overall survival for the subgroups was based on the Kaplan-Meier curves. As the base case overall survival within the trial period was modelled using the flexible spline-based Weibull function with 1 knot fitted to the ITT Kaplan-Meier curve, the results of the subgroups are presented alongside the results for the ITT population using the Kaplan-Meier curve. However, it is also possible to use

the ITT survival with the subgroup data. The mean CHOP INTEND score assigned to each health state and the mean rate of CHOP INTEND change used to estimate transition probabilities after trial follow-up are also modified to be subgroup specific.

Results in Table 6 reflect the results of the ENDEAR trial showing a better response in patients treated earlier. The QALYs gained in the “≤12 weeks disease duration” subgroup were 50% greater than those of the QALYs gained in the “>12 weeks disease duration” subgroup.

Table 6. Subgroup analysis - infantile onset with and without PAS

Population	Mean monthly rate of CHOP INTEND increase/decrease	Mean CHOP INTEND score per health state	List price Incremental cost (£)	List price Incremental QALY	List price ICER (£/QALY gained)	With PAS Incremental cost (£)	With PAS Incremental QALY	With PAS ICER (£/QALY gained)
ITT population	Nusinersen: [redacted] / RWC: [redacted]	ITT each arm	2,187,311	5.37	407,605	[redacted]	5.37	[redacted]
		ITT both arms	2,175,081	5.31	409,235	[redacted]	5.31	[redacted]
≤12 weeks disease duration	Nusinersen: [redacted] / RWC: [redacted]	≤ 12 weeks each arm	2,628,681	6.59	398,912	[redacted]	6.59	[redacted]
		≤ 12 weeks both arms	2,622,153	6.56	399,576	[redacted]	6.56	[redacted]
>12 weeks disease duration	Nusinersen: [redacted] / RWC: [redacted]	> 12 weeks each arm	1,747,737	4.13	422,874	[redacted]	4.13	[redacted]
		> 12 weeks both arms	1,743,436	4.12	423,603	[redacted]	4.12	[redacted]

Abbreviations: ICER, incremental cost-effectiveness ratio; QALY, Quality-adjusted life year;

B.2 Later-Onset SMA

2.1 Base case results

2.1.1 Base case incremental cost-effectiveness analysis results

Table 7 reports the lifetime costs, life years and QALYs for nusinersen and RWC. The greater costs and lower benefits in later onset patients compared with infantile onset combine to give an ICER of £1.25m per QALY gained. The inclusion of carer QALYs reduces the ICER to around £0.9m per QALY gained. The equivalent ICERs were approximately [redacted] and [redacted] per QALY gained with the PAS applied.

Table 7. Base case results - later onset SMA, patient QALYs

Technology	Total costs (£)	Total LYG	Total QALYs	Inc. costs (£)	Inc. LYG	Inc. QALYs	ICER inc. (£/QALY)
List Price							
RWC	184,312	19.61	14.52				
Nusinersen	3,148,754	20.99	16.88	2,964,442	1.38	2.37	1,252,991
PAS Price							
RWC	184,312	19.61	14.52				
Nusinersen	[redacted]	20.99	16.88	[redacted]	1.38	2.37	[redacted]

Abbreviations: ICER, incremental cost-effectiveness ratio; inc., incremental; LYG, life years gained; QALYs, quality-adjusted life years; RWC, real-world care; SMA, spinal muscular atrophy;

Table 8. Base case results - later onset SMA, patient and carer QALYs

Technology	Total costs (£)	Total LYG	Total QALYs	Inc. costs (£)	Inc. LYG	Inc. QALYs	ICER inc. (£/QALY)
List Price							
RWC	184,312	19.61	12.36				
Nusinersen	3,148,754	20.99	15.66	2,964,442	1.38	3.30	898,164
PAS Price							
RWC	184,312	19.61	12.36				
Nusinersen	[redacted]	20.99	15.66	[redacted]	1.38	3.30	[redacted]

Abbreviations: ICER, incremental cost-effectiveness ratio; inc., incremental; LYG, life years gained; QALYs, quality-adjusted life years; RWC, real-world care; SMA, spinal muscular atrophy;

2.2 Sensitivity analyses

2.2.1 Probabilistic sensitivity analysis

The methods of PSA were the same as those used in the infantile onset model.

As with infantile onset, it was not considered meaningful to present the cost-effectiveness acceptability curve based on conventionally accepted willingness to pay benchmarks due to the magnitude of the cost-effectiveness ratio. However, the PSA scatter plot for patient costs

and patient QALYs is presented to indicate the parameter-related uncertainty in the model (Figure 3).

Table 9. Probabilistic results - later onset SMA, patient QALYs with PAS

Technology	Total costs (£)	Total LYG	Total QALYs	Inc. costs (£)	Inc. LYG	Inc. QALYs	ICER (£/QALY)
RWC	182,627	19.61	14.55				
Nusinersen	[redacted]	20.93	16.82	[redacted]	1.32	2.27	[redacted]

Abbreviations: ICER, incremental cost-effectiveness ratio; inc., incremental; LYG, life years gained; QALYs, quality-adjusted life years; RWC, real-world care; SMA, spinal muscular atrophy;

Figure 3. Scatter plot on the cost-effectiveness plane - later onset SMA with PAS

[redacted]

Abbreviations: QALY, quality-adjusted life year; SMA, spinal muscular atrophy;

2.2.2 Deterministic sensitivity analysis

Table 10 reports the 10 variables with the largest range of impact on the ICER in terms of the overall spread between the ICER at the lower and upper bounds of each variable in OWSA. The table gives the base case value of each variable, the lower and upper bounds tested in OWSA and the ICERs associated with those limits. The base case ICER is [redacted] per QALY gained (Table 7). The same information is presented as a Tornado diagram in Figure 4.

Table 10. One-way sensitivity analysis - later onset SMA

Parameter	Base case	Lower bound	Upper bound	ICER at variable's	
				Lower bound	Upper bound
Patient utility: *Walks Unaided*	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Patient Utility: *Sits without Support but does not Roll*	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Nusinersen vial price: 5 mL at 2.4 mg/mL	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Factor to adjust later onset (type III) mortality risk	0.5	0.4	0.6	[redacted]	[redacted]
Patient utility: *Stands Unaided*	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Patient Utility: *Sits and Rolls Independently*	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Mean monthly rate of HFMSE increase - nusinersen	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Patient utility: *Stands/Walks with Assistance*	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Patient Utility: *Sits and Crawls with Hands and Knees*	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Percentage of patients that discontinue after scoliosis surgery	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: HFMSE, Hammersmith Functional Motor Scale-Expanded; ICER, incremental cost-effectiveness ratio; SMA, spinal muscular atrophy

Figure 4. Tornado diagram - later onset SMA with PAS

*The quadrant where the ICER falls is shown in the graph: I = quadrant 1; II = quadrant 2 (intervention dominated); III = quadrant 3 (less expensive and less effective); IV = quadrant 4 (intervention dominates)
Abbreviations: ICER, incremental cost-effectiveness ratio; HFMSE, Hammersmith Functional Motor Scale – Expanded; SMA, Spinal Muscular Atrophy

2.2.3 Scenario analysis

Scenario analyses explored the impact of varying the methodological approach to or data used to support model inputs, or varied modelling assumptions where data were absent (for example, long term survival). As noted in relation to the cost data, only one other data source was available in addition to the Bastida et al. (2016) study. The alternative to the CHERISH trial data for changes over time in HFMSE was a natural history study in SMA type II and III patients. The scenarios reported here are those which had the most significant impact on the results. Table 11 shows the input parameters which are the subject of scenario analyses, the approach adopted in the base case, the scenario(s) explored and the resulting ICER(s). The ICERs can be compared against the base case incremental cost per patient QALY gained of [redacted].

Table 11. Scenario analysis - later onset SMA with and without PAS

Input parameter	Base case analysis setting	Scenarios	List Price ICER (£)	PAS ICER (£)
			Patient perspective (upper), combined patient and carer perspective (lower)	
Base case ICER			**1,252,991** **898,164**	[redacted]
Time horizon (years)	Lifetime (80 years)	20	2,394,639 1,473,743	[redacted]
		40	1,528,733 1,027,641	[redacted]
		60	1,280,983 911,199	[redacted]
Cost perspective	Health and social care	Societal	1,150,976 825,038	[redacted]
Efficacy setting				
Apply higher long-term risk of death based on SMA type II adjusted general mortality rates	Apply	Don't Apply	1,227,736 886,694	[redacted]
Apply general population mortality rates to patients in motor milestones characteristic of later onset (type III) patients	Apply	Don't apply	2,324,278 1,285,987	[redacted]
Mortality risk factor	0.5	0.75	969,170 753,553	[redacted]
		1.00	734,749 614,044	[redacted]
Assumption that proportion of patients on treatment reaches a plateau; % of those reaching an improvement plateau who start getting worse	No	Yes 0%	1,371,100 983,437	[redacted]
Assumption that proportion of patients on treatment reaches a plateau; % of those reaching an improvement plateau who start getting worse	No	Yes 10%	1,393,262 997,921	[redacted]

Source for RWC arm HFMSE rate of decline	CHERISH	Kaufmann 2012(149)	1,268,258 911,947	[redacted]
Drug administration cost settings				
Inpatient/outpatient/day case	40% 30% 30%	100% 0% 0%	1,258,656 902,225	[redacted]
		0% 0% 100%	1,255,928 900,269	[redacted]
Health state cost settings				
Scenarios for health state costs	From published sources	Cost major clinical events only	1,276,308 914,878	[redacted]
Cost source	Bastida 2016	Klug 2016	1,258,136 901,852	[redacted]

Abbreviation: HFMSE, Hammersmith Functional Motor Scale-Expanded; ICER, incremental cost-effectiveness ratio; RWC, real-world care;

2.2.4 Summary of sensitivity analyses results

In common with the infantile onset model, the discount rates (excluded from the OWSA results) and nusinersen vial price were among the 5 variables which produced the largest spread around the base case ICER of £1,252,991 per QALY gained in the later onset model at the list price or [redacted] at the PAS price. Mortality rates were again important in later onset SMA but utilities had relatively greater prominence compared with the results for infantile onset SMA. The lowest ICER, of £832,517 per QALY ([redacted] per QALY at the PAS price), was obtained in OWSA with a utility associated with the ***Sits without Support but does not Roll*** health state of 1 (Table 10).

Shortening the time horizon increased the ICER relative to patient lifetime in the base case, substantially so at a time horizon below 20 years. Adopting a societal rather than a health and social care perspective reduces the ICER marginally in later onset patients. Changing assumptions about the source of health and social care costs, the setting for the administration of nusinersen or the approach to health state costs had a relatively minor impact on the ICER.

In later onset patients, uncertainty around the mortality of type II patients who achieved motor milestones characteristic of later onset (type III) patients resulted in wide variation around the ICER. Given evidence that type III patients have mortality similar to that of the general population, the model allows for a mortality adjustment factor. The following options are possible: the mortality of type II patients in type III milestones is set equal to the mortality of the general population (adjustment factor of 1), the mortality of type II patients (adjustment factor of 0), or somewhere in between. From a base case adjustment of 0.5, shifting the mortality risk of this group closer to that of the general population reduces the ICER and, when equalising it to the general population mortality rates, the ICER falls to around £735,000 per QALY gained ([redacted] at the PAS price) from a patient perspective and below £615,000 ([redacted] at the PAS price) including carer QALYs.

These scenario analyses serve to illustrate some of the key areas of uncertainty around the cost per QALY estimates. As with infantile onset patients, we reiterate that QALYs here are difficult to interpret and do not necessarily capture the full value of nusinersen.

2.3 Subgroup analysis

Subgroup analysis was conducted for subgroups based on disease duration (Table 12). In the CHERISH trial the subgroups were specified as <25 months, ≥25 months but <44 months, and ≥44 months. The model includes analyses for <25 months disease duration and ≥25 months disease duration. Cost effectiveness was modelled by applying the transition probabilities specific to the patient counts of the subgroups. The mean HFMSE score assigned to each health state and the mean rate of HFMSE change used to estimate transition probabilities after trial follow-up are also modified to be subgroup specific.

Table 12. Subgroup analysis - Later onset

			List Price			PAS Price		
Population	**Mean monthly rate of HFMSE increase/decrease**	**Mean HFMSE score per health state**	**Incremental cost (£)**	**Incremental QALY**	**ICER (£/QALY gained)**	**Incremental cost (£)**	**Incremental QALY**	**ICER (£/QALY gained)**
ITT population	Nusinersen: [redacted] / RWC: [redacted]	ITT each arm	2,964,442	2.37	1,252,991	[redacted]	2.37	[redacted]
		ITT both arms	2,963,298	2.34	1,265,944	[redacted]	2.34	[redacted]
<25 months disease duration	Nusinersen: [redacted] / RWC: [redacted]	<25 months each arm	2,947,814	2.33	1,263,457	[redacted]	2.33	[redacted]
		<25 months both arms	2,962,710	2.47	1,201,673	[redacted]	2.47	[redacted]
≥ 25 months disease duration	Nusinersen: [redacted] / RWC: [redacted]	≥ 25 months each arm	2,944,944	1.72	1,712,437	[redacted]	1.72	[redacted]
		≥ 25 months both arms	2,962,045	1.83	1,615,299	[redacted]	1.83	[redacted]

Abbreviations: ICER, incremental cost-effectiveness ratio; QALY, Quality-adjusted life year;

A higher rate of HFMSE increase results in faster transitions to the next best health state and a higher rate of HFMSE decrease results in faster transitions to the next worse health state. However, the ICER for the <25 months disease duration subgroup using the each-arm scenario is higher than the ICER for the ITT each arm scenario. This is due to the faster transition to worse health states in the <25 months subgroup for those patients in the nusinersen arm discontinuing treatment, which is associated with the higher rate of HFMSE decrease along with a smaller HFMSE score difference between the ***Walking unaided*** and ***Standing unaided*** health states in the RWC arm. If no patient is assumed to discontinue treatment, the ICER for the <25 months each arm subgroup is lower than the ICER for the ITT each arm scenario.

1

Nusinersen for treating spinal muscular atrophy: A Single Technology Appraisal

Addendum - ERG exploratory analyses results including Patient Access Scheme for nusinersen

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Introduction

This addendum presents the results of the ERG's exploratory analyses including the proposed Patient Access Scheme (PAS) for nusinersen. The PAS takes the form of a simple price discount of [redacted]

Accuracy of the company's analyses including the PAS

The ERG was able to reproduce most of the results contained within the company's PAS submission.[1] The only exception relates to the deterministic sensitivity analysis exploring the monthly rate of HFMSE increase in the nusinersen group in the later onset model. Within this scenario, the company's ICERs were [redacted] per QALY gained when only patient health gains were included, and [redacted] per QALY gained when caregiver QALY losses were also included. The results generated by the ERG were [redacted] per QALY gained when only patient health gains were included, and [redacted] per QALY gained when caregiver QALY losses were also included. The reason for these discrepancies are unclear.

ERG's exploratory analyses including the PAS

The results of the ERG's exploratory analyses for the early onset model (including the PAS) are presented in Table 1 and Table 2. The results of the ERG's exploratory analyses for the later onset model (including the PAS) are presented in Table 3 and Table 4. The results of these analyses should be interpreted alongside consideration of the ERG's concerns regarding the company's assumptions around health utilities, modelled survival advantages and motor function trajectories. A detailed critique of these issues is presented in the ERG report.[2]

Table 1: ERG preferred analysis, early onset (including PAS)

Option	QALYs (patient)	QALYs (patient+ caregiver)	Cost	Inc. QALYs (patient)	Inc. QALYs (patient+ caregiver)	Inc. cost	ICER (patient)	ICER (patient+ caregiver)
Company's base case								
Nusinersen	7.86	7.61	[redacted]	5.37	5.44	[redacted]	[redacted]	[redacted]
Usual care	2.49	2.17	£71,540	-	-	-	-	-
ERG exploratory analysis 1 – mean initial distribution applied to both treatment group								
Nusinersen	7.87	7.63	[redacted]	5.38	5.45	[redacted]	[redacted]	[redacted]
Usual care	2.49	2.18	£71,504	-	-	-	-	-
ERG exploratory analysis 2 - include end-of-life cost								
Nusinersen	7.87	7.63	[redacted]	5.38	5.45	[redacted]	[redacted]	[redacted]
Usual care	2.49	2.18	£71,504	-	-	-	-	-
ERG exploratory analysis 3 – patient utilities based on vignette study (Lloyd *et al*[3])								
Nusinersen	4.42	4.15	[redacted]	5.20	5.56	[redacted]	[redacted]	[redacted]
Usual care	-0.78	-1.42	£71,504	-	-	-	-	-
ERG exploratory analysis 4 - caregiver utilities based on Bastida *et al*[4]								
Nusinersen	7.87	5.88	[redacted]	5.38	3.65	[redacted]	[redacted]	[redacted]
Usual care	2.49	2.23	£71,504	-	-	-	-	-
ERG exploratory analysis 5 - ERG preferred analysis (including ERG analyses 1, 2, 3 and 4)								
Nusinersen	4.42	2.43	[redacted]	5.20	3.47	[redacted]	[redacted]	[redacted]
Usual care	-0.78	-1.04	£71,504	-	-	-	-	-

Table 2: Additional exploratory analyses undertaken using the ERG preferred model, early onset (including PAS)

Option	QALYs (patient)	QALYs (patient+ caregiver)	Cost	Inc. QALYs (patient)	Inc. QALYs (patient+ caregiver)	Inc. cost	ICER (patient)	ICER (patient+ caregiver)
ERG exploratory analysis 6a - patient utilities based on Bastida *et al*[4]								
Nusinersen	3.87	1.88	[redacted]	3.23	1.49	[redacted]	[redacted]	[redacted]
Usual care	0.64	0.38	£71,504	-	-	-	-	-
ERG exploratory analysis 6b - patient HRQoL estimates based on clinical judgement								
Nusinersen	6.69	4.70	[redacted]	5.99	4.25	[redacted]	[redacted]	[redacted]
Usual care	0.70	0.44	£71,504				-	-
ERG exploratory analysis 7 - no mortality adjustment								
Nusinersen	1.16	0.45	[redacted]	1.95	1.49	[redacted]	[redacted]	[redacted]
Usual care	-0.78	-1.04	£71,504	-	-	-	-	-
ERG exploratory analysis 8a- 5% nusinersen patients lose milestones each cycle								
Nusinersen	4.00	2.27	[redacted]	4.79	3.31	[redacted]	[redacted]	[redacted]
Usual care	-0.78	-1.04	£71,504	-	-	-	-	-
ERG exploratory analysis 8b- 10% nusinersen patients lose milestones each cycle								
Nusinersen	3.45	1.98	[redacted]	4.23	3.02	[redacted]	[redacted]	[redacted]
Usual care	-0.78	-1.04	£71,504	-	-	-	-	-
ERG exploratory analysis 8c- 20% nusinersen patients lose milestones each cycle								
Nusinersen	2.01	1.04	[redacted]	2.79	2.09	[redacted]	[redacted]	[redacted]
Usual care	-0.78	-1.04	£71,504	-	-	-	-	-
ERG exploratory analysis 8d – all patients stay in final state indefinitely after end of ENDEAR								
Nusinersen	-0.66	-1.03	[redacted]	0.09	-0.01	[redacted]	[redacted]	[redacted]
Usual care	-0.76	-1.02	£71,504	-	-	-	-	-
ERG exploratory analysis 8e – all patients lose all milestones after end of ENDEAR								
Nusinersen	-1.03	-1.37	[redacted]	-0.25	-0.33	[redacted]	[redacted]	[redacted]
Usual care	-0.78	-1.04	£71,504	-	-	-	-	-

Table 3: ERG preferred analysis, later onset (including PAS)

Option	QALYs (patient)	QALYs (patient+ caregiver)	Cost	Inc. QALYs (patient)	Inc. QALYs (patient+ caregiver)	Inc. cost	ICER (patient)	ICER (patient+ caregiver)
Company's base case								
Nusinersen	16.88	15.66	[redacted]	2.37	3.30	[redacted]	[redacted]	[redacted]
Usual care	14.52	12.36	£184,312	-	-	-	-	-
ERG exploratory analysis 1 – mean initial distribution applied to both treatment group								
Nusinersen	16.95	15.76	[redacted]	2.47	3.47	[redacted]	[redacted]	[redacted]
Usual care	14.48	12.29	£185,686	-	-	-	-	-
ERG exploratory analysis 2 - include end-of-life cost								
Nusinersen	16.95	15.76	[redacted]	2.47	3.47	[redacted]	[redacted]	[redacted]
Usual care	14.48	12.29	£189,688	-	-	-	-	-
ERG exploratory analysis 3 – patient utilities based on vignette study (Lloyd *et al*[3])								
Nusinersen	8.53	7.34	[redacted]	7.37	8.37	[redacted]	[redacted]	[redacted]
Usual care	1.15	-1.03	£185,686	-	-	-	-	-
ERG exploratory analysis 4 - caregiver utilities based on Bastida *et al*[4]								
Nusinersen	16.95	13.54	[redacted]	2.47	-0.14	[redacted]	[redacted]	[redacted]
Usual care	14.48	13.68	£185,686	-	-	-	-	-
ERG exploratory analysis 5 - ERG preferred analysis (including ERG analyses 1, 2, 3 and 4)								
Nusinersen	8.53	5.12	[redacted]	7.37	4.76	[redacted]	[redacted]	[redacted]
Usual care	1.15	0.36	£189,688	-	-	-	-	-

Table 4: Additional exploratory analyses undertaken using the ERG preferred model, later onset (including PAS)

Option	QALYs (patient)	QALYs (patient+ caregiver)	Cost	Inc. QALYs (patient)	Inc. QALYs (patient+ caregiver)	Inc. cost	ICER (patient)	ICER (patient+ caregiver)
ERG exploratory analysis 6a - patient utilities based on Bastida *et al*[4]								
Nusinersen	6.97	3.56	[redacted]	4.80	2.19	[redacted]	[redacted]	[redacted]
Usual care	2.16	1.37	£189,688	-	-	-	-	-
ERG exploratory analysis 6b - patient HRQoL estimates based on clinical judgement								
Nusinersen	15.44	12.03	[redacted]	3.54	0.93	[redacted]	[redacted]	[redacted]
Usual care	11.89	11.10	£189,688	-	-	-	-	-
ERG exploratory analysis 7 - no mortality adjustment								
Nusinersen	7.49	4.42	[redacted]	6.34	4.07	[redacted]	[redacted]	[redacted]
Usual care	1.15	0.35	£189,517	-	-	-	-	-
ERG exploratory analysis 8a- 5% nusinersen patients lose milestones each cycle								
Nusinersen	6.78	4.03	[redacted]	5.63	3.67	[redacted]	[redacted]	[redacted]
Usual care	1.15	0.36	£189,688	-	-	-	-	-
ERG exploratory analysis 8b- 10% nusinersen patients lose milestones each cycle								
Nusinersen	4.97	2.88	[redacted]	3.81	2.52	[redacted]	[redacted]	[redacted]
Usual care	1.15	0.36	£189,688	-	-	-	-	-
ERG exploratory analysis 8c- 20% nusinersen patients lose milestones each cycle								
Nusinersen	2.49	1.28	[redacted]	1.34	0.92	[redacted]	[redacted]	[redacted]
Usual care	1.15	0.36	£189,688	-	-	-	-	-
ERG exploratory analysis 8d – all patients stay in final state indefinitely after end of CHERISH								
Nusinersen	2.85	1.72	[redacted]	0.81	0.73	[redacted]	[redacted]	[redacted]
Usual care	2.04	0.98	£184,309	-	-	-	-	-
ERG exploratory analysis 8e – all patients lose all milestones after end of CHERISH								
Nusinersen	0.91	0.20	[redacted]	0.04	0.03	[redacted]	[redacted]	[redacted]
Usual care	0.88	0.17	£192,038	-	-	-	-	-

ERG comment on the company's proposed data collection strategy

The ERG makes the following observations regarding the company's proposed data collection strategy:

- Section 5.4 of the document states that no comparative data will be collected. Thus, whilst the proposed data collection strategy may reduce uncertainty surrounding longer-term outcomes for nusinersen-treated patients, it will not address uncertainty surrounding outcomes for patients receiving best supportive care. The ERG considers this a significant limitation of the proposal.
- The table presented beneath Section 5.7 of the company's document states that EQ-5D data will be collected for older children. Given the young age of patients with early onset SMA, some consideration should be given to alternative preference-based HRQoL instruments, such as the HUI-2 and the CHU-9D.
- The proposed data collection strategy will not provide information on outcomes for patients with Type 0 SMA or Type IV SMA.

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