Lead team presentation

Nusinersen for treating spinal muscular atrophy [ID1069]

Clinical effectiveness

1st Appraisal Committee meeting

Committee C

Lead team: Kamal Balakrishnan, Andrea Manca, David Chandler

Evidence Review Group: ScHARR

NICE technical team: Lulieth Torres, Ian Watson

Company: Biogen

27 June 2018

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

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
  - The lack of SMN protein causes the motor neurones to malfunction, deteriorate and eventually die
- Long term degenerative condition causing muscle weakness, and results in gradually worsening physical disabilities and mobility loss.
- Estimated that ~100 people are born with SMA per year, and 1,200–2,500 children and adults currently living with SMA, in the UK

Classification and subtypes of SMA

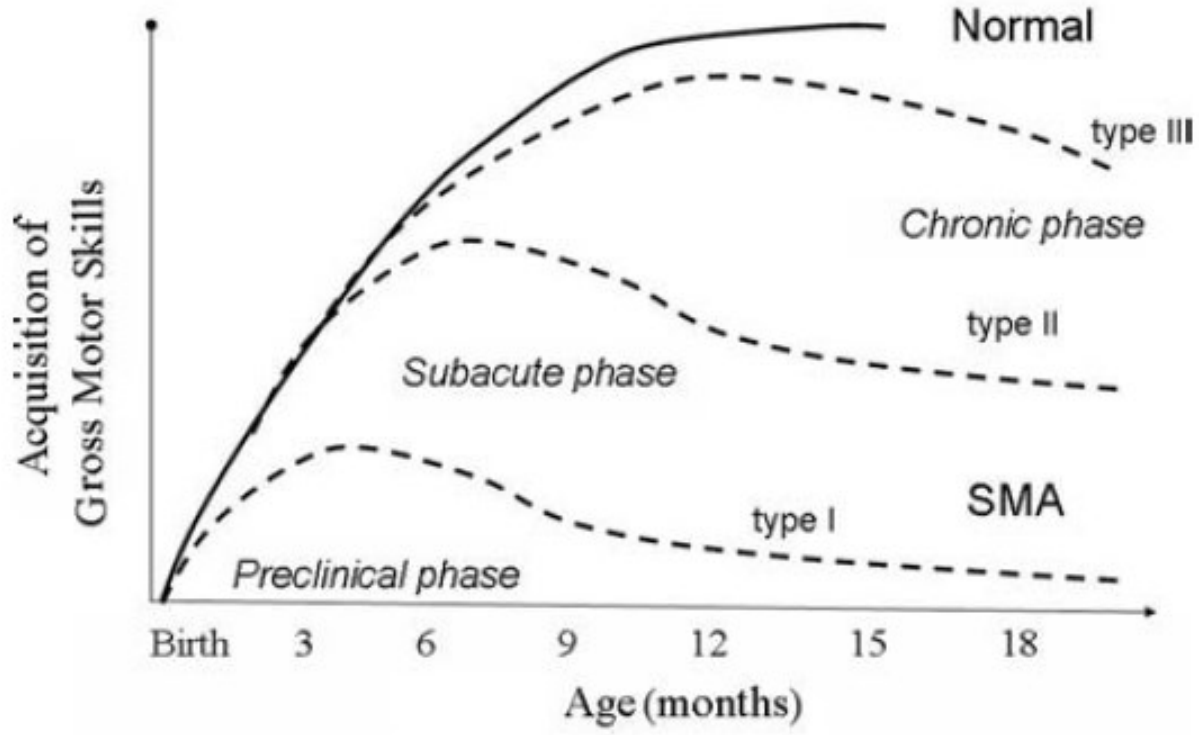
	Age of onset	Max. motor milestone	Motor ability and additional features	Survival
Type 0	Before birth	None	Severe hypotonia; unable to sit and roll	Respiratory insufficiency at birth: death within weeks
Type 1	2 weeks (Ia) 3 months (Ib) 6 months (Ic)	None	Severe hypotonia; unable to sit and roll	Death/ventilation 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.

Symptoms and complications (1)

- Pre-symptomatic period → rapidly progressive functional loss → relatively static phase with slow progression
- The severity of the symptoms is heterogeneous
- 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, shoulder and pelvic girdle muscle are most affected
  - Chest infections due to muscle weakness
  - Nutritional and gastrointestinal complications: difficulties eating, swallowing, breathing and bowel movements
  - Orthopaedic problems: posture, contractures, scoliosis, hip subluxation
  - Fatigue
- Despite these symptoms, cognitive ability is normal

Symptoms and complications (2)



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

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' group *submissions*

- "*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.*" - **Muscular Dystrophy UK**

- *"There is currently no treatment for SMA. Nusinersen is an innovative treatment that addresses a totally unmet need and has the potential to life-saving and life-changing benefits to patients."* - **The SMA Trust**

- *"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."* - **Spinal Muscular Atrophy Support UK**

- *"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."* –**TreatSMA**

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

Important issues:

- Variability of type 1
- Do not neglect type 2 and 3
- Real life perception v trial data
- Improvement and slowing deterioration
- Reliance on carers
- Importance of independence
- Psychosocial effects
  - Anxiety, depression, frustration

Dealing with the prognosis:

- Confronting premature death
- Difficult treatment choices
- Financial pressure
- Lost expectations

Living with symptoms:

- Loss of sleep, stress
- Uncertainty, helplessness
- Fear at loss of abilities

Social interactions:

- Social discomfort and stigma
- Limitations on social activities
- Struggle to achieve independence

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

- **Physical burden,**
  - Lifting and carrying
  - Deterioration of quality of life due to lack of sleep.
- **Emotional suffering**
  - Stress
  - Need for constant vigilance
  - Effects on wider family, particularly siblings and grandparents
- **Financial pressure**
  - Need for equipment and adaptations
  - Reduced income

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

"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"

"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 "

"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"

"*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*"

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 Simple discount PAS proposed (not formally approved; to be discussed in Part 2)
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	Children with 5q SMA with infantile (type 1) or later onset (types 2/3)	Narrower than the marketing authorisation (all patients with 5q SMA). Evidence focuses on children with types 1–3 SMA, 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

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 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	• People with SMA type 1 • Two copies of the *SMN2* gene • Onset <6 months of age, <7 months of age at screening	• People with SMA type 2–3 • Onset >6 months of age • Age 2–12 years • Sit independently but never walk independently • HFMSE score of 10 to 54
Dosing	12 mg on days 1, 15, 29, and 64, then every 4 months	12 mg on days 1, 29, 85, then 6 months later

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

Clinical evidence: ENDEAR and CHERISH (2)

	ENDEAR (early onset)	CHERISH (later onset)
Outcomes	• Motor function (CHOP INTEND and HINE-2) milestones (HINE-2) • Event-free survival	• Motor function (HFMSE) • Motor milestones (e.g. WHO milestones) • Upper limb function (RULM)

- Primary outcome of ENDEAR based on 'HINE-2 responders', defined as: ≥2-point increase 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
  - Novel outcome – not previously used, unclear whether there is evidence of an associated with functionally important outcomes

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

	Nusinersen (N=80)	Control (N=41)
Female	54%	59%
[redacted]	[redacted]	[redacted]
Age at symptom onset - mean (range), week	7.9 *(2–18)*	9.6 *(1–20)*
Disease duration at screening - mean (range), week	13.2 *(0–26)*	13.9 *(0–23)*
Age at first dose - mean (range), week	32.6 *(10–48)*	36.2 *(6–52)*
[redacted]	[redacted]	[redacted]
SMA symptoms (%)		
Hypotonia	100	100
Developmental motor delay	89	95
Paradoxical breathing	89	66
Pneumonia or respiratory symptoms	35	22
Swallowing or feeding difficulties	51	29
Use of a ventilation support	26%	15%
Use of a gastrointestinal tube, n (%)	9%	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)

HINE-2 - Module 2 of the Hammersmith Infant Neurological Examination; CHOP INTEND, Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders.

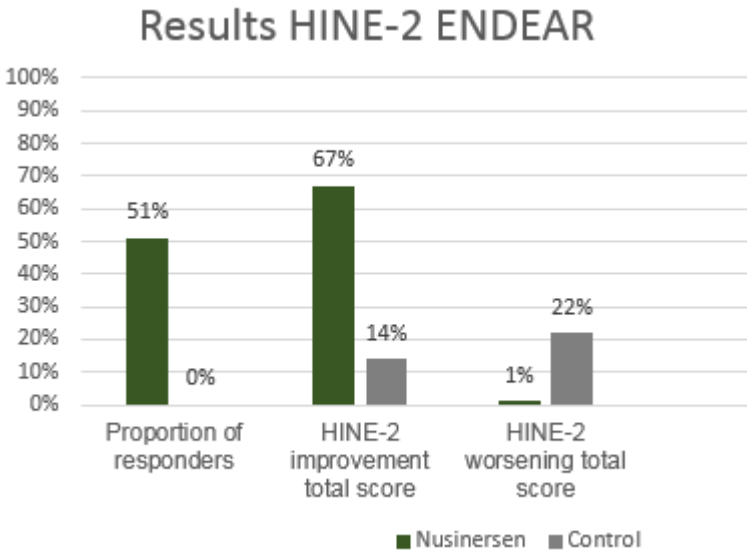
Baseline characteristics – **CHERISH** *(later onset)*

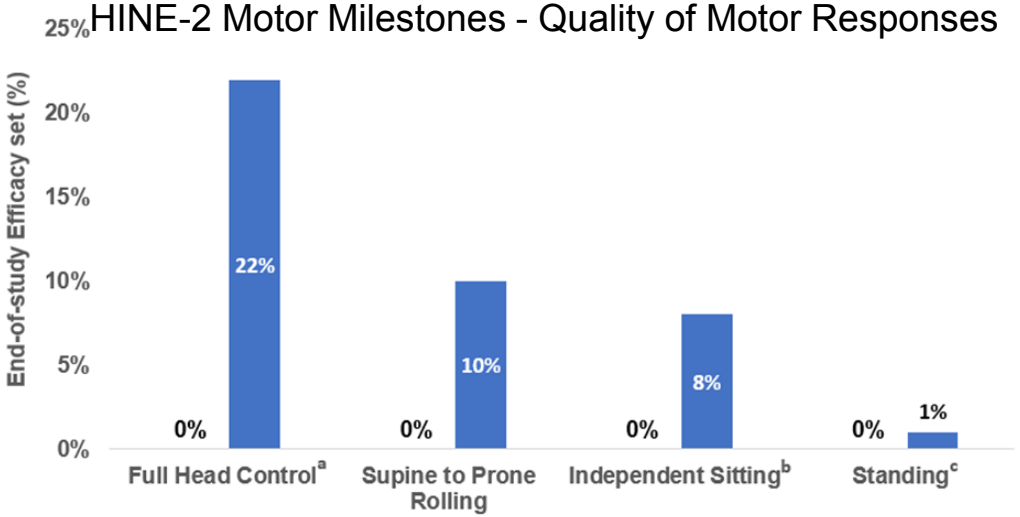
	Nusinersen (N=84)	Control (N=42)
Female	55%	50%
White	76%	71%
Age at symptom onset - median (range), months	10.0 (6–20)	11.0 (6–20)
Age at screening - median (range), months	48 (24–108)	36 (24–84)
Disease duration - median (range), months	39.3 (8–94)	30.2 (10–80)
Disease duration - median (range), months	39.3 (8–94)	30.2 (10–80)
SMN2 copy number, 2/3/4/unknown, %	7/88/2/2	10/88/2/0
Children who have ever achieved motor milestone Sat without support Walked with support Stood without support Walked ≥15 feet independently	 100% 24% 13% 0%	 100% 33% 29% 05
Children using a wheelchair	76%	69%
Mean (SD) HFMSE total score	22.4 (8.3)	19.9 (7.2)

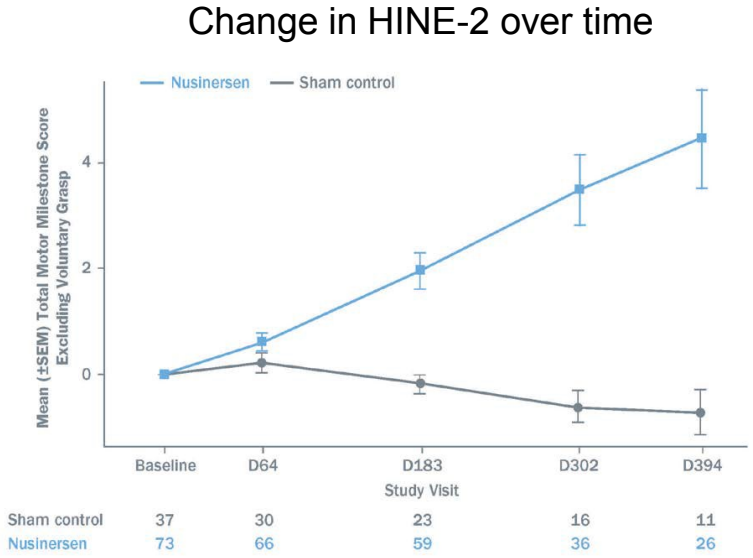
Results – **ENDEAR** *(early onset)* Motor function

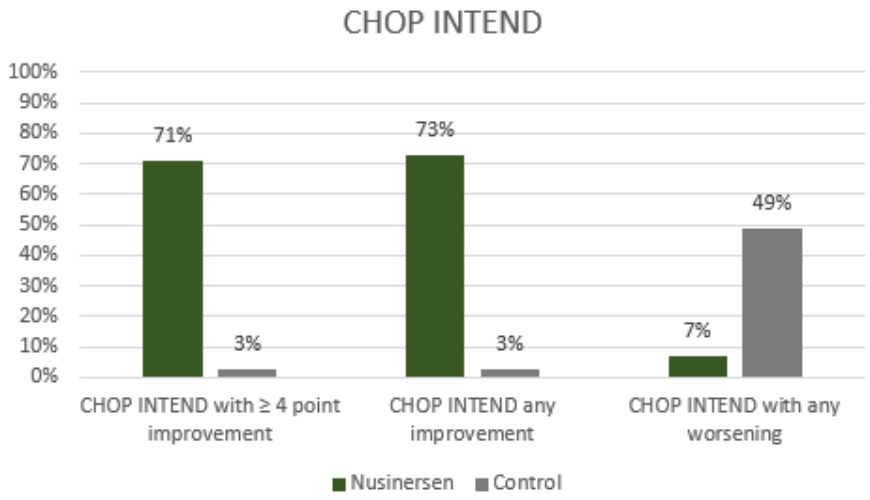
Outcome	Nusinersen	Control	Difference (95% CI)
Proportion of motor milestone responders (HINE-2) • improvement in total score • worsening in total score	37 (51%) 49 (67%) 1 (1%)	0 (0%) 5 (14%) 8 (22%)	[redacted] p<0.0001
CHOP INTEND with ≥4 point improvement	52 (71%)	1 (3%)	[redacted] p<0.001
CHOP INTEND 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

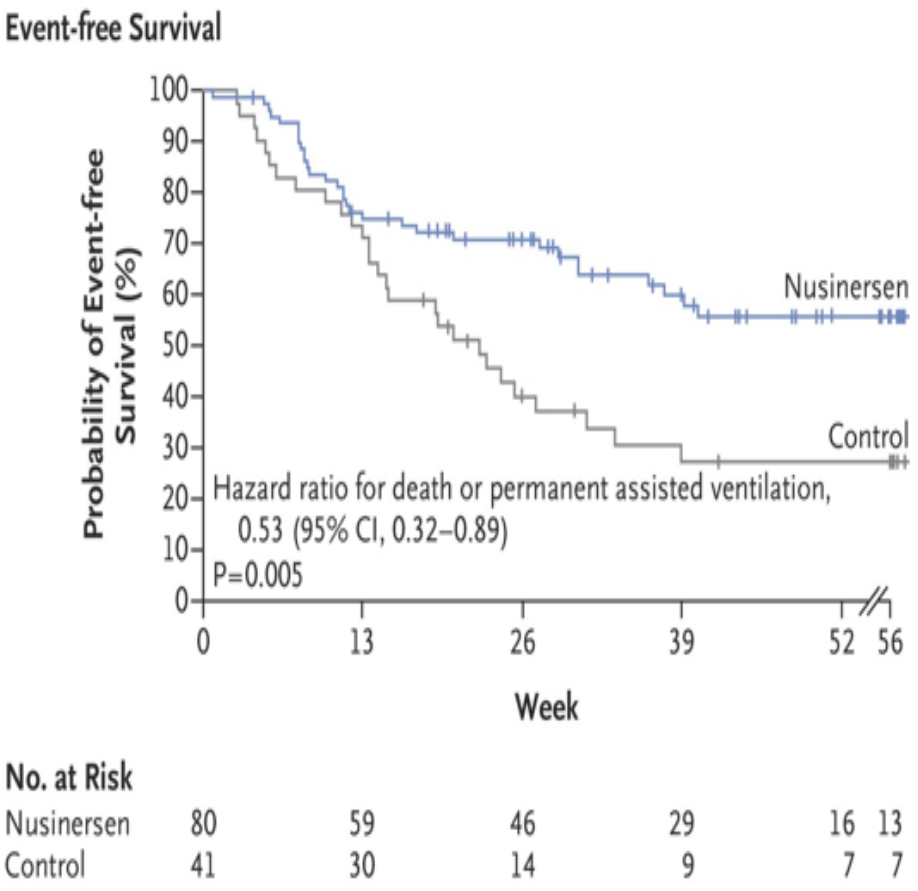


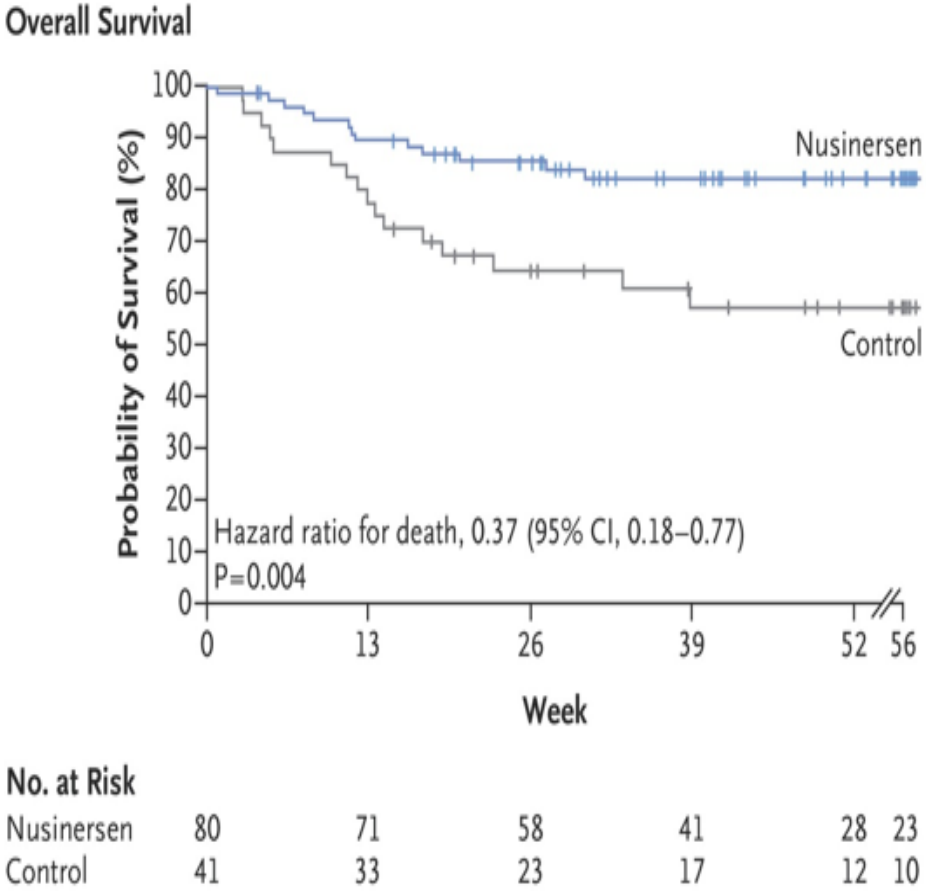






Results – **ENDEAR** (early onset) Event-free survival and overall survival





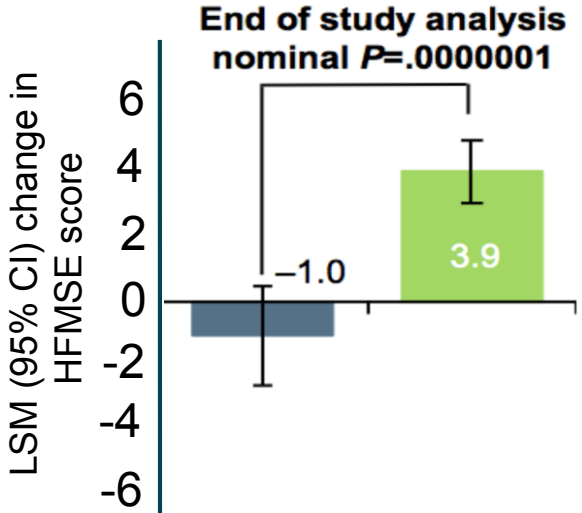
Statistically significant increases in both EFS (p=0.005) and OS (p=0.004) were observed for the nusinersen group

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

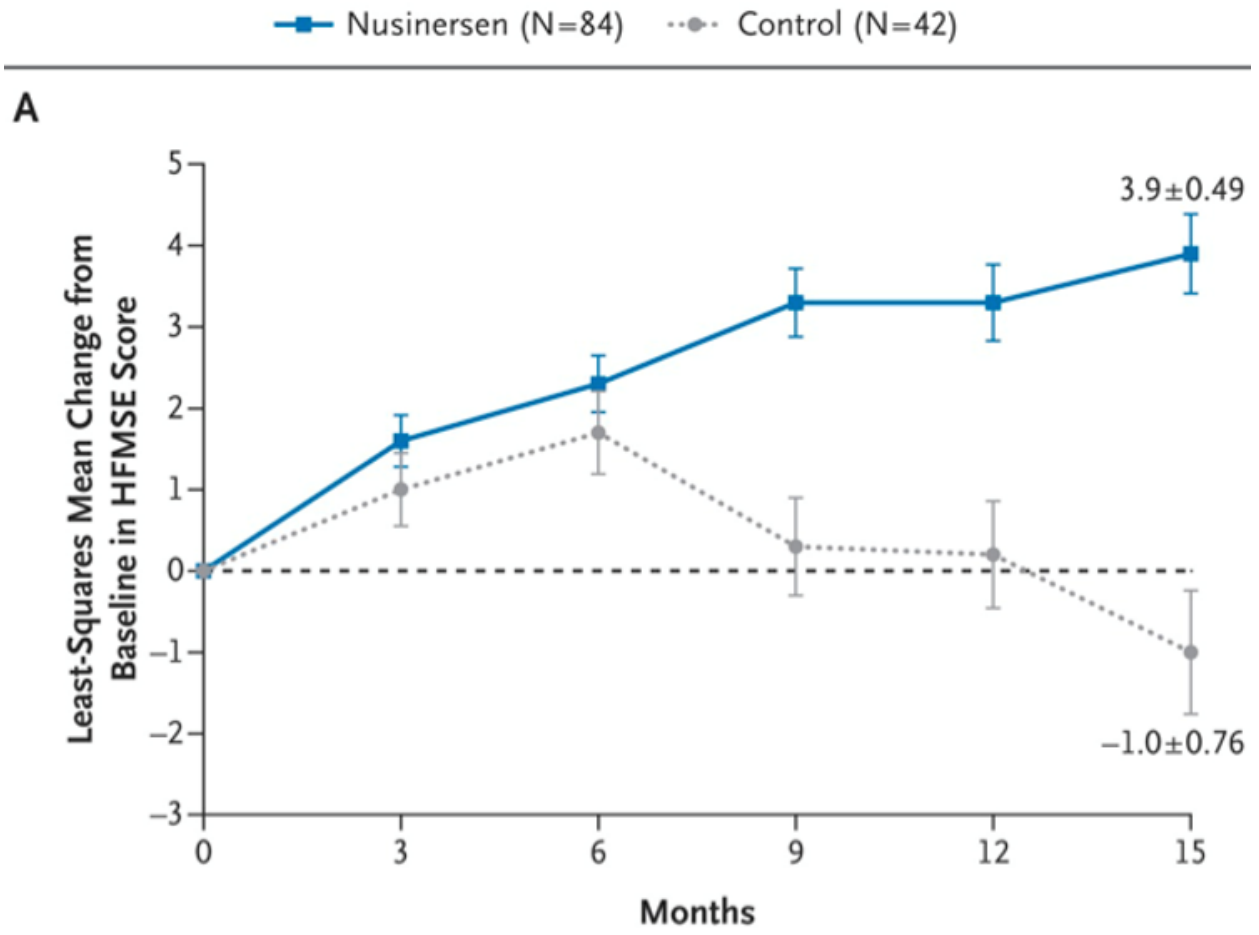
	Nusinersen	Control	
Respiratory function: annualised rate of serious respiratory events	[redacted]	[redacted]	[redacted]
Ventilation: % time on ventilator (LSM adjusted for baseline age and disease duration)	[redacted]	[redacted]	[redacted]
Hospitalisations: Adjusted annualised rate (per yr) Overall 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)
- Infants in the interim analysis had been in the study for a median of 317.5 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

- Greater treatment benefits were observed for younger children and those treated earlier in their disease course
- ENDEAR (below):
  - 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 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
- **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 had moderate risk of bias – concerns about blinding, outcome reporting and imbalance in dropouts
- 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
  - 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

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  - Dosing regimen
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- How effective is nusinersen?
  - Early and later-onset SMA
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Lead team presentation

Nusinersen for treating spinal muscular atrophy [ID1069]

Cost effectiveness

1st Appraisal Committee meeting

Committee C

Lead team: Kamal Balakrishnan, Andrea Manca, David Chandler

Evidence Review Group: ScHARR

NICE technical team: Lulieth Torres, Ian Watson

Company: Biogen

27 June 2018

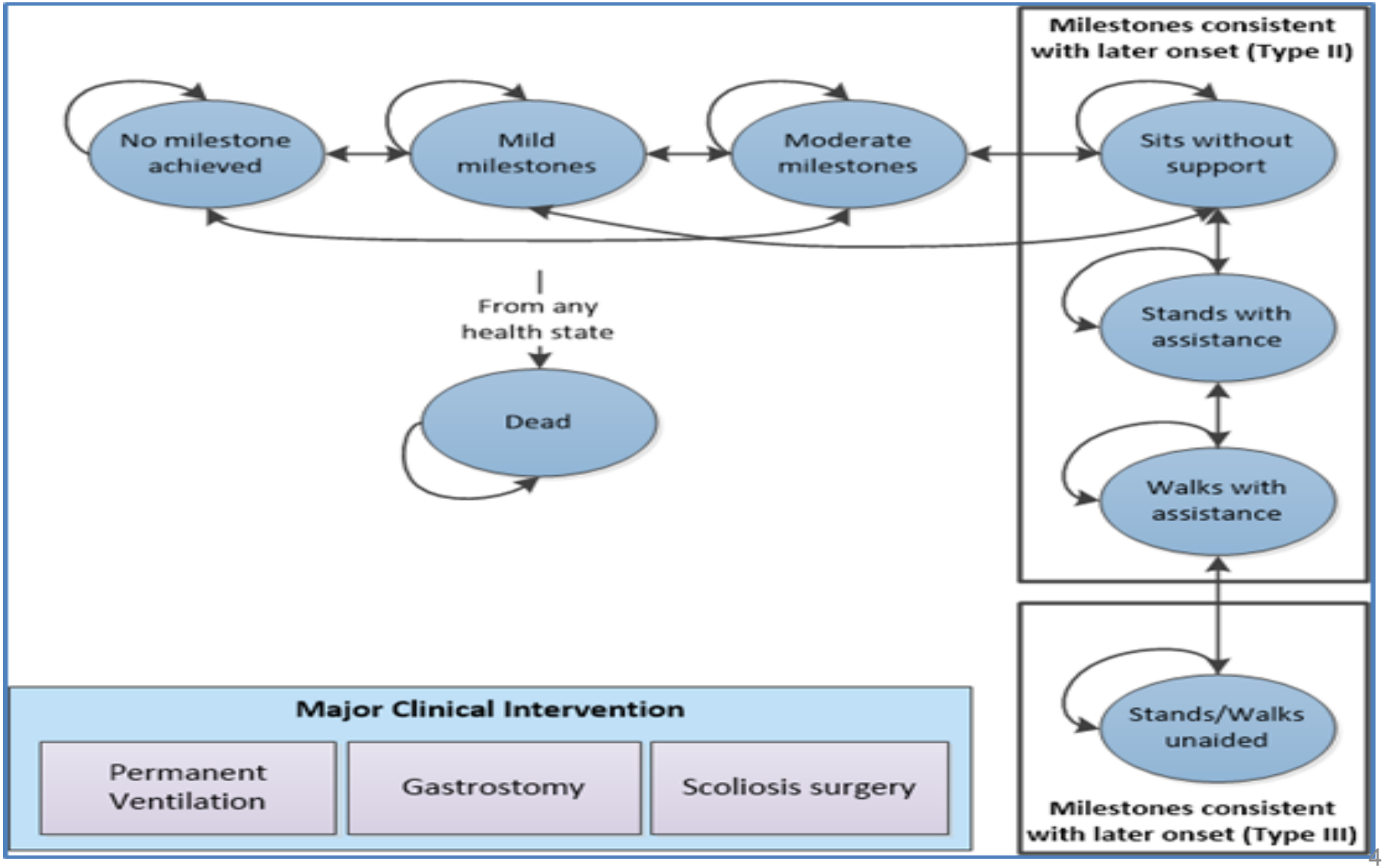
Key issues
Cost effectiveness

- 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?

Economic model – approach

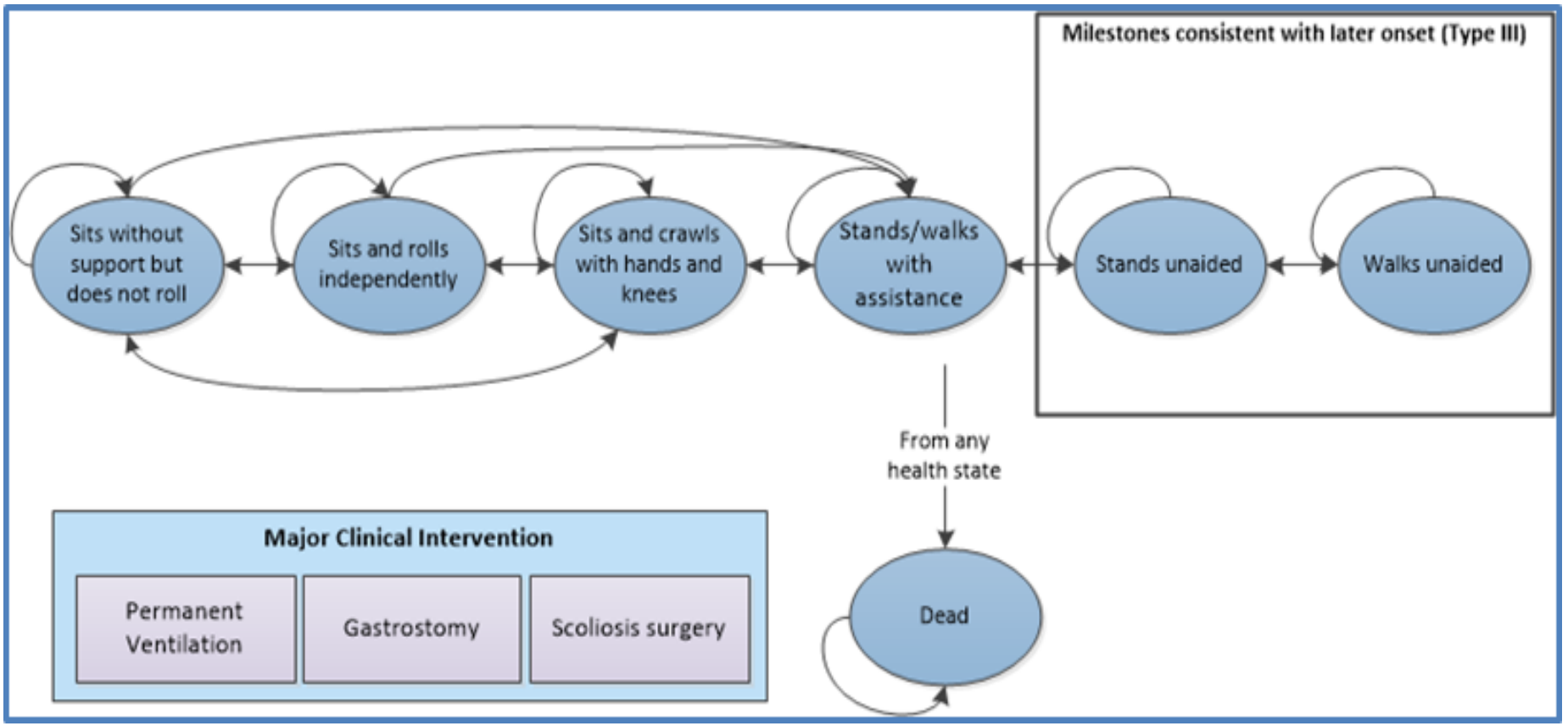
- Company presented 2 separate models:
  - **Early-onset**: SMA type 1
    - Initial age: 5.58 months
  - **Later-onset**: SMA type 2/3
    - Initial age: 43.71 months
- State transition approach, based on motor function milestones
  - Early-onset: HINE-2
  - Later-onset: HFMSE and WHO criteria
- Nusinersen 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

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:
  - During study follow-up: observed data (ENDEAR and CHERISH, supplemented by phase II trials)
  - 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

Overall survival (1)

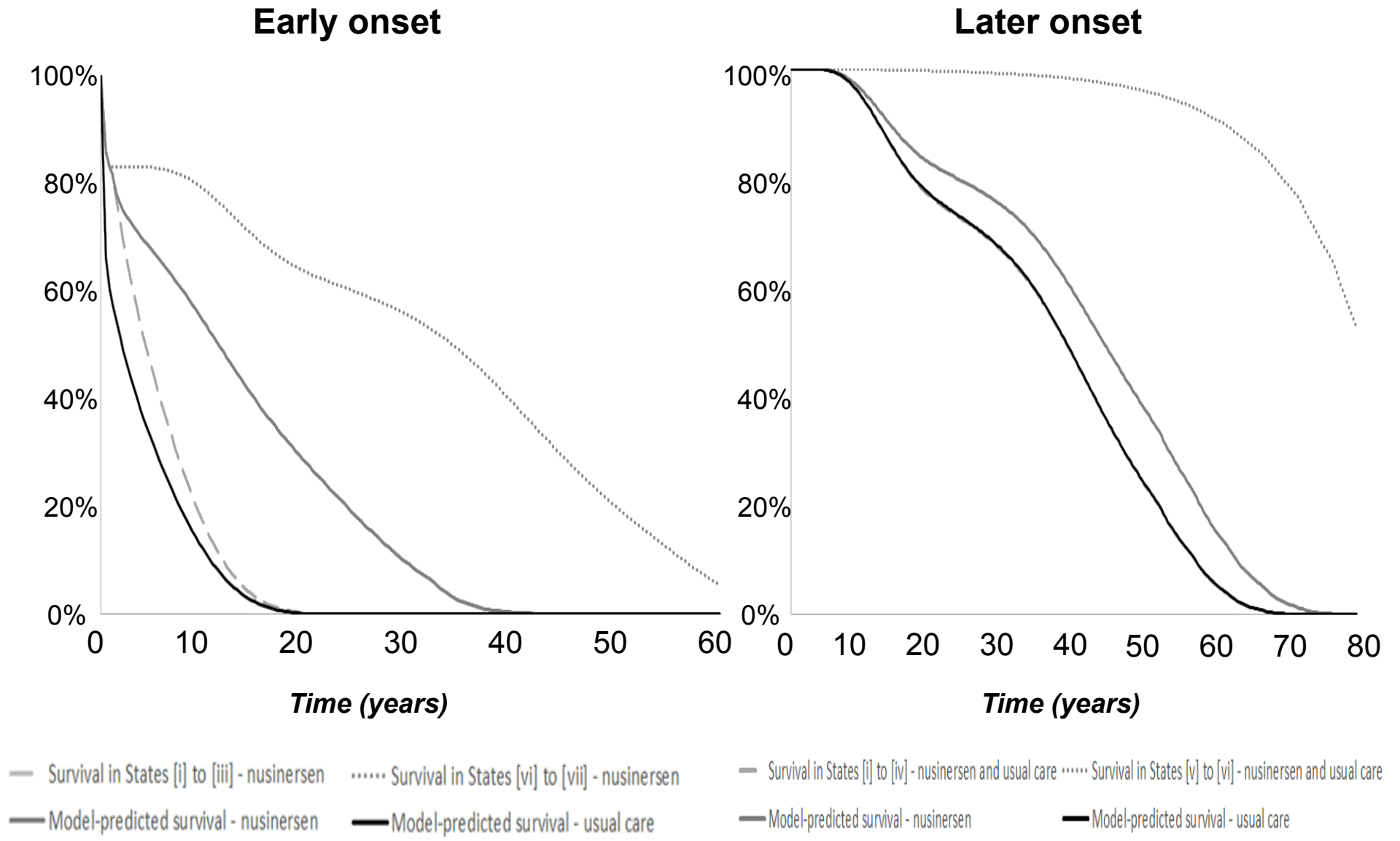
- In both models, after trial follow-up the company applied a mortality adjustment to the best health states, such that patients had a similar mortality risk to people with less-severe forms of SMA
  - **Early onset**: states 4–7: survival based on 10% of SMA type 1 mortality risk and *90% of SMA type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



Health-related quality of life

Patients

- 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
- Alternative analyses based on utilities obtained using vignettes

Carers

- Impact of SMA on carers captured by applying carer dis-utilities to each health state
  - Based on cross-sectional study of SMA patients (Bastida et al: [redacted]), adjusted for each health state and compared with general population utility
- Disutility due to bereavement: -0.04

Treatment cost

- Nusinersen acquisition cost: list price £75,000 per 12-mg vial
  - PAS proposed (not formally approved; to be discussed in Part 2)
- Administered via lumbar puncture
  - 40% inpatient, 30% outpatient, 30% day case: £606–£1,359 per admin
- 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

- Sourced from cross-sectional SMA study (Bastida et al)
  - Caregivers and people with SMA provided information about professional and informal care, expenditure and disease-related resource use
  - 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 and scenario analyses

DSA

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

Scenario analyses

- Company presented scenario analyses exploring time horizon, effectiveness/disease progression, costs and utilities
- Results varied as follows:

Early onset	
Lowest ICER (list price)	**Highest ICER** (list price)
100% SMA2 mortality risk: £347,082	No SMA2 mortality risk: £872,257
Later onset	
Lowest ICER (list price)	**Highest ICER*** (list price)
100% SMA3 mortality risk: £734,749	No SMA3 mortality risk: £2,324,278

*Slightly higher ICER seen in scenario with 20-year time horizon

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 comments – Modelling approach

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

ERG comments – Transition probabilities (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 – some patients improving and some deteriorating

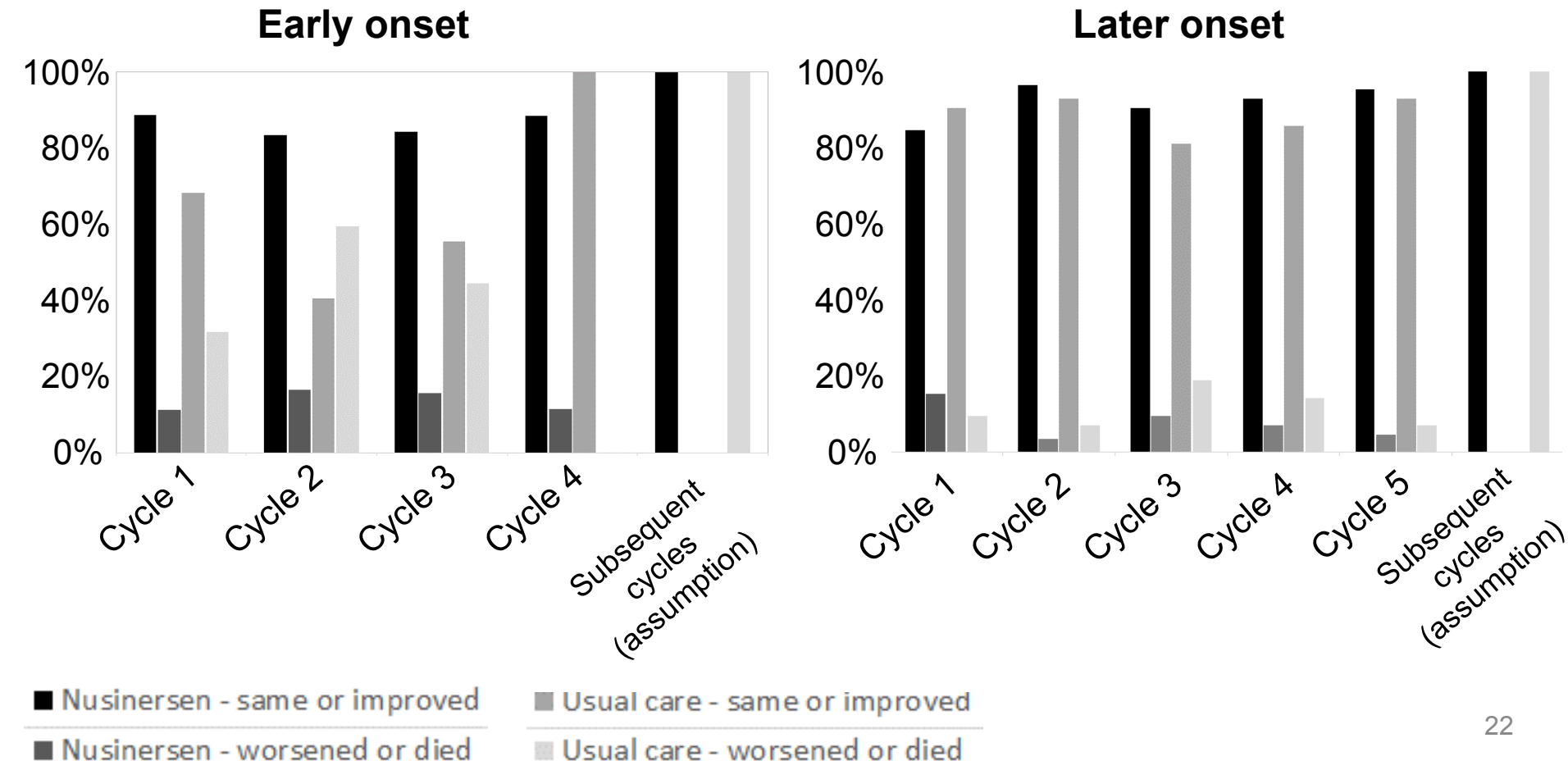
Calculation of transition probabilities

- 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

ERG comments – Transition probabilities (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

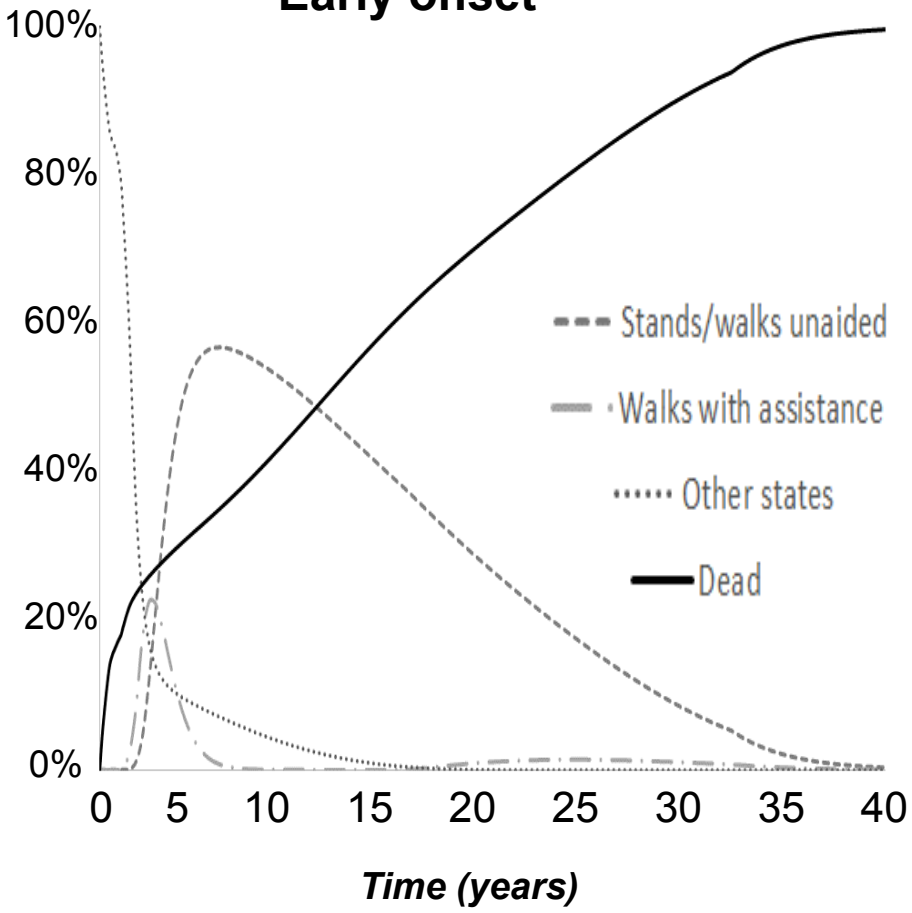


ERG comments – Transition probabilities (3)

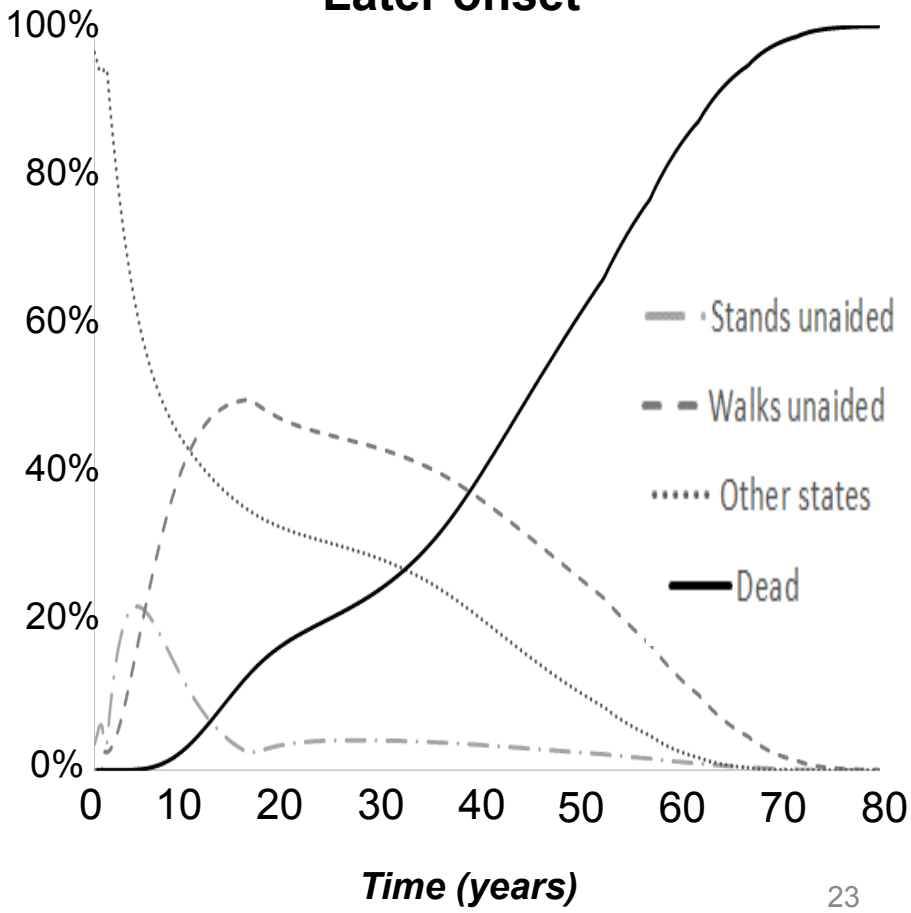
Consistency between observed and modelled data (cont)

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

Early onset



Later onset



ERG comments – Overall survival

ERG: the modelled overall survival was optimistic

- Complexity of approach
  - Key assumptions in company approach were insufficiently justified
  - Simpler parametric extrapolation may be more plausible and transparent
- Use of external data
  - Gregoretti et al: unclear if results are applicable to clinical practice and ENDEAR
  - Zerres et al: unclear if population was similar to CHERISH
  - General population: proportional hazards assumption unlikely to hold
- Treatment effect – ***key concern***
  - OS benefit primarily driven by lower mortality in better health states (adjustment to type 2 SMA mortality)
  - ***Weight applied to type 2 SMA mortality (90%) insufficiently justified***
    - ***Clinical advisers considered this a large and optimistic assumption***

ERG comments – Health-related quality of life

Patients

- Company's utility values had poor face validity – high valuations in poor health states, limited range
- Mapping for PedsQL is limited – based on healthy children aged 11–15, uses adult valuation set, analysis used OLS
- Alternative utilities available from Bastida et al (parent proxy, by SMA type) and Lloyd et al (vignettes valued by clinicians)
  - Do not have the same methodological limitations, but still have limited face validity – e.g. very low valuations
  - Although none were ideal, of the 3 sources ERG preferred the vignette study

Carers

- Company's approach was not sufficiently justified
  - Carer impact is proportional to the impact of disease for each state
  - Limitations of patient utilities affects calculation of carer utilities
  - Calculations are arbitrary
- Alternative carer utilities (by SMA type) are available from Bastida et al

Health-related quality of life – summary of utility values

Early onset	Patients		Carers	
	Base case	Lloyd et al	Base case	Bastida et al
No milestones	[redacted]	-0.24	[redacted]	[redacted]
Mild milestones	[redacted]	-0.12	[redacted]	[redacted]
Moderate milestones	[redacted]	-0.17	[redacted]	[redacted]
Sits wo support	[redacted]	-0.04	[redacted]	[redacted]
Stands w assistance	[redacted]	0.04	[redacted]	[redacted]
Walks w assistance	[redacted]	0.52	[redacted]	[redacted]
Stand/walks wo assistance	[redacted]	0.71	[redacted]	[redacted]

Later onset	Patients		Carers	
	Base case	Lloyd et al	Base case	Bastida et al
Sits wo support	[redacted]	0.04	[redacted]	[redacted]
Sits and rolls	[redacted]	0.04	[redacted]	[redacted]
Sits and crawls	[redacted]	0.10	[redacted]	[redacted]
Stands/walks w assistance	[redacted]	0.39	[redacted]	[redacted]
Stands wo assistance	[redacted]	0.72	[redacted]	[redacted]
Walks wo assistance	[redacted]	0.72	[redacted]	[redacted]

Utilities in the best and worst states have most influence on the results

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 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 (1)

- Company considers end of life criteria to apply to the early onset population
  - Company: 'survival free of permanent ventilation' is more relevant than overall survival, as permanent ventilation may not be used

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 may not reflect current practice; some patients with less-severe disease may survive to school age Mean survival with usual care in the model: 3.87 years

End-of-life (2)

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?